

# Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents

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## Supporting Information

**ABSTRACT:** Despite their wide use in academia as metal-carbene precursors, diazo compounds are often avoided in industry owing to concerns over their instability, exothermic decomposition, and potential explosive behavior. The stability of sulfonyl azides and other diazo transfer reagents is relatively well understood, but there is little reliable data available for diazo compounds. This work first collates available sensitivity and thermal analysis data for diazo transfer reagents and diazo compounds to act as an accessible reference resource. Thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and accelerating rate calorimetry (ARC) data for the model donor/acceptor diazo compound ethyl (phenyl)-diazoacetate are presented. We also present a rigorous DSC dataset with 43 other diazo compounds, enabling direct comparison to other energetic materials to provide a clear reference work to the academic and industrial chemistry communities. Interestingly, there is a wide range of onset temperatures ( $T_{\text{onset}}$ ) for this series of compounds, which varied between 75 and 160 °C. The thermal stability variation depends on the electronic effect of substituents and the amount of charge delocalization. A statistical model is demonstrated to predict the thermal stability of differently substituted phenyl diazoacetates. A maximum recommended process temperature ( $T_{\text{D24}}$ ) to avoid decomposition is estimated for selected diazo compounds. The average enthalpy of decomposition ( $\Delta H_{\text{D}}$ ) for diazo compounds without other energetic functional groups is  $-102 \text{ kJ mol}^{-1}$ . Several diazo transfer reagents are analyzed using the same DSC protocol and found to have higher thermal stability, which is in general agreement with the reported values. For sulfonyl azide reagents, an average  $\Delta H_{\text{D}}$  of  $-201 \text{ kJ mol}^{-1}$  is observed. High-quality thermal data from ARC experiments shows the initiation of decomposition for ethyl (phenyl)diazoacetate to be 60 °C, compared to that of 100 °C for the common diazo transfer reagent *p*-acetamidobenzenesulfonyl azide (*p*-ABSA). The Yoshida correlation is applied to DSC data for each diazo compound to provide an indication of both their impact sensitivity (IS) and explosivity. As a neat substance, none of the diazo compounds tested are predicted to be explosive, but many (particularly donor/acceptor diazo compounds) are predicted to be impact-sensitive. It is therefore recommended that manipulation, agitation, and other processing of neat diazo compounds are conducted with due care to avoid impacts, particularly in large quantities. The full dataset is presented to inform chemists of the nature and magnitude of hazards when using diazo compounds and diazo transfer reagents. Given the demonstrated potential for rapid heat generation and gas evolution, adequate temperature control and cautious addition of reagents that begin a reaction are strongly recommended when conducting reactions with diazo compounds.

**KEYWORDS:** differential scanning calorimetry, diazo compound, diazo transfer, sulfonyl azide, process safety

## INTRODUCTION

The choice of synthetic route in process development is multifactorial and often governed by reagent costs, product yield and purity, environmental impact, robustness, and, most importantly, safety.<sup>1,2</sup> Chemical transformations from commercial reagents to the desired product are evaluated holistically with these principles in mind, and a route is devised using available synthetic methods. Certain classes of reagents are essentially excluded from a process chemist's toolkit due to safety concerns. To determine whether reagents are acceptable to use in a scaled process requires the practical assessment of specific hazardous properties.<sup>3</sup>

Energetic materials pose specific explosive hazards, resulting from the high quantities of heat and gas that can be released upon rapid decomposition. There are several metrics commonly used to assess a reagent.<sup>4</sup> These can be grouped into risk assessment categories determining the likelihood or severity of an unwanted decomposition. The likelihood will be proportional to the activation energy term of an Arrhenius equation for the decomposition reaction. Thermal stability is a measure of the temperature at which a compound is observed

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to pyrolyze. Sensitivity to several stimuli can be exhibited by energetic materials, defined by specialist tests with results quoted in comparison to well-known sensitive materials. The cause of sensitive behavior is a complex phenomenon, and there is currently no theoretical way to predict sensitivity.<sup>5</sup> Impact (or shock) sensitivity (IS)<sup>6</sup> can be the most relevant for a chemical process, but friction, electrostatic discharge (ESD), or other sensitivities such as to light may also be relevant.<sup>7</sup> On the other hand, metrics related to severity will be primarily concerned with the magnitude of the heat produced in an exothermic process ( $\Delta H_R$ ). Other important considerations include whether a material can sustain a detonation<sup>8</sup> and the amount of pressure generated by evolved gases.

These concepts are defined from an experimental basis, with reference to well-studied materials; so, there is no inherent property to determine. 1,3,5-Trinitro-1,3,5-triazinane (RDX) is often used as a reference compound by explosive material scientists;<sup>9</sup> for organic or process chemists, 1,3-dinitrobenzene (*m*-DNB) is a more appropriate, conservative reference.<sup>10</sup> These tests are notorious for reproducibility as a large number of factors can alter the result: from test methodology to the presence of air bubbles in liquid samples,<sup>10</sup> or the crystal structure<sup>5b</sup> or particle morphology of a solid sample.<sup>4</sup> The measurement obtained will therefore depend upon the idiosyncrasies of the specific method used, and as such, full and accurate reporting of all experimental aspects is vital. Ideally, measurements should be conducted on the same setup and performed at the same time. Such tests require specialist test equipment not commonly available outside energetic material labs and consume decagram quantities of material.

Differential scanning calorimetry (DSC) is a valuable screening tool in process safety, providing information on both likelihood and severity characteristics related to a reaction or compound. The energy change of a sample crucible is monitored vs an inert reference crucible as the temperature is controlled, usually following a steady temperature ramp. Thermal stability and exotherm magnitude can be easily and rapidly obtained using this technique from small quantities of a sample (~mg). However, DSC lacks the high sensitivity of other techniques and does not provide valuable pressure data, such as with accelerating rate calorimetry (ARC). Energetic compounds, which evolve gas upon decomposition, must be analyzed in a sealed DSC crucible capable of withstanding the generated pressure to avoid misleading results.<sup>11</sup>

DSC results generally include the enthalpy of decomposition ( $\Delta H_D$ ), which indicates the energetic yield of the decomposition, as well as initiation ( $T_{init}$ ) and/or extrapolated onset temperatures ( $T_{onset}$ ), which represent thermal stability.  $T_{init}$  is defined by the temperature at which the heat flow is measured to be  $>0.01 \text{ W g}^{-1}$  from the baseline.  $T_{onset}$  is defined by the intersection of the extrapolated maximum peak slope and the baseline, often determined by DSC software. Typically, for process safety purposes, only  $T_{init}$  is used, and to complicate matters, it is often named  $T_{onset}$ . It is important to note that unlike melting points, decomposition reactions have a kinetic factor and decomposition will occur at lower temperatures than  $T_{init}$  albeit at an exponentially slower rate.

Diazo compounds are energetic materials that find extensive application in chemical synthesis as versatile synthetic intermediates, but almost exclusively in academic labs.<sup>12</sup> Such compounds present powerful bond-forming potential via the (catalytic) generation of metal carbenes and offer important synthetic disconnections, relevant to the preparation

of pharmaceutically relevant motifs. The most valuable transformation is arguably the reaction with alkenes to form cyclopropanes.<sup>13,14</sup> In a rare large-scale example, a styryl-diazoester was employed by Bristol-Myers Squibb in an enantioselective cyclopropanation in a multikilogram synthesis of Beclabuvir,<sup>15</sup> using the  $\text{Rh}_2(\text{S-DOSP})_4$  catalyst reported by Davies.<sup>16</sup> Carbene C–H insertion processes are becoming increasingly controlled, with potential to streamline synthetic routes.<sup>17</sup> Similarly, heteroatom X–H insertion reactions ( $X = \text{O}, \text{N}, \text{S}, \text{and P}$ )<sup>18–20</sup> and cycloaddition reactions<sup>21</sup> can install important pharmaceutically relevant functionality and heterocycles. Despite these available transformations, the diazo functional group is essentially avoided for reactions at process scale, due to the potential explosion hazard.<sup>22</sup>

The available data on the thermal hazards of diazo compounds is limited and disparate. Rarely is thermal hazard data presented, and it is common in the academic literature to make general comments as to the potential stability hazards, along the lines, of “Caution: while we never experienced any problems, diazo compounds are presumed to be potentially explosive”. Here, we have collated all available data on diazo compounds from the literature (Table 1). This data is largely from DSC experiments, though other results are quoted where this is not available. We have included  $\Delta H_D$  in  $\text{J g}^{-1}$  and in  $\text{kJ mol}^{-1}$ . For process safety, the  $\Delta H$  value is often reported in  $\text{J g}^{-1}$ , as this can be divided by the specific heat capacity ( $c_p$  in  $\text{J g}^{-1} \text{K}^{-1}$ ) to gauge the adiabatic temperature rise ( $\Delta T_{ad}$ ) of a defined mixture to give an idea of the severity of a runaway exotherm.<sup>2</sup> Impact sensitivity (IS) is given where it is available. If an explosion has been reported, it is noted though the root cause is often unclear and an absence of reports should not be interpreted as an absence of explosive behavior. The data presented in Table 1 should be treated with caution as exact details of experimental methods are often not reported and there are inconsistencies in the use of terminology within the reported literature.

