One-Pot Three-Component Reaction for Synthesis of Highly Substituted Pyrazolo[1,2-a][1,2,4]triazole Derivatives

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Abstract: A straightforward, simple and efficient method is described for the synthesis of pyrazolo[1,2-a][1,2,4]triazole derivates *via* one-pot three-component reaction between isocyanides, dialkyl acetylenedicarboxylate and 4-phenyl urazole (as a NH-acid) in acetone without using any catalyst at ambient temperature. This method offers several advantages such as high yield of products, easy work-up procedure and mild reaction conditions.

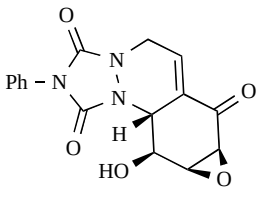
Keywords: Dialkyl acetylenedicarboxylate, isocyanide, multi-component reaction, pyrazolo[1,2-a][1,2,4]triazole, urazole.

INTRODUCTION

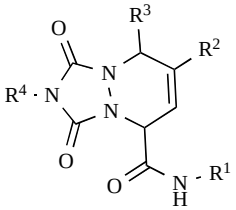
The design of novel multi-component reactions (MCRs) has attracted great attention from research groups in medicinal chemistry, drug discovery and materials science due to their significant advantages over conventional liner-type syntheses, simple procedures, environmental friendliness, atom economy, and their ability to generate architecturally complex molecules in one synthetic step [1].

In the last decades, pyrazole derivatives have played an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. They have been reported to possess wide variety of biological activities including anticancer [2], PGE2 inhibitory [3], anti-inflammatory [3, 4], anti-microbial [5], antibacterial [6], analgesic, anti-hypoxic and anti-pyretic activities [7].

On the other hand, during the last decades, heterocycles containing an urazole moiety have received considerable attention in pharmaceutical researches due to their activities such as anticonvulsant [8], fungicidal [9], inhibitor of HSP induction [10], thrombolin inhibitor and protease inhibitor (Scheme **1**) [11].



Inhibitore of HSP induction[10]



Protease inhibitor[11b]

Scheme 1.

In the recent years, many procedures have been described in the literature for preparation of heterocyclic compounds by the isocyanide-based multi-component reactions [12-23]. As a result, it is necessary to further develop more efficient procedures, which allow the ready synthesis of urazole polycyclic systems. In continuing our interest in isocyanide-based multi-component reactions [24-28], here we report a simple and efficient synthesis of dialkyl 7-(alkyl or arylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo [1,2-a][1,2,4]triazole-5,6-dicarboxylate **4** from one-pot three-component reaction between isocyanide **1**, dialkyl acetylenedicarboxylate **2** and 4-phenyl urazole **3** without using any catalyst at ambient temperature in acetone (Scheme **2**).

RESULTS AND DISCUSSION

First of all, to optimize the reaction conditions, the reaction of 2,6-dimethylphenyl isocyanide (1 mmol), dimethyl acetylenedicarboxylate (1mmol) and 4-phenyl urazole (1 mmol) was selected as a model reaction, and its behavior was studied in the different solvents at ambient temperature. The results are summarized in Table **1**. As it is shown in Table **1**, the best result was obtained in acetone. When the reaction was carried out under solvent-free conditions, the product was obtained in a moderate yield (41 %) that may be due to the lack of effective interaction between reactants.

Using the optimized reaction conditions, several reactions between isocyanide **1**, dialkyl acetylenedicarboxylate **2** and urazole **3** were examined, and the results are summarized in Table **2**. All reactions proceeded smoothly at ambient temperature in acetone, to produce the pyrazolo[1,2-a][1,2,4]triazole **4** within 24 h in 54-89 % yields. TLC and ^{1}H NMR spectra of the crude products clearly indicated formation of pyrazolo[1,2-a][1,2,4]triazole **4**.

The essential structures of the products **4a-h** were characterized from their elemental analysis, IR, ^{1}H and ^{13}C NMR, and mass spectra. The mass spectra of these compounds showed molecular ion peaks at appropriate *m/z* values, and initial fragmentation involving the loss of the side chains.

