Eclectic 1-Aryl-1,2-diazabuta-1,3-dienes: Valuable Tools for the Preparation of Pyrrol-2-ones, 1-Arylpyrazoles, 2-(3-Oxopyrazol-4-yl)malonates and 4-(2-Oxopyrrol-3-yl)pyrazol-3-ones

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Abstract: 1-Aryl-1,2-diazabuta-1,3-dienes react with dimethyl malonate to give hydrazonic intermediates that in turn are converted into pyrrol-2-ones, 1-arylpyrazoles and 2-(3-oxopyrazol-4-yl)malonates. The latter compounds represent an useful entry to 4-(2-oxopyrrol-3-yl)pyrazol-3-ones, by means of the addition of another molecule of 1,2-diazabuta-1,3-diene and subsequent cyclization of the adducts.

Key words: 1,2-diazabuta-1,3-dienes, Michael additions, cyclizations, pyrroles, pyrazoles

The azo-ene system of 1,2-diazabuta-1,3-dienes can be influenced by the presence of electron-rich or electron-poor groups on terminal carbon and/or nitrogen.[1–6] Although the terminal carbon remains the preferential target of nucleophilic attacks, electron-donating groups reduce the electrophilic character of this atom, while electron-withdrawing ones enhance it. The reaction of these substrates with activated methylene compounds generates a variety of α-substituted hydrazones as a consequence of 1,4-conjugated addition (Michael-type). The formation of this new carbon-carbon single bond is important both in itself and in view of subsequent five or six-membered cyclization processes.[3,4,6]

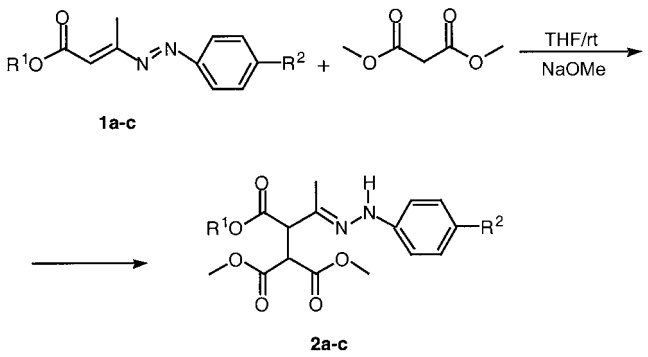
Here we report on the reaction of 1-aryl-1,2-diazabuta-1,3-dienes with dimethyl malonate. The presence of an aryl substituent instead of amido or ester group on the terminal nitrogen atom of the azo-ene system reduces its electrophilic character. In fact, we observed that the addition of dimethyl malonate to 1-aryl-1,2-diazabuta-1,3-dienes to give hydrazonic intermediates proceeds with lower yields and longer times with respect to the same reactions carried out using 1-aminocarbonyl- or 1-alkoxycarbonyl-1,2-diazabuta-1,3-dienes as described by some of us in a previous work.[6]

At the same time, the lack of electron-withdrawing groups on the nitrogen substantially influences the subsequent cyclization process of hydrazone intermediates. These latter compounds were demonstrated to be useful as versatile tools in the synthesis of different classes of heterocycles, using different reaction conditions. In fact, in the presence of sodium methoxide we obtained pyrrol-2-ones,[6] using $CuCl_2$ or $Cu(OTf)_2$ we prepared 1-arylpyrazoles, while in acidic medium we isolated 2-(3-oxopyrazol-4-yl)malonates.

Furthermore, we have also investigated the subsequent formation of 4-(2-oxopyrrol-3-yl)pyrazol-3-ones starting from these latter substrates and a further molecule of 1,2-diazabuta-1,3-diene.

1-Aryl-1,2-diazabuta-1,3-dienes **1a–c** are prepared from methyl or ethyl 2-chloroacetoacetate with phenyl- or 4-chlorophenylhydrazine, according to the typical procedures described in literature.[7]

In the presence of sodium methoxide (0.5 equiv) in tetrahydrofuran at room temperature, the reaction between compounds **1a–c** and dimethyl malonate gives rise to α-substituted hydrazone derivatives **2a–c** (Scheme 1). Yields and reaction times of **2a–c** are listed in Table 1.



Scheme 1

Table 1 Yields and Reaction Times Required for Hydrazones **2a–c**

Starting Material	R^1	R^2	Product	Reaction Time (h)	Yield[a] (%)
1a	Me	H	**2a**	50	59
1b	Et	H	**2b**	47	61
1c	Me	Cl	**2c**	54	51

[a] Yield of pure isolated products.

