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Regiocontrolled Synthesis of 1-Substituted-3(5)-carboxyalkyl-1*H*-pyrazoles Using Trichloromethyl Enones

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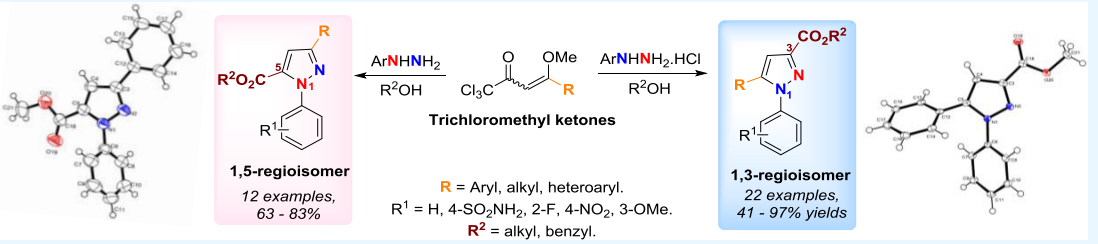

ABSTRACT: In this work, we present a regiocontrolled methodology to prepare 1-substituted-3(5)-carboxyalkyl-1*H*-pyrazoles using trichloromethyl enones as starting materials. It was found that the selectivity of the reaction depends on the nature of the hydrazine: when using arylhydrazine hydrochlorides, synthesis of the 1,3-regioisomer was achieved (22 examples, 37−97% yields), while the corresponding free hydrazine led exclusively to the 1,5-regioisomer (12 examples, 52−83% yields). The trichloromethyl group was used as a precursor for the carboxyalkyl moiety, furnishing a one-pot three-component regioselective protocol suitable for preparing both isomers at moderate to excellent yields. The selectivity of the reaction was investigated through NMR analyses and the structures of the products were unambiguously determined by SCXR analyses.

INTRODUCTION

Pyrazoles belong to a privileged class of heterocyclic compounds and are known for their use in drugs and agrochemicals.[1−6] Carboxy alkyl-substituted pyrazoles are known to act as CB1 receptor antagonists (antiobesity activity)[7,8] and have also been used as suitable starting materials for inhibitors of *Helicobacter pylori* dihydroorotate dehydrogenase,[9] and for nicotinic acid receptors.[10] More recently, carboxyethyl-substituted pyrazoles have been used as models to study the clipping reaction in the preparation of [2]rotaxanes and its behavior in the crystalline state.[11]

It is well known that usually only one of the regioisomers possesses the activity of interest (or enhanced activity over the other). Thus, methods that furnish high regioisomeric ratios for these targeted carboxyalkyl pyrazoles are of great interest. The main method known for preparing these substituted pyrazoles is the [3+2] cyclocondensation reaction between 1,3-dicarbonyl compounds (derivatives of ethyl 2,4-dioxo-4-substituted alkanoates—see Scheme 1a) and substituted hydrazines. Even though this is a very well-known method, it is usually accompanied by poor regioselectivity, furnishing a mixture of 1,3- and 1,5-regioisomers, which results in tedious and laborious purification procedures.[12−15] For instance, using the same starting carbonyl compound and phenylhydrazine, a mixture of the 1,5- and 1,3- regioisomers was obtained in 46 and 40% yields, respectively.[16] By adding trifluoroacetic acid, the ratio was inverted, furnishing the 1,5-regioisomer in 12−20% yields and the 1,3-regiosiomer in 61−74% yields (Scheme 1a).[17]

Improvement in the regioisomeric ratio is usually observed when (i) there are some structural changes in the starting materials[18] (e.g., presence of a strong electron-withdrawing group, use of protecting groups in either the enone[19] or the dinucleophile[20,21]), (ii) the influence of the solvent's nature is evaluated,[22,23] or (iii) catalysts are used.[24−26] Trichloroacetyl enol ethers **1** (Scheme 1b) have been successfully used in the synthesis of 5-carboxyalkyl pyrazoles (the corresponding 1,3-regioisomer is far less accessible[21]) and, as a matter of fact, the 1,3-regioisomer usually shows enhanced activity over the 1,5-regioisomer.[27,28]

Scheme 1 outlines the selective methods for selectively preparing either 1,5- or 1,3-regioisomers using trichloroacetyl enol ethers **1** as starting materials. Initially, arylhydrazine hydrochlorides (in the presence of sodium hydroxide) are used to furnish the 1,5-regioisomer,[29] and the use of protected phenylhydrazines (in the form of 1-phenylsemicarbazide)[21] furnishes the 1,3-regioisomers (Scheme 1). All other attempts to prepare the 1,3-regioisomer as the sole product have only

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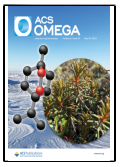
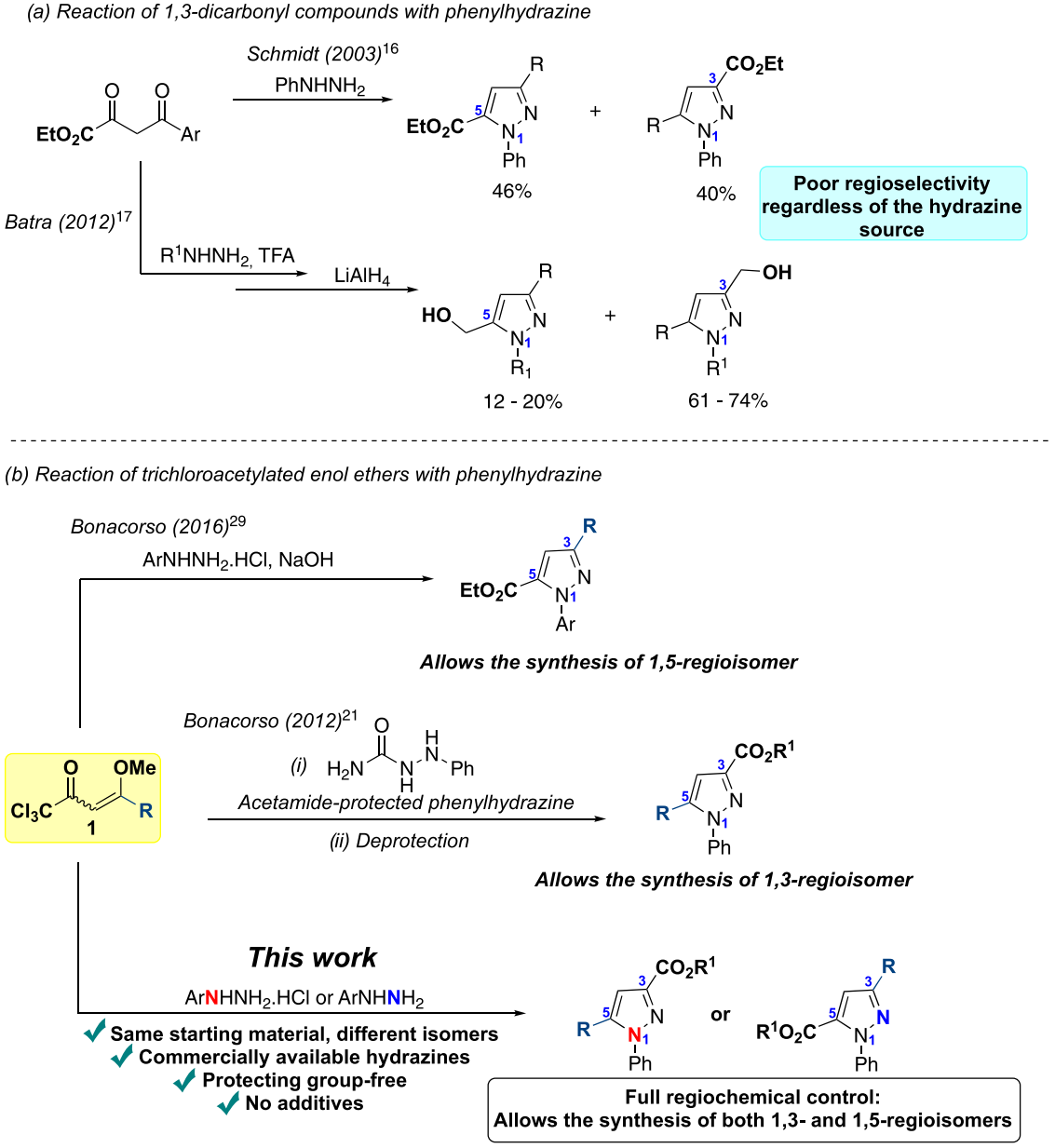


Scheme 1. Comparison of the Methods for Preparing Carboxyalkyl Pyrazoles[a]



[a](a) Those already reported and (b) the one presented herein, which enable control of the cyclocondensation reaction between enones **1** and aryl hydrazines.

furnished ratios of up to 90:10 (with a very narrow reaction scope),[30] in accordance with the conditions applied. To overcome this lack of selectivity, this present work uses a regiocontrolled protocol to prepare 1,3- and 1,5-regioisomers as sole products, based on the reaction between (*E*)/(*Z*)-1,1,1-trichloro-4-alkoxy-4-alkyl/aryl/heteroaryl-but-3-en-2-ones (enones **1**) and commercially available phenylhydrazines in both free form and hydrochloride form, to provide full regiochemical control in a protecting group and additive-free protocol.

