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# Synthesis of Diaminoacetic Acid Derivatives as a Promising Scaffold for the Synthesis of Polyheterocyclic Cage Compounds

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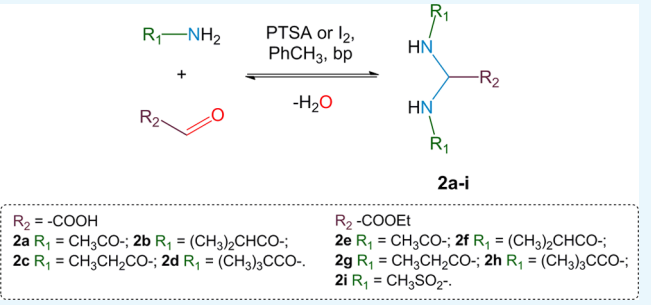
**ABSTRACT:** Here, we explored in detail an acid-catalyzed condensation of glyoxylic acid or its ethyl ester with several carboxamides of different basicity, or with mesyl amide, to furnish diaminoacetic acid derivatives. The most suitable synthesis conditions and the reaction catalysts were identified. Properties such as structure and basicity of the starting amides were demonstrated to influence the condensation process. Elemental iodine was used for the first time herein as an acid catalyst for the condensation of glyoxylic acid or its ester, which gave access to diaminoacetic acid derivatives in higher yields in most cases, as opposed to p-toluenesulfonic acid (PTSA). An abnormally high activity of mesyl amide when condensed with ethyl glyoxylate was noticed, which may evidence a special impact of the sulfonyl moiety in the amide molecule on the condensation.




## INTRODUCTION

The evolution of defense technology is directly linked with the development of new high-energy materials that are superior in energy-mass and performance characteristics to the existing ones.

Heterocyclic and polyheterocyclic nitramines are the most common class of high-energy compounds widely used in various composite explosives, rocket propellants, gun propellants, and specialty formulations. For instance, 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX, hexogen) and 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (HMX, octogen) (Figure 1) have gained a wide application in civil and defense industries.

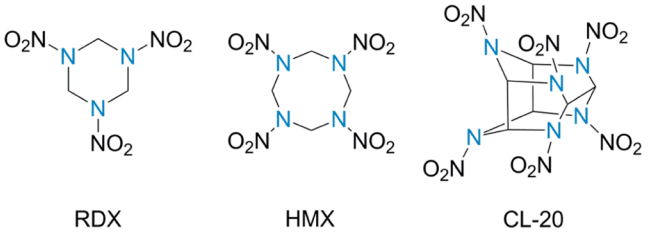



**Figure 1.** Structural formulas of RDX, HMX, and CL-20.

One of the effective ways to enhance the energetic performance of explosive compounds is by incorporating strained moieties such as three-, four- or five-membered rings or complex two-dimensional (2D) or three-dimensional (3D) molecules (cages) into them. This approach is applicable to cyclic and polycyclic nitramines. The estimations demonstrate that cage nitramines are much more attractive in finding high-energy materials because they possess a higher energetic performance and a lower sensitivity.[1] The density of nitramines increases as the molecular rigidity rises.[2]

The most common nitramine bearing a strained polyheterocyclic cage is 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0$^{3,11}$.0$^{5,9}$]dodecane (CL-20, hexanitrohexaazaisowurtzitane, HNIW) (Figure 1). This chemical entity is one of the most powerful explosives domesticated by humankind ($\rho$ = 2.044 g/cm$^3$, V$^0$D = 9.36 ($\varepsilon$) km/s).[3−5] CL-20 is considered as a promising component of composite explosives and as an eco-friendly high-energy oxidizer of rocket propellants, exhibiting high specific impulse and oxygen balance.[6]

Despite the merits of the strained cage nitramines, they have not found wide application, mainly due to the high production cost. One of the trends focused on solving this problem is to develop new approaches for the synthesis of these compounds.

Nitrogen heterocycles and polyheterocycles comprising a few readily nitratable N-substituents and two or more primary amino groups are promising scaffolds for the synthesis of polyheterocyclic cage molecules as precursors of cage nitramines. In particular, of interest are heterocyclic and polyheterocyclic products resulting from the condensation of

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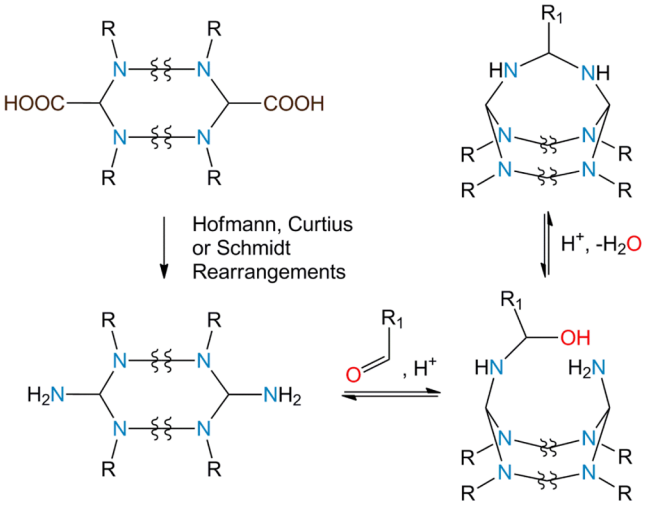
diaminoacetic acid or its derivatives with aldehydes. These compounds structurally contain carboxyl or ester groups that can be transfunctionalized into amino groups by the Schmidt reaction, Hofmann, and/or Curtius rearrangements.