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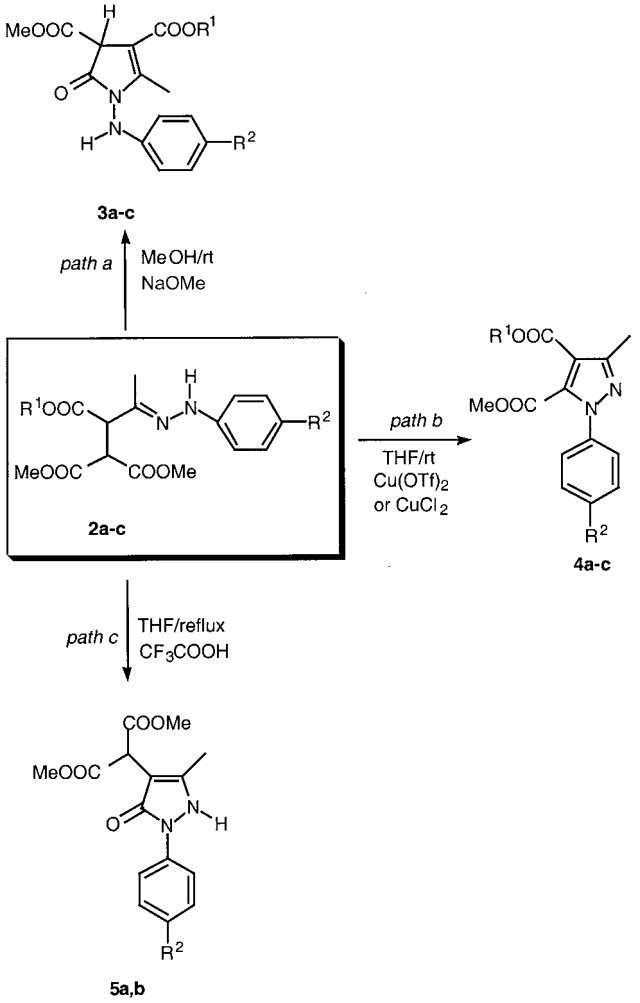
The configuration of C=N double bond of these intermediates was determined by NOE experiments, carried out on compound **2c**. It shows considerable NOE enhancement of NH by irradiation of CH_3, and vice versa. This evidence suggests the proximity of these two groups, in agreement with *E*-configuration of the C=N centre.

It is worth underlining that these common and useful intermediates like **2a–c** can be submitted to interesting transformations, by only varying the reaction conditions, due to the lack of a strong electron-withdrawing group on the nitrogen atom in position 1.

As expected, the treatment of compounds **2a–c** with sodium methoxide (0.3 equiv) in tetrahydrofuran at room temperature leads to pyrrol-2-ones **3a–c**[6] by means of an intramolecular nucleophilic attack of the central hydrazone nitrogen atom to the ester group of malonate, with consequent loss of an alcohol molecule (Scheme 2, *path a*). Yields and reaction times of **3a–c** are listed in Table 2.

In the presence of $CuCl_2$ or $Cu(OTf)_2$ in tetrahydrofuran at room temperature, the same hydrazones **2a–c** are converted into 1-arylpyrazoles **4a–c** (Scheme 2, *path b*). The use of $CuCl_2$ rather than of $Cu(OTf)_2$ is more convenient because of the higher yields and faster reaction times (see Table 3), as well as lower costs. This method represents a



Scheme 2

Table 2 Yields and Reaction Times Required for Pyrrol-2-ones **3a–c**

Starting Material	R^1	R^2	Product	Reaction Time (h)	Yield[a] (%)
2a	Me	H	**3a**	5.0	71
2b	Et	H	**3b**	4.5	68
2c	Me	Cl	**3c**	5.5	75

[a] Yield of pure isolated products based on **2a–c**.

new, mild and simple route to 1-arylpyrazoles which contributes to increase the literature examples reported for their synthesis.[8]

We also attempted to submit the hydrazones, previously prepared from 1-aminocarbonyl- or 1-alkoxycarbonyl-1,2-diazabuta-1,3-dienes and dimethyl malonate,[6] to the same treatment, but no reaction was detected.

The same compounds **2a–c**, in the presence of trifluoroacetic acid in tetrahydrofuran under reflux, yield 2-(3-oxopyrazol-4-yl)malonates **5a**,**b** (Scheme 2, *path c*).[9] In acidic medium, the reaction proceeds by means of an intramolecular nucleophilic attack of the terminal nitrogen atom of hydrazones **2a–c** to the ester group in the γ position derived from 1,2-diazabuta-1,3-diene, with loss of an alcohol molecule.[10] This event is ascribable to the stronger nucleophilic character of the terminal nitrogen atom due to the absence of electron-withdrawing group. In fact, hydrazones obtained from 1-aminocarbonyl or 1-alkoxycarbonyl-1,2-diazabuta-1,3-dienes do not exhibit this reaction. Yields and reaction times for the preparation of **5a**,**b** are given in Table 4.

This procedure represents the first example in literature in which, even if the cyclization on the carbonyl group derived from dimethyl malonate to give pyrrolones is possible, as previously described by some of us,[6] the annulation occurs on the ester group derived from 1,2-diazabuta-1,3-dienes to give pyrazolone derivatives.

2-(3-Oxopyrazol-4-yl)malonates **5a**,**b** are significant in the synthetic point of view: in fact they are susceptible for a further 1,4-addition of another molecule of 1,2-diazabuta-1,3-diene **6a**,**b** in tetrahydrofuran in the presence of sodium methoxide to give 3-hydrazono-1-(5-oxopyrazol-4-yl)butanes **7a**,**b** (Scheme 3).