RESULTS AND DISCUSSION

Initially, a series of 4-alkoxyvinyl trichloromethyl ketones was prepared through the acylation reaction of enol ethers (readily available or generated in situ from the corresponding dimethyl acetals) with trichloroacetyl chloride in the presence of pyridine.[31] For the initial tests, we considered conditions from the literature that deal with similar compounds.[32] We initially considered enone **1a** and phenylhydrazine (in both hydrochloride **2a** and free form **2a′**) as *N*,*N*-dinucleophiles, and methanol was chosen as the solvent, since it dissolves phenylhydrazine **2a** better (see Scheme 2). Tests using different solvents (MeCN, DMF, DMSO, and $CHCl_3$) did not result in the formation of the pyrazole, and only starting enone **1a** was recovered. Based on the literature, we expected the formation of the corresponding trichloromethyl pyrazole; however, with the use of MeOH as solvent, methanolysis of the $-CCl_3$ group was observed (Scheme 2).

Surprisingly, by varying the nature of the phenylhydrazine used (**2a** or **2a′**), the regioisomeric composition of the corresponding methyl 1,3-diphenyl-1*H*-pyrazole-5(3)-carboxylate **3a** or **4a** was greatly affected. Using the same reaction

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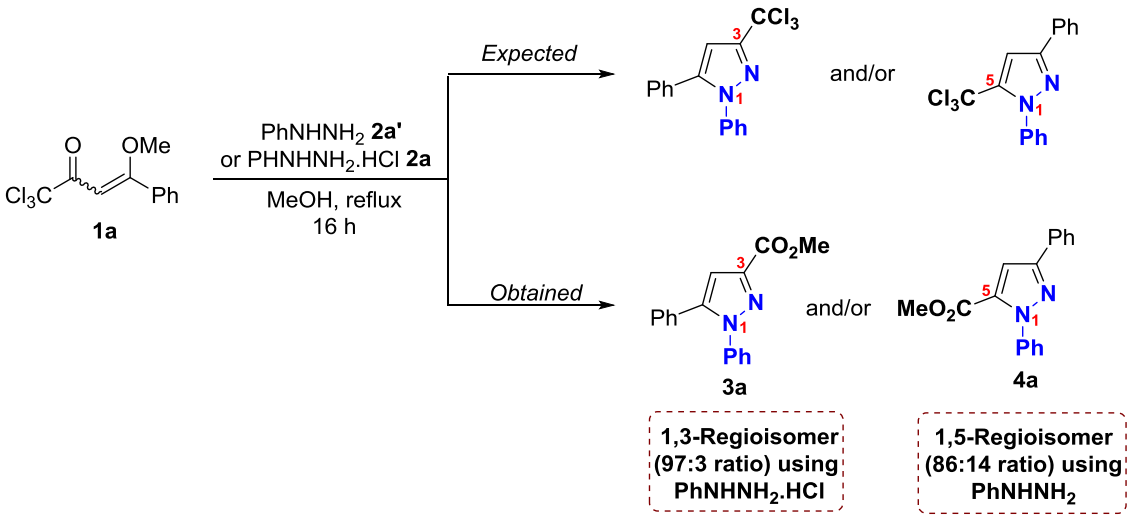
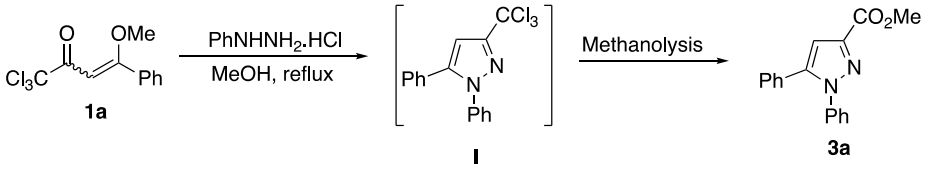
Scheme 2. Initial Reaction Tests between Enone 1a and Phenylhydrazine Hydrochloride 2a or Phenylhydrazine 2a′[a]



[a]The expected and obtained products, as well as the regioisomeric composition determined by ^{1}H NMR, are shown. Reaction conditions: Enone **1a** (1 mmol, 279 mg), phenylhydrazine hydrochloride **2a** (1.2 mmol, 173 mg) or phenylhydrazine **2a′** (1.2 mmol, 0.118 mL), and MeOH (10 mL).

Table 1. Optimization of the Reaction Conditions for the Synthesis of the 1,3-Regiosiomer 3a



			composition (%)[b]		
entry	$PhNHNH_2$·HCl (equiv)	time (h)	**1a**	**I**	**3a**
1[a]	1.2	4	100	—[d]	—[d]
2[a]	1.2	16	100	—[d]	—[d]
3	1.2	1	72	25	3
4	1.2	2	42	48	10
5	1.2	4	—[d]	57	43
6	1.2	6	—[d]	25	75
7	1.2	8	—[d]	19	81
8	1.2	11	—[d]	13	87
9	1.2	16	—[d]	—[d]	100 (85)[c]
10	2.0	16	—[d]	—[d]	100 (84)[c]
11	1.0	16	7	77	16

[a]Reaction carried out at room temperature. [b]Determined by ^{1}H NMR. [c]Isolated yield after column chromatography. During the experiments, a constant value of 2−3% of the 1,5-regioisomer (determined by ^{1}H NMR) was observed in all entries. Reaction conditions: Enone **1a** (1 mmol, 279 mg), $PhNHNH_2$·HCl **2a** (variable amounts), MeOH (10 mL), and reflux. [d]Not detected.

conditions, phenylhydrazine hydrochloride **2a** furnished the 1,3-regioisomer at a ratio of 97:3 (91:9 when using EtOH[30]), whereas free phenylhydrazine **2a′** furnished the 1,5-regioisomer at a ratio of 86:14. It is important to note that the 1,3-regioisomer is far less accessible and is often obtained only when using protecting groups.[20,21,26]

Despite the regioisomeric ratio obtained for the 1,3-regioisomer already being very high, optimization of the reaction conditions was performed to improve both the regioisomeric ratio and isolated yield (Table 1). When the reaction was done at room temperature (rt), only the starting enone **1a** was recovered (entries 1 and 2). When the reaction was heated, it took 4 h to totally consume enone **1a** (entry 5); however, the 1,5-diphenyl-3-(trichloromethyl)-1*H*-pyrazole **I** was not fully converted into the carboxymethyl ester. Thus, the reaction was continued until complete conversion in the second step was observed (16 h). The product was then isolated (by column chromatography), at 85% yield. Increasing the amount of phenylhydrazine hydrochloride **2a** to 2 equiv. and using the same optimal experimental conditions (from entry 9) did not improve the isolated yield (84%), which is in agreement with the observations, since the full consumption of the starting enone **1a** is observed with 4 h of reaction. The corresponding 1,5-regioisomer was detected as only noise signals (2−3%) during this step.

With the reaction conditions optimized, we next sought to explore the reaction scope (Scheme 3), since these condensation reactions can be very sensitive to smaller or bulkier substituents in the starting materials. Initially, different aryl moieties at the *β*-position of starting enone **1** were used

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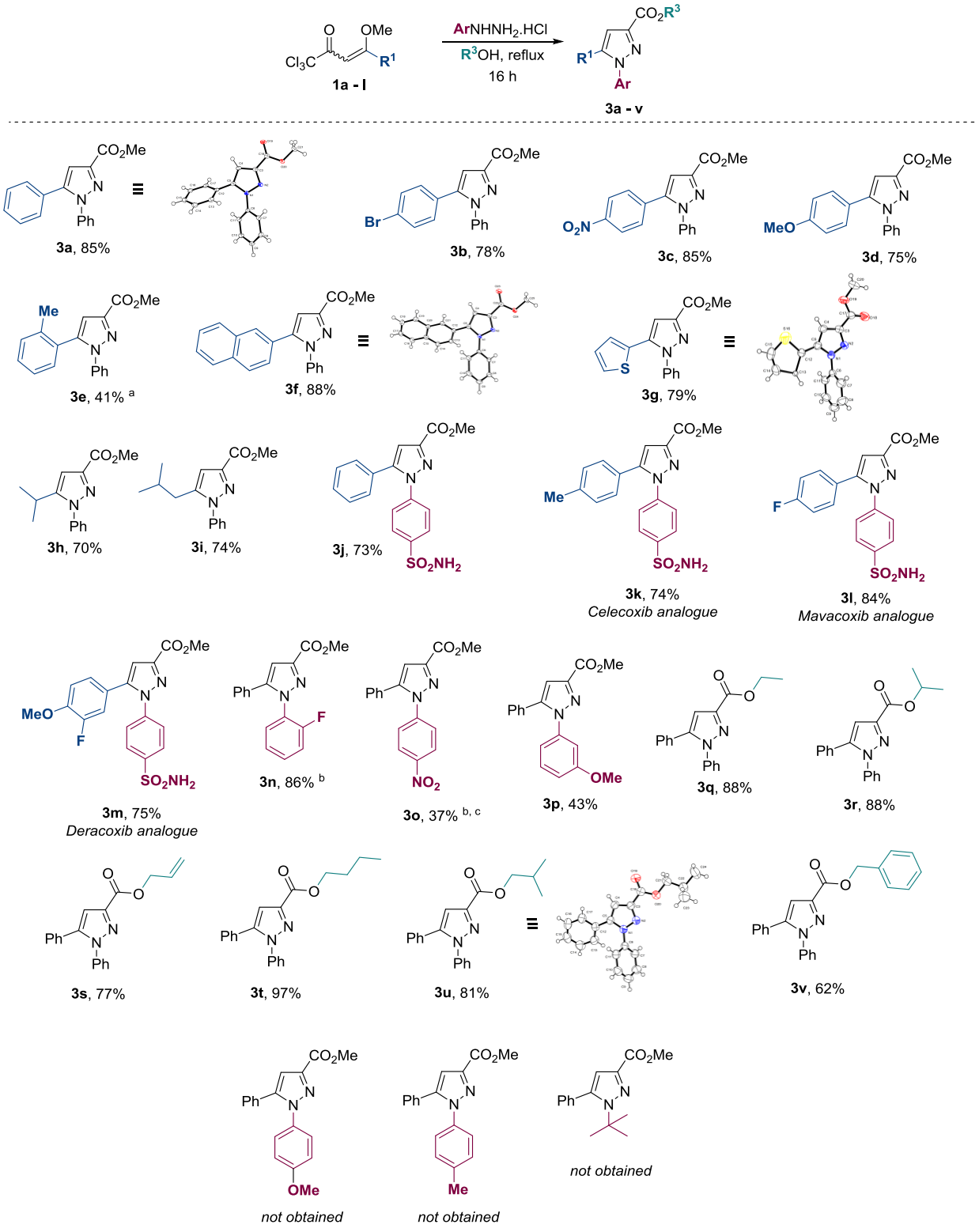
Scheme 3. Reaction Scope for the Synthesis of 3a−v, Varying the Substituents in the Starting Enone 1, Aryl Hydrazine 2, and Alcohol Used as Solvent