The ^{1}H NMR spectrum of compound **4a** exhibited two singlets at δ 2.33 and 2.40 ppm for methyl protons on

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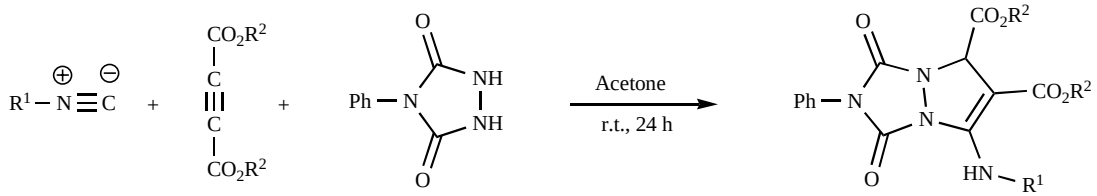


1 **2** **3** **4**

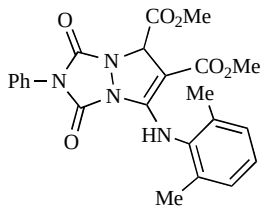
Scheme 2. Synthesis of pyrazolo[1,2-a][1,2,4]triazole **4**

Table 1. Optimization of the Reaction Conditions for the Reaction of 2,6-dimethylphenyl Isocyanide, Dimethyl Acetylenedicarboxylate and 4-phenyl Urazole at Ambient Temperature

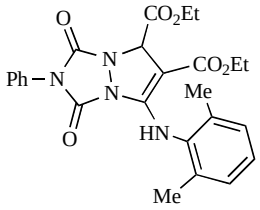
Entry	Solvent	Time (h)	Yield (%)[a]
1	CH_3CN	24	73
2	EtOH	24	35
3	MeOH	24	40
4	Acetone	24	89
5	Solvent-free	48	41

[a]Isolated Yield.

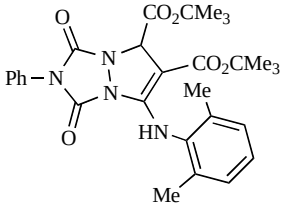
Table 2. Synthesis of Pyrazolo[1,2-a][1,2,4]triazole 4



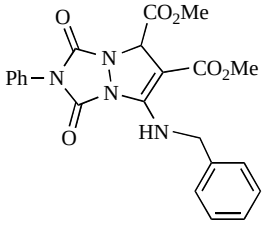
4a



4b



4c



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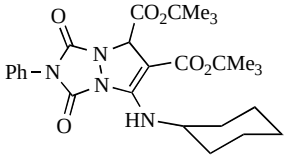

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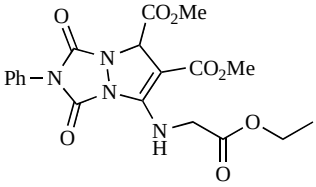

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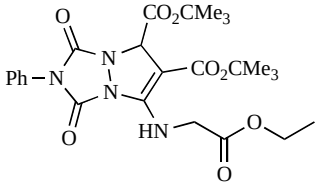
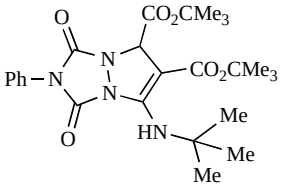