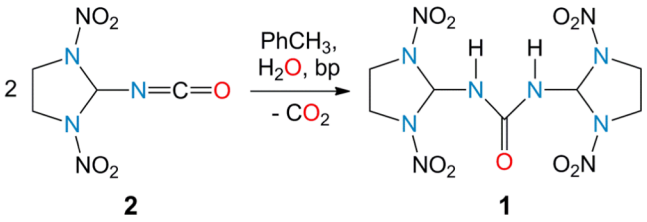
Scheme 1 illustrates a presumed synthetic route to cage compounds starting from diaminoacetic acid derivatives.

**Scheme 1. Synthesis of Polyheterocyclic Cage Molecules from Diaminoacetic Acid Derivatives**




Previously, we indirectly corroborated the possible transformation of the carboxyl group in the bis(nitroamino)acetic acid moiety (Scheme 2) into the amino group.[7] 1,3-Bis(1,3-dinitroimidazolidin-2-yl)urea (**1**) (37.5% yield) was prepared by reacting 1,3-dinitroimidazolidine-2-amine with 2-isocyanato-1,3-dinitroimidazolidine (**2**) (Scheme 2).

**Scheme 2. Synthesis of 1,3-Bis(1,3-dinitroimidazol-idin-2-yl)urea (1)**




The synthesis of polyheterocyclic cage compounds through the rearrangement of carboxyl groups into amino groups followed by cyclization is a new strategy for the preparation of these compounds.

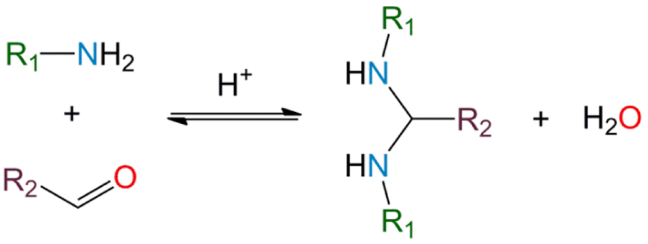
In the present study, a series of *N*,*N*-disubstituted diaminoacetic acid (**2**) derivatives were synthesized and the most favorable conditions for their formation were selected.

## RESULTS AND DISCUSSION

We previously revealed a negative inductive effect of two nitro groups in bis(nitroamino)acetic acid derivatives on the progress of the Curtius, Hofmann, or Schmidt rearrangement.[7] In this regard, we decided to examine the progress of the said rearrangements using other cyclic and polycyclic diaminoacetic acid derivatives with substituents having a lower negative inductive effect.

In this study, we explored the derivatization of **2** via the condensation of glyoxylic acid (OCHCOOH) or its ethyl glyoxylate (OCHCOOEt) with an array of amides: formamide ($HCONH_2$), acetamide ($CH_3CONH_2$), propionamide ($CH_3CH_2CONH_2$), isobutyramide ($(CH_3)_2CHCONH_2$), pyvalamide ($(CH_3)_3CCONH_2$), or mesyl amide ($CH_3SO_2NH_2$). The study aimed to establish the most suitable synthetic procedure, catalyst, and conditions for the formation of these compounds (Scheme 3).

**Scheme 3. Synthesis of Derivatives 2a−i**




$R_2$ = -COOH
**2a** $R_1$ = $CH_3CO$-; **2b** $R_1$ = $(CH_3)_2CHCO$-;
**2c** $R_1$ = $CH_3CH_2CO$-; **2d** $R_1$ = $(CH_3)_3CCO$-.

$R_2$ -COOEt
**2e** $R_1$ = $CH_3CO$-; **2f** $R_1$ = $(CH_3)_2CHCO$-;
**2g** $R_1$ = $CH_3CH_2CO$-; **2h** $R_1$ = $(CH_3)_3CCO$-;
**2i** $R_1$ = $CH_3SO_2$-.

While selecting amides, we took into account the basicity of the reagents and the ease of N-nitration of the condensation products, except for mesyl amide that is highly resistant to acidic medium and capable of generating polyheterocyclic cage compounds.[8−10] The basicity of amides and the tendency of their condensation products toward N-nitration depends on the value of the partially negative charge on the amide nitrogen atom. This charge is due to the inductive effect of the substituent and increases in the row: $CH_3SO_2NH_2$ < $HCONH_2$ < $CH_3CONH_2$ < $(CH_3)_2CHCONH_2$ < $CH_3CH_2CONH_2$ < $(CH_3)_3CCONH_2$. The force of the inductive effect can be assessed from $pK_a$ of acids corresponding to these amides: 0.6[11] < 3.75[12,13] < 4.75[12,13] < 4.83[13] < 4.87[13] < 5.03,[13] respectively.

The literature overview demonstrates that a staple method for the derivatization of diaminoacetic acid is the acid-catalyzed condensation between glyoxylic acid or its esters with carboxamides or substituted sulfonamides. The process is run in aqueous medium,[14,15] chlorophorm,[16] toluene,[17−20] benzene,[21] acetone,[15,22,23] or xylene.[24] Mixed phosphoric/sulfamic acids,[14] 2-naphthalenesulfonic acid[17,23] or p-toluenesulfonic acid,[18,21,25] are used as the acid catalysts. In addition to protic acids, Lewis acids can be employed as the catalyst. The condensation of substituted carboxamides[26] and sulfonamides[20] takes place in hot nitromethane over iron chloride (III)[24,26] or copper chloride (III)[26] and in toluene at reflux over boron trifluoride ethyl etherate.[20] In most cases, syntheses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are effected under reflux. In some instances, the resulting water is eliminated by a Dean−Stark trap.