[a]The ORTEP of compounds **3a** (CCDC: 2100776), **3f** (CCDC: 2111607), **3g** (CCDC: 2171149), and **3u** (CCDC: 2182363) are shown, and the thermal ellipsoids are drawn at the 50% probability level. 50% of the starting enone was observed in the NMR analysis. [b]Reaction time: 48 h. [c]56% of trichloromethyl pyrazole was observed in the NMR analysis.

and compounds **3a−g** were obtained in 41−88% yields (depending on the substituent used), thus showing that the reaction tolerates groups such as (2-thienyl, **3g**), bulkier (2-naphthalenyl, **3f**), and even 2-substituted aryl (2-methylphenyl, **3e**), which could greatly influence the selectivity of the reaction, as was previously shown for other selective protocols

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Scheme 4. (a) Prevention of $-CCl_3$ Methanolysis Caused by a EWG and (b) Elimination of the *N*-Substituent Caused by Electron-Donating Groups

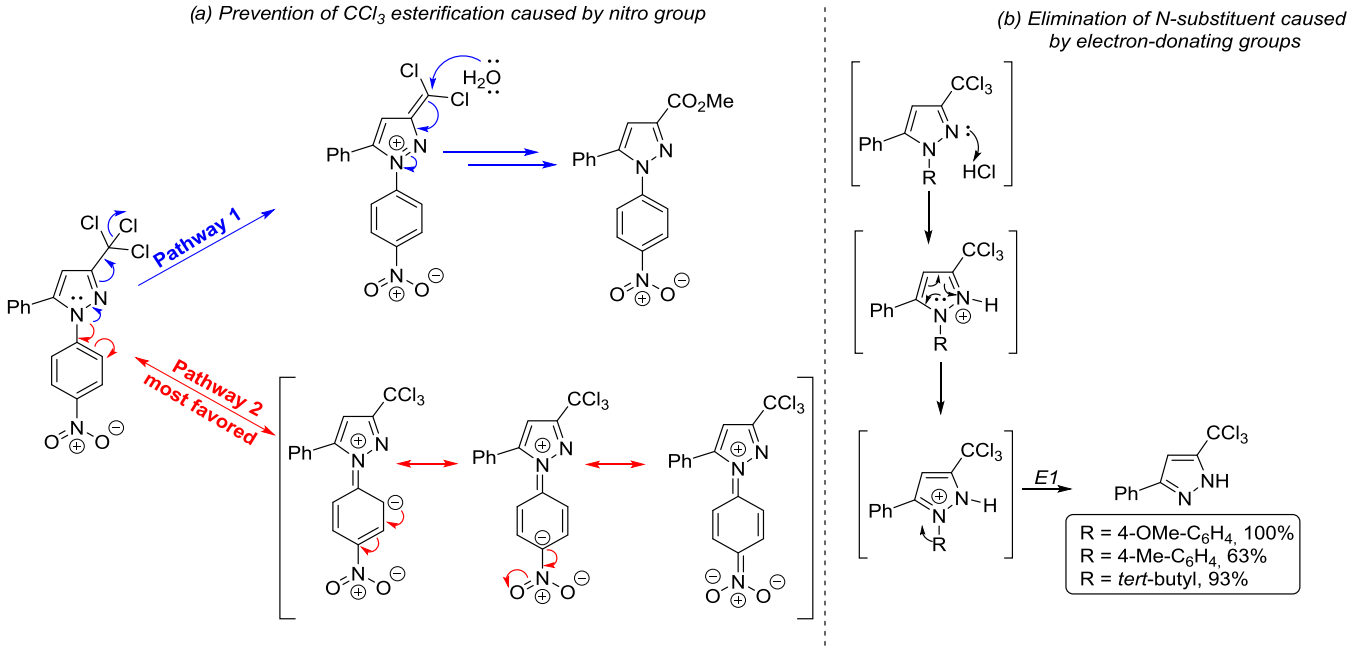
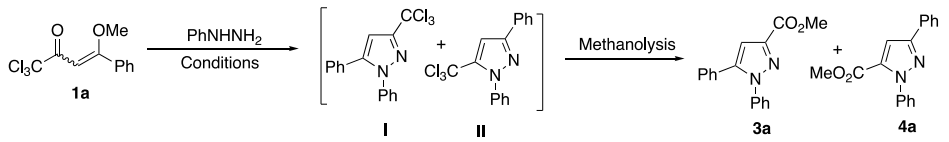


Table 2. Optimization of the Reaction Conditions for the Synthesis of the 1,5-Regiosiomer 4a



			composition (%)[a]			
entry	$PhNHNH_2$	conditions	**1a**	**II**	**3a**	**4a**
1	1.2	MeOH, reflux, 16 h	—[c]	—[c]	14	86
2	1.2	MeOH, rt 16 h	14	84	—[c]	2
3	1.2	(i) MeOH, rt 4 h, (ii) reflux, 16 h	—[c]	—[c]	9	91
4	1.2	(i) MeOH, rt, 16 h, (ii) reflux, 16 h	—[c]	—[c]	6	94
5	1.2	(i) $CHCl_3$, rt, 3 h, (ii) MeOH, reflux, 16 h	—[c]	21	20	59
6	1.2	(i) $CHCl_3$, reflux, 4 h, (ii) MeOH, reflux, 16 h	—[c]	8	24	68
7	1.5	(i) $CHCl_3$, reflux, 3 h, (ii) MeOH, reflux, 16 h	—[c]	—[c]	15	85
8	2.0	(i) $CHCl_3$, reflux, 3 h, (ii) MeOH, reflux, 16 h	—[c]	—[c]	—[c]	100 (70)[b]
9	2.0	(i) $CHCl_3$, reflux, 2 h, (ii) MeOH, reflux, 16 h	—[c]	—[c]	—[c]	100 (68)[b]

[a]Determined by ^1H NMR. [b]Isolated yield after column chromatography. Reaction conditions: Enone **1a** (1 mmol, 279 mg), $PhNHNH_2$ **2a′** (variable amounts), and solvent (10 mL). [c]Not detected.

for pyrazole synthesis.[22] The only important thing to note is that in the reaction to prepare **3e**, about 50% of the starting enone **1e** was observed after 16 h. In order to verify the influence of alkyl groups in the cyclocondensation reaction, enones substituted with *i*-Pr and *i*-Bu at the *β*-position were used; however, the yields (70 and 74%, respectively) and the selectivity of the reaction were the same as observed for the aryl groups. When replaced with a methyl group, the selectivity decreased to 82:18 for 1,3 and 1,5, respectively, and in the absence of a substituent at the *β*-position, similar selectivity (82:12) was observed. This shows that the reaction is tolerant to any changes in the *β*-position, but for smaller groups such as methyl, the regioselectivity decreases.

When using an *α*-branched enone ((*E*)-1,1,1-trichloro-4-ethoxy-3-methylbut-3-en-2-one), a regioisomeric mixture of 50:50 was observed, which could be attributed to both the absence of a substituent at the *β*-position and also the presence of the methyl group at C3, which forces the molecule out of planarity, thus making the conjugation of the double bond not efficient enough to direct all the initial attack in C4.[33]

By using the benzenesulfonamide group, carboxymethyl analogues of the commercial anti-inflammatory drugs celecoxib, mavacoxib, and deracoxib were prepared at good yields (compounds **3k−m**, 74−84% yields). Very different isolated yields were obtained when using other electron-withdrawing groups in the starting hydrazine. For example, compound **3n** was isolated at 86% yield (2-F-C_6H_4, 48 h) and **3o** was isolated in 37% yield (4-NO_2-C_6H_4, 48 h).

Scheme 3 shows the reaction scope for the synthesis of **3a−v**, varying the substituents in the starting enone **1**, aryl hydrazine **2**, and alcohol used as solvent, as well as the ORTEP projections of compounds **3a**, **3f**, **3g**, and **3u**.

