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Synthesis of Pyrazoles by 1,3-Dipolar Cycloaddition under Aqueous Micellar Catalysis

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Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday

Ethyl diazoacetate (EDA), which is easily prepared from ethyl glycinate and $NaNO_2$, reacts in situ with alkynes in a water micelle environment without organic solvent to form pyrazoles. The reaction is pH dependent, as in the presence of protic catalysis (H_2SO_4 4%, pH 3.5) a mixture of 3,5- and 4,5-disubstituted pyrazoles was obtained, while, at pH 5.5, only the 3,5-disubstituted isomer was obtained. The presence of the surfactant TPGS-750-M was crucial to secure clean crude reaction mixtures and high yields of the products. The same protocol was successfully applied to the synthesis of substituted pyrazolines.

Introduction

Ethyl diazoacetate (EDA), discovered about 140 years ago by Theodore Curtius,[1] is a relatively stable compound sold in toluene solution or practically pure with 10–15% CH_2Cl_2. Although EDA is considered safe for small-scale applications, it is fraught with danger when large quantities are needed for process development. Among the various synthetic methods to prepare diazo compounds, diazotisation of glycine derivatives is the simplest way to obtain diazoacetate esters.[2] This conversion requires $NaNO_2$ under acidic conditions and is generally carried out in a two-phase system[3] of water/CH_2Cl_2, $CHCl_3$ or other organic solvents. The diazo compound formed is extracted by the organic solvent to prevent acid-mediated degradation. This dried organic solution can be used for reactions requiring non-protic conditions.[4] Alternatively, the biphasic system can be used directly for reactions compatible with a protic environment. The "in situ" generation of EDA has recently been developed in continuous flow,[5,6] but even in this case the presence of organic solvents such as CH_2Cl_2, toluene or Et_2O is reported.

In search of a more sustainable way to use EDA, we have attempted to investigate the preparation and in situ cycloaddition with alkynes to produce pyrazoles in an aqueous/micellar environment.[7] Pyrazoles are present in several biologically relevant molecules used as drugs or agrochemicals.[8,9] While reactive electron-rich diazo compounds cyclise rapidly with alkynes, electron-poor diazocarbonyl molecules require special reaction conditions, such as Lewis's acid catalysis or solvent-free heating using convection or microwave sources.[10,7,11]

The use of surfactants is a straightforward solution to replace organic solvents with water.[12,13] The aqueous micellar environment enables the solubilization of organic lipophilic molecules in water and the creation of nanoreactors influences the reaction rate. Recently, the synthesis of pyrazoles in an ionic or zwitterionic micellar environment has been described.[14,15] The one-pot synthesis of pyrazoles by Pd-catalysed aromatic aminations and subsequent cyclisations in TPGS-750-M has also been reported.[16]

Results and Discussion

Based on successful experience with metal-catalysed reactions,[17,18,19] surfactant TPGS-750-M was chosen to explore the reaction. This is a non-ionic surfactant that is already used on a large scale and has lower environmental impact and toxicity compared to other surfactants.[20] Our idea was to generate EDA from glycine ethyl ester hydrochloride (**2**) and $NaNO_2$ in a micellar environment containing the dipolarophile to gradually capture EDA during its formation.

Methyl propiolate (**1**) was chosen as a model to study the transformation and to optimise the reaction conditions. When the reaction was carried out in water or water/CH_2Cl_2, a cycloaddition occurred that gave a modest yield of the

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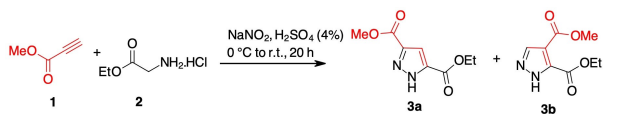
expected pyrazole (entry 2 in Table 1). An analogous result was observed when working with water/TPGS-750-M 3% and stirring the mixture at rt for 6 hours. The product was obtained as a mixture of regio-isomers (**3a** and **3b**) in 55 and 10% yields, respectively, isolated by column chromatography (entry 3, Table 1). Subsequently, different concentrations of TPGS-750-M were tried, also in the presence of small amounts of co-solvents. As shown in Table 1, the best results in terms of isolated yield of the major isomer **3a** were obtained with a 1.5% TPGS-750-M solution (68%, entry 5) or with 10% CH_2Cl_2 as co-solvent (76%, entry 7). Comparison with the results obtained in water alone or under the standard biphasic conditions with water/CH_2Cl_2 (entries 1 and 2 in Table 1) confirmed the role of the micellar nanoenvironment in this cycloaddition. Although satisfied with the in-situ generation of EDA in water without the presence of an organic solvent (entry 5 in Table 1), we were surprised by the formation of two regioisomers (**3a** and **3b** in Scheme 1) whose structure was determined by NMR comparison with literature data.