The condensation between the selected amides and ethyl glyoxylate or glyoxylic acid to furnish **2** was explored herein in chloroform, benzene, acetone, toluene, or xylene at reflux, as well as in aqueous medium at room temperature. The selected solvents are most often utilized in this process.[14−26] The starting compounds were used in stoichiometric quantities. In all experiments, the resulting water was removed by a Dean−Stark trap to shift the reaction toward the condensation products (the Le Chatelier−Brown principle).

The first reaction we studied was the condensation in aqueous medium over a wide range of acidity and different temperatures. This solvent was found to be unusable as the medium for the derivatization of **2**. Under highly acidic conditions, carboxamides in aqueous medium underwent hydrolysis to ammonium sulfate, and the reaction with glyoxylic acid and its ester was not detected. It is likely that under these conditions, the hydrolysis rate of carboxamides considerably exceeded that of condensation. Unlike carboxamides, more hydrolysis-resistant mesyl amide underwent condensation with ethyl glyoxylate to form ethyl bis-[(methylsulfonyl)amino]acetate (**2i**) in a 51% yield (the $H_2SO_4$ content in the mixture was 44 wt %).

We further examined the condensation in the selected aprotic solvents with the addition of 1.5 wt % PTSA, which is most commonly used in this process. The acid exhibited a sufficient catalytic activity and a moderate acidity, leading to no vigorous decomposition of carboxamides under the reaction conditions. The boiling points of chloroform, acetone, and benzene were found to be too low for an active condensation between most of the selected amides and ethyl glyoxylate or glyoxylic acid to derivatives of **2**. The best results (synthesis time, yield) were achieved in toluene. It is this solvent that we chose as the most suitable for derivatization of **2**.

Then, we examined the condensation between the selected amides and glyoxylic acid or ethyl glyoxylate to compounds **2a−i** in toluene at reflux without added catalyst (Table 1). It

**Table 1. Synthesis of Compounds 2a−i in Toluene at Reflux without Catalyst**

| entry | condensation product | yield, % |
|---|---|---|
| 1 | **2a** | 60.9 |
| 2 | **2b** | 62.5 |
| 3 | **2c** | 67.9 |
| 4 | **2d** | 61.2 |
| 5 | **2e** | no reaction |
| 6 | **2f** | 72.9 |
| 7 | **2g** | 73.9 |
| 8 | **2h** | below 30 |
| 9 | **2i** | 74.4 |

was interesting to find out to which extent the basicity of the selected amides would influence the condensation process under the experimental conditions and to obtain data on the practicability of the noncatalytic synthetic method for compounds **2a−i**. The experiments were performed for 6 h. In most cases, this time was enough to complete the process.

Autocatalytic condensations of the selected amides with glyoxylic acid for the specified time resulted in compounds **2a−d** in 61−68% yields (Table 1, entries 1−4). Mesyl amide was not observed to be condensed with glyoxylic acid in toluene at reflux (Table 1, entry 5), which is likely due to its low basicity. Formamide decomposed under the reaction conditions, forming no condensation products (the reaction mixture turned dark brown). Compounds **2f,g,i** were generated in 73−74% yields (Table 1, entries 6, 7, 9). Pyvalamide underwent condensation with ethyl glyoxylate, but the process completeness was only 20−30% within 6 h (Table 1, entry 8). The slow condensation rate of pyvalamide is explained by steric hindrances occurring during the condensation, which were due to the large size of the *tert*-butyl substituent.

Unexpectedly, the activation of the aldehyde group of glyoxylic acid by the substitution of the carboxyl hydrogen atom by the ethyl group turned out to be enough for the condensation to take place with low-basicity mesyl amide under the reaction conditions (Table 1, entry 9). At the same time, it was odd that acetamide with higher basicity did not react with ethyl glyoxylate under the same conditions (Table 1, entry 5). Because the process proceeded in the absence of an acid catalyst, acetamide could not be protonated. It can be hypothesized that the sulfonyl moiety in the molecule of the substituted sulfonamides somehow promoted the condensation with the aldehyde group.

Next, we examined how the PTSA acid catalyst influenced the condensation between the selected amides and glyoxylic acid or ethyl glyoxylate in toluene at reflux. The quantity of PTSA in the mixture and the synthesis time were varied in the experiments.

Table 2 summarizes data on the most favorable conditions for the formation of compounds **2a−i** from the PTSA-

**Table 2. Most Favorable Conditions in Which Compounds 2a−i Are Formed in Toluene at Reflux over the PTSA Catalyst**

| entry | condensation product | $\omega$ (PTSA), %[a] | t, h | yield, % |
|---|---|---|---|---|
| 1 | **2a** | 0.03 | 3 | 57.4 |
| 2 | **2b** | 0.06 | 5 | 71.2 |
| 3 | **2c** | 0.06 | 3 | 71.5 |
| 4 | **2d** | 0.06 | 4 | 64.5 |
| 5 | **2e** | 0.13 | 4 | 78.4 |
| 6 | **2f** | 0.19 | 3 | 73.6 |
| 7 | **2g** | 0.25 | 4 | 76.2 |
| 8 | **2h** | 0.12 | 3 | 77.1 |
| 9 | **2i** | 0.06 | 4 | 76.0 |

[a]Content by weight in the mixture (including toluene).

catalyzed condensation between the selected amides and glyoxylic acid or ethyl glyoxylate in toluene at reflux. Because PTSA and $I_2$ were soluble in toluene, their contents were expressed in wt % in the mixture.