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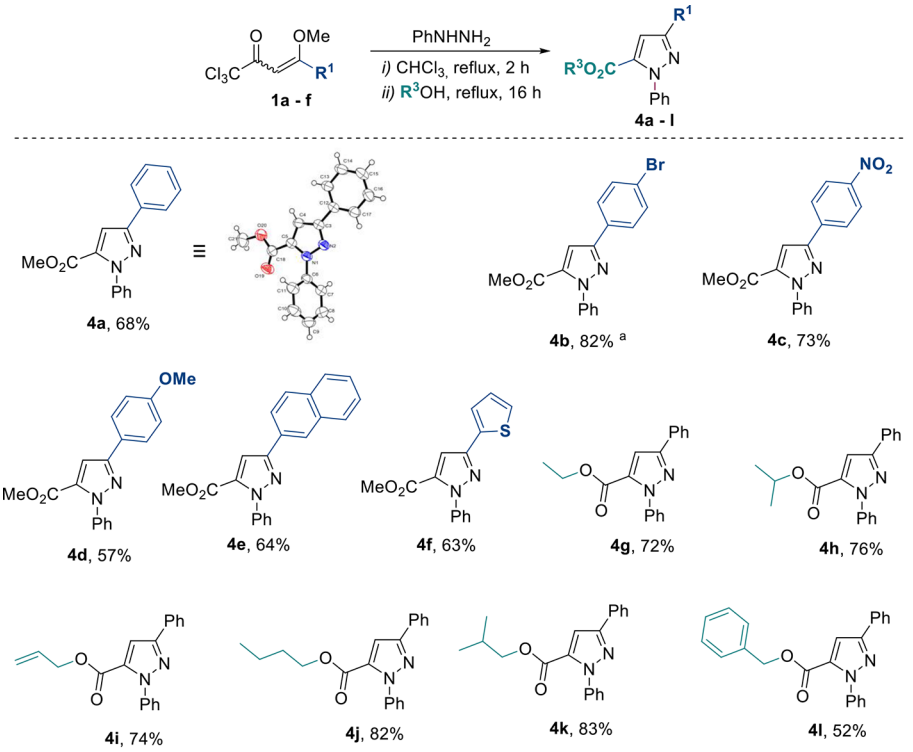
Scheme 5. Reaction Scope for the Synthesis of 4a–l, Varying the Substituents in the Starting Enone 1, with Alcohol Used as Solvent



[a]The ORTEP of compound **4a** (CCDC: 2168691) is shown, and the thermal ellipsoids are drawn at the 50% probability level.

For compound **3o**, full consumption of the starting enone was detected by thin-layer chromatography (TLC) analyses; however, the methanolysis of the trichloromethyl group is greatly harmed in the presence of such a strong EWG. The reaction time was increased from 48 to 72 h; however, no higher degree of methanolysis was observed in this case. A plausible explanation for this is presented in Scheme 4a, that is, the beginning of the reaction involves the pushing of the nitrogen's lone pair inside either the pyrazole ring or the phenyl ring. For the 4-nitrophenyl group, the favored one is the resonance to the phenyl ring over the pyrazole, furnishing 1-(4-nitrophenyl)-5-phenyl-3-(trichloromethyl)-1*H*-pyrazole as the major compound. For other EWGs such as 2-F and 4-SO_2NH_2, the mesomeric effects of fluorine and nitrogen favor the methanolysis reaction.

When electron-donating groups were used in the starting hydrazine, the elimination of the *N*-substituent was observed during the cyclocondensation reaction. In fact, this was earlier reported for the synthesis of 1-*tert*-butyl-3-(trifluoromethyl)-1*H*-pyrazoles[34] and was also observed in this work when using *tert*-butylhydrazine hydrochloride, which led to the corresponding unsubstituted *NH*-pyrazole being obtained in 93%, compared to 7% for the *N*-substituted one. This is explained by the initial protonation of the N_2, with the elimination reaction favored and the 1*H*-pyrazole and aryl cation being formed (Scheme 4b).[34] Other alkyl hydrazines (e.g., methylhydrazine hydrochloride) furnished low regioselectivity and, therefore, were not considered for further tests in this work.[30]

In the second part of this work, we focused on the regioselective preparation of the 1,5-regioisomer. Although the cyclocondensation reaction between enones **1** and phenylhydrazines (aiming for the synthesis of the 1-phenyl-5-trichloromethyl/carboxyethyl-1*H*-pyrazoles) has already been reported,[29,35] a detailed study that reports the regioisomeric composition of the products using different reaction conditions could not be found. When attempting to use starting materials that already possess the ester moiety, a mixture of regioisomers was always observed, which indicates the suitability of using trichloromethyl enones **1** as selective starting materials.[16,36]

Initially, we started with the same standard conditions as for the synthesis of **3a** (refluxing methanol for 16 h—see Table 2, entry 1). Consequently, we observed a regioisomeric mixture of 86:14 (for 1,5, and 1,3, respectively), demonstrating that the same reaction condition cannot be applied to selectively prepare each of the isomers as sole products. Thus, the reaction was conducted first at rt (16 h), but only 2% of the expected product was observed (along with starting enone **1** and 5-trichloromethylpyrazole **II**—see Table 2, entry 2). As no formation of the 1,3-regioisomer was observed at rt, the first step was done at rt followed by heating, which led to an improvement in the ratio (91:9 and 94:6 for entries 3 and 4, respectively, in Table 2).

Since the solvent plays an important role in the selectivity of these condensation reactions, we next sought to use $CHCl_3$ as solvent for the initial step (formation of 5-trichloromethylpyrazole **II**), and after full consumption of enone **1a** (determined by TLC), the solvent was removed and MeOH was added to allow the methanolysis of the trichloromethyl group. When using 1.2 and 1.5 equiv. of phenylhydrazine, a considerable amount of the 1,3-isomer was still observed (~15–20%—see entries 5–7 in Table 2). Upon increasing the amount to 2.0 equiv., only the 1,5-isomer was obtained (Table 2, entries 8 and 9).

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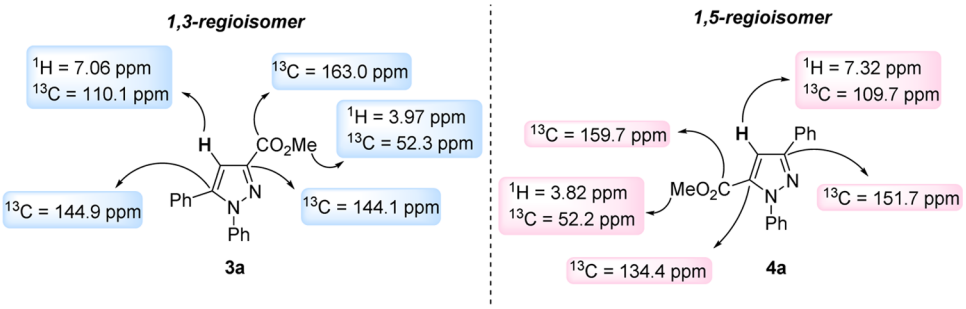
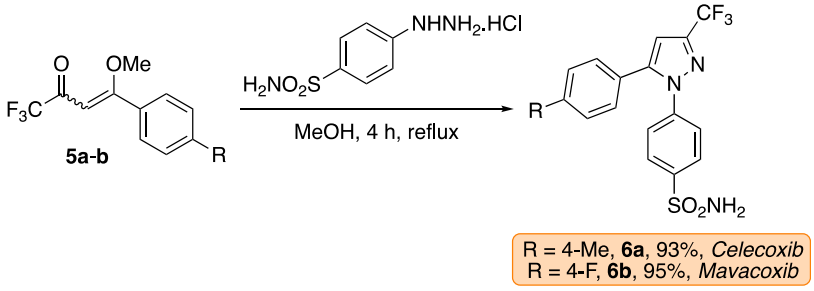


Figure 1. Comparison of ^{1}H (600 MHz) and ^{13}C (150 MHz) chemical shifts for the methyl 1,5-diphenyl-1*H*-pyrazole-3(5)-carboxylates **3a** and **4a**.

Scheme 6. Application of the Method Developed Herein in the Synthesis of 3-Trifluoromethyl Pyrazoles of Pharmacological Interest



With the optimal conditions in hand to prepare the 1,5-isomer as the sole product, we next explored the reaction scope by varying the substituent in the starting enone **1**. Given that the substituents did not play a significant role in selectively obtaining the 1,3-regioisomers in the first part of the work, and that alkyl substituents had already been reported in the literature,[37] we focused on preparing methyl 1-phenyl-3-aryl(heteroaryl)-1*H*-pyrazole-5-carboxylates **4a−l** (Scheme 5). The compounds were obtained in 57−82% yields when varying the substituent in the starting enones **1a−f**. When using other alcohols as solvents, in general the yield improved when comparing compounds **4g−k** (72−83%) and **4a** (68%), except for benzylic alcohol **4l** (52%). The 1,5-regioisomer was confirmed by SCXR analysis of the appropriate crystals of compound **4a** (obtained through slow evaporation of a $CHCl_3$ solution)—its ORTEP projection is shown in Scheme 5.