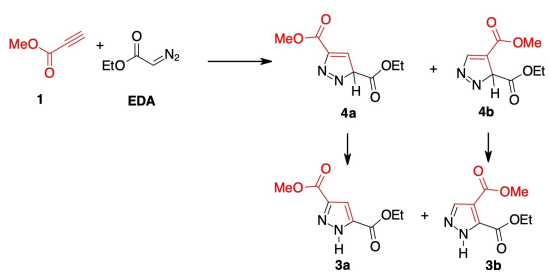
Table 1. Exploration of in situ formed EDA cycloaddition in water/TPGS-750-M.



1 2 3a 3b

Entry	Reaction conditions[a]	**3a** Yield[b]	**3b** Yield[b]
1	H_2O	50%	6%
2	H_2O/ CH_2Cl_2	55%	11%
3	5% wt TPGS-750-M/ H_2O	55%	10%
4	3% wt TPGS-750-M/ H_2O	57%	12%
5	1.5% wt TPGS-750-M/ H_2O	76%	8%
6	1.5% wt TPGS-750-M/10% GVL, H_2O	72%	6%
7	1.5% wt TPGS-750-M/ 10% CH_2Cl_2 /H_2O	79%	7%
8	1.5% wt TPGS-750-M/ 10% H_2O[c]	80%	-
9	1.5% wt TPGS-750-M/ 10% CH_2Cl_2 /H_2O[d]	12%	-
10	1.5% wt TPGS-750-M/H_2O[e]	72%	6%
11	1.5% wt TPGS-750-M/H_2O[e]	79%	-

[a] Reaction conditions: **2** (1.5 mmol), $NaNO_2$ (1.5 mmol), H_2SO_4 (0.04 mmol), 1 (1 mmol) in 7 mL of H_2O with surfactant at 0 °C followed by 20 h at rt. [b] Yield of isolated and fully characterized products. [c] **2** (1.5 mmol), $NaNO_2$ (1.5 mmol), H_2SO_4 (0.04 mmol),) in 1 mL of the solvent mixture, stirred at rt for 30 min. Then, addition of Na_2CO_3 (0.04 mmol) followed by **1** (1 mmol). Stirred at rt for 16 h. [d] Same condition than in [c] followed by neutralisation with 1.5 mmol of Na_2CO_3, final pH 9.4. [e] Reaction done as above but using commercially available EDA containing 13 wt. % of CH_2Cl_2.



1 EDA 4a 4b 3a 3b

Scheme 1. General mechanism for cycloaddition.

This behaviour has never been observed before in activation with Lewis acids.[21] The reaction between EDA and alkenes is a 1,3-cycloaddition, forming unstable 3H-pyrazoles (**4a** or **4b** in Scheme 1), which subsequently undergo a 1,5-sigmatropic shift to give the final aromatic pyrazole (Scheme 1).[22] When conjugated diazo compounds are used (such as EDA), activation of the alkyne is required.[23] Lewis acids are reported to activate alkynes containing a conjugated carbonyl group by coordination, presumably lowering the LUMO of the alkyne.[24] Analogously, the protic environment of our reaction could act on the LUMO of the alkyne without triggering the decomposition of the diazo. However, the acid should not influence the regiochemistry of the product. In order to better understand the mechanism of formation of the minor isomer, the reaction was carried out at different pH values. As shown in Table 1, the protic environment indeed influences the regiochemistry of the cycloaddition. In acidic environment (pH 3.5), we obtained a ratio of about 10:1 of the two regiosiomers (entry 7), while after neutralisation of H_2SO_4 with Na_2CO_3 (final pH 5.5), only the major isomer was obtained in good yield. A further increase of the pH to 9.4 led to a decrease in the pyrazole yield, as most of the EDA formed remained unreacted after 24 hours of stirring. Based on these observations, we changed our procedure. EDA was obtained "in situ" from **2**. As soon as the tlc analysis indicated the formation of EDA, the micellar acidic solution was neutralised with 4% Na_2CO_3.