These products are obtained as diastereoisomeric mixtures and used as such for the subsequent cyclization. ^1H and ^{13}C NMR spectra of **7a**,**b** show that they exist exclusively in 'CH' tautomeric form while the starting **5a**,**b** are in 'NH' tautomeric form. In fact, in ^1H NMR spectra, the H–D-exchange experiments revealed the presence of two groups of peaks ascribable to ureidic 'NH' and/or 'NH_2' of two diastereoisomers of **7a**,**b**. On the other hand, 90° DEPT experiments of the same **7a**,**b** shown four signals attributable to both 'CH' groups of the diastereoisomer mixtures. Yields and reaction times for the preparation of **7a**,**b** are listed in Table 5.

Table 3 Yields and Reaction Times Required for 1-Arylpyrazoles **4a–c**

Starting Material	R^1	R^2	Product	Reaction Time (h)[a]	Yield[b] (%)	Reaction Time (h)[c]	Yield[d] (%)
2a	Me	H	**4a**	7.0	47	19	41
2b	Et	H	**4b**	6.5	53	23	44
2c	Me	Cl	**4c**	7.0	56	20	41

[a] Reaction times using $CuCl_2$ as catalyst.
[b] Yields of pure isolated products based on **2a–c**, using $CuCl_2$ as catalyst.
[c] Reaction times using $Cu(OTf)_2$ as catalyst.
[d] Yields of pure isolated products based on **2a–c**, using $Cu(OTf)_2$ as catalyst.

Table 4 Yields and Reaction Times Required for 2-(3-Oxopyrazol-4-yl)malonates **5a**,**b**

Starting Material	R^1	R^2	Product	Reaction Time (h)	Yield[a] (%)
2a	Me	H	**5a**	6	64
2b	Et	H	**5a**	6	78
2c	Me	Cl	**5b**	6	81

[a] Yield of pure isolated products based on **2a–c**.

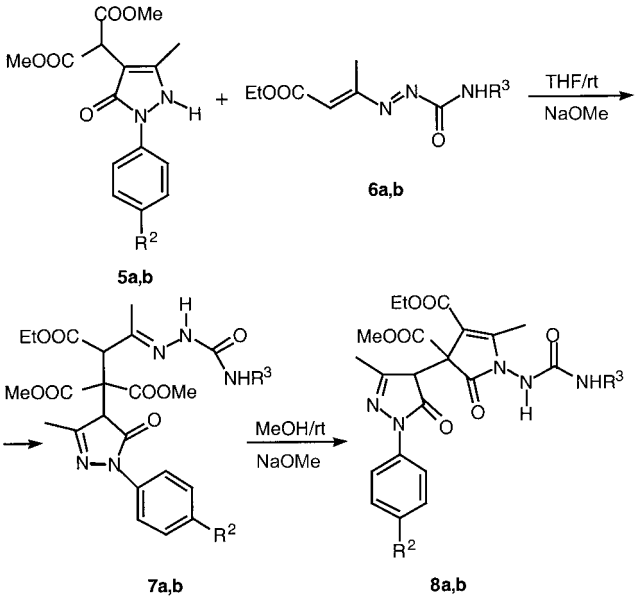
Compounds **7a**,**b** can be easily converted into the relative 4-(2-oxopyrrol-3-yl)pyrazol-3-ones **8a**,**b** using stoichiometric amount of sodium methoxide in methanol, by means of a second five-membered ring closure as described above for the formation of **3a–c** (Scheme 3). Also in this case, **8a**,**b** are obtained as diastereoisomeric mixtures (50:50) and 'CH' tautomeric form is observed, as revealed by ^{1}H-D–H-exchange experiments and 90° DEPT spectra of these latter compounds. Probably, products **7** and **8** are more sterically congested with respect to the starting compounds **5**, and therefore they adopt the less hindered 'CH' form, allowing the bulky substituent to lie away from the plane of the pyrazole ring. Yields and reaction times of **8a**,**b** are shown in Table 6.

In conclusion, this work describes the importance of the substituent on the terminal nitrogen atom of the azo-ene system and offers simple and convenient access to pyrrol-2-ones,[11] 1-arylpyrazoles[12] and pyrazol-5-ones,[3,12] which are of great interest both as products and intermediates in organic,[3,5,13–15] biological,[16] pharmaceutical,[17] analytical[18] and agricultural[19] chemistry.

Table 5 Yields and Reaction Times Required for 3-Hydrazono-1-(5-oxopyrazol-4-yl)butanes **7a**,**b**

Starting Materials				Product	Reaction	Yield[a]
5	R^2	**6**	R^3		Time (h)	(%)
5a	H	**6a**	H	**7a**	0.5	75
5b	Cl	**6b**	Ph	**7b**	0.5	68

[a] Yield of pure isolated products.



Scheme 3

Table 6 Yields and Reaction Times Required for 4-(2-Oxopyrrol-3-yl)pyrazol-3-ones **8a**,**b**

Starting Material	R^2	R^3	Product	Reaction Time (h)	Yield[a] (%)
7a	H	H	**8a**	6	83
7b	Cl	Ph	**8b**	6	71

[a] Yield of pure isolated products based on **7a**,**b**.

