# One-Pot Three-Component Synthesis of Highly Functionalized 2,3-Dihydro-1,3-dioxo-1*H*,5*H*-pyrazolo[1,2-*a*][1,2,4]triazoles

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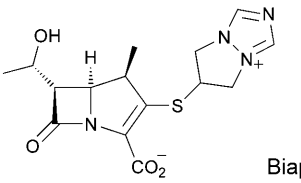
The reactive 1:1 zwitterionic intermediate formed by the addition of isocyanides to dialkyl acetylenedicarboxylates was trapped with 4-arylurazoles to produce the highly functionalized pyrazolo[1,2-*a*][1,2,4]triazoles **5** in good yields (*Table*). The structures of the products **5a**–**h** were corroborated spectroscopically (IR, $^1$H- and $^{13}$C-NMR), by EI-MS, and elemental analysis. A possible mechanism for this reaction is proposed (*Scheme*).

**Introduction.** – The development of simple synthetic routes towards widely used organic compounds from readily available starting materials is one of the major tasks in organic synthesis [1]. Bridgehead-nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities [2]. The interest in fused systems of the 1,5,7-triazabicyclo[3.3.0]octane type, with two ring-junction N-atoms and one extra N-atom, stems from the occurrence of partially or fully saturated pyrazolo[1,2-*a*]-[1,2,4]triazole ring systems in biologically active compounds [3–5]. For example, biapenem (**1**), is a broad-spectrum carbapenem active against both aerobic and anaerobic bacteria [6].



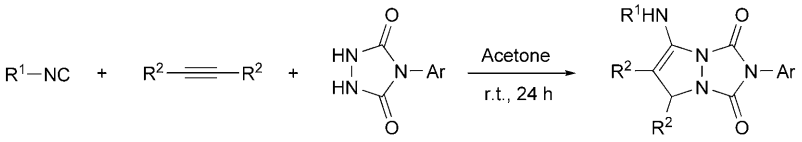

Biapenem (**1**)

So far, the most-common synthetic methods for the preparation of pyrazolo[1,2-*a*]-[1,2,4]triazole ring systems involve: *i*) ring synthesis from non-heterocyclic precursors [7]; *ii*) formation of a single bond [8]; *iii*) formation of two bonds *via* [3+2] atom fragments, one bond (or both) being adjacent to the ring-junction N-atom(s) [9]; or *iv*) formation of two bonds *via* [4+1] atom fragments, one bond being adjacent to a ring-junction N-atom [10]. As far as we know, there is no report concerning the synthesis of pyrazolo[1,2-*a*][1,2,4]triazoles by formation of *three* bonds. As part of our current studies on the development of new routes in heterocyclic synthesis [11–15], we would like to

report herein a simple method for the preparation of highly functionalized pyrazolo[1,2-*a*][1,2,4]triazoles by formation of three bonds from [1+2+2] atom fragments.

**Results and Discussion.** – We found that a mixture of the isocyanides **2**, the dialkyl acetylenedicarboxylates **3**, and the 4-arylurazoles **4** undergo a smooth 1:1:1 addition reaction in acetone at ambient temperature to provide the pyrazolo[1,2-*a*][1,2,4]triazoles **5** in 73–87% yield (*Table*). The structures of the isolated products were corroborated by IR, $^1$H- and $^{13}$C-NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of, *e.g.*, **5a** displayed the $M^+$ signal at *m*/*z* 471, which is consistent with the proposed 1:1:1 adduct of *tert*-butyl isocyanide (**2a**), dimethyl acetylenedicarboxylate (**3a**), and 4-(3,4-dichlorophenyl)urazole (**4a**). The $^1$H-NMR spectrum of **5a** exhibited four sharp *singlet*s arising from the *t*-Bu group ($\delta$(H) 1.43), two MeO functions ($\delta$(H) 3.68, 3.72), and one methine ($\delta$(H) 5.25). A broad signal at $\delta$(H) 7.05 was observed for the NH group, along with characteristic *signals* for three aromatic H-atoms. The $^1$H-decoupled $^{13}$C-NMR spectrum of **5a** showed 17 distinct resonances, in agreement with the proposed structure. Partial assignment of these resonances are given in *Exper. Part.*

Table. *One-Step Three-Component Preparation of Compounds* **5a**–**h**. For details, see *Exper. Part.*