Methyl propiolate **1** was added and, after 20 h of stirring at rt, we observed the exclusive formation of pyrazole **3a**, isolated in 80% yield (entry 8).

This pH-dependent behaviour was also observed when working with commercial EDA (containing 13% wt CH_2Cl_2). At acidic pH, a mixture of isomers was obtained, whereas at pH 5.5 only the main isomer was isolated (entries 10 and 11). The reaction scope was studied according to these two procedures starting from **2** and the results are summarised in Table 2.

Various alkynes conjugated to a carbonyl (ketones, esters or amides) gave the pyrazole cycloadducts in good yields in both procedures (entries 1–6 in Table 2). As expected, alkynes such as phenylacetylene without coordinating electron-withdrawing groups gave the cycloadducts in poor yields (see SI). Acetylene-dicarboxylates gave trisubstituted pyrazoles in good yield (entries 7 and 8 in Table 2), while more hindered 4-methyl-1-phenyl-1-pentyn-3-one showed poor reactivity (see SI). Various glycine esters or amides can also be converted to the corresponding diazoacetates to give differentially substituted 3,5- (or 4,5-) pyrazole dicarboxylates (entries 9 and 10).

In summary, two procedures were possible for the cycloadditon of EDA with activated alkynes under aqueous micellar catalysis: an "in situ" procedure with simultaneous generation of EDA and cycloaddition in acidic medium and a telescopic process in which EDA is generated in acid and subsequently neutralised and the dipolarophile is added in the same flask. The telescopic process is stereoselective and gives high yield of the 3,5-disubstituted isomer. However, it has the disadvantage that all of the EDA is generated in solution before the cycloaddition, which can lead to safety concerns when working on a large scale. The in-situ acid-catalysed process, on the other

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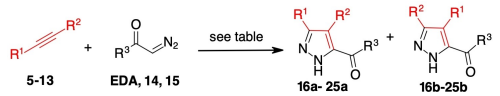
Table 2. Reaction scope.



Entry	Starting materials[a]	Isomer **a** yield (%, route)[b]	Isomer **b** yield (%, route)[b]
1	R^1 = COOEt, R^2 = H, (**5**); R^3 = OEt (EDA);	**16a** (78, A)	**16b** (7, A)
2	R^1 = $COO(CH_2)_2$t-Bu, R^2 = H, (**6**); R^3 = OEt (EDA)	**17a** (63, A)	**17b** (7, A)
3	R^1 = $COOcyclo C_5H_9$, R^2 = H, (**7**); R^3 = OEt (EDA)	**18a** (61, A; 69, B)	**18b** (10, A)
4	R^1 = $COOCHPhC_2H_5$, R^2 = H, (**8**); R^3 = OEt (EDA)	**19a** (63, A)	**19b** (8, A)
5	R^1 = CONMePh, R^2 = H, (**9**); R^3 = OEt (EDA)	**20a** (66, A; 73 B)	**20b** (10, A)
6	R^1 = COMe, R^2 = H, (**10**); R^3 = OEt (EDA)	**21a** (79, A; 84, B)	**21b** (4 A)
7	R^1 = COOEt, R^2 = COOEt, (**11**); R^3 = OEt (EDA)	**22a** (66, A)	
8	R^1 = COOMe, R^2 = COOMe, (**12**); R^3 = OEt (EDA)	**23a** (74, A)	
9	R^1 = COOEt, R^2 = H, (**5**); R^3 = OBn (**13**)	**24a** (75, A)	**24b** (4, A)
10	R^1 = COOEt, R^2 = H, (**5**); R^3 = NHBn (**14**)	**25a** (31, A)	**25b** (4, A)

[a] Reaction conditions: Route A. Glycine derivative (1.5 mmol), $NaNO_2$ (1.5 mmol), H_2SO_4 (0.04 mmol), alkyne (1 mmol) in 7 mL of H_2O /TPGS-750-M 1.5% wt at 0 °C followed by 20 h at rt. Route B Glycine derivative (1.5 mmol), $NaNO_2$ (1.5 mmol), H_2SO_4 (0.04 mmol),) in mL of H_2O /TPGS-750-M 1.5% wt, stirred at rt for 30 min. Then, addition of Na_2CO_3 (0.04 mmol) followed by alkyne (1 mmol). Stirred at rt for 20 h [b] Yields of isolated and fully characterized materials.