The structures of compounds **3** and **4** were unambiguously assigned by $^{1}H-^{13}C$ HMBC experiments—selected chemical shifts of hydrogen and carbons are highlighted in Figure 1. The greatest differences were observed in H4 and C3(5) directly connected to the phenyl and carboxymethyl moieties. For the 1,3-regioisomer, the H4 is 0.26 ppm more shielded, the carbon connected to the carboxymethyl group is 9.7 ppm more deshielded, and the carbon connected to the phenyl group is 6.8 ppm more shielded than in the 1,5-regioisomer.

Although several new synthetic routes for the synthesis of celecoxib and its analogues have been published,[38−40] direct and selective cyclocondensation or reactions with ynones[3,41,42] are still powerful methods in terms of reaction conditions, yield, and regioselectivity. In order to demonstrate the applicability of the method developed herein, the COX-2 inhibitors celecoxib and mavacoxib[43] were prepared by using the corresponding trifluoromethyl ketones **5a−b** (Scheme 6), which furnished exclusively 3-trifluoromethylpyrazoles **6a−b** in high yields (93−95%). It is important to note that no presence of the 5-trifluoromethylpyrazoles was detected by ^{1}H NMR analyses.

A proposed mechanism for the synthesis of both isomers is presented in Scheme 7. Both of the pathways proceed quite similarly, with a difference only at the very beginning, in which either the most or the least hindered nitrogen of the phenylhydrazine attacks the *β*-position. For phenylhydrazine hydrochloride, the least hindered (and most nucleophilic) nitrogen is in the non-nucleophilic (NH_3^+) salt form. Therefore, the only nitrogen capable of carrying out the attack on the *β*-position of the enone is the most hindered one (NH). Under basic or neutral conditions, phenylhydrazine is in its free form, thus the nucleophilic attack occurs by the least hindered and more nucleophilic nitrogen (NH_2); for better understanding of this, the formation of the 1,3-regioisomer will be detailed below. After the initial attack occurs, the formation of intermediate **I** rapidly eliminates a molecule of MeOH and HCl. The resulting NH_2 group of the *β*-enaminone **II** attacks the carbonylic carbon, furnishing cyclic intermediate **III**, which furnishes pyrazoline **IV** by prototropism and is spontaneously dehydrated (intermediates **V** and **VI**) to furnish 3-trichloromethylpyrazoles **VII** through the loss of H_2O and deprotonation of the nitrogen. The posterior methanolysis of the trichloromethyl group, which has already been reported in the literature,[44] involves the initial formation of the *gem*-dichloroalkene (**VIII**), water addition (**IX**), acyl chloride formation (**X**), and final addition of the corresponding alcohol (**XI** and **XII**) to furnish the final 3-carboxyalkylpyrazoles.

CONCLUSIONS

This work presented a regiocontrolled, one-pot, three-component protocol for the synthesis of both possible regioisomers (as sole products) of 3(5)-carboxyalkyl-1*H*-pyrazoles, using trichloromethyl enones and arylhydrazines. The nature of both the hydrazine and the solvent used for the reaction greatly influenced the selectivity of the reaction, and a

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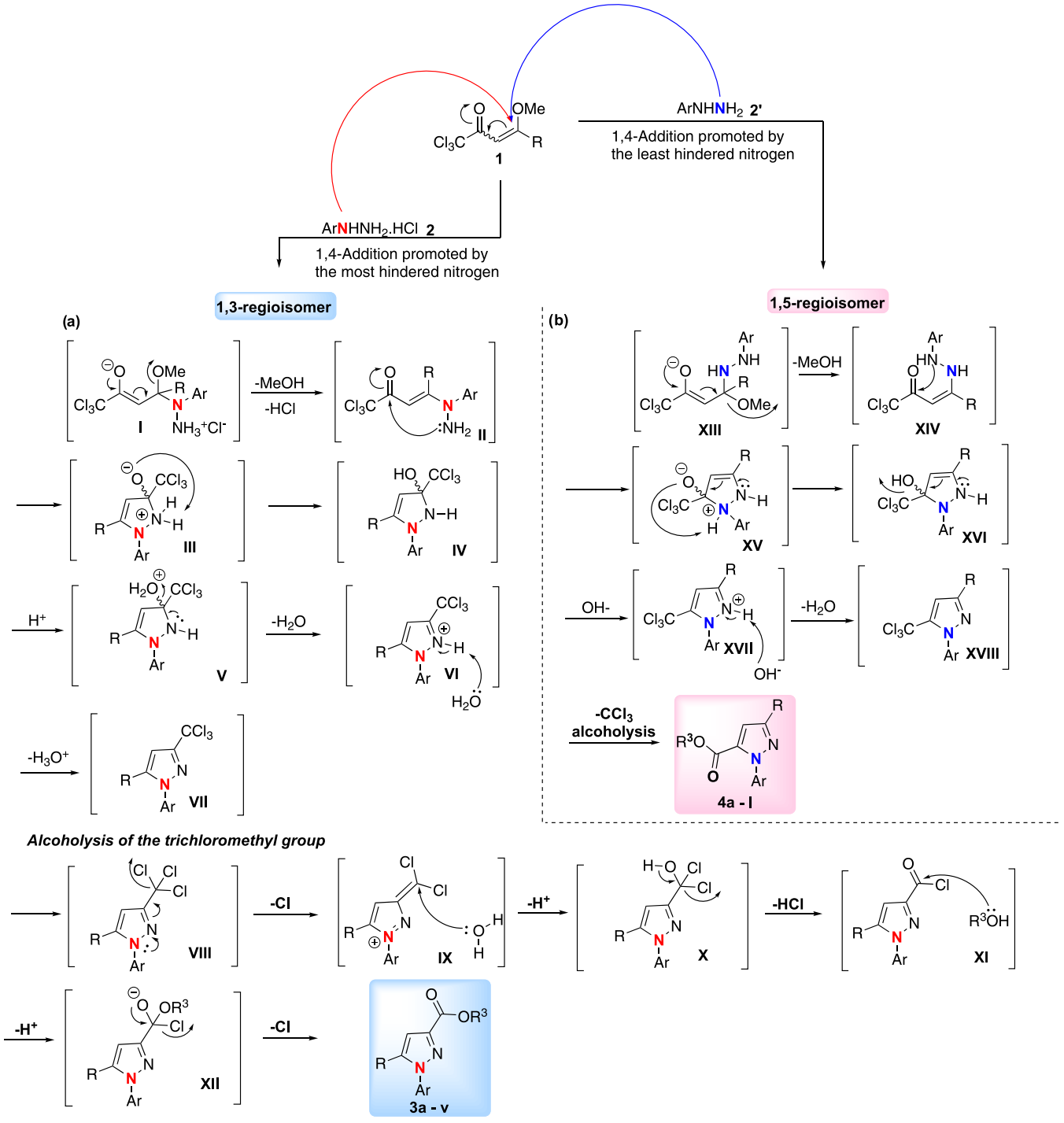
Scheme 7. Proposed Mechanism for the Synthesis of (a) 1,3-Regioisomers and (b) 1,5-Regioisomers of Carboxyalkyl Pyrazoles 3a−v and 4a−l



plausible mechanism was presented to corroborate these findings. Using the methodology developed herein, 34 examples of 3(5)-carboxyalkyl-1*H*-pyrazoles were prepared in moderate to excellent yields (41−97%). Using the same conditions, celecoxib and mavacoxib were regioselectively prepared at high yields.

EXPERIMENTAL SECTION

Reagents were purchased and used without further purification. Thin-layer chromatography (TLC) was performed using silica gel plates F-254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or stained with sulfuric vanillin, followed by heating. Most reactions were monitored by TLC for disappearance of the starting material. NMR spectra were carried out in $CDCl_3$ or DMSO-d_6 solutions using TMS as the internal standard. ^{1}H NMR spectra were recorded at 600 or at 400 MHz, chemical shifts δ are quoted in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). ^{13}C NMR spectra were recorded at 150 MHz or at 100 MHz. The low-resolution mass spectra were recorded on a gas chromatography−mass spectrometry (GC−MS) using EI mode (70 eV), and high-resolution mass

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spectra (HRMS) were recorded on an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. All melting points were determined on a melting point apparatus and are uncorrected. Single-crystal X-ray diffraction data were recorded in a diffractometer equipped with a four-circle Kappa goniometer, PHOTON 100 CMOS array detector, graphite monochromator, and Mo Kα (λ = 0.71073 Å) or Cu Kα radiation (λ = 1.54080 Å) source. Absorption correction was performed using multiscan methods. The structure was solved and refined with the *Olex2* program[45] (version 1.3), by means of *olex2.solve*[46] and *olex2.refine*,[46] respectively. Anisotropic displacement parameters for non-hydrogen atoms were applied.

General Experimental Procedure for the Synthesis of Enones 1. To an oven-dried round-bottom flask, anhydrous CH_2Cl_2 (50 mL) and trichloroacetyl chloride (25 mmol, 2.8 mL) were added under argon atmosphere. The solution was cooled to 0 °C, and a mixture of the corresponding dimethyl acetal (10 mmol) and anhydrous pyridine (25 mmol, 2.1 mL) dissolved in anhydrous CH_2Cl_2 (50 mL) was slowly added dropwise with the aid of a dropping funnel. After the addition was complete, the ice bath was kept for another hour, and then, the reaction was heated to reflux (56 °C, oil bath) and kept under vigorous stirring for 16 h. After this, the reaction mixture was cooled to room temperature and washed with diluted HCl (3%, 2 × 30 mL) and with brine (1 × 50 mL). The organic layer was lastly dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. The residue was purified through column chromatography using silica gel and a mixture of hexanes and ethyl acetate (80:20) to afford the pure enones **1**. Products **1a−d** and **1f−h** have been reported elsewhere[47,48] (purity was confirmed by ^{1}H NMR), and characterization has been done for the newly synthesized derivatives.