The comparison of the data given in Tables 1 and 2 shows that PTSA added to the mixture activated the condensation process, reduced the synthesis time for most of compounds **2a−i**, and slightly improved the yield of compounds **2c,d,f,g,i** (Table 2, entries 2, 4, 6, 7, 9). The yields of compounds **2b,h** were increased most of all (Table 2, entries 4, 8). Compound **2e** was generated in a 78% yield (Table 2, entry 5).

The PTSA quantity required for the activation of the process depended particularly on the amides' basicity and steric hindrances that occur during the condensation of the amide. For instance, the condensations of less sterically hindered



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acetamide and the most basic pyvalamide with ethyl glyoxylate required the least of PTSA (Table 1, entries 5, 8).

The electron-withdrawing groups present in the carboxamide substituent made it more amenable to hydrolysis. Since formamide and acetamide were the most liable to hydrolysis from among the selected amides when the acid catalyst was added to the mixture, we observed a decreased yield of compound **2a** and an activated decomposition of formamide.

Because most of the carboxamides are amenable to hydrolysis in acidic medium (especially at elevated temperature), it was interesting to explore "mild" catalysis of the reaction under study. We chose weak Lewis acid—elemental iodine ($I_2$)—as such a catalyst. The quantity of $I_2$ in the mixture and the synthesis time were varied in the experiments. The use of $I_2$ as the catalyst for the reaction between carboxamides and aldehydes was described earlier.[27]

Table 3 lists data on the most favorable conditions for the formation of compounds **2a−i** from the $I_2$-catalyzed condensation between the selected amides and glyoxylic acid or ethyl glyoxylate in toluene under reflux.

**Table 3. Most Favorable Conditions in Which Compound 1 Is Formed in Toluene at Reflux over the $I_2$ Catalyst**

| entry | condensation product | ω ($I_2$), %[a] | t, h | yield, % |
|---|---|---|---|---|
| 1 | **2a** | 0,33 | 4 | 62.9 |
| 2 | **2b** | 0,11 | 4 | 68.4 |
| 3 | **2c** | 0,11 | 4 | 63.5[b] |
| 4 | **2d** | 0,21 | 3 | 68.5 |
| 5 | **2e** | 0,40 | 5 | 78.4 |
| 6 | **2f** | 0,77 | 4 | 77.5 |
| 7 | **2g** | 0,33 | 4 | 79.5 |
| 8 | **2h** | 0,33 | 3 | 77.9 |
| 9 | **2i** | 0,54 | 5 | 72.8[b] |

[a]Content by weight in the mixture (including toluene). [b]The presence of $I_2$ decreases the yield.

The comparison of the data tabulated in Tables 1−3 shows that catalytic quantities of $I_2$ in the mixture activated the condensation and shortened the synthesis time of compounds **2a−i**. The yields of compounds **2a,c−h** increased (**2e,h** were formed in a 78% yield). The yields of compounds **2c,i** decreased, which is most likely due to side reactions involving $I_2$. Compared to PTSA, the $I_2$ catalysis gave less resinification products.

We failed to obtain condensation products of formamide and glyoxylic acid or ethyl glyoxylate over the PTSA or $I_2$ catalyst. Formamide was too unstable under the condensation conditions.

Table 4 summarizes the data on the yields of compounds **2a−i** at constant synthesis times and catalyst quantities (PTSA or $I_2$), allowing us to evaluate the condensation rate of the selected amides and glyoxylic acid or its ethyl glyoxylate.

It follows from the data presented in Table 4 that compounds **2a−d** were formed at different rates. The formation of compounds **2a,d** was slower (Table 4, entries 1, 4), which is likely due to a lower activity of glyoxylic acid that reacted slowly with the low-basicity and sterically hindered substituted carboxamides. The higher formation rate of compound **2e** can be explained by the smaller size of the substituent of the acetamide molecule (abated steric hindrances when it was condensed), as well as by the extremely low solubility of that compound in toluene, leading to its active precipitation from the reaction mixture (Le Chatelier−Brown principle).

**Table 4. Comparative Data on Yields of Compounds 2a−i at Constant Synthesis Times and Acid Catalyst Quantities**

| entry | condensation product | ω (PTSA/$I_2$), %[a] | t, h | yield (PTSA/$I_2$), % |
|---|---|---|---|---|
| 1 | **2a** | 0,06/0,11 | 4 | 49,9/50,1 |
| 2 | **2b** | 0,06/0,11 | 4 | 65,7/68.4 |
| 3 | **2c** | 0,06/0,11 | 4 | 66,9/63.5[b] |
| 4 | **2d** | 0,06/0,11 | 4 | 64,5/59,0 |
| 5 | **2e** | 0,13/0,33 | 3 | 78,2/77,8 |
| 6 | **2f** | 0,13/0,33 | 3 | 73,3/69,3 |
| 7 | **2g** | 0,13/0,33 | 3 | 73,7/76,3 |
| 8 | **2h** | 0,13/0,33 | 3 | 77.1/77.9 |
| 9 | **2i** | 0,13/0,33 | 3 | 53,3/71,0 |

[a]Content by weight in the mixture (including toluene). [b]The presence of $I_2$ decreases the yield.

The effect of the PTSA or $I_2$ catalyst on the condensation process is shown in Table 5 by the example of compounds **2a** and **2e**.