Methyl 2-chloroacetoacetate, ethyl 2-chloroacetoacetate, phenylhydrazine, 4-chlorophenylhydrazine sulphate, dimethyl malonate, NaOMe, trifluoroacetic acid, $CuCl_2$, copper(II) trifluoromethanesulphonate are commercial materials and were used without further purification. Solvents were purchased and were used without further purification with the exception of THF which was distilled from NaOH. 1-Aryl-1,2-diazabuta-1,3-dienes **1a–c** were prepared following the typical procedure reported in literature.[7] 1,2-Diazabuta-1,3-dienes **6a**,**b** were synthesized as standard *E*/*Z* isomeric mixture according to previously reported procedure.[20,21] Petroleum ether used had bp 40–60 °C.

Melting points were determined in open capillary tubes and are uncorrected. IR-FT spectra were obtained as Nujol mulls. Mass spectra were made at an ionizing voltage of 70 eV. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Chemical shifts (δ_H) are reported relative to TMS as internal standard. All coupling constants (*J*) values are given in Hz. Chemical shifts (δ_C) are reported relative to DMSO-d_6 or $CDCl_3$ as internal standard in a broad band decoupled mode; the multiplicities were obtained using 135 and 90° DEPT experiments to aid in assignment (q = methyl, t = methylene, d = methine, s = quaternary). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; all the NH and OH exchanged with D_2O. NOE enhancement factors were determined in degassed $CDCl_3$ 0.01 M solution at 300 K, using NOEDIF pulse program of Varian. Irradiation time was 4 sec, with power level of 10. Precoated silica gel plates 0.25 mm were employed for analytical TLC and silica gel 35–70 μm for column chromatography. All new compounds showed satisfactory elemental analysis (C ±0.35; H ±0.30; N ±0.30).

Hydrazones 2a–c; General Procedure

To a magnetically stirred solution of dimethyl malonate (132.12 mg, 1 mmol) and NaOMe (27.01 mg, 0.5 mmol) in THF (5 mL), a solution of the 1-aryl-1,2-diazabuta-1,3-dienes **1a–c** (1 mmol) in THF (5 mL) was added. The reaction was allowed to stand at r.t. until the complete disappearance of the reagents (47–54 h, monitored by TLC). The solvent was evaporated under reduced pressure and products **2a–c** were purified by chromatography on a silica gel column (elution mixture: cyclohexane–EtOAc, 70:30) and then crystallized from EtOAc–petroleum ether.

Trimethyl (*E*)-3-(2-Phenylhydrazono)butane-1,1,2-tricarboxylate (2a)

Yield: 199 mg (59%); white powder (EtOAc–petroleum ether); mp 136–137 °C.

IR (Nujol): 3333, 1747, 1717 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.12 (d, *J* = 11.2 Hz, 1 H, CH), 4.43 (d, *J* = 11.2 Hz, 1 H, CH), 6.84 (t, *J* = 8.8 Hz, 1 H_{arom}), 7.01 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.05–7.26 (m, 3 H_{arom} and NH).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 14.78 (q), 51.98 (d), 52.84 (q), 53.00 (q), 53.17 (q), 53.29 (d), 113.10 (d), 120.44 (d), 129.40 (d), 138.61 (s), 145.14 (s), 168.48 (s), 168.74 (s), 170.85 (s).

MS: *m*/*z* (%) = 336 (M^+, 60), 304 (29), 272 (68), 245 (100).

Anal. Calcd for $C_{16}H_{20}N_2O_6$ (336.35): C, 57.14; H, 5.99; N, 8.33. Found: C, 57.28; H, 5.79; N, 8.39.

2-Ethyl 1,1-Dimethyl (*E*)-3-(2-phenylhydrazono)butane-1,1,2-tricarboxylate (2b)

Yield: 214 mg (61%); white powder (EtOAc–petroleum ether); mp 141–143 °C.

IR (Nujol): 3317, 1761, 1722 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.93 (s, 3 H, CH_3), 3.58 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.91 (d, *J* = 11.2 Hz, 1 H, CH), 4.10 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.18 (d, *J* = 11.2 Hz, 1 H, CH), 6.70 (t, *J* = 8.6 Hz, 1 H_{arom}), 7.01 (d, *J* = 8.6 Hz, 2 H_{arom}), 7.06–7.22 (m, 3 H_{arom} and NH).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 14.28 (q), 14.79 (q), 51.96 (d), 52.96 (q), 53.00 (q), 53.14 (d), 61.79 (t), 113.07 (d), 120.36 (d), 129.38 (d), 138.74 (s), 145.22 (s), 168.55 (s), 168.74 (s), 170.28 (s).

MS: *m*/*z* (%) = 350 (M^+, 38), 304 (43), 272 (50), 259 (18), 245 (100).

Anal. Calcd for $C_{17}H_{22}N_2O_6$ (350.38): C, 58.28; H, 6.33; N, 8.00. Found: C, 58.41; H, 6.28; N, 8.18.

Trimethyl (*E*)-3-[2-(4-Chlorophenyl)hydrazono]butane-1,1,2-tricarboxylate (2c)

Yield: 189 mg (51%); white powder (EtOAc–petroleum ether); mp 139–140 °C.