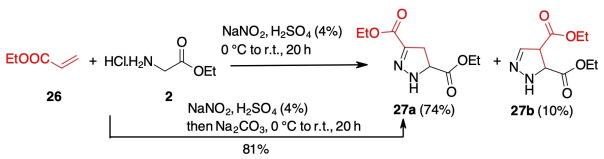
hand, allows access to 4,5-disubstituted pyrazoles, although in small amounts, which are difficult to obtain using other synthetic approaches.

These two protocols were also applied to the cycloaddition of EDA with ethyl acrylate **26**, leading to the corresponding substituted pyrazolines **27a** and **27b** (Scheme 2). Again, protic catalysis gave a mixture of regioiomers, whereas the reaction at a higher pH gave a single isomer in higher yield.

Conclusions

In summary, we have established that EDA can be prepared in situ from glycine esters or amides and used for cycloaddition with alkynes or alkenes to give disubstituted pyrazoles or pyrazolines.

The micellar nanoenvironment provided by TPGS-750-M is responsible for the higher yields compared to water alone,



Scheme 2. Cycloaddition with ethyl acrylate.

while the regiochemistry was independent due to the presence of the surfactant, as pH alone seems to be responsible for the formation of the 4,5-disubstituted pyrazoles. It is possible to perform an "in situ" route, where EDA is generated and reacted directly in the same acidic environment required for its preparation. Alternatively, a telescopic process is possible in which the reaction conditions are manipulated before the reactant is added to the medium in which EDA is produced. The reactions are metal-free and were always carried out in water with 1.5% surfactant as the only additive. Extraction of the final product was carried out using sustainable EtOAc and purification of the resulting 3,5-disubstituted pyrazoles can be carried out by crystallisation where possible, providing a sustainable alternative to standard pyrazole syntheses in organic solvents.

Experimental Section

5-Ethyl 3-methyl 1*H*-pyrazole-3,5-dicarboxylate 3a. General procedure, route B In an open reaction environment, a cold suspension of $NaNO_2$ (308.0 mg, 4.46 mmol) in 1.5 wt% TPGS-750-M/H_2O (1 mL) was added dropwise to a suspension of glycine ethyl ester hydrochloride (616.1 mg, 4.46 mmol) in 1.5 wt% TPGS-750-M/H_2O (6 mL). After stirring at 0 °C for 30 minutes, H_2SO_4 (0.227 mL, 4 mol%) was added dropwise over a period of 2 minutes and the mixture was stirred at the same temperature for a further 30 minutes. Na_2CO_3 (12.6 mg, 0.12 mmol) was added followed by methyl propiolate **2** (0.264 mL, 2.98 mmol) and the reaction mixture was stirred for 20 h at room temperature. It was then diluted with water (10 mL), the aqueous phase was extracted with EtOAc (3× 20 mL) and the combined organic layers were washed with brine (1×25 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash column chromatography eluted with PE:EtOAc (8:2) gave 474 mg **3a** as a pale yellow solid (yield: 80%).^{1}H NMR (600 MHz, DMSO): δ 14.61 (s, 1H), 7.19 (d, J=2.0, 1H), 4.30 (qd, J=7.1, 1.6, 2H), 3.83 (d, J=1.5, 3H), 1.29 (td, J=7.1, 1.6, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.90, 160.23, 139.96, 139.52, 111.25, 61.56, 52.29, 14.02 ppm. MS (ESI) 221 $[M+Na]^+$. Mp 82–86 °C. Calcd for $C_8H_{10}N_2O_4$ C 48.48, H 5.09, N 14.14, O 32.29; found C 48.51, H 5.08, N 14.16.