**Table 5. Most Favorable Conditions in Which Compound 1 Is Formed in Toluene at Reflux over the $I_2$ Catalyst**

| entry | condensation product | ω (PTSA/$I_2$), %[a] | t (PTSA/$I_2$), h | yield (PTSA/$I_2$), % |
|---|---|---|---|---|
| 1 | **2a** | no catalyst | 4 | 50.4 |
| 2 | **2a** | 0.016/0.11 | 4 | 51.1/50.5 |
| 3 | **2a** | 0.03/0.22 | 4 | 54,5/59.7 |
| 4 | **2a** | 0.047/0.33 | 4 | 52.4/62.9 |
| 5 | **2a** | 0,06/0.44 | 4 | 49.9/59.3 |
| 6 | **2e** | no catalyst | 4 | no formation |
| 7 | **2e** | 0.05/0.22 | 3/4 | 71.4/29.8 |
| 8 | **2e** | 0.08/0.34 | 3/4 | 77.5/77.0 |
| 9 | **2e** | 0.11/0.45 | 3/4 | 78.2/76.7 |
| 10 | **2e** | 0.13/0.67 | 3/4 | 77.7/4.1 |

[a]Content by weight in the mixture.

It follows from the data presented in Table 5 that the change in the yields of compounds **2a,e**, when the quantity of PTSA in the mixture was varied, was smooth. Compound **2a** was formed more actively when the quantity of PTSA in the mixture was about 0.03% (Table 5, entry 3), whereas for compound **2e**—at the quantity of about 0.11% (Table 5, entry 9). The activation of the condensation process by elemental $I_2$ required a higher quantity of the catalyst. The condensation between acetamide and glyoxylic acid began to be active when the quantity of $I_2$ in the mixture was about 0.22% (Table 5, entry 3), whereas when reacted with ethyl glyoxylate, it was active when the catalyst content was about 0.34% (Table 5, entries 8). The need for the higher quantity of PTSA to activate the condensation process between acetamide and ethyl glyoxylate is explained by the autocatalytic condensation reaction of glyoxylic acid. When the content of $I_2$ in the reaction mixture was increased to 0.67% (Table 5, entry 10) in the condensation between acetamide and ethyl glyoxylate, the yield of compound **2e** decreased sharply. It is more likely that the higher content of $I_2$ activated side reaction(s) and/or deactivated the starting compounds.



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Irrespective of the catalyst used, the highest yields of *N,N*-disubstituted diaminoacetic acid derivatives were achieved by reacting the amides with ethyl glyoxylate.

## CONCLUSIONS

In summary, the acid-catalyzed condensation between glyoxylic acid or its ethyl ester and a series of carboxamides with different basicity or mesyl amide to furnish diaminoacetic acid derivatives was examined in detail. The most suitable method, catalyst, and synthetic conditions for the compounds were selected. The effect of the substituents in the carboxamide molecules on the condensation process was demonstrated.

The synthesis of diaminoacetic acid derivatives without added catalyst may be justified in case when glyoxylic acid is condensed with low-basicity substituted carboxamides such as acetamide or several moderate-basicity substituted carboxamides such as propionamide. Ethyl glyoxylate was condensable in a higher yield with moderate-basicity carboxamides such as isobutyramide and propionamide, as well as with the sulfonamides.

PTSA appeared to be the best catalyst for the condensation reaction between glyoxylic acid and the moderate-basicity substituted carboxamides such as ispbutyramide and propionamide, as well as for the condensation reaction of ethyl glyoxylate with high-basicity substituted carboxamides such as pyvalamide and the sulfonamide. $I_2$ demonstrated itself as the best catalyst for the condensation reaction between the low-basicity and high-basicity substituted carboxamides such as acetamide and pyvalamide, as well as for the condensation reaction between ethyl glyoxylate and the substituted carboxamides differing in basicity. Elemental iodine has been used for the first time as the catalyst for the condensation reaction between glyoxylic acid or ethyl glyoxylate and amides. Even though we did not investigate the condensation of other glyoxylic esters with substituted carboxamides, it can be said with high confidence that elemental iodine will be the best catalyst for this process, as opposed to PTSA. This study resulted in seven new derivatives of diaminoacetic acid.

Mesyl amide when condensed with ethyl glyoxylate without a catalyst was found to have an abnormally high activity. The sulfonyl moiety in the mesyl amide molecule has probably a special impact on the condensation process.

## EXPERIMENTAL SECTION

**General Information.** Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Commercially available compounds were used without further purification, unless otherwise stated. Melting points were determined on a Stuart SMP30 melting point apparatus (Bibby Scientific Ltd, U.K.). Infrared (IR) spectra were recorded on a Simex FT-801 Fourier transform infrared spectrometer in KBr pellets or in liquid film. $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-400 instrument (Bruker Corporation) at 400 and 100 MHz. Chemical shifts are expressed in ppm ($\delta$). Elemental analysis was performed on a Thermo Fisher FlashEA 1112 elemental analyzer (Thermo Fisher).

During the experiments, the starting reagents and the reaction products were weighed on an analytical balance. The syntheses were run in round-bottom flasks fitted with a magnetic stirrer. Silicon bath was used for the heat-up.