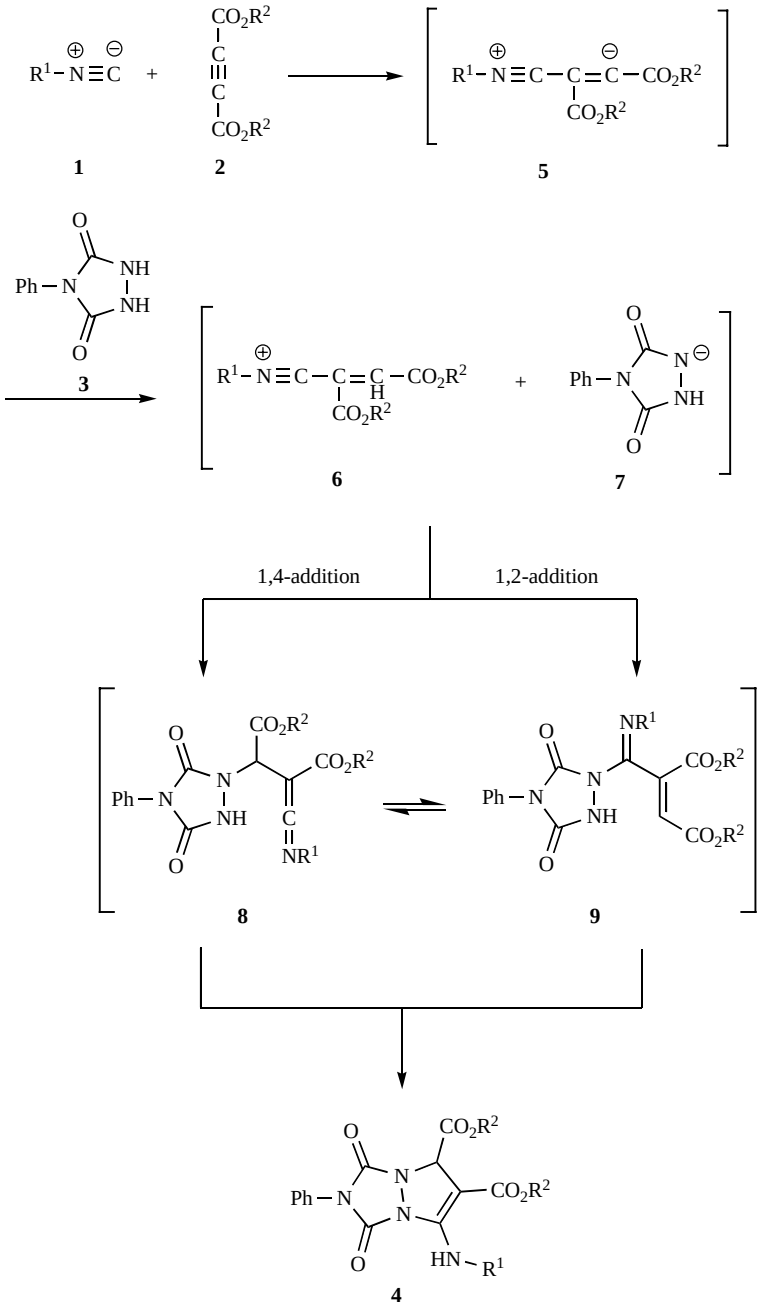
4g



4h

Entry	R^1	R^2	Product	Yield (%)[a]
1	2,6-diMe-C_6H_3	Me	**4a**	89
2	2,6-diMe-C_6H_3	Et	**4b**	85
3	2,6-diMe-C_6H_3	CMe_3	**4c**	88
4	$PhCH_2$	Me	**4d**	70
5	cyclohexyl	CMe_3	**4e**	54
6	$EtOOCCH_2$	Me	**4f**	81
7	$EtOOCCH_2$	CMe_3	**4g**	59
8	CMe_3	CMe_3	**4h**	84

[a]Isolated yields.



Scheme 3. The proposed mechanism for synthesis of pyrazolo[1,2-a][1,2,4]triazole.

benzene ring. The methyl protons of carbmethoxy groups were observed as two singlets at δ 3.80 and 3.87 ppm and the methine proton appeared as singlet at δ 5.47 ppm. The aromatic protons were shown as two multiplets at δ 7.12-7.17 ppm and δ 7.34-7.45 ppm. A broad signal for the NH proton at δ 8.61 ppm, indicated intramolecular hydrogen bond formation with vicinal carbonyl group. The ^{13}C NMR spectrum of compound **4a** showed 20 distinct resonances consistent with the pyrazolotriazole structure. The structural assignments of compounds **4a-h** made on the basis of NMR spectra were supported by their IR spectra. The IR spectrum of these compounds, in general, exhibited the strong carbonyl absorption band around 1769-1650 cm^{-1} and fairly broad NH absorption at nearly 3320-3255 cm^{-1}.