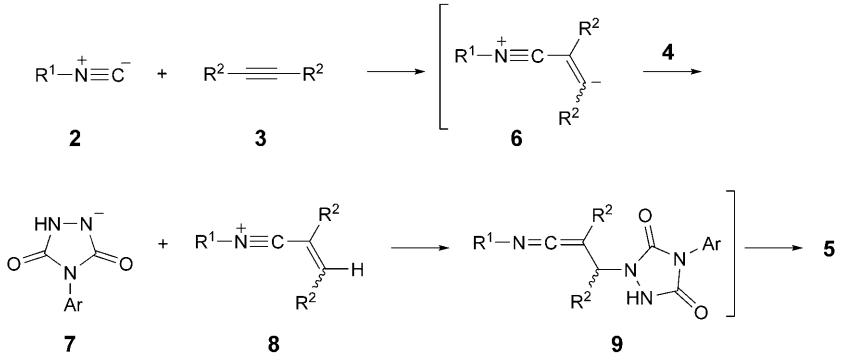

**2** **3** **4** **5**

| Series | $R^1$ | $R^2$ | Ar | Yield [%] |
|---|---|---|---|---|
| **a** | *t*-Bu | $MeO_2C$ | 3,4-$Cl_2C_6H_3$ | 77 |
| **b** | *t*-Bu | $EtO_2C$ | 3,4-$Cl_2C_6H_3$ | 75 |
| **c** | *t*-Bu | $MeO_2C$ | $C_6H_5$ | 87 |
| **d** | *t*-Bu | $EtO_2C$ | $C_6H_5$ | 73 |
| **e** | $C_6H_{11}$ | $MeO_2C$ | 3,4-$Cl_2C_6H_3$ | 85 |
| **f** | $C_6H_{11}$ | $EtO_2C$ | 3,4-$Cl_2C_6H_3$ | 79 |
| **g** | $C_6H_{11}$ | $MeO_2C$ | $C_6H_5$ | 84 |
| **h** | $C_6H_{11}$ | $EtO_2C$ | $C_6H_5$ | 82 |

The $^1$H- and $^{13}$C-NMR spectra of the products **5b**–**h** were similar to those of **5a**, except for the 2-aryl substituents, the 7-alkylamino function, and the ester groups in positions 5 and 6, respectively; they all exhibited characteristic signals with appropriate chemical shifts and coupling constants.

On the basis of the well-established chemistry of isocyanides [16–20], mechanistically, it is reasonable to assume that the pyrazolo[1,2-*a*][1,2,4]triazoles **5** result from initial addition of the isocyanide to the acetylenedicarboxylate, followed by subsequent protonation of the resulting 1:1 zwitterionic adduct **6** by the 4-arylurazole **4** (*Scheme*). The resulting anion **7** would then react with the cation **8** to the ketenimine **9**, which is cyclized, under these reaction conditions, to the observed heterocycles **5**.

*Scheme*



In summary, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of 4-arylurazoles provides a simple one-pot procedure for the efficient synthesis of polyfunctional pyrazolo[1,2-*a*][1,2,4]triazoles of potential synthetic and pharmacological interest. Our method has the advantage that it can be performed under neutral conditions, requiring no activation or modification of the starting materials.

This research project was supported by the *Research Council of the University of Tehran* (No. 6102036/1/02).

## Experimental Part

*General.* Dimethyl and diethyl acetylenedicarboxylates, as well as *tert*-butyl and cyclohexyl isocyanides were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. The compounds **4** were prepared according to a literature procedure [21]. Column chromatography (CC): silica gel *60* (*Merck*). Melting points (m.p.): *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in $cm^{-1}$. $^1H$- and $^{13}C$-NMR spectra: *Bruker DRX-500-Avance* instrument; at 500.1 and 125.8 MHz, resp., in $CDCl_3$; $\delta$ in ppm rel. to $Me_4Si$ (=0 ppm), $J$ in Hz. EI-MS (20 eV): *Finnigan MAT-8430* mass spectrometer; in *m/z* (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

*General Procedure for the Preparation of Compounds* **5**. To a magnetically stirred soln. of **3** (1 mmol) and **4** (1 mmol) in anh. acetone (6 ml) was added dropwise a soln. of **2** (1 mmol) in anh. acetone (2 ml) at r.t. over 10 min. The mixture was stirred for 24 h. The solvent was removed, and the crude products were purified by CC ($SiO_2$; hexane/AcOEt 3:1) and recrystallization (hexane/AcOEt 1:1).