5-Ethyl 4-methyl 1*H*-pyrazole-4,5-dicarboxylate 3b General procedure route A. In an open reaction environment, a cold suspension of $NaNO_2$ (308.0 mg, 4.46 mmol) in 1.5 wt% TPGS-750-M/H_2O (1 mL) was added dropwise to a suspension of glycine ethyl ester hydrochloride (616.1 mg, 4.46 mmol) in 1.5 wt% TPGS-750-M/H_2O (6 mL). The mixture was stirred at 0 °C for 30 minutes, then H_2SO_4 (0.227 mL, 4 mol%) was added dropwise over a period of 2 minutes, followed by methyl propiolate **2** (0.264 mL, 2.98 mmol). The reaction mixture was stirred at room temperature for 20 hours and then quenched with a saturated solution of $NaHCO_3$ (15 mL). The aqueous phase was extracted with EtOAc (3×20 mL), and the combined organic layers were washed with brine (1×25 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The oily residue obtained was purified by flash column chromatography. Elution with PE:EtOAc (9:1) gave 44.5 mg **3b** as a white solid. (yield: 8%). ^{1}H NMR (600 MHz, DMSO): δ 7.58 (s, 1H), 4.39 (q, J=7.1, 2H), 3.92 (s, 3H), 1.32 (t, J=7.1, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.74, 159.03, 157.05, 156.57, 109.87, 63.09, 53.28, 14.21 ppm. MS (ESI) 221 $[M+Na]^+$. Mp 45–47 °C. HRMS (ESI) calcd for $C_8H_{10}N_2O_4$ $(M+1)^+$ 199.0719; found 199.0721.

Diethyl 1*H*-pyrazole-3,5-dicarboxylate 16a.[25] Pale yellow solid, 421.6 mg (yield: 78%). ^{1}H NMR (600 MHz, DMSO): δ 14.59 (s, 1H),

7.18 (s, 1H), 4.30 (q, $J=7.1$, 4H), 1.30 (t, $J=7.1$, 6H). ^{13}C NMR. MS (ESI) 235 $[M+Na]^+$. Mp 50–52 °C. Lit. m.p. 54–55 °C[25]

Diethyl 1*H*-pyrazole-4,5-dicarboxylate 16 b.[11] Colorless oil, 39.4 mg (yield: 7%). ^1H NMR (600 MHz, DMSO): δ 7.55 (s, 1H), 4.38 (q, $J=7.1$, 4H), 1.32 (q, $J=9.8$, 8.4, 6H). MS (ESI) 235 $[M+Na]^+$. HRMS (ESI) calcd for $C_9H_{12}N_2O_4$ $(M+1)^+$ 213.0876 found 213.0875.

3-(3,3-Dimethylbutyl) 5-ethyl 1*H*-pyrazole-3,5-dicarboxylate 17 a. Pale yellow solid, 275.2 mg (yield: 63%). ^1H NMR (600 MHz, DMSO): δ 14.62 (s, 1H), 7.46–6.42 (m, 1H), 4.31 (q, $J=7.1$, 4H), 1.62. ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.53, 11.33, 63.53, 61.77, 41.80, 29.92, 29.70, 14.34 ppm. MS (ESI) 269 $[M+H]^+$. Mp 32–34 °C. HRMS (ESI) calcd for $C_{13}H_{20}N_2O_4$ $(M+1)^+$ 269.1502; found 269.1503.

4-(3,3-Dimethylbutyl) 5-ethyl 1*H*-pyrazole-4,5-dicarboxylate 17 b. Colorless oil, 30.5 mg (yield: 7%). ^1H NMR (600 MHz, DMSO): δ 7.53 (d, $J=1.9$, 1H), 4.50–4.30 (m, 4H), 1.65 (td, $J=7.2$, 2.0, 2H), 1.32 (td, $J=7.1$, 2.0, 3H), 0.94 (d, $J=2.0$, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.11, 159.10, 157.01, 156.23, 109.61, 64.54, 62.76, 41.65, 29.94, 29.66, 14.22 ppm. MS (ESI) 269 $[M+H]^+$. HRMS (ESI) calcd for $C_{13}H_{20}N_2O_4$ $(M+1)^+$ 269.1502; found 269.1504.