*(E,Z)-1,1,1-Trichloro-4-methoxy-4-(2-methylphenyl)but-3-en-2-one (**1e**).* A light yellow oil, yield: 2.32 g (80%); isomers obtained in the proportion of 93% (*E*)- and 7% (*Z*)-. ^{1}H NMR (400 MHz, $CDCl_3$): δ [(*E*)-isomer] 7.29−7.25 (m, 1H), 7.20−7.14 (m, 2H), 7.11−7.06 (m, 1H), 6.23 (s, 1H), 3.86 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [(*E*)-isomer] 177.6, 176.5, 134.5, 133.5, 129.2, 128.7, 126.6, 124.8, 96.1, 91.6, 56.5, 17.3. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}Cl_3O_2$, 292.9903; found, 292.9895.

*(E,Z)-1,1,1-Trichloro-4-methoxy-4-(3-fluoro-4-methoxyphenyl)but-3-en-2-one (**1m**).* A light yellow oil, yield: 2.06 g (63%); isomers obtained in the proportion of 89% (*E*)- and 11% (*Z*)-. ^{1}H NMR (600 MHz, $CDCl_3$): δ [(*E*)-isomer] 7.31 (d, *J* = 8.6 Hz, 1H), 7.29−7.24 (m, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.15 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ [(*E*)-isomer] 179.1, 175.6 (d, *J* = 1.7 Hz), 152.4, 150.8, 150.1 (d, *J* = 10.3 Hz), 126.1 (d, *J* = 3.5 Hz), 117.1, 116.9, 112.4, 90.8, 57.3, 56.3. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}Cl_3FO_3$, 326.9758; found, 326.9775.

General Experimental Procedure for the Synthesis of 3-Carboxyalkyl Pyrazoles 3. To a round-bottom flask loaded with enones **1** (1 mmol), dissolved in the corresponding alcohol (10 mL for compounds **3a−n** and 2 mL for compounds **3o−s**), the corresponding hydrazine hydrochloride **2a−e** (1.2 mmol) was added in one portion. The reaction was kept under vigorous stirring at rt for 15 min and then heated to reflux for another 16 h (when alcohols with higher boiling point were used, the temperature of the oil bath was 90 °C). After this time, the reaction mixture was cooled down to rt and the solvent was removed under vacuum. The residue was purified through column chromatography using silica gel with hexanes and ethyl acetate at different proportions as eluent.

*Methyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3a**).*[21] The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow solid (237 mg, 85% yield), mp: 99−102 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.36−7.30 (m, 8H), 7.22 (d, *J* = 7.3 Hz, 2H), 7.06 (s, 1H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 163.0, 144.9, 144.1, 139.6, 129.6, 129.1, 128.9, 128.7, 128.5, 125.8, 110.0, 52.3.

*Methyl-5-(4-bromophenyl)-1-phenyl-1H-pyrazole-3-carboxylate (**3b**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow solid (278 mg, 78% yield), mp: 113−115 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.44 (d, *J* = 8.4 Hz, 2H), 7.39−7.36 (m, 3H), 7.31 (dd, *J* = 6.0, 2.9 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.05 (s, 1H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.8, 144.2, 143.7, 139.3, 132.0, 130.3, 129.3, 128.8, 128.5, 125.8, 123.3, 110.1, 52.4. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}BrN_2O_2$, 357.0239; found, 357.0231.

*Methyl-5-(4-nitrophenyl)-1-phenyl-1H-pyrazole-3-carboxylate (**3c**).* The product was isolated by column chromatography (hexane−ethyl acetate 85:15) to furnish an orange solid (275 mg, 85% yield), mp: 155−158 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.17 (d, *J* = 8.0 Hz, 2H), 7.44−7.38 (m, 5H), 7.32 (d, *J* = 6.7 Hz, 2H), 7.18 (s, 1H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.5, 147.7, 144.5, 142.4, 139.0, 135.6, 129.5, 129.5, 129.3, 125.8, 124.0, 111.1, 52.5. HRMS (ESI$^+$): calcd for $C_{17}H_{14}N_3O_4$ [M + H], 324.0984; found, 324.1048.

*Methyl-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-3-carboxylate (**3d**).*[49] The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow solid (231 mg, 75% yield), mp: 74−76 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.37−7.32 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.99 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.97 (s, 3H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 163.1, 160.0, 144.7, 144.0, 139.7, 130.2, 129.1, 128.4, 125.8, 121.9, 114.2, 109.5, 55.4, 52.3.

*Methyl-5-(2-methylphenyl)-1-phenyl-1H-pyrazole-3-carboxylate (**3e**).* The product was isolated by column chromatography (hexane−ethyl acetate 90:10) to furnish a light yellow oil (119 mg, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.31−7.28 (m, 1H), 7.26 (brs, 5H), 7.19−7.17 (m, 3H), 6.95 (s, 1H), 3.98 (s, 3H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 163.0, 144.0, 143.8, 139.5, 137.2. 130.6, 130.5, 129.6, 129.4, 128.8, 127.9, 126.0, 124.3, 111.0, 52.2, 19.9. HRMS (ESI$^+$): calcd for $C_{18}H_{17}N_2O_2$ [M + H], 293.1290; found, 293.1283

*Methyl-5-(naphthalen-2-yl)-1-phenyl-1H-pyrazole-3-carboxylate (**3f**).* The product was isolated by column chromatography (hexane−ethyl acetate 85:15) to furnish a yellow solid (289 mg, 88% yield), mp: 98−102 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.82−7.72 (m, 4H), 7.50 (p, *J* = 6.8 Hz, 2H), 7.39−7.31 (m, 5H), 7.22 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.16 (s, 1H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 163.0, 144.9, 144.2, 139.7, 133.1, 133.1, 129.2, 128.6, 128.4, 128.4, 127.8, 127.1, 127.0, 126.8, 126.0, 125.8, 110.4, 52.3. HRMS (ESI$^+$): calcd for $C_{21}H_{17}N_2O_2$ [M + H], 329.1290; found, 329.1332.

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*Methyl-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole-3-carboxylate (**3g**).*[49] The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow solid (225 mg, 79% yield), mp: 110−113 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.46−7.40 (m, 5H), 7.29 (d, J = 5.0 Hz, 1H), 7.10 (s, 1H), 6.94 (t, J = 4.1 Hz, 1H), 6.84 (d, J = 3.5 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.7, 144.0, 139.3, 138.9, 130.2, 129.4, 129.2, 127.9, 127.6, 127.3, 126.7, 109.6, 52.3.

*Methyl-1-phenyl-5-(isopropyl)-1H-pyrazole-3-carboxylate (**3h**).* The product was isolated by column chromatography (hexane−ethyl acetate 90:10) to furnish a yellow oil (171 mg, 70% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.51−7.46 (m, 3H), 7.43−7.41 (m, 2H), 6.79 (s, 1H), 3.93 (s, 3H), 3.00 (sep, J = 6.8 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 163.3, 152.4, 143.6, 129.3, 129.2, 126.4, 105.7, 52.1, 25.7, 22.9. HRMS (ESI$^+$): calcd for $C_{14}H_{17}N_2O_2$ [M + H], 245.1290; found, 245.1288.

*Methyl-1-phenyl-5-(isobutyl)-1H-pyrazole-3-carboxylate (**3i**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow oil (191 mg, 74% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.50−7.44 (m, 3H), 7.42−7.39 (m, 2H), 6.77 (s, 1H), 3.93 (s, 3H), 2.51 (d, J = 7.2 Hz, 2H), 1.88−1.80 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 163.2, 145.0, 143.6, 139.4, 129.3, 129.0, 126.3, 108.6, 52.1, 35.1, 28.4, 22.4. HRMS (ESI$^+$): calcd for $C_{15}H_{19}N_2O_2$ [M + H], 259.1447; found, 259.1452.

*Methyl-5-phenyl-1-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate (**3j**).* The product was isolated by column chromatography (hexane−ethyl acetate 40:60) to furnish a white solid (260 mg, 73% yield), mp: 200−201 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.87 (d, J = 8.6 Hz, 2H), 7.54−7.51 (m, 4H), 7.43−7.40 (m, 3H), 7.30 (dd, J = 7.0, 2.2 Hz, 2H), 7.18 (s, 1H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ (ppm) 161.8, 144.6, 143.8, 143.7, 141.3, 129.1, 128.7, 128.7, 128.6, 126.7, 125.7, 110.1, 51.8. HRMS (ESI$^+$): calcd for $C_{17}H_{16}N_3O_4S$ [M + H], 358.0862; found, 358.0948.

*Methyl-5-(4-methylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate (**3k**).*[50] The product was isolated by column chromatography (hexane−ethyl acetate 30:70) to furnish a white solid (276 mg, 74% yield), mp: 215−217 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.88 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 6.6 Hz, 4H), 7.21 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.12 (s, 1H), 3.87 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 161.9, 144.7, 143.8, 143.8, 141.5, 138.8, 129.4, 128.7, 126.8, 125.8, 125.8, 110.0, 51.9, 20.8.