*Dimethyl 7-[(*tert*-Butyl)amino]-2-(3,4-dichlorophenyl)-2,3-dihydro-1,3-dioxo-1*H*,5*H*-pyrazolo[1,2-*a*]-[1,2,4]triazole-5,6-dicarboxylate* (**5a**). Yield: 77%. Pale-yellow crystals. M.p. 131–135°. IR (KBr): 3300 (NH); 1794*m*, 1744*s*, 1675 (C=O); 1606, 1464, 1436, 1374, 1268, 1216, 1122, 1087, 1023, 785. $^1H$-NMR (500 MHz, $CDCl_3$): 1.43 (*s*, 9 H); 3.68 (*s*, 3 H); 3.72 (*s*, 3 H); 5.25 (*s*, 1 H); 7.05 (br. *s*, 1 H); 7.34 (*dd*, $J$=2.2, 8.6, 1 H); 7.49 (*d*, $J$=8.6, 1 H); 7.61 (*d*, $J$=2.2, 1 H). $^{13}C$-NMR (125 MHz, $CDCl_3$): 30.25; 51.18; 53.07; 57.94; 62.16; 85.54; 125.01; 127.61; 130.15; 130.83; 132.99; 133.18; 148.45; 149.93; 153.11; 165.27; 169.10. EI-MS: 471 (4, $M^+$), 411 (49), 355 (100), 255 (9), 240 (12), 208 (13), 168 (14), 136 (15), 57 (41), 41 (30), 29 (18). Anal. calc. for $C_{19}H_{20}Cl_2N_4O_6$ (471.30): C 48.42, H 4.28, N 11.89; found: C 48.6, H 4.4, N 11.7.

*Diethyl 7-[(*tert*-Butyl)amino]-2-(3,4-dichlorophenyl)-2,3-dihydro-1,3-dioxo-1*H*,5*H*-pyrazolo[1,2-*a*]-[1,2,4]triazole-5,6-dicarboxylate* (**5b**). Yield: 75%. Pale-yellow crystals. M.p. 90–102°. IR (KBr): 3250

(NH); 1801*m*, 1753*s*, 1668 (C=O); 1614, 1477, 1380, 1335, 1221, 1096, 1028, 874, 646. $^1$H-NMR (500 MHz, $CDCl_3$): 1.16 (*t*, *J* = 7.1, 3 H); 1.18 (*t*, *J* = 7.1, 3 H); 1.37 (*s*, 9 H); 4.05 (*dq*, *J* = 10.8, 7.1, 1 H); 4.12 (*q*, *J* = 7.1, 2 H); 4.14 (*dq*, *J* = 10.8, 7.1, 1 H); 5.19 (*s*, 1 H); 6.97 (br. *s*, 1 H); 7.31 (*dd*, *J* = 2.4, 8.6, 1 H); 7.43 (*d*, *J* = 8.6, 1 H); 7.57 (*d*, *J* = 2.4, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 14.05; 14.33; 30.28; 57.85; 59.97; 62.28; 62.41; 86.13; 124.96; 127.58; 130.24; 130.81; 132.92; 133.17; 148.46; 149.81; 153.13; 164.93; 168.69. EI-MS: 499 (11, $M^+$), 443 (10), 425 (59), 369 (100), 341 (6), 182 (7), 154 (13), 57 (60), 41 (31), 29 (74). Anal. calc. for $C_{21}H_{24}Cl_2N_4O_6$ (499.35): C 50.51, H 4.84, N 11.22; found: C 50.8, H 5.0, N 11.0.

*Dimethyl 7-[(*tert-*Butyl)amino]-2,3-dihydro-1,3-dioxo-2-phenyl-1*H,5H-*pyrazolo[1,2-*a*][1,2,4]triazole-5,6-dicarboxylate* (**5c**). Yield: 87%. Colorless crystals. M.p. 129–131°. IR (KBr): 3285 (NH); 1788*m*, 1735*s*, 1652 (C=O); 1606, 1488, 1449, 1400, 1365, 1223, 1148, 1092, 765. $^1$H-NMR (500 MHz, $CDCl_3$): 1.40 (*s*, 9 H); 3.64 (*s*, 3 H); 3.68 (*s*, 3 H); 5.24 (*s*, 1 H); 7.06 (br. *s*, 1 H); 7.27–7.35 (*m*, 1 H); 7.37–7.40 (*m*, 4 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 30.30; 51.12; 52.95; 57.86; 62.13; 85.26; 126.09; 128.93; 129.30; 130.78; 149.24; 150.28; 153.82; 165.45; 169.16. EI-MS: 402 (2, $M^+$), 343 (70), 287 (100), 228 (7), 168 (18), 136 (20), 57 (17), 41 (15), 29 (6). Anal. calc. for $C_{19}H_{22}N_4O_6$ (402.41): C 56.71, H 5.51, N 13.92; found: C 56.7, H 5.7, N 13.6.