The extremely unstable and explosive nature of alkyl diazo compounds has been evident since their discovery in the late 1890s,<sup>45</sup> and they are rarely isolated as a result. Diazomethane **1** is the simplest diazo compound and is a highly sensitive, explosive gas.<sup>46</sup> Widely known to explode at the slightest provocation, including exposure to direct sunlight, chipped glassware, or ground-glass joints,<sup>24</sup> its extreme sensitivity and gaseous nature are a barrier to precisely investigating the initiation of the decomposition using standard techniques. While generally agreed to decompose above  $100 \text{ }^\circ\text{C}$ ,<sup>25</sup> the difficulty in ensuring the reaction is triggered thermally makes the accurate determination of the thermal stability impractical.<sup>26</sup> Given the well-known hazards, the specter of diazomethane is perhaps one reason that diazo compounds are often avoided in the pharmaceutical industry. There are a few examples of industrial interest in diazomethane, leveraging continuous flow processes to generate and consume the reagent in situ with increased safety.<sup>47</sup>

Pure phenyl diazomethane **2**,<sup>28</sup> the 4-methoxyphenyl-analogue **3**,<sup>29</sup> and diazoacetonitrile **4**<sup>30,31</sup> are reported to explode spontaneously, although this list is not exhaustive. When required, these monosubstituted, low-molecular-weight diazo compounds are generally prepared in situ for immediate use in one-pot protocols or continuous flow processes.<sup>48</sup> Due to their violently short-lived nature, the isolation of quantities sufficient for stability or sensitivity testing is impractical. The so-called “semistabilized” diazo compounds with a conjugated

Table 1. Impact Sensitivity (IS), Thermal Stability, and Exotherm Data Previously Reported for Diazo Compounds<sup>10,15,24–44</sup>

entry	diazo compound	IS (J)	explosion reported?	thermal analysis <sup>23</sup>				ref	
				heating rate (°C min <sup>-1</sup> )	T <sub>init</sub> (°C) <sup>a</sup>	T <sub>onset</sub> (°C) <sup>a</sup>	ΔH <sub>D</sub> (J g <sup>-1</sup> ) <sup>a</sup>		ΔH <sub>D</sub> (kJ mol <sup>-1</sup> ) <sup>a</sup>
1		very sensitive	24, 25, 26, 27	n.a. <sup>b</sup>	>100	est. -4300 to -7000	est. -180 to -297	26	
2		very sensitive	yes					28	
3		very sensitive	yes	reported to slowly decompose at -80 °C				29	
4		very sensitive	yes					30, 31	
5			yes					32	
6			yes					33	
7	EDA		cannot sustain detonation <sup>34</sup>	5 n.a. <sup>d</sup> n.a. <sup>b</sup>	55 <sup>d</sup> 65 <sup>e</sup>	101 <sup>e</sup> -1499 <sup>e</sup> -1560 <sup>d</sup> -1358	-171 <sup>e</sup> -178 <sup>d</sup> -155	35 36	
8	DDNP	1.5 <sup>37</sup>	primary explosive <sup>37</sup>	5 10		178 <sup>f</sup> 155	-2075 -436	38 10	
9				5		201 <sup>f</sup>		38	
10				5		203 <sup>f</sup>		38	
11				n.a. <sup>b</sup>	90 <sup>e</sup>	120 <sup>e</sup>		39	
12				n.a. <sup>b</sup> 5	86 <sup>e</sup> 77 <sup>e</sup>	115 <sup>e</sup> 108 <sup>e</sup>	-706 -863	-124 -152	40 41
13				n.a. <sup>b</sup>		77 <sup>g</sup>	-900	-182	42
14				n.a. <sup>b</sup>		108 <sup>h</sup>			43
15				n.a. <sup>b</sup>		42 <sup>g</sup>	-872	-176	15
16				10	90 <sup>e</sup>	91	-658	-255	44
17				10	76 <sup>e</sup> 190 <sup>e,j</sup>	102 194 <sup>j</sup>	-293 -112	-175 -67 <sup>j</sup>	44
18				n.a. <sup>b</sup>	125 <sup>e</sup> 205 <sup>e,j</sup>	152 <sup>e</sup> 220 <sup>e,j</sup>	-805 -496 <sup>j</sup>	-186 -115 <sup>j</sup>	36

<sup>a</sup>Measured by DSC unless otherwise noted. <sup>b</sup>Heating rate not given. <sup>c</sup>DSC of 40% weight ethyl diazoacetate (EDA) in toluene. ΔH<sub>D</sub> reported was -602 J g<sup>-1</sup>, which was extrapolated to 100% weight EDA assuming a linear relationship. <sup>d</sup>Measured by ARC on neat EDA, a much more sensitive instrument and slower heating rate and so T<sub>onset</sub> is lower and ΔH<sub>D</sub> is higher than a typical DSC experiment. <sup>e</sup>Estimated from DSC plot given in Supporting Information. <sup>f</sup>DSC peak maxima temperatures. <sup>g</sup>Distinction between T<sub>init</sub> and T<sub>onset</sub> was unclear; so, we have assumed T<sub>init</sub> as defined in this work. <sup>h</sup>Measured by thermogravimetric analysis (TGA). <sup>i</sup>Interestingly, this compound is reported to cyclize into a pyrazole rather than evolving N<sub>2</sub> gas. <sup>j</sup>Distinct second decomposition is observed.

aryl or alkenyl  $\pi$ -system are similarly handled in solution for brief periods of time.<sup>49</sup>

Ethyl diazoacetate (EDA) is the most commonly used diazo compound, and DSC data is available on a dilute solution<sup>35</sup> and neat sample.<sup>36</sup> Diazodinitrophenol (DDNP) is a well-studied primary explosive,<sup>37</sup> which, along with its derivatives (7 and 8), is less appropriate for fine chemical synthesis.<sup>38</sup> Disubstituted donor/acceptor diazo compounds are often isolated, depending on the structure, but there remains very little data on their stability in the literature. Data were reported for aryl diazoacetates 9–11, and  $\alpha$ -diazo- $\beta$ -keto sulfoxide 12; however, in each case, full experimental details of the thermal analysis were not reported.<sup>40–43</sup> Recently, hypervalent iodine diazoacetates 14 and 15 for photoredox chemistry and redox-active *N*-hydroxyphthalimidoyl diazoacetate (NHPI-DA) 16 were reported with accompanying DSC data.<sup>36,44</sup>

There are several possible routes for the preparation of diazo compounds, which themselves involve energetic reagents (Figure 1). Diazotization is limited to simple diazo

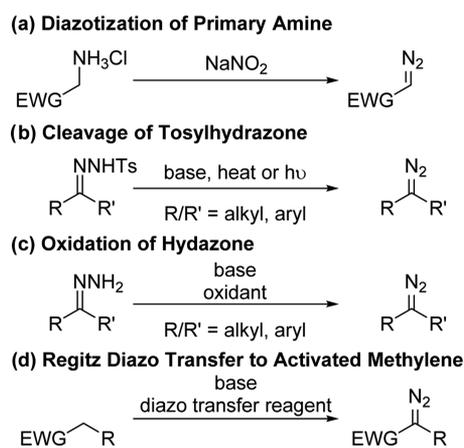


Figure 1. General synthetic methods to prepare diazo compounds.

compounds.<sup>50</sup> Aryl or alkyl diazo compounds can be prepared from *N*-sulfonylhydrazones, which are cleaved with base,<sup>51</sup> thermolytically or photolytically<sup>52</sup> though forcing conditions may decompose the diazo product. Unsubstituted hydrazones can be dehydrogenated using oxidizers.<sup>53</sup> Regitz diazo transfer to an activated methylene compound is the most widely used method to access complex diazo compounds with at least one electron-withdrawing group. The  $N_2$  transfer is typically effected by sulfonyl azide reagents, though recently, other azides have been developed that effect the same reaction.<sup>54,55</sup>

Sulfonyl azides are commonly used diazo transfer reagents that have known hazardous properties.<sup>56</sup> Several explosions have been reported,<sup>57–61</sup> and so, these compounds have been relatively well studied. Available literature thermal analysis and sensitivity data for sulfonyl azide and other diazo transfer reagents are collated in Table 2. Though generally more thermally stable than diazo compounds, the sulfonyl azide functional group confers a significantly higher energetic yield. Sulfonyl azides have been reported to be impact-sensitive;<sup>62–64</sup> however, another report claimed that impurities were the cause, i.e., pure  $MsN_3$  was not impact-sensitive but a slightly impure sample was highly sensitive.<sup>67</sup> Pure  $TsN_3$  has been reported to explode,<sup>57,58</sup> but the root cause of these incidents was not conclusively demonstrated to be the azide, and the only report of explosive power comes from an unpublished

private correspondence.<sup>62</sup> It has been noted that preparations of sulfonyl azide using an alcohol as solvent lead to impurities, which may be the cause of the observed impact sensitivity, and so, the preparation of sulfonyl azides in acetone/water is recommended to avoid this possibility.<sup>81</sup>