Although the mechanism of this reaction has not been established experimentally, on the basis of the proposed mechanism in the literature [12-14], it is reasonable to assume that compound **4** resulted from initial addition of the isocyanide **1** to dialkyl acetylenedicarboxylate **2** and subsequent protonation of the 1:1 adduct **5** by 4-phenyl urazole **3** (NH-acid) affording the vinylisonitrilium cation **6**. Then, vinylisonitrilium cation **6** is probably attacked by the anion of the NH-acid **7** on the two possible electrophilic sites (1,2-addition and 1,4-conjugate addition) to generate two possible intermediate **8** and **9** in equilibrium with each other. Finally, these intermediates apparently isomerize under the reaction conditions, to produce the fused heterocyclic system **4** (Scheme **3**).

EXPERIMENTAL

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^1H and ^{13}C NMR spectra were obtained on BRUKER DRX-250 and 400 AVANCE instruments with $CDCl_3$ as a solvent. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. All reagents and solvents were obtained from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and were used without further purification.

General Procedure for the Synthesis of Compounds 4

To a magnetically stirred solution of isocyanide **1** (1mmol) and 4-phenyl urazole **3** (1mmol) in acetone (20 mL) was added dropwise a mixture of dialkyl acetylenedicarboxylate **2** (1 mmol) in acetone (2 mL) at ambient temperature over 15 min. The reaction mixture was stirred at ambient temperature for 24 h. After completion of the reaction, as indicated by TLC, the solvent removed under reduced pressure and the solid residue was washed with diethyl ether (3 × 2 mL) to give the pure product **4**.

Dimethyl 7-(2,6-dimethylphenylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4a**): White powder, mp 153-155 °C. IR (KBr) (υ_{max}/cm^{-1}): 3291 (NH), 2984, 1758, 1721, 1660, 1620; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.33 (3H, s, CH_3), 2.40 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.47 (1H, s, CHN), 7.12-7.17 (3H, m, ArH), 7.34-7.45 (5H, m, ArH), 8.61 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.63 (CH_3), 18.97 (CH_3), 51.39 (OCH_3), 53.18 (OCH_3), 62.02 (NCH), 82.50 (*C*=C–N), 126.14, 127.76, 128.31, 128.41, 128.90, 129.28, 135.34, 136.25, 136.26, 147.85 (C=*C*–N), 150.65 (NC=O), 153.31 (NC=O), 165.55 (C=O), 169. 41 (C=O); MS *m/z* (%): 450 (M$^+$, 9), 391 (100), 330 (14), 240 (48), 183 (18), 149 (33), 119 (40), 91 (8), 77 (15); Anal. Calcd for $C_{23}H_{22}N_4O_6$: C 61.33, H 4.92, N 12.44; Found: C 61.49, H 4.99, N 12.49.

Diethyl 7-(2,6-dimethylphenylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4b**): white powder, mp 125-127 °C. IR (KBr) (υ_{max}/cm^{-1}): 3259 (NH), 2980, 1750, 1728, 1663, 1617; ^1H NMR (250 MHz, $CDCl_3$) δ = 1.31 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.32 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 2.31 (3H, s, CH_3), 2.37 (3H, s, CH_3), 4.13-4.33 (4H, m, $2OCH_2CH_3$), 5.43 (1H, s, CHN), 7.07-7.15 (3H, m, ArH), 7.34-7.39 (5H, m, ArH), 8.61 (1H, br s, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 14.12 (OCH_2CH_3), 14.42 (OCH_2CH_3), 18.59 (CH_3), 18.96 (CH_3), 60.04 (OCH_2CH_3), 62.17 (NCH), 62.26 (OCH_2CH_3), 82.12 (*C*=C–N), 126.05, 127.65, 128.25, 128.33, 128.77, 129.19, 135.31, 136.21, 136.30, 147.80 (C=*C*–N), 15057 (NC=O), 153.26 (NC=O), 165.33 (C=O), 168.90 (C=O); MS *m/z* (%): 478 (M$^+$, 5), 405 (100), 377 (3), 359 (2), 302 (15), 240 (39), 212 (16), 149 (84), 119 (31), 91 (31), 77 (27), 57 (53); Anal. Calcd for $C_{25}H_{26}N_4O_6$: C 62.75, H 5.48, N 11.71; Found: C 62.68, H 5.43, N 11.77.