*Diethyl 7-[(*tert-*Butyl)amino]-2,3-dihydro-1,3-dioxo-2-phenyl-1*H,5H-*pyrazolo[1,2-*a*][1,2,4]triazole-5,6-dicarboxylate* (**5d**). Yield: 73%. Colorless crystals. M.p. 68–70°. IR (KBr): 3280 (NH); 1786*m*, 1732*s*, 1651 (C=O); 1606, 1435, 1399, 1328, 1211, 1089, 1023, 769. $^1$H-NMR (500 MHz, $CDCl_3$): 1.18 (*t*, *J* = 7.1, 3 H); 1.19 (*t*, *J* = 7.1, 3 H); 1.41 (*s*, 9 H); 4.07 (*dq*, *J* = 10.7, 7.1, 1 H); 4.13 (*q*, *J* = 7.1, 2 H); 4.14 (*dq*, *J* = 10.7, 7.1, 1 H); 5.23 (*s*, 1 H); 7.04 (br. *s*, 1 H); 7.28–7.34 (*m*, 1 H); 7.36–7.40 (*m*, 4 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 14.05; 14.34; 30.31; 57.77; 59.86; 62.12; 62.34; 85.88; 126.03; 128.83; 129.25; 130.86; 149.23; 150.16; 153.81; 165.09; 168.77. EI-MS: 431 (4, $[M+1]^+$), 383 (10), 357 (75), 301 (100), 273 (8), 182 (6), 154 (13), 111 (5), 57 (17), 41 (15), 29 (27). Anal. calc. for $C_{21}H_{26}N_4O_6$ (430.46): C 58.60, H 6.09, N 13.02; found: C 58.7, H 6.2, N 12.9.

*Dimethyl 7-(Cyclohexylamino)-2-(3,4-dichlorophenyl)-2,3-dihydro-1,3-dioxo-1*H,5H-*pyrazolo[1,2-*a*][1,2,4]triazole-5,6-dicarboxylate* (**5e**). Yield: 85%. Pale-yellow crystals. M.p. 147–151°. IR (KBr): 3280 (NH); 1783*m*, 1734*s*, 1666 (C=O); 1608, 1521, 1464, 1398, 1222, 1125, 1095, 1029, 800, 779. $^1$H-NMR (500 MHz, $CDCl_3$): 1.18–2.00 (*m*, 10 H); 3.63 (*s*, 3 H); 3.68 (*s*, 3 H); 3.96 (*m*, 1 H); 5.20 (*s*, 1 H); 7.23 (br. *s*, 1 H); 7.30 (*dd*, *J* = 2.2, 8.7, 1 H); 7.44 (*d*, *J* = 8.7, 1 H); 7.57 (*d*, *J* = 2.2, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 24.39; 24.44; 25.16; 33.76; 34.16; 50.95; 52.96; 55.96; 61.82; 80.70; 124.99; 127.55; 130.17; 130.77; 132.91; 133.08; 147.81; 149.96; 152.30; 165.41; 169.16. EI-MS: 497 (3, $M^+$), 437 (100), 383 (10), 355 (42), 301 (6), 281 (11), 266 (11), 206 (23), 168 (12), 140 (15), 55 (30), 41 (22), 29 (10). Anal. calc. for $C_{21}H_{22}Cl_2N_4O_6$ (497.33): C 50.72, H 4.46, N 11.27; found: C 50.9, H 4.6, N 11.2.