*p*-Acetamidobenzenesulfonyl azide (*p*-ABSA) is considered to be a “safer” diazo transfer reagent and generally preferred over mesyl ( $MsN_3$ ) or tosyl azide ( $TsN_3$ ) for batch diazo preparation. The key reasons for this can be seen in Table 2; while the thermal stability ( $T_{init}$  and  $T_{onset}$ ) is similar, it is significantly less sensitive to impact and has an apparently lower  $\Delta H_D$ . It has not been demonstrated that *p*-ABSA can sustain a detonation, as the only result is unclear.<sup>68</sup> *p*-Dodecylbenzenesulfonyl azide (*p*-DBSA) and 4,6-dimethoxy-1,3,5-triazine (ADT) have been demonstrated to be non-impact-sensitive alternative diazo transfer reagents.<sup>55,62–64</sup> Polystyrene-supported benzenesulfonyl azide 23 has been suggested as another safer, if costly, option.<sup>73</sup> Both  $TsN_3$  and  $MsN_3$  have been prepared and used in flow,<sup>82</sup> where the sulfonyl azide is maintained in a solution throughout the protocol and thus the explosive properties of the neat material are avoided.<sup>83</sup> Among the more reactive diazo transfer reagents,  $NfN_3$ ,<sup>79</sup> 2-azido-1,3-dimethylimidazolium hexafluorophosphate (ADMP),<sup>54</sup> and 25<sup>74</sup> have been demonstrated to be insensitive alternatives to the explosive  $TfN_3$ . Friction and ESD sensitivity data are available for the imidazole-1-sulfonyl azide salts 24–29<sup>74</sup> and  $NfN_3$ .<sup>79</sup>

Diazo compounds and diazo transfer reagents are valuable synthetic tools, but the question of explosive potential discourages their use. Table 2 compiles a large amount of thermal and explosive hazard data on diazo transfer reagents available in the literature. It is apparent that similar information is scarce for diazo compounds, which are generally regarded to pose similar hazards in the chemical laboratory. Here, we present a rigorous DSC dataset of diazo compounds and offer a direct comparison to diazo transfer reagents and other energetic materials to provide a clear reference work to the academic and industrial chemistry communities. Thermal stability data on 44 diazo compounds using DSC is reported, and the effects of various substituents on these properties are explored. Onset temperatures were found to be 75–160 °C, with electron-rich substituents generally giving lower thermal stability. Energetic yields were around 102 kJ mol<sup>-1</sup> unless other energetic functional groups were included. Furthermore, the Yoshida correlation is applied to the DSC data to predict the impact sensitivity and explosivity of the tested diazo compounds. None are predicted to be explosive, but many are predicted to exhibit impact sensitivity with exothermic decomposition. The implications of these results are that the scale-up of reactions using sulfonyl azides or diazo compounds should be undertaken with caution, ensuring that adequate thermal control and overpressure relief mechanisms are in place and that the initiating reagent is added at an appropriate rate.

## RESULTS AND DISCUSSION

**DSC Analysis of Diazo Compounds.** In this study, the thermal stability and energetic yield of 44 diazo compounds were measured using DSC. In a typical measurement, 5 mg of the diazo compound was weighed into a high-pressure crucible, sealed, and equilibrated at 25 °C. The sample was then heated at 5 °C min<sup>-1</sup> while the heat flow was monitored vs an empty reference crucible. The use of high-pressure crucibles ensured

Table 2. Impact Sensitivity, Thermal Stability, and Exotherm Data Previously Reported for Sulfonyl Azide and Other Diazo Transfer Reagents<sup>11,23,41,54,55,57–80</sup>

entry	diazo transfer reagent	IS (J)	explosion reported?	thermal analysis <sup>23</sup>					ref
				heating rate (°C min <sup>-1</sup> )	T <sub>init</sub> (°C) <sup>a</sup>	T <sub>onset</sub> (°C) <sup>a</sup>	ΔH <sub>D</sub> (J g <sup>-1</sup> )	ΔH <sub>D</sub> (kJ mol <sup>-1</sup> )	
1		4.9	yes <sup>57,58</sup>	10	120		-1696	-334	62, 63, 64
				5	121	156	-1583	-312	65
				5	128	158	-1057	-209	11
2		4.9	yes, <sup>66</sup> no if pure <sup>67</sup>	10	125		-2330	-282	62, 63, 64
3		>14.7 <sup>b</sup>		10	151		-703	-246	62, 63, 64
4		25 (3/25) >13.4 <sup>b</sup>		n.a. <sup>c</sup>	180 <sup>d</sup>				68
				10	120		-720	-173	69, 64
				n.a. <sup>c</sup>	125	148	-912	-219	41
5		29.4 (3/6)		10	163		-987	-224	62, 63, 64
				10	148 <sup>e</sup>	167	-1140	-259	70
6				10	122 <sup>e</sup>	157	-1104	-251	70
7		25 (9/25)		n.a. <sup>e</sup>	166 <sup>d</sup>				68
8		4.9		10	118		-2088	-477	64
9		25 (9/25)	yes, <sup>68f</sup> no <sup>71g</sup>	n.a. <sup>e</sup>	162 <sup>d</sup>				68
10		>25 <sup>b</sup> 29.4 (4/6)	yes <sup>72h</sup>	n.a. <sup>e</sup>	166 <sup>d</sup>				68
				10	139		-1506	-327	63, 64
11		29.4 (6/6)		10	127		-1186	-310	63, 64
12		25 (2/25)	yes <sup>68f</sup>	n.a. <sup>e</sup>	173 <sup>d</sup>				68
13		29.4 (5/6)		10	146		-1159	-270	62, 63, 64
14		>29.4 <sup>b</sup>		10	136		-845	-261	62, 63, 64
15		>40 <sup>b</sup>		n.a. <sup>e</sup>	130	166	-275	-183	73
16		6	yes <sup>59</sup>	5		102			74
17	X = Cl								
17	X = H <sub>2</sub> SO <sub>4</sub>	40		5		131			74
18	X = OMs	40		5		88			74
19	X = OTs	30		5		114			74
20	X = ClO <sub>4</sub>	<1		5		140			74
21	X = BF <sub>4</sub>	40		5		146			74
22		<1		5		112			74

Table 2. continued

entry	diazo transfer reagent	IS (J)	explosion reported?	thermal analysis <sup>23</sup>					ref
				heating rate (°C min <sup>-1</sup> )	T <sub>init</sub> (°C) <sup>a</sup>	T <sub>onset</sub> (°C) <sup>a</sup>	ΔH <sub>D</sub> (J g <sup>-1</sup> )	ΔH <sub>D</sub> (kJ mol <sup>-1</sup> )	
23	<b>31</b> 		yes <sup>61</sup>	n.a. <sup>c</sup>	112 <sup>f</sup>				75
24	<b>ADMP</b> 	>25 <sup>b</sup>		10	200				54
25	<b>32</b> 			n.a. <sup>c</sup>	160				76
	X = SO <sub>2</sub> CF <sub>3</sub>								
26	<b>TfN<sub>3</sub></b> 	very sensitive <sup>k</sup>	yes <sup>60</sup>						77
27	<b>NfN<sub>3</sub></b> 	>25.5 <sup>b</sup>		n.a. <sup>c</sup>	120 <sup>d</sup>				78
				10		141	-419	-136	79
28	<b>ADT</b> 	>100 <sup>b</sup>		n.a. <sup>c</sup>		195 <sup>d</sup>			80
				5	159	150			55
				5		187	-1135	-207	11

<sup>a</sup>Measured by DSC unless otherwise noted. <sup>b</sup>Sample reached the upper test limit with no reaction. <sup>c</sup>Heating rate not given. <sup>d</sup>Method not clear from the report. <sup>e</sup>Estimated from the DSC plot given in the report. <sup>f</sup>Explosion judged by the report<sup>68</sup> of audible sound effect upon thermal decomposition, indicative of a supersonic detonation. <sup>g</sup>Pure 17 reported to decompose “quietly” at approx 105 °C but crude product exploded. <sup>h</sup>Explosion occurred on the addition of a spiro azepanindole species to neat azide. <sup>i</sup>The root cause of this explosion is unclear. <sup>j</sup>Reported from TGA as DSC was not run to decomposition. <sup>k</sup>No data has been published, but the pure form is reported to spontaneously explode and so testing would be difficult. <sup>l</sup>Initially reported as +30 kJ mol<sup>-1</sup> endothermic decomposition due to DSC measurement in open crucibles.