IR (Nujol): 3324, 1751, 1719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H, CH_3), 3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.11 (d, *J* = 11.2 Hz, 1 H, CH), 4.40 (d, *J* = 11.2 Hz, 1 H, CH), 6.93 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.10 (br s, 1 H, NH), 7.16 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 15.10 (q), 52.04 (d), 53.04 (q), 53.15 (q), 53.36 (q), 53.42 (d), 114.19 (d), 124.92 (s), 129.20 (d), 139.32 (s), 143.64 (s), 168.27 (s), 168.47 (s), 170.55 (s).

MS: *m*/*z* (%) = 372 (M^+ + 2, 38), 370 (M^+, 48), 340 (11), 338 (33), 308 (16), 306 (49), 281 (33), 279 (100).

Anal. Calcd for $C_{16}H_{19}ClN_2O_6$ (370.74): C, 51.83; H, 5.16; N, 7.56. Found: C, 51.92; H, 5.11; N, 7.71.

NOE Enhancement factors: CH_3{NH} 16%; NH{CH_3} 5%.

Pyrrol-2-ones 3a–c; General Procedure

To a magnetically stirred solution of hydrazones **2a–c** (1 mmol) in MeOH (10 mL) was added NaOMe (16.2 mg, 0.3 mmol). The reaction was allowed to stand at r.t. until the complete disappearance of **3a–c** (4.5–5.5 h, monitored by TLC). The solvent was evaporated under reduced pressure and the products **3a–c** were obtained as oils by chromatography on a silica gel column (elution mixture: cyclohexane–EtOAc, 60:40).

Dimethyl 1-Anilino-2-oxo-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylate (3a)

Yield: 216 mg (71%); yellow oil.

IR (Nujol): 3317, 1753, 1728, 1713 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.30 (s, 1 H, CH), 6.42 (s, 1 H, NH), 6.71 (d, *J* = 7.6 Hz, 2 H_{arom}), 6.95 (t, *J* = 7.6 Hz, 1 H_{arom}), 7.21–7.26 (m, 2 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 11.65 (q), 51.44 (q), 52.02 (d), 53.14 (q), 102.29 (s), 112.90 (d), 122.10 (d), 129.47 (d), 145.57 (s), 157.77 (s), 163.47 (s), 166.17 (s), 170.38 (s).

MS: *m*/*z* (%) = 304 (M^+, 29), 272 (100).

Anal. Calcd for $C_{15}H_{16}N_2O_5$ (304.31): C, 59.21; H, 5.30; N, 9.21. Found: C, 59.03; H, 5.44; N, 9.34.

4-Ethyl 3-Methyl 1-Anilino-2-oxo-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylate (3b)

Yield: 217 mg (68%); yellow oil.

IR (Nujol): 3308, 1741, 1731, 1706 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.48 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 4.19–4.30 (m, 3 H, CH and OCH_2CH_3), 6.26 (s, 1 H, NH), 6.75 (d, *J* = 7.6 Hz, 2 H_{arom}), 6.97 (t, *J* = 7.6 Hz, 1 H_{arom}), 7.23–7.28 (m, 2 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 11.50 (q), 13.96 (q), 53.67 (d), 53.72 (q), 60.16 (t), 106.38 (s), 112.68 (d), 122.06 (d), 129.28 (d), 145.25 (s), 160.09 (s), 162.26 (s), 168.55 (s), 171.61 (s).

MS: *m*/*z* (%) = 318 (M^+, 25), 287 (16), 242 (100).

Anal. Calcd for $C_{16}H_{18}N_2O_5$ (318.33): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.44; H, 5.78; N, 8.91.

Dimethyl 1-(4-Chloroanilino)-2-oxo-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylate (3c)
Yield: 254 mg (75%); yellow oil.

IR (Nujol): 3303, 1741, 1736, 1712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.30 (s, 1 H, CH), 6.28 (s, 1 H, NH), 6.66 (d, *J* = 8.4 Hz, 2 H_{arom}), 7.21 (d, *J* = 8.4 Hz, 2 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 11.92 (q), 51.82 (q), 52.26 (d), 53.52 (q), 102.87 (s), 114.57 (d), 127.55 (s), 129.78 (d), 144.42 (s), 157.47 (s), 163.64 (s), 166.32 (s), 170.52 (s).

MS: *m*/*z* (%) = 340 (M^+ + 2, 9), 338 (M^+, 27), 308 (33), 306 (100).

Anal. Calcd for $C_{15}H_{15}ClN_2O_5$ (338.75): C, 53.19; H, 4.46; N, 8.27. Found: C, 53.29; H, 4.33; N, 8.41.

1-Arylpyrazoles 4a–c; General Procedure
To a magnetically stirred solution of the hydrazone **2a–c** (1 mmol) in THF (10 mL) was added $CuCl_2$ (134.35 mg, 1.0 mmol) or $Cu(OTf)_2$ (361.68 mg, 1.0 mmol). The reaction was allowed to stand at r.t. until the complete disappearance of **2a–c** (6.5–23.0 h, monitored by TLC). The solvent was evaporated under reduced pressure and the products **4a–c** were obtained as oils by chromatography on a silica gel column (elution mixture: cyclohexane–EtOAc, 80:20).