3-Cyclopentyl 5-ethyl 1*H*-pyrazole-3,5-dicarboxylate 18 a. Pale yellow oil, 324.8 mg (yield: 69%). ^1H NMR (600 MHz, DMSO): δ 14.58 (s, 1H), 7.15 (d, $J=1.1$, 1H), 5.28 (dq, $J=6.1$, 2.6, 1H), 4.29 (q, $J=7.1$, 2H), 1.90 (dq, $J=11.7$, 5.9, 5.5, 2H), 1.74 (d, $J=11.5$, 4H), 1.64–1.54 (m, 2H), 1.29 (t, $J=7.2$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.75, 160.17, 78.85, 61.70, 32.82, 23.87, 14.35 ppm. MS (ESI) 253 $[M+H]^+$. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4$ $(M+1)^+$ 253.1189; found 253.1187.

4-Cyclopentyl 5-ethyl 1*H*-pyrazole-4,5-dicarboxylate 18 b. Colorless oil, 47.6 mg (yield: 10%). ^1H NMR (600 MHz, DMSO): δ 7.54 (d, $J=1.2$, 1H), 5.36 (dt, $J=6.1$, 3.1, 1H), 4.38 (q, $J=7.1$, 2H), 2.00–1.81 (m, 2H), 1.87–1.68 (m, 4H), 1.60 (qd, $J=7.3$, 6.9, 2.9, 2H), 1.32 (t, $J=7.1$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.42, 159.14, 156.96, 155.98, 109.49, 100.11, 80.16, 62.73, 32.77, 23.80, 14.22 ppm. MS (ESI) 253 $[M+H]^+$. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4$ $(M+1)^+$ 253.1189; found 253.1188.

5-Ethyl 3-(1-phenylpropyl) 1*H*-pyrazole-3,5-dicarboxylate 19 a. Pale yellow oil, 252.9 mg (yield: 63%). ^1H NMR (600 MHz, DMSO): δ 14.68 (s, 1H), 7.42 (d, $J=7.6$, 2H), 7.36 (dd, $J=8.5$, 6.8, 2H), 7.32–7.28 (m, 1H), 7.27 (s, 1H), 5.84 (d, $J=1.6$, 1H), 4.31 (d, $J=7.1$, 2H), 2.02–1.82 (m, 2H), 1.30 (t, $J=7.1$, 3H), 0.87 (t, $J=7.3$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.58, 159.75, 139.83, 128.65, 128.30, 126.78, 111.94, 79.01, 61.79, 29.40, 14.35, 10.08 ppm. MS (ESI) 303 $[M+H]^+$. HRMS (ESI) calcd for $C_{16}H_{18}N_2O_4$ $(M+1)^+$ 303.1345; found 303.1347.

5-Ethyl 4-(1-phenylpropyl) 1*H*-pyrazole-4,5-dicarboxylate 19 b. Colorless oil, 32.0 mg (yield: 8%). ^1H NMR (600 MHz, DMSO): δ 7.69 (d, $J=1.2$, 1H), 7.47–7.42 (m, 2H), 7.41–7.36 (m, 2H), 7.35–7.30 (m, 1H), 5.90 (t, $J=6.8$, 1H), 4.39 (qd, $J=7.1$, 1.2, 2H), 2.06-1.87 (m, 2H), 1.33 (td, $J=7.1$, 1.2, 3H), 0.87 (td, $J=7.4$, 1.2, 3H).^{13}C NMR (150 MHz, $CDCl_3$): δ 162.13, 159.12, 157.02, 155.58, 139.07, 128.77, 126.84, 109.82, 80.31, 62.77, 29.28, 14.24, 10.01 ppm. MS (ESI) 303 $[M+H]^+$. HRMS (ESI) calcd for $C_{16}H_{18}N_2O_4$ $(M+1)^+$ 303.1345; found 303.1347.