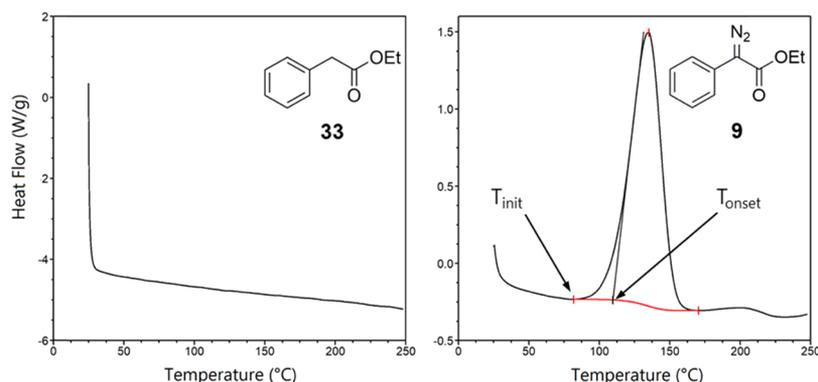


Figure 2. Comparison of the DSC plot for ethyl (phenyl)acetate **33** and ethyl (phenyl)diazoacetate **9**.

containment of all gaseous decomposition products, which otherwise led to erroneous endothermic peaks.<sup>11,84</sup> The results for  $T_{\text{init}}$ ,  $T_{\text{onset}}$ , and  $\Delta H_{\text{D}}$  were measured for two samples and averaged (Table 3). For selected results, this analysis was repeated on different DSC equipment at GlaxoSmithKline (GSK) using a slightly different method with a 2 °C min<sup>-1</sup> temperature ramp, which resulted in lower  $T_{\text{init}}$  and  $T_{\text{onset}}$  due to the higher resolution. Repeatability criteria were 2% for  $T_{\text{init}}$  and  $T_{\text{onset}}$  and 10% for  $\Delta H_{\text{D}}$ ,<sup>3a</sup> though the majority of results were well within this range; any results falling outside this range were repeated.

The DSC plots for the donor/acceptor diazo compound ethyl (phenyl)diazoacetate **9** and analogous ethyl (phenyl)acetate **33** are shown in Figure 2.<sup>85</sup> Both compounds are liquid at 25 °C and thus do not exhibit melting points, typically observed as a sharp endothermic peak for solids. A clear exothermic decomposition is observed in the DSC plot of **9**,

which corresponds to the dissociation of the diazo to form N<sub>2</sub> gas and a highly reactive carbene. This decomposition is also evident in the thermogravimetric analysis (TGA) plot of **9** (Figure 3), which clearly shows a sharp mass loss initiating around 85 °C (99.6% of the starting mass) and corresponding to a 14.8% mass loss by 126 °C. The molecular mass of N<sub>2</sub> (28.01 g mol<sup>-1</sup>) is exactly 14.73% of the molecular mass of **9** (190.2 g mol<sup>-1</sup>). The average DSC for **9** (Table 3, entry 1) shows an agreement with both our result (Table 3, entry 2) and existing literature report (Table 1, entry 10; heating rate and  $\Delta H_{\text{D}}$  were not reported).

Diazo compound **9** was then compared to a variety of other aryl diazoacetates to investigate the effect of substituents on thermal stability.  $T_{\text{onset}}$  was used for this comparison, as it was found to give more consistent results. Changing the ester alkyl group did not have a significant effect on  $T_{\text{onset}}$ , which represents thermal stability. *tert*-Butyl (phenyl)diazoacetate **34**

Table 3. Averaged DSC Results for Diazo Compounds

entry	compound <sup>a</sup>	structure	R	T <sub>init</sub> (°C)	T <sub>onset</sub> (°C)	ΔH <sub>D</sub> (J g <sup>-1</sup> )	ΔH <sub>D</sub> (kJ mol <sup>-1</sup> )
1	<b>9<sup>b</sup></b>			87	109	-539	-103
2	<b>9<sup>c</sup></b>		H	80	107	-562	-107
3	<b>10</b>			85	108	-574	-101
4	<b>10<sup>c</sup></b>		-	80	98	-554	-98
5	<b>34</b>		H	76	108	-479	-105
6	<b>35</b>		4-Br	98	115	-344	-102
7	<b>36</b>		-	87	110	-360	-106
8	<b>37</b>		-	84	100	-395	-116
9	<b>38</b>		4-OMe	63	81	-467	-103
10	<b>39</b>		4-Me	79	103	-486	-99
11	<b>40</b>		4-F	72	101	-503	-105
12	<b>41</b>		4-Cl	97	115	-448	-101
13	<b>42</b>		4-Br	98	114	-380	-102
14	<b>43</b>		4-CF <sub>3</sub>	96	123	-416	-107
15	<b>44</b>		4-NO <sub>2</sub>	113	131	-578	-136
16	<b>45</b>		3-OMe	86	110	-472	-104
17	<b>46</b>		3-Me	82	109	-485	-99
18	<b>47</b>		3-F	88	116	-451	-94
19	<b>48</b>		3-Cl	95	117	-464	-104
20	<b>49</b>		3-CF <sub>3</sub>	92	117	-394	-102
21	<b>50</b>		2-OMe	61	84	-521	-115
22	<b>50<sup>c</sup></b>		2-OMe	57	75	-443	-98
23	<b>51</b>		2-F	72	98	-503	-105
24	<b>52</b>		2-Cl	71	94	-464	-104
25	<b>53</b>		2-CF <sub>3</sub>	79	104	-407	-105
26	<b>54</b>		3,4-Cl	97	116	-376	-97
27	<b>55</b>		3,4-Me	82	101	-465	-101
28	<b>56</b>		3,4-OMe	71 <sup>d</sup>	84 <sup>e</sup>	-437 <sup>e</sup>	-109 <sup>e</sup>
29	<b>57</b>		3,4,5-OMe	72 <sup>d</sup>	97 <sup>e</sup>	-323 <sup>e</sup>	-90 <sup>e</sup>
30	<b>57<sup>c</sup></b>		3,4,5-OMe			-225	-63
31	<b>58</b>		4-OPh	81	95	-385	-109
32	<b>59</b>		4-Ph	80 <sup>f</sup>	108	-396	-105
33	<b>60</b>		-	110	133	-435	-83 <sup>f</sup>
34	<b>61</b>		H	88	108	-494	-94
35	<b>62</b>		Cl	100	114	-468	-106



strong  $\sigma$ -acceptor (such as  $\text{CF}_3$  **43**, **49**) and  $\pi$ -acceptor substituents such as  $\text{NO}_2$  (**44**) serve to stabilize the diazo compound leading to  $T_{\text{onset}}$  of approx 120 and 130 °C, respectively.

Using the data from Table 3, we developed a statistical model to predict the thermal stability of novel diazo compounds of the substructure shown in Figure 5, using

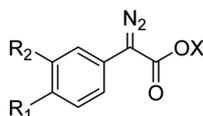


Figure 5. Model diazo compound.

only the Hammett parameter of substituent  $R_1$  or  $R_2$  (eq 1). We propose that this model could be used as a prediction of stability (as  $T_{\text{onset}}$  with a 5 °C  $\text{min}^{-1}$  ramp) on novel diazo compounds of this type, to provide an estimate of the thermal stability before synthesis. The model was tested by the synthesis of previously unknown phenoxyaryl-substituted diazo compound **58**, which was predicted by eq 1 to have a  $T_{\text{onset}}$  of 93 °C ( $\sigma_p^+ = -0.50$ , experimental result 95 °C; Table 1, entry 31) and biphenyl diazoacetate **59**, with a predicted  $T_{\text{onset}}$  of 102 °C ( $\sigma_p^+ = -0.18$ , experimental result 108 °C; Table 1, entry 32). While phenoxy **58** had excellent predictive accuracy, biphenyl **59** was slightly more stable than expected. This data is also plotted in Figure 4 for comparison. It is possible that this difference is due to the resonance stabilization of the diazo moiety, as the enhanced delocalization of charge is not captured in the Hammett parameter

$$T_{\text{onset}} \text{ (}^\circ\text{C)} = (28.69 \times \sigma_m \text{ or } \sigma_p^+) + 107.5 \quad (1)$$

Ortho-substituted examples were found to be less thermally stable than meta or para analogues, depending on the steric bulk of the substituent. Chlorophenyl diazo **52** and trifluoromethylphenyl diazo **53** gave a significant reduction in  $T_{\text{init}}$  and  $T_{\text{onset}}$ , with onset temperatures approximately 20 °C lower, whereas less bulky substituents such as methoxyphenyl diazo **50** and fluorophenyl diazo **51** had comparable thermal stability to para-substituted **38** and **40**, respectively. This suggests a steric clash with the larger functional groups, reducing the conjugation of the aryl ring with the diazoester due to the out-of-plane twisting of the aromatic ring despite the proximity of electron-withdrawing aryl substituents.