Dimethyl 3-Methyl-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4a)
Yield: 129 mg (47%) using $CuCl_2$, 113 mg (41%) using $Cu(OTf)_2$; yellow oil.

IR (Nujol): 1777, 1714 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.85 (s, 6 H, 2 OCH_3), 7.44-7.49 (m, 5 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 13.69 (q), 51.97 (q), 53.53 (q), 113.37 (s), 123.95 (d), 129.02 (d), 129.57 (d), 137.91 (s), 139.08 (s), 151.44 (s), 161.98 (s), 163.27 (s).

MS: *m*/*z* (%) = 274 (M^+, 45), 242 (100).

Anal. Calcd for $C_{14}H_{14}N_2O_4$ (274.28): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.50; H, 5.21; N, 10.09.

4-Ethyl 5-Methyl 3-Methyl-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4b)
Yield: 153 mg (53%) using $CuCl_2$, 127 mg (44%) using $Cu(OTf)_2$; yellow oil.

IR (Nujol): 1751, 1712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.53 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.30 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 7.41–7.50 (m, 5 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 13.68 (q), 14.44 (q), 53.45 (q), 60.81 (t), 113.53 (s), 123.94 (d), 129.00 (d), 129.58 (d), 137.79 (s), 139.09 (s), 151.50 (s), 162.07 (s), 162.80 (s).

MS: *m*/*z* (%) = 288 (M^+, 36), 242 (100).

Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.31): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.40; H, 5.48; N, 9.79.

Dimethyl 1-(4-Chlorophenyl)-3-methyl-1*H*-pyrazole-4,5-dicarboxylate (4c)
Yield: 173 mg (56%) using $CuCl_2$, 127 mg (41%) using $Cu(OTf)_2$; yellow oil.

IR (Nujol): 1732, 1716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 7.42 (s, 4 H_{arom}).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 13.67 (q), 52.06 (q), 53.67 (q), 115.93 (s), 125.22 (d), 129.76 (d), 134.90 (s), 137.56 (s), 137.84 (s), 151.69 (s), 161.80 (s), 163.14 (s).

MS: *m*/*z* (%) = 310 (M^+ + 2, 26), 308 (M^+, 77), 279 (33), 277 (100).

Anal. Calcd for $C_{14}H_{13}ClN_2O_4$ (308.72): C, 54.47; H, 4.24; N, 9.07. Found: C, 54.39; H, 4.38; N, 9.21.

2-(3-Oxopyrazol-4-yl)malonates 5a,b; General Procedure
A solution of the hydrazone **2a–c** (1 mmol) in THF (10 mL) was refluxed with trifluoroacetic acid (0.8 mL) for 6 h until the disappearance of **2a–c** (monitored by TLC). The mixture was neutralized by addition of $NaHCO_3$ until pH ~7 and filtered. The solvent was evaporated under reduced pressure and products **5a**,**b** were purified by chromatography on a silica gel column (elution mixture: cyclohexane–EtOAc, 40:60) and then crystallized from EtOAc–petroleum ether.

Dimethyl 2-(5-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)malonate (5a)
Yield: 195 mg (64%) from **2a**, 237 mg (78%) from **2b**; white powder (EtOAc–petroleum ether); mp 64–66 °C.

IR (Nujol): 3224, 1742, 1690, 1602 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, CH_3), 3.65 (s, 6 H, 2 OCH_3), 4.54 (s, 1 H, CH), 7.06–7.18 (m, 3 H_{arom}), 7.39 (d, *J* = 7.6 Hz, 2 H_{arom}), 10.74 (br s, 1 H, NH).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 25.74 (q), 46.54 (d), 52.98 (q), 96.61 (s), 119.93 (s), 121.30 (d), 126.30 (d), 128.96 (d), 136.22 (s), 147.90 (s), 169.05 (s).

MS: *m*/*z* (%) = 304 (M^+, 63), 272 (21), 245 (100).

Anal. Calcd for $C_{15}H_{16}N_2O_5$ (304.31): C, 59.21; H, 5.30; N, 9.21. Found: C, 59.03; H, 5.44; N, 9.41.

Dimethyl 2-[2-(4-Chlorophenyl)-5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl]malonate (5b)
Yield: 274 mg (81%); white powder (EtOAc–petroleum ether); mp 75–77 °C.

IR (Nujol): 3228, 1740, 1695, 1600 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 3.71 (s, 6 H, 2 OCH_3), 4.54 (s, 1 H, CH), 7.17 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.41 (d, *J* = 8.8 Hz, 2 H_{arom}), 9.40 (br s, 1 H, NH).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 26.78 (q), 46.51 (d), 53.00 (q), 95.66 (s), 119.89 (s), 122.14 (d), 128.78 (d), 131.47 (s), 134.74 (s), 148.19 (s), 168.84 (s).

MS: *m*/*z* (%) = 340 (M^+ + 2, 15), 338 (M^+, 45), 281 (33), 279 (100).

Anal. Calcd for $C_{15}H_{15}ClN_2O_5$ (338.75): C, 53.19; H, 4.46; N, 8.27. Found: C, 53.33; H, 4.51; N, 8.11.