**Synthetic Methods.** *Synthetic Protocols for Bis-(acetylamino)acetic acid (**2a**), Bis[(2-methylpropanoyl)-amino]acetic acid (**2b**), Bis(propanoylamino)acetic acid (**2c**), and Bis[(2,2-dimethylpropanoyl)amino]acetic acid (**2d**) in Toluene at Reflux over PTSA or $I_2$ Catalyst.* A mixture of aqueous OCHCOOH (0.74 g, 5 mmol, 50%), corresponding amide (10 mmol; $CH_3CONH_2$, $CH_3CH_2CONH_2$, $(CH_3)_2CHCONH_2$ or $(CH_3)_3CCONH_2$), toluene (15 mL), and a catalytic quantity of PTSA or $I_2$ (or no catalyst) was refluxed in a round-bottom flask (50 mL) equipped with a Dean−Stark trap and a reflux condenser.

The whole product after synthesis was held for 18−20 h at room temperature, the resulting precipitates were dispersed, and the reaction mixture was diluted twice with acetone (**2a**) or diethyl ether (**2b−d**), stirred for 30 min, and filtered. The filter cake was washed twice with the same solvent used for dilution and dried at room temperature to constant weight. The result was a white or pale brown needle-like sediment.

*Compound **2a** $CH_3CONH_2$ (0.59 g).* The process was catalyzed with $I_2$ (0.048 g), and the synthesis time was 4 h. Yield: 0.548 g, 3.147 mmol (62.9% on an OCHCOOH basis).

In the catalyst-free process, the synthesis time was 6 h. Yield: 0.531 g, 3.049 mmol (60.9% on an OCHCOOH basis).

MP = 205−207 °C (dec.) (6:1 v/v acetone: water). IR (KBr): $\nu$ = 3343, 3105, 2944, 1722, 1655, 1619, 1567, 1513, 1428, 1377, 1355, 1324, 1307, 1264, 1237, 1146, 1101, 1027, 976, 706, 685, 656, 604 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): $\delta$ = 1.84 (s, 6H), 3.4 (br s, 1H; overlapped $H_2O$), 5.50 (t, $J$ = 7.7 Hz, 1H), 8.65 (d, $J$ = 7.7 Hz, 2H) ppm. $^{13}$C{$^1$H} NMR (DMSO-$d_6$): $\delta$ = 22.6, 56.4, 56.3, 169.7, 170.5 ppm. Elemental analysis calcd (%) for $C_6H_{10}N_2O_4$ (174.15): C, 41.38; H, 5.79; N, 16.09; found: C, 41.41; H, 5.81; N, 16.09.

*Compound **2b** $(CH_3)_2CHCONH_2$ (0.87 g).* The process was catalyzed with PTSA (0.01 g), and the synthesis time was 5 h. Yield: 0.820 g, 3.561 mmol (71.2% on an OCHCOOH basis).

The process was catalyzed with $I_2$ (0.016 g), and the synthesis time was 4 h. Yield: 0.787 g, 3.418 mmol (68.4% on an OCHCOOH basis).

In the catalyst-free process, the synthesis time was 6 h. Yield: 0.719 g, 3.122 mmol (62.5% on an OCHCOOH basis).

MP = 233−235 °C (dec.) (isopropanol). IR (KBr): $\nu$ = 3340, 3293, 3075, 2969, 2942, 2933, 2910, 2874, 1742, 1656, 1603, 1545, 1469, 1415, 1376, 1284, 1251, 1227, 1204, 1175, 1120, 1099, 1055, 1005, 939, 898, 842, 751, 673, 652, 621 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): $\delta$ = 0.97 (t, $J$ = 6.0 Hz, 12H), 2.43−2.49 (m, 2H), 5.49 (t, $J$ = 7.7 Hz, 1H), 8.45 (d, $J$ = 7.7 Hz, 2H), 12.72 (br s, 1H) ppm. $^{13}$C{$^1$H} NMR (DMSO-$d_6$): $\delta$ = 19.66, 19.73, 33.7, 56.3, 170.5, 176.5 ppm. Elemental analysis for $C_{10}H_{18}N_2O_4$ (230.26): calcd (%) C, 52.16; H, 7.88; N, 12.17; found: C, 52.21; H, 7.89; N, 12.19.

*Compound **2c** $CH_3CH_2CONH_2$ (0.73 g).* The process was catalyzed with PTSA (0.01 g), and the synthesis time was 3 h. Yield: 0.723 g, 3.575 mmol (71.5% on an OCHCOOH basis).

In the catalyst-free process, the synthesis time was 6 h. Yield: 0.687 g, 3.397 mmol (67.9% on an OCHCOOH basis).

MP = 208−209 °C (dec.) (isopropanol). IR (KBr): $\nu$ = 3315, 3286, 3069, 2979, 2939, 2909, 2879, 1720, 1650, 1542, 1529, 1461, 1433, 1370, 1354, 1340, 1313, 1236, 1218, 1150, 1092, 1067, 1030, 929, 807, 701, 627, 610 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): $\delta$ = 0.97 (t, $J$ = 7.5 Hz, 6H), 2.13 (q, $J_1$ = 15.1 Hz, $J_2$ = 7.6 Hz, 4H), 5.53 (t, $J$ = 7.7 Hz, 1H), 8.51 (d, $J$ = 7.7 Hz, 2H), 12.8 (br s, 1H) ppm. $^{13}$C{$^1$H} NMR (DMSO-$d_6$): $\delta$ = 10.0, 28.3, 56.3, 170.5, 173.3 ppm. Elemental analysis for



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$C_8H_{14}N_2O_4$ (202.21): calcd (%) C, 47.52; H, 6.98; N, 13.85; found: C, 47.52; H, 6.99; N, 13.87.