In multisubstituted systems, similar trends in thermal stability are observed. Ethyl (3,4-dichlorophenyl)diazoacetate **54** and ethyl (3,4-dimethylphenyl)diazoacetate **55** have a similar  $T_{\text{onset}}$  to their 3- and 4-substituted analogues. Ethyl (3,4-dimethoxyphenyl) diazoacetate **56** is significantly stabilized compared to 4-OMe **38**, due to *meta*-methoxy being  $\sigma$ -electron-withdrawing. Indeed, the presence of another methoxy group in 3,4,5-trimethoxyphenyl example **57** conferred another improvement to thermal stability.<sup>87</sup>

Ethyl (pyridin-4-yl)diazoacetate **60** was more thermally stable due to the electron-poor 4-pyridyl substituent. On the other hand, ethyl (pyridin-3-yl)diazoacetate **61** and 6-chloropyridin-3-yl **62**, which cannot delocalize a negative charge of a potential carbene onto the nitrogen atom, displayed no significant difference vs benzo-analogues **9** and **41**. Interestingly, the pyridin-2-yl diazo compound **63** adopts the triazolo tautomer and has a thermal stability far surpassing the diazo compounds in this study.

Acceptor/acceptor-type diazo compounds can be contrasted to the donor/acceptor compounds. Ethyl diazoacetate (EDA) has comparable thermal stability to ethyl (phenyl)diazoacetate **9**, though the initiation is observed at a lower temperature. While another electron-withdrawing substituent clearly increases the thermal stability of the diazo compound for diazoesters (**64–69**), cyanodiazo compounds (**70–72**) have comparable or lower onset temperatures even with an  $\alpha$ -carbonyl. The onset temperature for benzyl ester **71** is comparable to that for ethyl esters with electron-poor aromatics such as **62**. Donor/acceptor aryl trifluoromethyldiazo compounds **73** and **74** also have lower onset temperatures than their aryl ester analogues **9** and **42**.

The mean  $\Delta H_D$  for diazo compounds **9**, **10**, and **34–74** (excluding EDA, **44**, **64**, and **65**) is  $-102 \text{ kJ mol}^{-1}$ , which confirms that diazo compound energetic yield is significantly lower than sulfonyl azides. Sulfone **65** and nitro-containing **44** and **64** are exceptions, where adding additional energetic functional groups clearly increases the enthalpy of decomposition of the single main transition, indicating that the other energetic functional groups concurrently or sequentially pyrolyze during the diazo decomposition, increasing the measured enthalpy. This average value is on the order of 50  $\text{kJ mol}^{-1}$  lower than previous reports of similar diazo compounds **9** and **10**, which could be attributed to differences in equipment and methodology, particularly the heating rate and how the exothermic peak is integrated, and in the case of  $\alpha$ -vinyl diazo compound **13**, a different decomposition pathway. EDA has a significantly higher  $\Delta H_D$  than the average diazo compound, as was also previously reported, indicating that the decomposition involves both the loss of  $\text{N}_2$  and additional processes.

**DSC Analysis of Sulfonyl Azides and Other Diazo Transfer Reagents.** DSC data for thermal stability and energetics of decomposition were also collected for several common diazo transfer reagents (Table 4). They are generally

Table 4. DSC Analysis of Selected Diazo Transfer Reagents

entry	compound <sup>a</sup>	$T_{\text{init}}$ (°C)	$T_{\text{onset}}$ (°C)	$\Delta H_D$ ( $\text{J g}^{-1}$ )	$\Delta H_D$ ( $\text{kJ mol}^{-1}$ )
1	TsN <sub>3</sub>	128	158	-1057	-208
2	<i>p</i> -ABSA	130	156	-790	-190
3	<i>p</i> -ABSA <sup>b</sup>	120	138	-928	-223
4	<i>p</i> -CBSA	148	167	-923	-210
5	<i>m</i> -CBSA	93 <sup>c</sup>	155	-920	-209
6	<i>o</i> -NBSA	123	151	-1541	-352
7	ADMP	167	202	-793	-226
8	NfN <sub>3</sub>	102	136	-582	-189
9	ADT	159	186	-1135	-207

<sup>a</sup>Results using DSC method A and average results, where  $n = 2$  unless otherwise noted. <sup>b</sup>Using DSC method B and  $n = 1$ . <sup>c</sup>Reported as the initiation of melting point, which obscures exotherm initiation.

more thermally stable than diazo compounds, but the decomposition has a larger energetic yield. The data were broadly similar to previous reports (cf. Table 2) although both TsN<sub>3</sub> and *ortho*-nitrobenzenesulfonyl azide (*o*-NBSA) were found to be almost 30% less energetic. For the same decomposition of an energetic functional group, the  $\Delta H_D$  per mole might be expected to be quite similar, which is not seen in the broad range of sulfonyl azide results in the literature (Table 2,  $-334$  to  $-136 \text{ kJ mol}^{-1}$ ). With DSC data,

it is important to make comparisons between compounds using the same technique, ideally on the same machine. The sulfonyl azide data in Table 4 has an average of  $-201 \text{ kJ mol}^{-1}$  (excluding *o*-NBSA, ADMP, and ADT), similar to all of the literature sulfonyl azide DSC data (average  $-226 \text{ kJ mol}^{-1}$ ); however, the literature  $\Delta H_D$  data has a much broader range and higher sample standard deviation (139.6 vs 10.7 for the data in Table 4), which is likely to be a reflection of the different methods and equipment used. This dataset therefore provides a more standardized set of measurements for comparison of the thermal stability of these reagents.

**Prediction of Sensitivity and Explosion Hazards: Yoshida Correlation.** In a seminal work, Yoshida conducted impact sensitivity and explosive propagation (EP) experiments on a number of energetic materials and developed a correlation to predict these properties from DSC results.<sup>10,88</sup> The Yoshida correlations (eqs 2 and 3) use  $T_{\text{onset}}$  (in  $^{\circ}\text{C}$ ) and  $\Delta H_D$  (as  $Q$ , an inverse value in  $\text{cal g}^{-1}$  representing energy output) and give a dimensionless number. A value  $>0$  predicts that a material will exhibit impact sensitivity (IS) and/or explosive propagation (EP), while a value  $<0$  predicts it will not. Additionally, even a sample that gives a null prediction could still result in a safety incident if the exothermic decomposition is not respected

$$\begin{aligned} \text{impact sensitivity (IS)} \\ = \log_{10}(Q) - 0.72[\log_{10}(T_{\text{onset}} - 25)] - 0.98 \end{aligned} \quad (2)$$

$$\begin{aligned} \text{explosive propagation (EP)} \\ = \log_{10}(Q) - 0.38[\log_{10}(T_{\text{onset}} - 25)] - 1.67 \end{aligned} \quad (3)$$

Process safety scientists at Pfizer recently published an assessment of peptide coupling reagents, where the authors used a more conservative version of this correlation (eqs 4 and 5), where the  $Q$  term was reduced by 25% and  $T_{\text{init}}$  was used instead of  $T_{\text{onset}}$ <sup>3a</sup>

$$\begin{aligned} \text{impact sensitivity (IS)} \\ = \log_{10}(Q) - 0.54[\log_{10}(T_{\text{init}} - 25)] - 0.98 \end{aligned} \quad (4)$$

$$\begin{aligned} \text{explosive propagation (EP)} \\ = \log_{10}(Q) - 0.285[\log_{10}(T_{\text{init}} - 25)] - 1.67 \end{aligned} \quad (5)$$

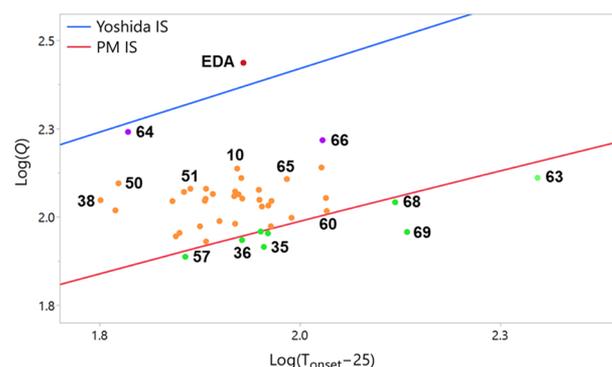
We applied both correlations to the literature DSC data for diazo transfer reagents from Table 2 to predict impact sensitivity and explosive properties, which will give an indication of sensitivity and explosivity hazards for compounds for which DSC is reported, but the specialist tests have not been undertaken. For those with specialist data reported, the IS and EP predictions were compared with those reports (Table S2).