*Diethyl 7-(Cyclohexylamino)-2-(3,4-dichlorophenyl)-2,3-dihydro-1,3-dioxo-1*H,5H-*pyrazolo[1,2-*a*][1,2,4]triazole-5,6-dicarboxylate* (**5f**). Yield: 79%. Pale-yellow crystals. M.p. 113–116°. IR (KBr): 3365 (NH); 1783*m*, 1736*s*, 1669 (C=O); 1622, 1520, 1464, 1401, 1339, 1288, 1219, 1198, 1157, 1088, 1026, 776. $^1$H-NMR (500 MHz, $CDCl_3$): 1.18 (*t*, *J* = 7.1, 3 H); 1.19 (*t*, *J* = 7.1, 3 H); 1.20–2.01 (*m*, 10 H); 3.90–4.20 (*m*, 5 H); 5.21 (*s*, 1 H); 7.26 (br. *s*, 1 H); 7.33 (*dd*, *J* = 8.6, 2.3, 1 H); 7.46 (*d*, *J* = 8.6, 1 H); 7.60 (*d*, *J* = 2.3, 1 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 14.03; 14.38; 24.40; 24.45; 25.20; 33.75; 34.22; 55.88; 59.69; 62.08; 62.20; 81.11; 124.97; 127.54; 130.24; 130.78; 132.88; 133.11; 147.80; 149.82; 152.34; 165.15; 168.77. EI-MS: 525 (6, $M^+$), 479 (3), 451 (100), 369 (30), 309 (47), 280 (50), 264 (13), 220 (41), 187 (14), 161 (15), 55 (39), 41 (27), 29 (59). Anal. calc. for $C_{23}H_{26}Cl_2N_4O_6$ (525.39): C 52.58, H 4.99, N 10.66; found: C 52.6, H 5.1, N 10.6.

*Dimethyl 7-(Cyclohexylamino)-2,3-dihydro-1,3-dioxo-2-phenyl-1*H,5H-*pyrazolo[1,2-*a*][1,2,4]triazole-5,6-dicarboxylate* (**5g**). Yield: 84%. Colorless crystals. M.p. 85–88°. IR (KBr): 3290 (NH); 1783*m*, 1734*s*, 1663 (C=O); 1598, 1487, 1453, 1399, 1218, 1094, 1023, 751. $^1$H-NMR (500 MHz, $CDCl_3$): 1.20–2.05 (*m*, 10 H); 3.65 (*s*, 3 H); 3.70 (*s*, 3 H); 4.05 (*m*, 1 H); 5.26 (*s*, 1 H); 7.20–7.25 (*m*, 2 H); 7.39–7.42 (*m*, 4 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 24.34; 24.38; 25.10; 33.69; 34.07; 50.75; 52.70; 55.81; 61.78; 80.52; 126.01; 128.75; 129.11; 130.76; 148.62; 150.27; 153.02; 165.43; 169.17. EI-MS: 428 (5, $M^+$), 397 (10), 370 (65), 288 (100), 216 (56), 168 (70), 140 (66), 111 (80), 86 (95), 55 (82), 41 (25). Anal. calc. for $C_{21}H_{24}N_4O_6$ (428.44): C 58.87, H 5.65, N 13.08; found: C 59.0, H 5.7, N 13.0.

*Diethyl 7-(Cyclohexylamino)-2,3-dihydro-1,3-dioxo-2-phenyl-1*H,5H-*pyrazolo[1,2-*a*][1,2,4]triazole-5,6-dicarboxylate* (**5h**). Yield: 82%. Colorless crystals. M.p. 70–72°. IR (KBr): 3295 (NH); 1791*m*,

1751*s*, 1695 (C=O); 1618, 1497, 1452, 1389, 1219, 1142, 1097, 770, 642. $^1$H-NMR (500 MHz, $CDCl_3$): 1.15 (*t*, *J* = 7.1, 3 H); 1.17 (*t*, *J* = 7.1, 3 H); 1.20–1.99 (*m*, 10 H); 3.90–4.20 (*m*, 5 H); 5.15 (*s*, 1 H); 7.20–7.25 (*m*, 2 H); 7.29–7.34 (*m*, 4 H). $^{13}$C-NMR (125.8 MHz, $CDCl_3$): 13.99; 14.34; 24.40; 24.45; 25.19; 33.77; 34.20; 55.81; 59.56; 62.01; 62.03; 80.97; 126.05; 128.80; 129.18; 130.84; 148.63; 150.19; 153.09; 165.26; 168.87. EI-MS: 457 (2, $[M+1]^+$), 456 (1, $M^+$), 383 (100), 301 (46), 280 (9), 220 (10), 182 (7), 154 (11), 119 (10), 55 (18), 41 (13), 29 (25). Anal. calc. for $C_{23}H_{28}N_4O_6$ (456.50): C 60.52, H 6.18, N 12.27; found: C 60.6, H 6.2, N 12.1.

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*Received March 2, 2006*