*Compound* **2d** *($(CH_3)_3CCONH_2$ (1.01 g).* The process was catalyzed with PTSA (0.01 g), and the synthesis time was 4 h. Yield: 0.833 g, 3.225 mmol (64.5% on an OCHCOOH basis).

The process was catalyzed with $I_2$ (0.032 g), and the synthesis time was 3 h. Yield: 0.885 g, 3.426 mmol (68.5% on an OCHCOOH basis).

MP = 117−119 °C (dec.) (ethyl acetate). IR (KBr): $\nu$ = 3334, 2972, 2955, 2874, 1746, 1638, 1535, 1479, 1402, 1371, 1338, 1309, 1273, 1221, 1060, 1026, 1202, 1121, 999, 943, 914, 866, 830, 798, 777, 653 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.22 (s, 18H), 5.48 (t, $J$ = 6.7 Hz, 1H), 6.33 (br s, 1H), 7.42 (d, $J$ = 6.3 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 27.1, 38.7, 57.7, 169.7, 180.2 ppm. Elemental analysis for $C_{12}H_{22}N_2O_4$ (258.31): calcd (%) C, 55.80; H, 8.58; N, 10.84; found: C, 55.84; H, 8.59; N, 10.84.

*Synthetic Protocols for Ethyl Bis(acetylamino)acetate (**2e**), Ethyl Bis[(2-methylpropanoyl)amino]acetate (**2f**), Ethyl Bis(propanoylamino)acetate (**2g**), Ethyl Bis[(2,2-dimethylpropanoyl)amino]acetate (**2h**), and Ethyl Bis-[(methylsulfonyl)amino]acetate (**2i**) in Toluene at Reflux over PTSA or $I_2$ Catalyst.* A mixture of newly distilled (over $P_2O_5$) OCHCOOEt (0.51 g, 5 mmol), corresponding amide (10 mmol; $CH_3CONH_2$, $CH_3CH_2CONH_2$, $(CH_3)_2CHCONH_2$, $(CH_3)_3CCONH_2$ or $CH_3SO_2NH_2$), toluene (15 mL), and a catalytic quantity of PTSA or $I_2$ (or no catalyst) was refluxed in a round-bottom flask (50 mL) fitted with a Dean−Stark trap and a reflux condenser.

In the synthesis of compounds **2e−g,i**, the reaction mixture after synthesis was held for 18−20 h at room temperature and the resulting precipitates were dispersed, diluted twice with diethyl ether (**2e−g**) or isopropyl alcohol, stirred for 30 min, and filtered. If necessary, a small amount of acetone was added to the mixture for better purification from the polar impurities. The filter cake was washed twice with the same solvent used for dilution and dried at room temperature to constant weight.

In the synthesis of compound **2h**, the reaction mixture after synthesis was held for 18−20 h at room temperature and then filtered. The filter cake was washed with toluene. The filtrate and toluene after washing were combined, washed with 3% aqueous $NaHCO_3$ (10 mL; in PTSA catalysis) or 3% aqueous $Na_2SO_3$ (10 mL; in $I_2$ catalysis), and two times with water (10 mL). The washed organic layer was dried over $Na_2SO_4$ and evaporated at reduced pressure to dryness in a rotary evaporator to furnish a white or pale brown needle-like sediment.

*Compound* **2e** *$CH_3CONH_2$ (0.591 g).* The process was catalyzed with PTSA (0.02 g), and the synthesis time was 4 h. Yield: 0.793 g, 3.922 mmol (78.4% on an OCHCOOEt basis).

The process was catalyzed with $I_2$ (0.048 g), and the synthesis time was 5 h. Yield: 0.793 g, 3.922 mmol (78.4% on an OCHCOOEt basis).

MP = 214−215 °C (EtOAc). IR (KBr): $\nu$ = 3305, 3077, 2991, 2953, 2911, 2839, 1741, 1649, 1550, 1475, 1446, 1371, 1329, 1268, 1226, 1145, 1089, 1025, 949, 864, 738, 710, 681, 608 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): $\delta$ = 1.17 (t, $J$ = 7.1 Hz, 3H), 1.85 (s, 6H), 4.09 (q, $J_1$ = 14.2 Hz, $J_2$ = 7.1 Hz, 2H), 5.54 (t, $J$ = 7.6 Hz, 1H), 8.76 (d, $J$ = 7.6 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-$d_6$): $\delta$ = 14.4, 22.6, 56.4, 61.5, 169.0, 169.9 ppm. Elemental analysis for $C_8H_{14}N_2O_4$ (202.21): calcd (%) C, 47.52; H, 6.98; N, 13.85; found: C, 47.56; H, 7.02; N, 13.86.

*Compound* **2f** *$(CH_3)_2CHCONH_2$ (0.871 g).* The process was catalyzed with PTSA (0.03 g), and the synthesis time was 3 h. Yield: 0.950 g, 3.678 mmol (73.6% on an OCHCOOEt basis).

The process was catalyzed with $I_2$ (0.111 g), and the synthesis time was 4 h. Yield: 1.001 g, 3.875 mmol (77.5% on an OCHCOOEt basis).

In the catalyst-free process, the synthesis time was 6 h. Yield: 0.941 g, 3.643 mmol (72.9% on an OCHCOOEt basis).