Ethyl 3-(methyl(phenyl)carbamoyl)-1*H*-pyrazole-5-carboxylate 20 a. Yellow solid, 131.1 mg (yield: 73%). ^1H NMR (600 MHz, DMSO): δ 14.21 and 14.07 (s, 1H overall), 7.52–7.44 (m, 2H), 7.38–7.34 (m, 2H), 7.25–7.16 (m, 1H), 4.24 (q, $J=7.1$, 1H), 4.13 (q, $J=7.1$, 2H), 3.35 (d, $J=10.8$, 3H), 1.24 and 1.17 (t, $J=7.2$ and t, $J=7.1$, 3H overall). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.76, 159.68, 142.62, 142.76, 138.60, 130.16, 129.06, 127.59, 110.34, 61.02, 38.73, 14.19 ppm. MS (ESI) 274 $[M+H]^+$. Mp 151–154 °C. . Calcd for $C_{14}H_{15}N_3O_3$ C 61.53, H 5.53, N 15.38, O 17.56; found C 61.56, H 5.50, N 15.39.

Ethyl 4-(methyl(phenyl)carbamoyl)-1*H*-pyrazole-5-carboxylate 20 b. Pale yellow solid, 42.6 mg (yield: 10%). ^1H NMR (600 MHz, DMSO): δ 7.46-7.41 (m, 2H), 7.41–7.38 (m, 1H), 7.38–7.35 (m, 2H), 6.23 (s, 1H), 4.28 (q, $J=7.1$, 2H), 3.38 (s, 3H), 1.24 (t, $J=7.2$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.94, 159.25, 156.74, 155.96, 141.92, 130.02, 128.84, 127.06, 108.08, 62.45, 38.49, 14.11 ppm. MS (ESI) 274 $[M+H]^+$. Mp 88–89 °C. Calcd for $C_{14}H_{15}N_3O_3$ C 61.53, H 5.53, N 15.38, O 17.56; found C 61.59, H 5.48, N 15.40.

Ethyl 3-acetyl-1*H*-pyrazole-5-carboxylate 21 a. White solid 525.8 mg (yield: 79%). ^1H NMR (600 MHz, DMSO): δ 14.50 (s, 1H), 7.29 (s, 1H), 4.31 (q, $J=7.1$, 2H), 2.51 (d, $J=2.3$, 3H), 1.30 (t, $J=7.1$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.72, 160.43, 110.12, 61.92, 26.91, 14.30 ppm. MS (ESI) 205 $[M+Na]^+$. Mp 112–114 °C. Calcd for $C_8H_{10}N_2O_3$: C 52.74, H 5.53, N 15.38, O 26.35; found C 52.78, H 5.50, N 15.40.

Ethyl 4-acetyl-1*H*-pyrazole-5-carboxylate 21 b. Yellow waxy material, 24.7 mg (yield: 4%). ^1H NMR (600 MHz, DMSO): δ 7.75 (s, 1H), 4.39 (q, $J=7.1$, 2H), 2.59 (s, 3H), 1.32 (t, $J=7.1$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.14, 167.98, 159.14, 157.25, 107.77, 62.83, 27.49, 14.25 ppm. MS (ESI) 205 $[M+Na]^+$. HRMS (ESI) calcd for $C_8H_{10}N_2O_3$ $(M+Na)^+$ 205.0589; found 205.0590.

Triethyl 1*H*-pyrazole-3,4,5-tricarboxylate 22 a.[11] Pale yellow solid, 274.5 mg (yield: 66%). ^1H NMR (600 MHz, DMSO): δ 15.08–14.84 (m, 1H), 4.28 (dq, $J=10.5$, 7.0, 6H), 1.27 (q, $J=7.2$, 9H). MS (ESI) 285 $[M+H]^+$. Mp 89–92 °C. Lit. mp 92 °C.[11]

5-Ethyl 3,4-dimethyl 1*H*-pyrazole-3,4,5-tricarboxylate 23 a.[26] White solid, 333.2 mg (yield: 74%). ^1H NMR (600 MHz, $CDCl_3$): δ 4.40 (qd, $J=7.1$, 1.6, 2H), 3.94 (dd, $J=6.4$, 1.7, 6H), 1.37 (td, $J=7.1$, 1.7, 3H). MS (ESI) 279 $[M+Na]^+$. Mp 98–100 °C. Lit. mp 98 °C[26]

5-Benzyl 3-ethyl 1*H*-pyrazole-3,5-dicarboxylate 24 a.[23] Yellow solid, 317 mg (yield: 75%). ^1H NMR (600 MHz, $CDCl_3$): δ 13.08 (s, 1H), 7.40–7.32 (m, 3H), 7.29 (t, $J=6.8$, 2H), 7.28 (s, 1H), 5.29 (s, 2H), 4.31 (q, $J=7.1$, 2H), 1.29 (t, $J=7.1$, 3H). MS (ESI) 297 $[M+Na]^+$. Mp 82–84 °C. Calcd for $C_{14}H_{14}N_2O_4$: C 61.31, H 5.15, N 10.21; O 23,33; found C 61.34, H 5.14, N 10.20.