The Yoshida correlation correctly flags all diazo transfer reagents, which are reported to be impact-sensitive with the exception of naphthalene-2-sulfonyl azide 21. The more conservative Pfizer-modified correlation on the other hand flags  $\text{NfN}_3$  and ADT, both of which have been experimentally demonstrated to be insensitive to impact.<sup>55,79</sup> *para*-Carboxybenzenesulfonyl azide (*p*-CBSA) and *p*-ABSAs are predicted to be insensitive to impact; however, there are reports of some impact sensitivity and they are categorized as “less sensitive” and infrequently react to impact loadings of almost 30 J.<sup>64,68</sup>

Both correlations correctly predict explosivity for reagents that are known to detonate; the Pfizer-modified correlation may be overly conservative as it flags several commonly used compounds that do not appear to be explosive, such as *p*-ABSAs. Any reagent flagged by the less conservative Yoshida EP correlation, which from the literature data is only *p*-bromobenzenesulfonyl azide 19, should be regarded as explosive unless further testing is undertaken. *p*-DBSA, *m*-CBSA, naphthalene-2-sulfonyl azide 21, triisopropylbenzenesulfonyl azide 22, polystyrene-supported benzenesulfonyl azide 23, and ADT are predicted to be nonexplosive.<sup>89</sup>

Application of the correlations to literature DSC data for diazo compounds highlighted that both allyl (phenyl) diazoacetate 11 and vinyl diazoester 13 are predicted to be impact-sensitive and explosive by the Yoshida correlation, primarily due to the reportedly low onset temperatures. Hypervalent iodine diazoacetates 14 and 15 and NHPI-DA 16 are not predicted to be impact-sensitive or explosive.

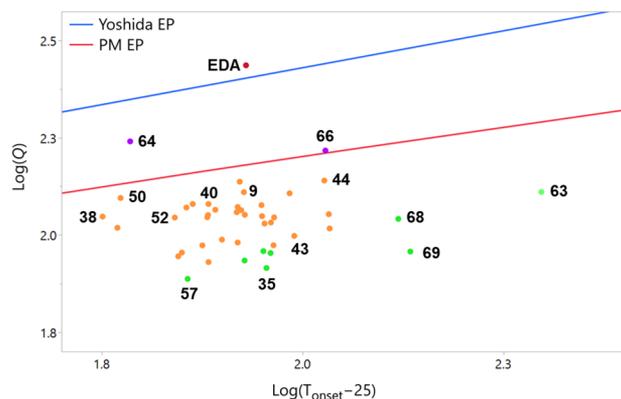
**Prediction of the Sensitivity and Explosion Hazards of Diazo Compounds.** Both correlations were applied to all diazo compound DSC results from Table 3 to predict impact sensitivity or explosive properties (see Table S3 for data). Figure 6 plots the DSC results and compares the Yoshida



**Figure 6.** Plot of  $\log(Q)$  vs  $\log(T_{\text{onset}} - 25)$  for diazo compounds 9, 10, and 34–74 compared to the IS correlation limits, with selected compounds highlighted. See SI for further details.

correlation and the more conservative Pfizer-modified prediction. While the Yoshida correlation predicts that none of the tested compounds are impact-sensitive, the Pfizer-modified correlation predicts many of the diazo compounds to be impact-sensitive. Only 35, 36, 42, 54, triazolo 63, and 69 are predicted to be insensitive using the Pfizer-modified IS correlation. Interestingly, the compounds flagged as insensitive contain more “molecular ballast”, i.e., compounds with bromo-, dichloro-, phosphonyl-, or menthyl-functionality, with a lower proportion of the overall molecular weight being due to the energetic functional group. This reduces the energetic yield per unit mass, while the energetic yield per unit mole remains the same. Triazolo 63 is significantly stabilized in the dominant aromatic tautomer. None of the peptide-coupling reagents assessed by Sperry et al. were flagged by the Yoshida IS correlation, while six were flagged by the Pfizer-modified IS correlation.<sup>3a</sup> Of these, four compounds exhibited IS. Based on this, we suggest that the Yoshida correlation may not flag some impact-sensitive materials and the Pfizer-modified prediction more accurately predicts impact sensitivity for diazo compounds.

Figure 7 plots the same DSC results with both the Yoshida and Pfizer-modified EP predictions (see SI) and highlights that



**Figure 7.** Plot of  $\log(Q)$  vs  $\log(T_{\text{onset}} - 25)$  for diazo compounds 9, 10, and 34–74 compared to the EP correlation limits, with selected compounds highlighted. See SI for further details.

only ketodiazooacetate **66** is predicted to be capable of detonation by only the more conservative PM correlation. The Pfizer study determined that all compounds flagged by the modified EP correlation but not the Yoshida correlation were not considered explosive. We therefore do not predict explosivity for any of the tested diazo compounds.

**Estimation of Maximum Recommended Process Temperature To Avoid Hazardous Thermal Decomposition.** Exotherms of the magnitude typically observed for diazo compounds and sulfonyl azides are a cause for concern. To initially determine safe process operating conditions at GSK, the formula given in eq 6 is used,<sup>2</sup> with  $T_{\text{init}}$  (in °C) from a DSC experiment collected at a 2 °C min<sup>-1</sup> heating rate. This allows for a conservative first approximation of safe operating temperature with a reasonable margin of safety, from a simple experiment using readily available DSC equipment.

$$T_{\text{D24}} = 0.7 \times T_{\text{init}} - 46 \quad (6)$$

$T_{\text{D24}}$  is the temperature at which the time to maximum rate under adiabatic conditions ( $\text{TMR}_{\text{ad}}$ ) becomes >24 h. This equation relies on the assumptions that at the detection limit of an exotherm in the DSC experiment ( $T_{\text{init}}$ ), the conversion is close to zero and thus the heat release rate is equal to the detection limit, as well as the conservative assumptions of a relatively low activation energy (50 kJ mol<sup>-1</sup>) and zero-order kinetics for the decomposition. Because of the limited sensitivity of the DSC test, values are given to the nearest 5 °C.

$T_{\text{D24}}$  was determined for selected diazo compounds using DSC data generated by method B (Table 5). For the donor/acceptor diazo compounds 9, 10, 50, and 57, the  $T_{\text{D24}}$  was found to be below 20 °C, which means that these compounds

**Table 5.** Estimated Maximum Recommended Process Temperatures for Selected Diazo Compounds

entry	compound	$T_{\text{D24}}$ (°C)
1	9	10
2	10	10
3	50	-5
4	57	0
5	66	25

should not be processed above ambient temperature as some amount of decomposition may occur. If temperature control is not applied, it could lead to a thermal runaway and explosion, depending on the quantity of the diazo compound. Acceptor/acceptor diazo compound **66** (Table 5, entry 5) had a  $T_{\text{D24}}$  of 25 °C, indicative of its higher thermal stability.

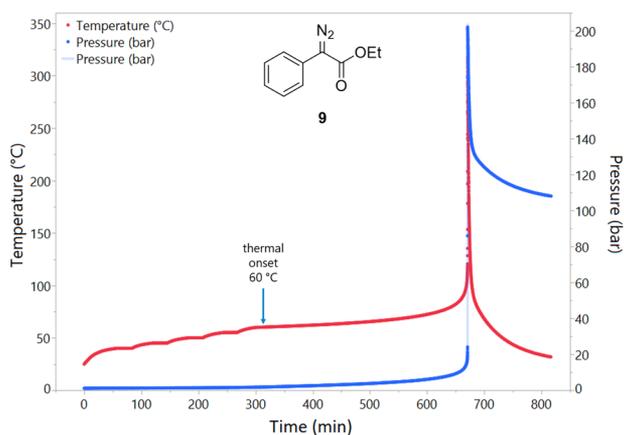
Though the formula is not directly applicable to DSC data using a 5 °C min<sup>-1</sup> heating rate, which gives higher  $T_{\text{init}}$  than the 2 °C min<sup>-1</sup>, it can be used to give an indication of a safe operating window. We found that despite the higher  $T_{\text{D24}}$  using this data, most diazo compounds in Table 3 had a value below 25 °C; so, it is not recommended to prepare or use these compounds with heating and that additional cooling measures should be considered. Only triazolo **63**, ethyl (4-nitrophenyl)-diazooacetate **44**, acceptor/acceptor amide/ester **67**, malonate **68**, and phosphonyl/ester **69** were found to have a  $T_{\text{D24}}$  above ambient temperature using the 5 °C min<sup>-1</sup> data.

It is important to note that for a process scale reaction, more complex and reliable thermal safety assessments may be conducted. For example, using ARC or reaction calorimeters on a case-by-case basis, which would seek to understand other process and reaction parameters and interactions. This enables a suitable basis of safety to be defined for the process to be scaled up safely.