MP = 218−220 °C ($CHCl_3$). IR (KBr): $\nu$ = 3312, 3069, 2969, 2932, 2872, 1745, 1646, 1545, 1531, 1470, 1368, 1322, 1247, 1218, 1174, 1133, 1099, 1059, 1020, 1001, 937, 908, 694, 673, 659, 628, 608 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.16 (d, $J$ = 6.8 Hz, 12H), 1.28 (t, $J$ = 7.1 Hz, 3H), 2.39−2.46 (m, 2H), 4.26 (q, $J_1$ = 14.2 Hz, $J_2$ = 7.1 Hz, 2H), 5.44 (t, $J$ = 6.8 Hz, 1H), 7.1 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 14.0, 19.1, 19.2, 34.9, 57.2, 62.4, 168.0, 177.5 ppm. Elemental analysis for $C_{12}H_{22}N_2O_4$ (258.31): calcd (%) C, 55.80; H, 8.58; N, 10.84; found: C, 55.81; H, 8.60; N, 10.81.

*Compound* **2g** *$CH_3CH_2CONH_2$ (0.731 g).* The process was catalyzed with PTSA (0.04 g), and the synthesis time was 4 h. Yield: 0.877 g, 3.809 mmol (76.2% on an OCHCOOEt basis).

The process was catalyzed with $I_2$ (0.048 g), and the synthesis time was 4 h. Yield: 0.915 g, 3.974 mmol (79.5% on an OCHCOOEt basis).

In the catalyst-free process, the synthesis time was 6 h. Yield: 0.851 g, 3.696 mmol (73.9% on an OCHCOOEt basis).

MP = 199−203 °C (4:1 v/v $CHCl_3$:PhMe). IR (KBr): $\nu$ = 3310, 3073, 2978, 2962, 2939, 2907, 2877, 1745, 1648, 1546, 1533, 1462, 1426, 1368, 1321, 1274, 1222, 1146, 1097, 1067, 1028, 924, 894, 867, 810, 710, 675 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.15 (t, $J$ = 7.6 Hz, 6H), 1.28 (t, $J$ = 7.1 Hz, 3H), 2.27 (q, $J_1$ = 15.1 Hz, $J_2$ = 7.6 Hz, 4H), 4.26 (q, $J_1$ = 14.2 Hz, $J_2$ = 17.1 Hz, 2H), 5.48 (t, $J$ = 7.0 Hz, 1H), 7.38 (d, $J$ = 6.6 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 9.3, 14.0, 28.9, 57.1, 62.4, 168.2, 174.4 ppm. Elemental analysis for $C_{10}H_{18}N_2O_4$ (230.26): calcd (%) C, 52.16; H, 7.88; N, 12.17; found: C, 52.20; H, 7.91; N, 12.18.

*Compound* **2h** *$(CH_3)_3CCONH_2$ (1.011 g).* The process was catalyzed with PTSA (0.02 g), and the synthesis time was 3 h. Yield: 1.104 g, 3.855 mmol (77.1% on an OCHCOOEt basis).

The process was catalyzed with $I_2$ (0.048 g), and the synthesis time was 3 h. Yield: 1.115 g, 3.894 mmol (77.9% on an OCHCOOEt basis).

MP = 121−123 °C (heptane). IR (KBr): $\nu$ = 3326, 3094, 2972, 2941, 2908, 2872, 1753, 1657, 1547, 1513, 1479, 1461, 1400, 1369, 1323, 1297, 1273, 1205, 1128, 1098, 1030, 993, 944, 918, 899, 864, 823, 810, 773, 759, 687, 642, 630 $cm^{-1}$. $^1H$ NMR (acetone-$d_6$): $\delta$ = 1.17 (s, 18H), 1.22 (t, $J$ = 7.1 Hz, 3H), 4.15 (q, $J_1$ = 14.2 Hz, $J_2$ = 7.1 Hz, 2H), 5.61 (t, $J$ = 7.8 Hz, 1H), 7.73 (d, $J$ = 6.6 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (acetone-$d_6$): $\delta$ = 13.5, 38.1, 57.0, 61.2, 168.7, 177.9 ppm. Elemental analysis for $C_{14}H_{26}N_2O_4$ (286.37): calcd (%) C, 58.72; H, 9.15; N, 9.78; found: C, 58.77; H, 9.17; N, 9.79.

*Compound* **2i** *$CH_3SO_2NH_2$ (0.951 g).* The process was catalyzed with PTSA (0.01 g), and the synthesis time was 4 h. Yield: 1.042 g, 3.798 mmol (76.0% on an OCHCOOEt basis).

In the catalyst-free process, the synthesis time was 6 h. Yield: 1.020 g, 3.718 mmol (74.4% on an OCHCOOEt basis).

MP = 170−172 °C (acetone). IR (KBr): $\nu$ = 3282, 3255, 3042, 3019, 2987, 2939, 1748, 1442, 1410, 1390, 1369, 1340, 1317, 1209, 1151, 1127, 1044, 1013, 997, 972, 910, 891, 845, 808, 768, 706, 632 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): $\delta$ = 1.24 (t, $J$ = 7.1 Hz, 3H), 3.0 (s, 6H), 4.18 (q, $J_1$ = 14.2 Hz, $J_2$ = 7.1 Hz,



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2H), 5.24 (t, $J$ = 8.6 Hz, 1H), 8.43 (d, $J$ = 8.6 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-$d_6$): $\delta$ = 14.3, 42.3, 62.5, 63.8, 167.9 ppm. Elemental analysis for $C_6H_{14}N_2O_6S_2$ (274.31): calcd (%) C, 26.27; H, 5.14; N, 10.21; found: C, 26.26; H, 5.14; N, 10.22.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05916.

IR, UV, and NMR spectra for new or appropriate compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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