5-Benzyl 4-ethyl 1*H*-pyrazole-4,5 -dicarboxylate 24 b. Colorless oil, 15.0 mg (yield: 4%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.45 (d, $J=7.2$, 2H), 7.39 (td, $J=11.4$, 9.6, 4.2, 3H), 7.30 (s, 1H), 5.43 (s, 2H), 4.45 (q, $J=7.1$, 2H), 1.42 (t, $J=7.2$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.18, 158.96, 156.84, 156.14, 134.67, 128.98, 128.89, 128.84, 109.77, 68.25, 62.86, 29.84, 14.23 ppm. MS (ESI) 297 $[M+Na]^+$. HRMS (ESI) calcd for $C_{14}H_{14}N_2O_4$ $(M+Na)^+$ 297.0851; found 297.0852.

Ethyl 5-(benzylcarbamoyl)-1*H*-pyrazole-3-carboxylate 25 a.[27] White solid, 136.0 mg (yield: 31%). ^1H NMR (600 MHz, DMSO): δ 14.28 (s, 1H), 9.14 (s, 1H), 7.36–7.20 (m, 5H), 4.46 (s, 2H), 4.30 (s, 2H), 1.30 (t, $J=7.4$, 3H). MS (ESI) 296 $[M+Na]^+$. Mp 183–185 °C. Calcd for $C_{14}H_{15}N_3O_3$: C 61.53, H 5.53, N 15.38; O,17.56; found C 61.56, H 5.51, N 15.36.

Ethyl 5-(benzylcarbamoyl)-1*H*-pyrazole-4-carboxylate 25 b. Pale yellow solid, 17.4 mg (yield: 4%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (h, $J=6.6$, 6.1, 5H), 7.16 (d, $J=5.8$, 1H), 4.64 (d, $J=5.9$, 2H), 4.45 (q, $J=7.1$, 2H), 1.42 (t, $J=7.1$, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.97, 159.08, 157.80, 156.30, 137.15, 129.02, 128.09, 128.06, 109.01, 62.80, 43.81, 14.24 ppm. MS (ESI) 296 $[M+Na]^+$. Mp 56–58 °C. Calcd for $C_{14}H_{15}N_3O_3$: C 61.53, H 5.53, N 15.38; O,17.56; found C 61.57, H 5.50, N 15.35.

Diethyl 4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylate 27 a.[28] Yellow oil, 433.2 mg (yield: 81%). ^1H NMR (600 MHz, $CDCl_3$): δ 6.15 (s, 1H), 4.39 (ddd, $J=12.6$, 5.5, 2.0, 1H), 4.26–4.19 (m, 2H), 4.14 (qd, $J=7.1$, 1.9, 2H), 3.23-3.21 and 3.14–3.08 (m, 2H overall), 1.27 (td, $J=7.2$, 1.9, 3H), 1.22 (td, $J=7.2$, 1.9, 3H). MS (ESI) 237 $[M+Na]^+$. HRMS (ESI) calcd for $C_9H_{14}N_2O_4$ $(M+Na)^+$ 237.0851; found 237.0853.

Diethyl 4,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate 27b. Pale yellow oil, 53.3 mg (yield: 10%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.17 (ddd, J = 11.5, 8.0, 1.3, 1H), 4.34 (qd, J = 7.2, 1.3, 2H), 4.25 (qt, J = 7.1, 1.1, 2H), 3.53–3.45 (m, 2H), 1.35 (td, J = 7.1, 1.3, 3H), 1.30 (td, J = 7.1, 1.3, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.98, 159.97, 151.15, 79.97, 62.47, 62.37, 37.68, 14.17, 14.15. MS (ESI) 237 $[M+Na]^+$. HRMS (ESI) calcd for $C_9H_{14}N_2O_4$ $(M+Na)^+$ 237.0851; found 237.0852.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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