3-Hydrazono-1-(5-oxopyrazol-4-yl)butanes 7a,b; General Procedure
To a magnetically stirred solution of **5a**,**b** (1 mmol) and NaOMe (27.01 mg, 0.5 mmol) in THF (5 mL) was added a solution of **6a**,**b** (1.0 mmol) in THF (5 mL). The reaction was allowed to stand at r.t. for 0.5 h until the complete disappearance of the reagents (monitored by TLC). The solvent was evaporated under reduced pressure and the products **7a**,**b** were purified by chromatography on a silica gel column (elution mixture: cyclohexane–EtOAc, 70:30) and then crystallized from EtOAc–petroleum ether.

1,1-Dimethyl 2-Ethyl 3-[2-(Aminocarbonyl)hydrazono]-1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)butane-1,1,2-tricarboxylate (7a)
Yield: 367 mg (75%); white powder (EtOAc–petroleum ether); mp 177–179 °C.

IR (Nujol): 3558, 3435, 3221, 3132, 1766, 1737, 1712, 1678, 1561 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.13–1.17 (m, 3 H, OCH_2CH_3), 1.76 and 1.77 (2 s, 3 H, CH_3), 2.19 and 2.21 (2 s, 3 H, CH_3), 3.58 and 3.63 (2 s, 3 H, OCH_3), 3.65 and 3.69 (2 s, 3 H, OCH_3), 4.11–4.18 (m, 3 H, OCH_2CH_3 and CH), 4.46 and 4.48 (2 s, 1 H, CH), 6.21 (br s, 2 H, NH_2), 7.19–7.24 (m, 1 H_{arom}), 7.41–7.44 (m, 2 H_{arom}), 7.65–7.68 (m, 2 H_{arom}), 9.34 and 9.36 (s, 1 H, NH).

^{13}C NMR (100.56 MHz, DMSO-d_6): δ = 13.79 (q), 13.85 (q), 16.50 (q), 16.52 (q), 16.96 (q), 16.97 (q), 51.99 (d), 52.00 (d), 52.97 (q), 53.00 (q), 53.08 (q), 53.10 (q), 55.53 (d), 55.57 (d), 57.40 (s), 57.48 (s), 61.40 (t), 61.42 (t), 118.56 (d), 118.59 (d), 125.12 (d), 125.13 (d), 128.68 (d), 136.93 (s), 136.96 (s), 140.05 (s), 140.07 (s), 156.25 (s), 156.26 (s), 158.53 (s), 158.55 (s), 165.60 (s), 165.90 (s), 168.30 (s), 168.32 (s), 171.06 (s), 171.10 (s).

MS: *m*/*z* (%) = 490 (M^+ + 1, 19), 489 (M^+, 78), 444 (9), 430 (25), 400 (22), 341 (69), 304 (100).

Anal. Calcd for $C_{22}H_{27}N_5O_8$ (489.49): C, 53.98; H, 5.56; N, 14.31. Found: C, 53.81; H, 5.44; N, 14.38.

1,1-Dimethyl 2-Ethyl 3-[2-(Anilinocarbonyl)hydrazono]-1-[1-(4-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl]butane-1,1,2-tricarboxylate (7b)
Yield: 408 mg (68%); white powder (EtOAc–petroleum ether); mp 186–188 °C.

IR (Nujol): 3564, 3240, 3116, 1774, 1741, 1702, 1668, 1559 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.30 (m, 3 H, OCH_2CH_3), 1.97 and 1.98 (2 s, 3 H, CH_3), 2.34 and 2.35 (2 s, 3 H, CH_3), 3.66 and 3.68 (2 s, 3 H, OCH_3), 3.76 and 3.80 (2 s, 3 H, OCH_3), 4.19–4.24 (m, 2 H, OCH_2CH_3), 4.41 and 4.44 (2 s, 1 H, CH), 4.63 and 4.66 (2 s, 1 H, CH), 7.05–7.33 (m, 5 H_{arom}), 7.47–7.73 (m, 4 H_{arom}), 8.30 and 8.32 (2 s, 1 H, NH), 9.30 and 9.35 (2 s, 1 H, NH).

^{13}C NMR (100.56 MHz, $CDCl_3$): δ = 13.93 (q), 13.99 (q), 16.70 (q), 16.73 (q), 26.84 (q), 26.88 (q), 52.40 (d), 52.96 (d), 53.09 (q), 53.27 (q), 53.32 (q), 55.50 (d), 55.70 (d), 57.75 (s), 57.92 (s), 62.09 (t), 62.24 (t), 119.01 (d), 119.83 (d), 120.06 (d), 120.21 (d), 123.18 (d), 123.37 (d), 128.50 (d), 128.85 (d), 130.53 (s), 130.61 (s), 135.79 (s), 135.86 (s), 137.91 (s), 138.05 (s), 141.76 (s), 141.91 (s), 153.64 (s), 159.24 (s), 159.40 (s), 166.29 (s), 166.66 (s), 166.70 (s), 166.81 (s), 168.71 (s), 171.80 (s).

MS: *m*/*z* (%) = 601 (M^+ + 2, 11), 599 (M^+, 33), 508 (33), 506 (100).

Anal. Calcd for $C_{28}H_{30}ClN_5O_8$ (600.03): C, 56.05; H, 5.04; N, 11.67. Found: C, 56.11; H, 5.12; N, 11.58.