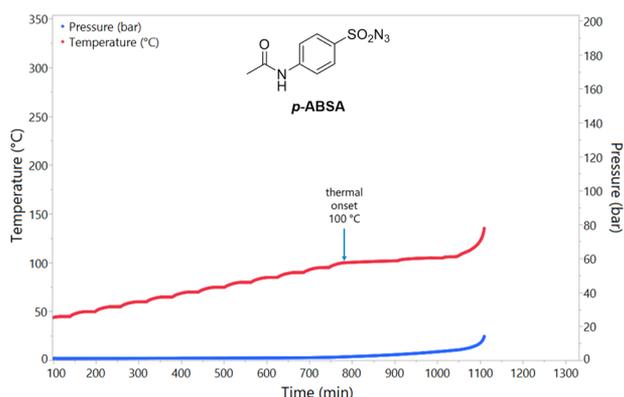
**Accelerating Rate Calorimetry (ARC).** DSC is used as an initial screening test by process safety at GSK when considering a reaction that is intended to be undertaken on a laboratory scale. Any sample exhibiting an exotherm above 300 J g<sup>-1</sup> may be classed as self-reactive as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals and would therefore be submitted for further testing. ARC gives an approximately 10-fold more sensitive determination of  $T_{\text{init}}$  by operating in a heat-wait-search mode: a sample is heated in predefined temperature steps (typically 5 °C), stabilized at each temperature where the ARC searches for an exotherm at a predefined sensitivity. When the sample begins exothermic decomposition, the ARC heating matches the self-heating rate of the sample to simulate adiabatic conditions. The rate of pressure and temperature rise is measured. Compared to DSC, the technique is more sensitive but requires significantly more time and sample (typically between 3 and 7 g).

To provide highly accurate thermal stability data, ethyl (phenyl)diazooacetate **9** (3.355 g) was tested in an ARC using the heat-wait-search mode, and the temperature and pressure plots were recorded (Figure 8). The decomposition initiated at 60 °C, which was followed by a long incubation time where the temperature rise rate remained below 0.1 °C min<sup>-1</sup>; the  $\text{TMR}_{\text{ad}}$  was calculated to be 183 min. The maximum rate of temperature rise was 4110 °C min<sup>-1</sup>, and the maximum rate of pressure rise was 3094 bar min<sup>-1</sup>.<sup>90</sup> The maximum temperature was 340 °C, and the maximum pressure was 202 bar. Sperry suggests that materials exhibiting a rate of pressure rise of >17 000 bar min<sup>-1</sup> should be considered for further explosivity testing, albeit using the faster modified “ScanARC” method.<sup>3a,8a</sup> This adds further evidence that diazo compound **9** is not predicted to be explosive, but the significant rate of heat and pressure generation must be respected.

Diazo transfer reagent *p*-ABSA (3.699 g) was analyzed using the same ARC protocol (Figure 9). The decomposition initiated at 100 °C, and the initial decomposition was much less smooth than the diazo compound, exhibiting small jumps in temperature due to the initially very slow rate. The



**Figure 8.** Plot of temperature and pressure during the ARC experiment with **9**.

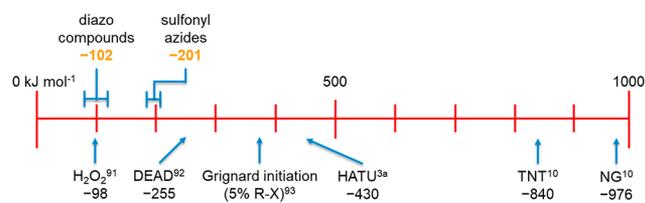


**Figure 9.** Plot of temperature and pressure during the ARC experiment with *p*-ABSA.

experiment had to be stopped as the decomposition developed to protect the ARC equipment and only the initial stages were measured. Using the same ARC protocol, another diazo transfer reagent ADT (2.107 g) was also analyzed (Figure S104); the thermal onset was found to be 125 °C, and the  $TMR_{ad}$  was calculated to be 123 min; the maximum temperature was 350 °C, with a maximum rate of temperature rise of 2314 °C  $min^{-1}$ , and the maximum pressure was 284 bar, with a maximum rate of pressure rise of 13,461 bar  $min^{-1}$ .<sup>90</sup>

#### Contextualizing the Hazards of Diazo Compounds.

The energy release from an uncontrolled decomposition of sulfonyl azides or diazo compounds is typically rapid and results in thermal runaway under adiabatic conditions. Sulfonyl azides are clearly more energetic than diazo compounds, which have a similar  $\Delta H_D$  to the decomposition of hydrogen peroxide (see Figure 10 for comparisons).<sup>3a,10,91–93</sup> In the context of a reaction, any process that intends to decompose these



**Figure 10.** Indicative scale of  $\Delta H_D$  for known exothermic reagents.

compounds to effect the desired chemistry would be best conducted with adequate cooling and slow addition of initiator to manage exotherm development.

From the literature diazo transfer reagent IS data in Table 2, it can be seen that some reagents are classed as sensitive and should be handled with extreme care when neat ( $TsN_3$ ,  $MsN_3$ , *o*-NBSA,  $TfN_3$ ) if at all; most other reagents fall into the less sensitive category (including *p*-ABSA) or are insensitive to impact (ADMP,  $NfN_3$ , ADT). In the lab, impacts to neat reagent are most likely to be from manipulation during reaction preparation: handling with spatula, agitation with a stirrer or dropping a container. From our Yoshida correlation IS predictions, we recommend that neat diazo compounds are handled with similar care as impact sensitivity is a strong possibility for all but the most stable examples. Some impact sensitivities of well-defined energetic materials are given in Table S4 for comparison.

The principal hazard of using diazo compounds (ignoring toxicity), sulfonyl azides, and indeed many other exothermic reactions involving potentially unstable reagents is the risk of thermal runaway and pressure generation. Thermal runaway occurs because as the temperature of a reaction mixture increases, the rate of reaction (and thus heat output for exothermic processes) increases exponentially, whereas the rate of cooling remains linear. For this reason, scale-up should always be approached with appropriate caution. Metal-carbene chemistry relies upon the decomposition of the diazo compound, which is similarly exothermic to thermally induced decomposition and will evolve the same amount of  $N_2$  gas. For exotherms of the magnitude observed, on small scales (for example <1 mmol), the likelihood of thermal runaway is low due to effective cooling. Furthermore, the heat and pressure generated from a runaway decomposition are unlikely to present a major hazard due to the small reaction mass. Additionally, at dilute concentrations (for example, <0.3 M), the solvent mass acts as a heatsink for the energy generated. At larger scales, although there may be sufficient heatsink to prevent a hazard, there may be potential for serious consequences. More concentrated reaction mixtures present the possibility for the solvent mass to be heated rapidly and vaporized. Thus, any significant scale-up would require its own detailed thermal hazard assessment to enable safe reaction design.

Any chemist conducting this type of reaction should pay careful attention to the scale, concentration, temperature control of reaction vessel, and rate of addition when initiating the reaction and to err on the side of caution if in doubt. The addition of the initiating reagent should be slow to allow the effective management of the developing exotherm by the temperature control unit. Reaction vessel choice should seek to maximize surface-area-to-volume ratio and have an appropriate overpressure relief mechanism to manage the evolved  $N_2$ .

## CONCLUSIONS

Diazo compounds offer powerful synthetic routes to complex molecules but are often avoided due to justifiable concerns about the potential hazards. Though the perils of diazomethane are well known, there is little data available to describe the hazards of more complex diazo compounds despite their frequent appearance in the literature; when results are presented, vital experimental detail is often absent. We have presented consistent DSC data for 44 donor/acceptor and acceptor/acceptor diazo compounds. Onset temperatures were

found to be in the range of 75–160 °C, and the thermal stability was significantly affected by substituents. Generally, electron-withdrawing groups were found to improve thermal stability and increase  $T_{\text{init}}$  and  $T_{\text{onset}}$ , whereas electron-donating groups have the opposite effect. More complex resonance effects were also noted, as steric clashes resulted in out-of-plane twisting and therefore reduced the conjugation of the diazo functional group with the aryl ring, leading to a destabilizing effect. A statistical model was demonstrated to reasonably predict  $T_{\text{onset}}$  for hypothetical alkyl (phenyl)-diazoacetates based on the Hammett parameter  $\sigma_m$  or  $\sigma_p^+$  of the aryl substituent.

A formula was used to estimate the maximum recommended process temperature to avoid unwanted decomposition; for most of the tested compounds, to avoid decomposition, it is not recommended to use above 25 °C or store above 0 °C, excepting particularly stabilized acceptor/acceptor diazo compounds. The diazo compounds were found to have a mean  $\Delta H_D$  of  $-102 \text{ kJ mol}^{-1}$ , and it is expected that a similar  $\Delta H_D$  would be observed for similar compounds where the diazo functional group is the only source of exothermic decomposition. Several diazo transfer reagents were also tested using the same DSC method and found to have generally higher thermal stability in agreement with the reported data and, for sulfonyl azides, a mean  $\Delta H_D$  of  $-201 \text{ kJ mol}^{-1}$ . Considerable variation in  $T_{\text{onset}}$  and  $\Delta H_D$  results was found in the literature, likely due to different (and unreported) heating rates, highlighting the importance of exhaustive experimental detail in reporting DSC results. High-quality thermal hazard data from the ARC is presented on ethyl (phenyl)diazoacetate **9**, which was found to initiate decomposition at 60 °C. The diazo transfer reagent *p*-ABSA was found to initiate decomposition at 100 °C. Significant pressure development was measured in addition to the exotherm and constitutes a considerable explosion hazard if the compounds are heated without an overpressure relief.