Di-tert-butyl 7-(2,6-dimethylphenylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4c**): White powder, mp 164-166 °C. IR (KBr) (υ_{max}/cm^{-1}): 3270, (NH), 2978, 1765, 1729, 1657, 1622; ^1H NMR (250 MHz, $CDCl_3$) δ = 1.51 (9H, s, $C(CH_3)_3$), 1.54 (9H, s, $C(CH_3)_3$), 2.30 (3H, s, CH_3), 2.38 (3H, s, CH_3), 5.23 (1H, s, CHN), 7.05-7.08 (3H, m, ArH), 7.30-7.37 (5H, m, ArH), 8.62 (1H, br s, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 18.54 (CH_3), 19.14 (CH_3), 27.98 ($C(CH_3)_3$), 28.52 ($C(CH_3)_3$), 63.37 (CHN), 80.98 ($C(CH_3)_3$), 83.13 ($C(CH_3)_3$), 83.74 (*C*=C–N), 125.98, 127.41, 128.21, 128.60, 129.15, 130.82, 135.21, 136.53, 147.80 (C=*C*–N), 150.20 (NC=O), 153.25 (NC=O), 165.25 (C=O), 167.89 (C=O); MS *m/z* (%): 534 (M$^+$, 2), 433 (26), 405 (11), 377 (51), 240 (24), 212 (11), 149 (78), 119 (16), 91 (35), 73 (31), 57 (100); Anal. Calcd for $C_{29}H_{34}N_4O_6$: C 65.15, H 6.41, N 10.48; Found: C 65.27, H 6.50, N 10.56.

Dimethyl 7-(benzylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4d**): Yellow powder, mp 95-97 °C. IR (KBr) (υ_{max}/cm^{-1}): 3255 (NH), 2982, 1758, 1728, 1650, 1620; ^1H NMR (250 MHz, $CDCl_3$) δ = 3.73 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.92 (2H, d, *J* = 5.5 Hz, CH_2), 5.35 (1H, s, CHN), 7.30-7.42 (5H, m, ArH), 7.46-7.50 (5H, m, ArH), 7.61 (1H, br s, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 50.70 (CH_2), 51.21 (OCH_3), 53.08 (OCH_3), 62.14 (CHN), 81.50 (*C*=C–N), 126.09, 127.37, 127.94, 128.89, 129.08, 129.38, 130.69, 137.30, 149.08 (C=*C*–N), 150.94 (NC=O), 153.12 (NC=O), 165.51 (C=O), 169.16 (C=O); MS *m/z* (%): 437 (M+1, 5), 405 (3), 377 (100), 226 (7), 140 (3), 119 (15), 91 (72); Anal. Calcd for $C_{22}H_{20}N_4O_6$: C 60.55, H 4.62, N 12.84; Found: C 60.82, H 4.59, N 12.90.

Di-tert-butyl 7-(cyclohexylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4e**): White powder, mp 178-180 °C. IR (KBr) (υ_{max}/cm^{-1}): 3320, (NH), 2995, 1769, 1724, 1668, 1635; ^1H NMR (250 MHz, $CDCl_3$) δ = 1.28-2.20 (10H, m. CH_2 cyclohexyl), 1.50 (9H, s, $C(CH_3)_3$), 1.53 (9H, s, $C(CH_3)_3$), 4.07 (1H, m, NCH cyclohexyl), 5.15 (1H, s, CHN), 7.17 (1H, br, NH), 7.44-7.53 (5h, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.60, 25.38, 25.47 (CH_2 cyclohexyl), 27.95 ($C(CH_3)_3$), 28.50 ($C(CH_3)_3$), 33.28 (CH_2 cyclohexyl), 54.15 (NCH_2 cyclohexyl), 62.98 (CHN), 81.05 ($C(CH_3)_3$), 83.30 ($C(CH_3)_3$), 87.96 (*C*=C–N), 125.94, 129.22, 129.37, 130.61, 149.14 (C=*C*–N), 149.77 (NC=O), 153.50 (NC=O), 165.70 (C=O), 169.38 (C=O); MS *m/z* (%): 512 (M$^+$, 1), 510 (12), 368 (53), 313 (34), 236 (60), 211 (19), 177 (35), 119 (39), 97 (65), 57 (100); Anal. Calcd for $C_{27}H_{36}N_4O_6$: C 63.26, H 7.08, N 10.93; Found: C 63.49, H 7.17, N 11.02.