*Methyl-5-(4-fluorophenyl)-1-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate (**3l**).*[50] The product was isolated by column chromatography (hexane−ethyl acetate 50:50) to furnish a white solid (258 mg, 69% yield), mp: 235−236 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.88 (d, J = 8.5 Hz, 2H), 7.54−7.51 (m, 4H), 7.39−7.34 (m, 2H), 7.27 (t, J = 8.8 Hz, 2H), 7.19 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 163.2, 161.9, 161.6, 143.8, 143.7, 141.3, 131.3 (d, J = 8.6 Hz), 126.8, 125.9, 125.2 (d, J = 3.0 Hz), 115.9 (d, J = 22.0 Hz), 110.4, 52.0.

*Methyl-5-(3-fluoro-4-methoxyphenyl)-1-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylate (**3m**).* The product was isolated by column chromatography to furnish a white solid (304 mg, 75% yield), mp: 222−223 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.89 (d, J = 8.5 Hz, 2H), 7.56−7.52 (m, 4H), 7.24 (dd, J = 12.1, 1.9 Hz, 1H), 7.19 (t, J = 8.8 Hz, 1H), 7.16 (s, 1H), 7.03 (dd, J = 8.5, 1.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 161.8, 151.8, 150.2, 147.8 (d, J = 10.2 Hz), 143.8 (d, J = 9.8 Hz), 143.4, 141.3, 126.8, 125.8, 125.6 (d, J = 2.9 Hz), 121.1 (d, J = 7.3 Hz), 116.5 (d, J = 19.5 Hz), 114.0, 110.2, 56.1, 51.9. HRMS (ESI$^+$): calcd for $C_{18}H_{16}FN_3O_5S$ [M + H], 406.0873; found, 406.0863.

*Methyl-1-(2-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**3n**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow oil (255 mg, 86% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.51 (td, J = 7.7, 1.5 Hz, 1H), 7.42−7.38 (m, 1H), 7.34−7.27 (m, 3H), 7.25−7,20 (m, 3H), 7.11−7.05 (m, 2H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.8, 156.8 (d, J = 253.8 Hz), 146.7, 144.9, 131.1 (d, J = 7.7 Hz), 129.2, 129.2, 129.0, 128.7, 128.0, 124.8, 124.8, 116.7 (d, J = 19.7 Hz), 109.0, 52.3. HRMS (ESI$^+$): calcd for $C_{17}H_{13}FN_2NaO_2$ [M + Na], 319.0859; found, 319.0856.

*Methyl-1-(4-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**3o**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (115 mg, 37% yield), mp: 145−147 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.21 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.9 Hz, 2H), 7.44−7.37 (m, 3H), 7.24 (d, J = 7.2 Hz, 2H), 7.07 (s, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.5, 146.9, 145.4, 145.3, 144.3, 129.6, 129.2, 129.0, 129.0, 125.8, 124.6, 111.3, 52.5. HRMS (ESI$^+$): calcd for $C_{17}H_{14}N_3O_4$ [M + H], 324.0984; found, 324.0987.

*Methyl-1-(3-methoxyphenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**3p**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow solid (132 mg, 43% yield), mp: 103−106 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.34−7.30 (m, 3H), 7.25−7.20 (m, 3H), 7.05 (s, 1H), 6.92−6.88 (m, 2H), 6.85 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 163.0, 160.0, 144.9, 144.0, 140.5, 129.8, 129.6, 128.9, 128.8, 128.7, 118.1, 114.9, 111.1, 110.0, 55.5, 52.3. HRMS (ESI$^+$): calcd for $C_{18}H_{17}N_2O_3$ [M + H], 309.1239; found, 309.1244.

*Ethyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3q**).*[16,51] The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a yellow solid (257 mg, 88% yield), mp: 56−59 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.36−7.29 (m, 8H), 7.21 (dd, J = 7.9, 1.4 Hz, 2H), 7.05 (s, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.6, 144.8, 144.5, 139.7, 129.7, 129.1, 128.9, 128.8, 128.7, 128.5, 125.9, 110.1, 61.3, 14.6.

*Isopropyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3r**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange oil (270 mg, 88% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.34−7.28 (m, 8H), 7.21 (dd, J = 8.0, 1.5 Hz, 2H), 7.02 (s, 1H), 5.34 (sep, J = 6.3 Hz, 1H), 1.41 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.2, 144.8, 144.6, 139.7, 129.7, 129.1, 128.9, 128.8, 128.7, 128.4, 125.9, 110.0, 68.8, 22.0. HRMS (ESI$^+$): calcd for $C_{19}H_{19}N_2O_2$ [M + H], 307.1447; found, 307.1445.

*Allyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3s**).* The product was isolated by column chromatography (hexane−

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ethyl acetate 80:20) to furnish an orange solid (234 mg, 77% yield), mp: 64−67 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.35−7.29 (m, 8H), 7.21 (dd, J = 7.9, 1.4 Hz, 2H), 7.06 (s, 1H), 6.07 (ddt, J = 16.3, 10.6, 5.8 Hz, 1H), 5.43 (dd, J = 17.2, 1.4 Hz, 1H), 5.30 (dd, J = 10.4, 0.8 Hz, 1H), 4.89 (d, J = 5.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.2, 144.8, 144.1, 139.6, 132.2, 129.6, 129.1, 128.9, 128.9, 128.7, 128.5, 125.8, 118.9, 110.1, 65.8. HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O_2$ [M + H], 305.1290; found, 305.1302.

*Butyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3t**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (311 mg, 97% yield), mp: 40−44 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.35−7.29 (m, 8H), 7.21 (dd, J = 7.9, 1.5 Hz, 2H), 7.03 (s, 1H), 4.39 (t, J = 6.8 Hz, 2H), 1.79 (qui, J = 6.9 Hz, 2H), 1.48 (sex, J = 7.5, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.6, 144.7, 144.4, 139.6, 129.7, 129.1, 128.9, 128.8, 128.7, 128.4, 125.8, 110.0, 65.1, 30.9, 19.3, 13.9. HRMS (ESI$^+$): calcd for $C_{20}H_{21}N_2O_2$ [M + H], 321.1603; found, 321.1606.

*Isobutyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3u**).* The product was isolated by column chromatography (hexane−ethyl acetate 90:10) to furnish a yellow solid (260 mg, 81% yield), mp: 77−80 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.35−7.30 (m, 8H), 7.22 (dd, J = 8.0, 1.6 Hz, 2H), 7.02 (s, 1H), 4.18 (d, J = 6.9 Hz, 2H), 2.14 (non, J = 6.8 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.6, 144.7, 144.4, 139.7, 129.7, 129.1, 128.9, 128.8, 128.7, 128.4, 125.8, 110.0, 71.1, 28.0, 19.3. HRMS (ESI$^+$): calcd for $C_{20}H_{21}N_2O_2$ [M + H], 321.1603; found, 321.1608.

*Benzyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**3v**).* The product was isolated by column chromatography (hexane−ethyl acetate 90:10) to furnish a brown solid (220 mg, 62% yield), mp: 91−94 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.49 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.35−7.29 (m, 9H), 7.20 (dd, J = 8.0, 1.4 Hz, 2H), 7.04 (s, 1H), 5.44 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 162.4, 144.8, 144.1, 139.6, 136.1, 129.6, 129.1, 128.9, 128.9, 128.7, 128.7, 128.6, 128.5, 128.4, 125.8, 110.2, 66.8. HRMS (ESI$^+$): calcd for $C_{23}H_{19}N_2O_2$ [M + H], 355.1447; found, 355.1451.

General Experimental Procedure for the Synthesis of 5-Carboxyalkyl Pyrazoles 4. Method A: To a round-bottom flask loaded with enones **1** (1 mmol) dissolved in chloroform (10 mL), phenylhydrazine **2a′** (2 mmol, 0.2 mL) was added and stirred at rt for 15 min, and, after this time, the reaction was heated to reflux for additional 2 h. After this time, the solvent was removed under vacuum and the corresponding alcohol (10 mL for compounds **4a−f** and 2 mL for compounds **4g−l**) was added to the residue. The reaction was heated to reflux (when alcohols with higher boiling point were used, the temperature of the oil bath was 90 °C) for 16 h. After this time, the solvent was removed under vacuum and the crude reaction mixture was subjected to column chromatography using hexanes and ethyl acetate at different proportions as eluent.

Method B: To a round-bottom flask loaded with enones **1** (1 mmol) dissolved in the corresponding alcohol (10 mL), phenylhydrazine **2a′** (2 mmol, 0.2 mL) was added and stirred at rt for 24 h. After this time, the reaction was heated to reflux (when alcohols with higher boiling point were used, the temperature of the oil bath was 90 °C) for 16 h. After this time, the solvent was removed under vacuum and the crude reaction mixture was subjected to column chromatography using hexanes and ethyl acetate at different proportions as eluent.

*Methyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4a**).*[52] The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (190 mg, 68% yield), mp: 109−110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.88 (dd, J = 8.2, 1.1 Hz, 2H), 7.51−7.41 (m, 7H), 7.37−7.34 (tt, J = 7.44, 1.2 Hz, 1H), 7.32 (s, 1H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.7, 151.7, 140.4, 134.4, 132.2, 128.9, 128.9, 128.8, 128.6, 126.2, 125.9, 109.7, 52.2.