Yoshida's predictive correlation and a more conservative modified form from Pfizer were applied to the DSC data to screen for impact sensitivity and explosive propagation. Many of the diazo compounds tested are predicted to be impact-sensitive as a neat substance, though all are predicted to be less sensitive than the borderline compound *m*-DNB. It is therefore recommended to treat diazo compounds with particular caution when neat, particularly to avoid impacts or physical processing at scale, especially for lower-molecular-weight examples. None of the diazo compounds tested are predicted to be explosive. All of the compounds still demonstrate a significant exothermic decomposition, which must be respected, particularly when utilizing the reaction of diazo compounds with a metal catalyst for metal-carbene chemistry. As such, the addition of the "initiator" in the preparation and use of diazo compounds should always be conducted slowly and with adequate temperature control. While some of these observations may be in line with the perceived knowledge, we believe that this study will provide a valuable reference and standard set of experimental conditions for those working with these reagents. While on a small scale, diazo compounds will continue to be widely used, there are clear challenges to adapting these reagents to process scales. Part of the evaluation of the industrial viability and safety of any diazo transfer reagent or diazo compound should include DSC (and follow-up ARC) to determine safe operating conditions.

## EXPERIMENTAL SECTION

**DSC Experimental Terminology.**  $T_{\text{init}}$  is defined by the temperature at which the heat flow is measured to be  $>0.01 \text{ W g}^{-1}$  from the baseline.  $T_{\text{onset}}$  is defined by the intersection of the extrapolated maximum peak slope and the baseline.  $\Delta H_D$  is obtained by integration of the peak. Averaged DSC results reported where individual results have  $<2\%$  difference from the average for  $T_{\text{init}}$  and  $T_{\text{onset}}$  and  $<10\%$  difference from the average for  $\Delta H_D$ . Where noted, if a melting point overlaps with the decomposition, the melt endotherm was removed and blended with adjacent data to allow  $T_{\text{onset}}$  and  $\Delta H_D$  to be more accurately determined. In these cases, if  $T_{\text{init}}$  cannot be determined due to the melt endotherm, the temperature where the melt commences is used.

**DSC Method A.** DSC analysis was performed using a TA Instruments Q2000 DSC with a liquid nitrogen cooling system (LNCS). Approx 5 mg was accurately weighed to 1 d.p. into a reusable PerkinElmer B0182901 stainless steel high-pressure crucible with a disposable gold-plated copper seal rated to 150 bar and sealed under air with the appropriate B0182864 sealing tool. After equilibrating at 25 °C, samples were heated at  $5 \text{ °C min}^{-1}$  to a maximum temperature of 250 °C for diazo compounds and 300 °C for other compounds. Data analysis was conducted using TA Instruments Universal Analysis 2000 software version 4.5.0.5.

**DSC Method B.** DSC analysis was performed using a Mettler Toledo DSC 823e. Approx 5 mg was accurately weighed to 1 d.p. into a Mettler Toledo ME-26731 gold-plated 40  $\mu\text{L}$  high-pressure crucible with seal insert and lid rated to 150 bar and sealed under air with the appropriate sealing press. After equilibrating at 25 °C, samples were heated at  $2 \text{ °C min}^{-1}$  to a maximum temperature of 350 °C. Data analysis was conducted using a Mettler Toledo STARE software version 12.00 build 5342.

**TGA Method.** TGA analysis was performed using a Mettler Toledo TGA/DSC 1LF/UMX. A tare weight was obtained for a Mettler Toledo 70  $\mu\text{L}$  platinum crucible (open, medium, product no. 51119654) in the TGA before approx 30 mg was weighed into the crucible and reweighed in the TGA. A purge gas flow rate of  $50 \text{ mL min}^{-1} \text{ N}_2$  was used. After equilibrating at 25 °C, the sample was heated at  $5 \text{ °C min}^{-1}$  to a maximum temperature of 300 °C. The data was visualized with JMP Pro version 14.3.0.

**ARC Method.** Approx 3.5 g of sample was accurately weighed into a Hastelloy ARC test cell (or "bomb"). The ARC test cell was placed in a Thermal Hazard Technology ES ARC and thermocouple attached by an equatorial clip. The experiment was performed using a heat-wait-search method starting at 40 °C, and the test cell was heated in  $5 \text{ °C}$  increments to a maximum temperature of 280 °C, a pressure of 35 bar, or user intervention. At the end of the experiment, the ARC cools the test cell with compressed air. Data analysis was performed using Thermal Hazard Technology's ARCCal+ software version 1.6.2, which applies the  $\Phi$  factor to correct the ARC thermal onset temperature and adiabatic temperature rise (ATR) results for the thermal inertia of the test cell using eq 7

$$\Phi = 1 + (M_b \times C_b) + (M_{cl} \times C_{cl}) / (M_s \times C_s) \quad (7)$$

where  $M$  is the mass (g),  $C$  is the specific heat capacity ( $\text{J kg}^{-1} \text{ K}^{-1}$ ),  $b$  is the bomb (test cell),  $cl$  is the clip attached to the bomb, and  $s$  is the sample. The time to maximum rate under

adiabatic conditions ( $TMR_{ad}$ ) was calculated from the ARC data at the exotherm onset using eq 8

$$TMR_{ad} = (t_{max} - t_0) / \Phi \quad (8)$$

where  $t_{max}$  is the time at the maximum self-heat rate, and  $t_0$  is the time at the start of the exotherm.

The data was visualized with JMP Pro version 14.3.0.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.9b00422>.

DSC plots for all compounds, synthetic details, full table of Hammett  $\sigma$  parameters correlated to DSC results, abnormalities observed in DSC plots, full table of Yoshida correlation output for all compounds, and  $^1H$  and  $^{13}C$  NMR spectra for **49** and **58** (PDF)  
Full table of Yoshida and Pfizer-modified correlation output (XLSX)

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### Notes

The authors declare no competing financial interest.

All characterization data for synthesized compounds, raw DSC data for all compounds, raw TGA data for **9** and raw ARC data for **9**, *p*-ABSA, and ADT can be found at <https://doi.org/10.14469/hpc/6274>.

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(7) Though thermal stability or impact sensitivity are most commonly used to define an unstable substance, there are a number of other sensitivities, which can be considered. Friction sensitivity is measured by placing the material between two plates and applying a defined load in a back-and-forth motion. Electrostatic discharge (ESD) sensitivity is measured with an applied electrical flow. Both tests are less common than impact sensitivity and suffer from more reproducibility issues. See ref 4. Some energetic compounds can also exhibit instability to light. Experimental values will be reported in the SI where they exist but due to the lack of available data and variability concerns will not be commented on further.

(8) If a combustion reaction is autocatalytic (or self-sustaining) a decomposition front is observed, where the energy released from exothermic decomposition of a molecule triggers decomposition of adjacent molecules, propagating through the material. Both TNT and wood can be considered materials with high energy content but differ in the velocity of a decomposition front. The decomposition is defined as deflagration (burning) if the front is subsonic, or detonation if the front moves faster than the speed of sound, creating a shockwave. This is measured by a variety of specialist tests, such as the Mk. III Ballistic Mortar; a sample of primary explosive such as PETN is placed in a shell containing the test material and detonated. If the shockwave can initiate detonation of the test material, it can be considered an explosive. As most chemists will not have access to this testing, Bodman and Chervin developed an alternative screening test using a modified ARC with ultra-fast pressure sensing in the sample capsule. (a) Bodman, G. T.; Chervin, S. Use of ARC in Screening for Explosive Properties. *J. Hazard. Mater.* **2004**, *115*, 101–105. Upon decomposition, the maximum rate of pressure rise can be measured

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(83) Phlegmatization (or desensitization) is when a sensitive material is diluted in solvent or plasticizer to reduce the sensitivity. In this case, the sulfonyl azide is never handled out of solution and thus at far lesser risk of detonation.

(84) Distinct endotherms were observed from gas loss when the DSC experiment was conducted in an unsealed crucible.

(85) The initial drop in heat flow is an artefact from using the heavier high-pressure crucibles, which are required to avoid energy loss when gas is evolved. For more details, see: Thomas, L. C. *Interpreting Unexpected Events and Transitions in DSC Results*; TA039, 2018; pp 1–5. Retrieved from: <http://www.tainstruments.com/pdf/literature/TA039.pdf> (August 2018).

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(88) The threshold was defined based on borderline sensitive *m*-DNB with a degree of conservatism. This plot was repeated for substances known to propagate an explosion (detonate) and those that cannot, defined by borderline explosives ammonium nitrate and 90% benzoyl peroxide in water.

(89) It is important to note this prediction only relates to the neat substance and does not preclude these compounds exploding if decomposition is triggered in a sealed vessel or reaction mixture, due to the significant amounts of heat and gas evolved.

(90) The rates of temperature and pressure rise are exponentially linked to sample size, so the rate data is only comparable to other ARC tests with the same sample size. For rates above  $1000\text{ }^{\circ}\text{C min}^{-1}$ , there is a large margin of error due to the limits of detection speed. The same is true for large pressure rise rates.

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