Dimethyl 7-((ethoxycarbonyl)methylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4f**): Yellow powder, mp 110-112 °C. IR (KBr) (υ_{max}/cm^{-1}): 3320 (NH), 2990, 1762, 1726, 1660, 1624; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.30 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.24-4.29 (m, 2H, NCH_2), 4.44-4.60 (m, 2H, OCH_2CH_3), 5.38 (s, 1H, CHN), 7.42-7.54 (m, 5H, ArH), 7.78 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.11 (OCH_2CH_3), 47.75 (NCH_2), 51.37 (OCH_3), 53.15 (OCH_3), 61.85 (OCH_2CH_3), 62.17 (CHN), 82.25 (*C*=C–N), 126.07, 129.20,

129.37, 130.56, 149.21 (C=*C*–N), 150.35 (NC=O), 152.90 (NC=O), 165.10 (C=O), 169.04 (C=O), 169.44 (C=O); MS *m/z* (%): 432 (M^+, 7), 373 (100), 355 (15), 248 (39), 227 (24), 171 (30), 157 (8), 119 (26), 77 (19); Anal. Calcd for $C_{19}H_{20}N_4O_8$: C 52.78, H 4.66, N 12.96; Found: C 52.95, H 4.74, N 13.05.

Di-tert-butyl 7-((ethoxycarbonyl)methylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4g**): White powder, mp 182-185 °C. IR (KBr) (υ_{max}/cm^{-1}): 3328 (NH), 2990, 1758, 1720, 1667, 1633; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31 (3H, t, J = 6.9 Hz, OCH_2CH_3), 1.51 (9H, s, $C(CH_3)_3$), 1.53 (9H, s, $C(CH_3)_3$), 4.24-4.56 (4H, m, NCH_2, OCH_2CH_3), 5.19 (1H, s, CHN), 7.39-7.51 (5H, m, ArH), 7.74 (1H, br, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.98 (OCH_2CH_3), 27.10 ($C(CH_3)_3$), 28.68 ($C(CH_3)_3$), 47.96 (NCH_2), 60.97 (OCH_2CH_3), 63.40 (CHN), 80.56 ($C(CH_3)_3$), 82.99 ($C(CH_3)_3$), 84.11 (*C*=C–N), 126.00, 129.18, 129.52, 130.71, 149.45 (C=*C*–N), 149.72 (NC=O), 153.18 (NC=O), 165.21 (C=O), 168.92 (C=O), 169.51 (C=O); MS *m/z* (%): 515 (M^+-1, 1), 415 (5), 359 (13), 256 (15), 213 (10), 177 (100), 149 (45), 119 (88), 69 (80), 43 (750; Anal. Calcd for $C_{25}H_{32}N_4O_8$: C 58.13, H 6.24, N 10.85; Found: C 58.34, H 6.32, N 10.96.

Di-tert-butyl 7-(tert-butylamino)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-5,6-dicarboxylate (**4h**): White powder, mp 174-176 °C. IR (KBr) (υ_{max}/cm^{-1}): 3302 (NH), 2975, 1747, 1730, 1664, 1615; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.47 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$), 5.13 (1H, s, CHN), 7.41 (1H, br s, NH) 7.44-7.49 (5H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 27.93 ($OC(CH_3)_3$), 28.41 ($OC(CH_3)_3$), 30.35 ($NC(CH_3)_3$), 57.52 ($NC(CH_3)_3$), 63.56 (CHN), 80.84 ($OC(CH_3)_3$), 83.13 ($OC(CH_3)_3$), 88.31 (*C*=C–N), 125.97, 128.71, 129.26, 131.03, 149.35 (C=*C*–N), 149.70 (NC=O), 154.00 (NC=O), 164.65 (C=O), 167.92 (C=O); MS *m/z* (%): 486 (M^+, 5), 429 (11), 405 (65), 385 (43), 284 (7), 227 (15), 212 (10), 147 (8), 119 (21), 91 (41), 57 (100); Anal. Calcd for $C_{25}H_{34}N_4O_6$: C 61.71, H 7.04, N 11.51; Found: C 61.90, H 7.13, N 11.44.

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