*Methyl-3-(4-bromophenyl)-1-phenyl-1H-pyrazole-5-carboxylate (**4b**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (293 mg, 82% yield), mp: 93−94 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.74 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.50−7.44 (m, 5H), 7.29 (s, 1H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.5, 150.6, 140.3, 134.5, 132.0, 131.2, 129.0, 128.8, 127.5, 126.1, 122.6, 109.5, 52.3. HRMS (ESI$^+$): calcd for $C_{17}H_{14}BrN_2O_2$ [M + H], 357.0239; found, 357.0218.

*Methyl-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-5-carboxylate (**4c**).* The product was isolated by column chromatography (hexane−ethyl acetate 85:15) to furnish a yellow solid (236 mg, 73% yield), mp: 203−204 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.29 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H), 7.54−7.48 (m, 5H), 7.41 (s, 1H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.3, 149.3, 147.7, 140.0, 138.5, 135.0, 129.3, 128.9, 126.4, 126.1, 124.3, 110.4, 52.4. HRMS (ESI$^+$): calcd for $C_{17}H_{14}N_3O_4$ [M + H], 324.0984; found, 324.0979.

*Methyl-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-5-carboxylate (**4d**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (176 mg, 57% yield), mp: 87−89 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.80 (d, J = 8.8 Hz, 2H), 7.50−7.44 (m, 5H), 7.25 (s, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 160.0, 159.8, 151.5, 140.4, 134.2, 128.8, 128.7, 127.2, 126.2, 125.0, 114.3, 109.2, 55.5, 52.2. HRMS (ESI$^+$): calcd for $C_{18}H_{17}N_2O_3$ [M + H], 309.1239; found, 309.1216.

*Methyl-3-(naphthalen-2-yl)-1-phenyl-1H-pyrazole-5-carboxylate (**4e**).* The product was isolated by column chromatography (hexane−ethyl acetate 90:10) to furnish a brown solid (213 mg, 65% yield), mp: 94−95 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.34 (s, 1H), 8.02 (dd, J = 8.5, 1.5 Hz, 1H), 7.91−7.87 (m, 2H), 7.86−7.83 (m, 1H), 7.57−7.44 (m, 8H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.7, 151.7, 140.4, 134.5, 133.6, 133.5, 129.6, 128.9, 128.8, 128.6, 128.4, 127.9, 126.5, 126.3, 126.2, 124.8, 124.0, 109.9, 52.3. HRMS (ESI$^+$): calcd for $C_{21}H_{17}N_2O_2$ [M + H], 329.1290; found, 329.1370.

*Methyl-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-5-carboxylate (**4f**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish a brown solid (179 mg, 63% yield), mp: 94−96 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.48−7.45 (m, 5H), 7.42 (dd, J = 3.6, 1.1 Hz, 1H), 7.30 (dd, J = 5.0, 1.1 Hz, 1H), 7.20 (s, 1H), 7.08 (dd, J = 5.0, 3.6 Hz, 1H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.5, 147.1, 140.1, 135.2, 134.3, 129.0, 128.8, 127.7, 126.2, 125.5, 124.8, 109.5, 52.3. HRMS (ESI$^+$): calcd for $C_{15}H_{13}N_2O_2S$ [M + H], 285.0698; found, 285.0700.

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*Ethyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4g**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (210 mg, 72% yield), mp: 65−67 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 7.2 Hz, 2H), 7.51−7.40 (m, 7H), 7.35 (t, J = 7.4 Hz, 1H), 7.33 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.3, 151.6, 140.5, 134.8, 132.3, 128.9, 128.8, 128.7, 128.5, 126.3, 125.9, 109.6, 61.3, 14.2. HRMS (ESI$^+$): calcd for $C_{18}H_{17}N_2O_2$ [M + H], 293.1290; found, 293.1301.

*Isopropyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4h**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (233 mg, 76% yield), mp: 64−67 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 7.5 Hz, 2H), 7.50−7.41 (m, 7H), 7.35 (t, J = 7.4 Hz, 1H), 7.31 (s, 1H), 5.12 (sep, J = 6.2 Hz, 1H), 1.23 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 158.8, 151.6, 140.7, 135.3, 132.3, 128.9, 128.8, 128.7, 128.5, 126.3, 125.9, 109.5, 69.2, 21.8. HRMS (ESI$^+$): calcd for $C_{19}H_{19}N_2O_2$ [M + H], 307.1447; found, 307.1459.

*Allyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4i**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (225 mg, 74% yield), mp: 52−54 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 7.3 Hz, 2H), 7.51−7.41 (m, 7H), 7.37−7.33 (m, 2H), 5.95−5.86 (m, 1H), 5.29 (dd, J = 17.2, 1.2 Hz, 1H), 5.25 (dd, J = 10.4, 0.9 Hz, 1H), 4.71 (d, J = 5.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 158.9, 151.7, 140.4, 134.4, 132.2, 131.6, 128.9, 128.8, 128.5, 126.2, 125.9, 119.0, 109.7, 65.8. HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O_2$ [M + H], 305.1290; found, 305.1294.

*Butyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4j**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (263 mg, 82% yield), mp: 52−54 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 7.1 Hz, 2H), 7.51−7.39 (m, 7H), 7.35 (t, J = 7.4 Hz, 1H), 7.32 (s, 1H), 4.20 (t, J = 6.6 Hz, 2H), 1.59 (qui, J = 7.5 Hz, 2H), 1.31 (sex, J = 7.5 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.4, 151.6, 140.6, 134.9, 132.3, 128.9, 128.8, 128.7, 128.5, 126.3, 126.0, 109.6, 65.3, 30.6, 19.2, 13.8. HRMS (ESI$^+$): calcd for $C_{20}H_{20}N_2NaO_2$ [M + Na], 343.1422; found, 343.1421.

*Isobutyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4k**).* The product was isolated by column chromatography (hexane−ethyl acetate 80:20) to furnish an orange solid (266 mg, 83% yield), mp: 80−82 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 7.3 Hz, 2H), 7.52−7.40 (m, 7H), 7.37−7.32 (m, 2H), 3.99 (d, J = 6.6 Hz, 2H), 1.90 (non, J = 6.7 Hz, 1H), 0.88 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.4, 151.6, 140.6, 134.9, 132.3, 128.9, 128.8, 128.8, 128.5, 126.3, 126.0, 109.6, 71.5, 27.8, 19.1. HRMS (ESI$^+$): calcd for $C_{20}H_{21}N_2O_2$ [M + H], 321.1603; found, 321.1618.

*Benzyl-1,3-diphenyl-1H-pyrazole-5-carboxylate (**4l**).* The product was isolated by column chromatography (hexane−ethyl acetate 90:10) to furnish an orange solid (184 mg, 52% yield), mp: 87−90 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.86 (d, J = 7.1 Hz, 2H), 7.48−7.39 (m, 7H), 7.36−7.33 (m, 5H), 7.29−7.27 (m, 2H), 5.24 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ (ppm) 159.0, 151.7, 140.5, 135.3, 134.5, 132.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 126.3, 126.0, 109.9, 67.0. HRMS (ESI$^+$): calcd for $C_{23}H_{19}N_2O_2$ [M + H], 355.1447; found, 355.1459.

General Experimental Procedure for the Synthesis of 3-Trifluoromethyl Pyrazoles 6. To a round-bottom flask loaded with enones **5a−b** (1 mmol), dissolved in MeOH (10 mL), 4-hydrazinylbenzenesulfonamide hydrochloride (1.2 mmol, 268 mg) was added in one portion. The reaction was kept under vigorous stirring at rt for 15 min and then heated to reflux for another 4 h. After this time, the reaction mixture was cooled down to rt and the solvent was removed under vacuum. The residue was purified through column chromatography using silica gel with hexanes and ethyl acetate at different proportions as eluent.

*4-(5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (**6a**).*[53] The product was isolated by column chromatography (hexane−ethyl acetate 40:60) to furnish a yellow solid (353 mg, 93% yield), mp: 159−162 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.88 (d, J = 8.7 Hz, 2H), 7.57−7.53 (m, 4H), 7.24−7.18 (m, 5H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ (ppm) 145.3, 144.0, 142.2 (q, J = 37.6 Hz), 141.2, 139.1, 129.5, 128.8, 126.8, 126.0, 125.4, 121.3 (q, J = 268.6 Hz), 106.2, 20.8.

*4-(5-(4-Fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (**6b**).*[53] The product was isolated by column chromatography (hexane−ethyl acetate 50:50) to furnish a yellow solid (366 mg, 95% yield), mp: 165−167 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.89 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.53 (s, 2H), 7.41−7.38 (m, 2H), 7.29 (t, J = 8.8 Hz, 2H), 7.25 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ (ppm) 162.6 (d, J = 247.2 Hz), 144.3, 144.1, 142.2 (q, J = 37.9 Hz), 140.9, 131.4 (d, J = 8.5 Hz), 126.9, 126.0, 124.8 (d, J = 3.1 Hz), 121.3 (q, J = 268.9 Hz), 116.0 (d, J = 21.9 Hz), 106.6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01879.

^{1}H and ^{13}C{^{1}H} NMR spectra of compounds and crystal parameters and ORTEP of compounds **3a**, **3f**, **3g**, **3u**, and **4a** are available (PDF)

Crystallographic data (ZIP)

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Notes

The authors declare no competing financial interest.

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