4-(2-Oxopyrrol-3-yl)pyrazol-3-ones 8a,b; General Procedure
To a magnetically stirred solution of **7a**,**b** (1 mmol) in MeOH (10 mL) was added NaOMe (54.02 mg, 1.0 mmol). The reaction was allowed to stand at r.t. for 6.0 h until the complete disappearance of **7a,b** (monitored by TLC). The solvent was evaporated under reduced pressure and the products **8a**,**b** were purified by chromatography on a silica gel column (elution mixture: cyclohexane–EtOAc, 70:30) and then crystallized from EtOAc–petroleum ether.

4-Ethyl 3-Methyl 1-[(Aminocarbonyl)amino]-5-methyl-3-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-2-oxo-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylate (8a)
Yield: 380 mg (83%); white powder (EtOAc–petroleum ether); mp 159–165 °C.

IR (Nujol): 3460, 3362, 3269, 1751, 1717, 1702, 1678, 1600 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.99–1.08 (m, 3 H, OCH_2CH_3), 1.98 and 2.01 (2 s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 3.58 and 3.59 (2 s, 3 H, OCH_3), 4.00–4.13 (m, 2 H, OCH_2CH_3), 5.09 (br s, 1 H, CH), 6.40 (br s, 2 H, NH_2), 7.18–7.40 (m, 1 H_{arom}), 7.39–7.47 (m, 2 H_{arom}), 7.66–7.73 (m, 2 H_{arom}), 8.81 (br s, 1 H, NH).

^{13}C NMR (100.56 MHz, DMSO-d_6): δ = 14.32 (q), 14.43 (q), 15.54 (q), 16.03 (q), 16.19 (q), 16.34 (q), 52.17 (d), 52.34 (d), 53.17 (q), 53.26 (q), 53.52 (s), 53.65 (s), 61.52 (t), 61.58 (t), 102.03 (s), 102.37 (s), 118.84 (d), 119.07 (d), 125.45 (d), 125.60 (d), 129.49 (d), 129.60 (d), 138.15 (s), 138.27 (s), 157.94 (s), 158.74 (s), 158.87 (s), 159.62 (s), 163.33 (s), 163.47 (s), 163.80 (s), 164.96 (s), 165.37 (s), 165.83 (s), 166.11 (s), 166.24 (s), 172.65 (s), 172.88 (s).

MS: *m*/*z* (%) = 458 (M^+ + 1, 21), 457 (M^+, 59), 414 (55), 398 (10), 355 (20), 309 (68), 205 (100).

Anal. Calcd for $C_{21}H_{23}N_5O_7$ (457.45): C, 55.14; H, 5.07; N, 15.31. Found: C, 55.21; H, 5.00; N, 15.51.

4-Ethyl 3-Methyl 1-[(Anilinocarbonyl)amino]-5-methyl-3-[3-methyl-5-oxo-1-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]-2-oxo-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylate (8b)
Yield: 403 mg (71%); white powder (EtOAc–petroleum ether); mp 161–166 °C.

IR (Nujol): 3458, 3340, 1749, 1710, 1698, 1665, 1595 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.03–1.11 (m, 3 H, OCH_2CH_3), 1.96 and 2.00 (2 s, 3 H, CH_3), 2.23 and 2.26 (2 s, 3 H, CH_3), 3.56 and 3.58 (2 s, 3 H, OCH_3), 4.02–4.18 (m, 2 H, OCH_2CH_3), 5.11 (br s, 1 H, CH), 7.05–7.36 (m, 5 H_{arom}), 7.48–7.57 (m, 2 H_{arom}), 7.70–7.79 (m, 2 H_{arom}), 8.36 (br s, 1 H, NH), 9.44 (br s, 1 H, NH).

^{13}C NMR (100.56 MHz, DMSO-d_6): δ = 14.34 (q), 14.47 (q), 15.54 (q), 15.99 (q), 16.23 (q), 16.40 (q), 52.22 (d), 52.43 (d), 53.19 (q), 53.32 (q), 53.57 (s), 53.68 (s), 61.55 (t), 61.59 (t), 102.07 (s), 102.38 (s), 119.01 (d), 119.09 (d), 120.03 (d), 120.11 (d), 120.22 (d), 120.43 (d), 123.18 (d), 123.33 (d), 128.86 (d), 129.01 (d), 130.41 (s), 130.55 (s), 135.79 (s), 135.81 (s), 138.11 (s), 138.21 (s), 158.00 (s), 158.69 (s), 158.99 (s), 159.51 (s), 163.31 (s), 163.49 (s), 163.91 (s), 164.93 (s), 165.40 (s), 165.91 (s), 166.13 (s), 166.27 (s), 172.69 (s), 172.91 (s).

MS: *m*/*z* (%) = 569 (M^+ + 2, 11), 568 (M^+ + 1, 8), 567 (M^+, 33), 450 (33), 448 (100).

Anal. Calcd for $C_{27}H_{26}ClN_5O_7$ (567.99): C, 57.10; H, 4.61; N, 12.33. Found: C, 57.21; H, 4.68; N, 12.28.

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