Synthesis of Some New 1,2,4-Triazole Derivatives by *Mitsunobu* Chemistry

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The reactive 1:1 intermediate produced in the reaction between triphenylphosphine and diisopropyl azodicarboxylate has been trapped by isocyanates or isothiocyanates to yield 1,2,4-triazole derivatives **2** (*Scheme 1*). The structures of the highly functionalized compounds **2** were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, EI-MS) and by elemental analyses. A mechanism for this type of cyclization is proposed (*Scheme 2*).

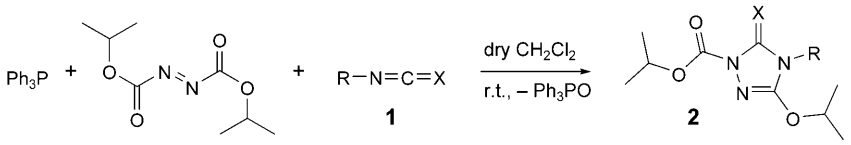
Introduction. – During the last few decades, considerable attention has been devoted to the synthesis of 1,2,4-triazole derivatives possessing diverse pharmacological properties such as antimicrobial [1][2], anti-inflammatory [3], analgesic [4], antitumor [5], antihypertensive [6], anticonvulsant, and antiviral activities [7]. On the other hand, 1,3,4-thiadiazoles also exhibit diverse biological activities possibly due to the presence of the =N–C–S moiety [8]. Moreover, some heterobicyclic compounds incorporating 1,3,4-thiadiazole or 1,2,4-triazole rings have been produced as antimicrobial agents [9]. Some azole derivatives used as common antibiotics such as *Amphotericin B* possess a toxic effect on humans as well as their antimicrobial effects [10]. Beside this, although antimicrobial agents having different structures are frequently used in treatment of microbial infections, there is an increasing resistance, to these drugs observed [10]. To overcome the problem of drug resistance it is crucial to synthesize new classes of antibiotics possessing chemical properties different from those commonly used.

In this paper, we report the synthesis of some new 1,2,4-triazole derivatives **2** by the reaction between Ph_3P and diisopropyl azodicarboxylate in the presence of isocyanates or isothiocyanates **1**.

Results and Discussion. – The reaction of Ph_3P with diisopropyl azodicarboxylate in the presence of an isocyanate or isothiocyanate **1** in dry CH_2Cl_2 proceeded spontaneously at room temperature and was completed within a few min. ^{1}H- and ^{13}C-NMR spectra of the crude product clearly indicated the formation of the 1,2,4-triazoles **2a**–**2f** (*Scheme 1*).

The structures of **2a**–**2f** were deduced from their IR, ^{1}H- and ^{13}C-NMR, and mass spectra. The EI-MS of **2a**–**2f** are fairly similar and display molecular-ion peaks at *m/z* 305, 319, 319, 285, 321, and 259, respectively, in addition to the more intensive $[M+1]^+$ peak, which is, in general, the base peak. Any initial fragmentation involves the loss of an i-Pr group. Typically, the ^{1}H-NMR spectrum of **2a** exhibited four characteristic signals that are readily recognized as arising from Me_2CH (2*d* at 1.36 and 1.39 ppm,

Scheme 1



1, 2	R	X	Yield of 2 [%]
a	Ph	O	98
b	*m*-MeC_6H_4	O	98
c	$PhCH_2$	O	80
d	*n*-Bu	O	70
e	Ph	S	95
f	Me	S	77

^3J(H,H) = 6.2 Hz), Me_2CHO (2*sept.* at 5.19 and 5.24 ppm, ^3J(H,H) = 6.2 Hz), and the Ph residue gave rise to characteristic signals in the aromatic region of the spectrum. The ^{13}C-NMR spectrum of **2a** showed signals for C(3) and C(5) at 149.86 and 148.12 ppm, respectively, indicating the presence of the triazole ring.

The ^{1}H- and ^{13}C-NMR spectra of **2b**–**2f** are similar to those of **2a** except for the signals of the *N*-aryl or *N*-alkyl groups, which exhibit characteristic signals with appropriate chemical shifts. On the basis of the well-established *Mitsunobu* chemistry [11–15], it is reasonable to assume that the triazoles **2** are formed either *via Route A* or *Route B* shown in *Scheme 2*.

Route A. The initial addition of Ph_3P to the diisopropyl azodicarboxylate and subsequent attack of the resulting zwitterion **3** to the isocyanate or isothiocyanate **1** yield betaine **5**, which apparently cyclizes under the reaction conditions employed, and loss of Ph_3PO leads to the triazoles **2**.

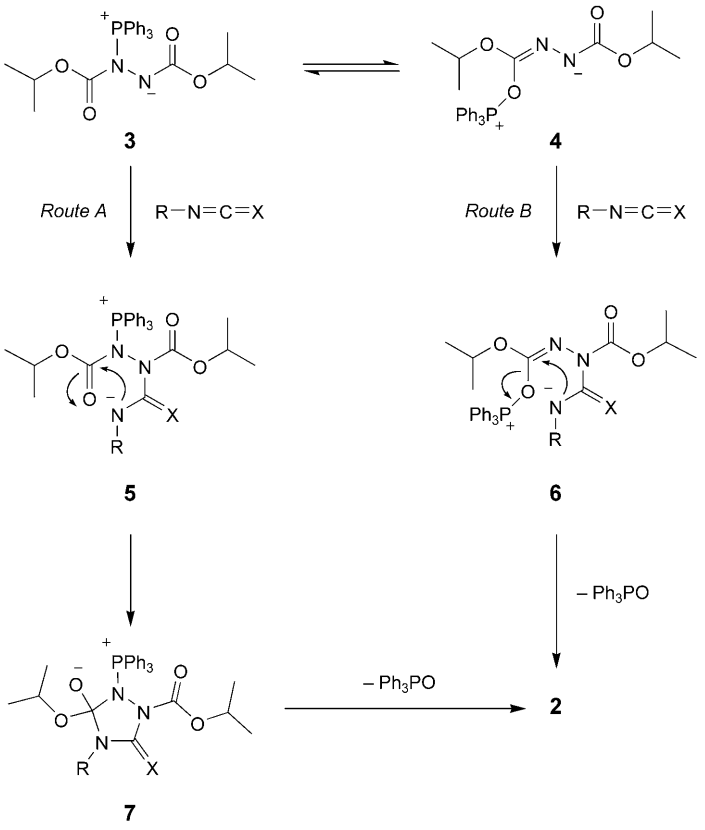
Route B. Although the *Morrison–Brunn–Huisgen* (MBH) betaine **3** is the established intermediate in the first step of this reaction, the P–O bonded tetracoordinate species of type **4** was also proposed as a possible intermediate in the earlier literature [16–18]. This zwitterion results from the addition of PPh_3 to the O-atom of the ester, or may be the result of the rearrangement of betaine **3**. These intermediates are in equilibrium with each other (**3** ⇌ **4**). According to the *Route B*, triazole **2** results from the addition of zwitterion **4** to **1** to yield betaine **6**, which cyclizes to give the triazoles **2**.

In conclusion, the method presented has the advantage that the reaction is performed under neutral conditions and at room temperature. The cyclization of the intermediate has been shown to be an excellent way for the synthesis of 1,2,4-triazole derivatives. It is worth mentioning that 1,3,4-oxadiazoles and 1,3,4-thiadiazole are not formed under the reaction conditions. The simplicity of the present procedure renders it an interesting alternative to complex multistep approaches.

Experimental Part

General. All reagents and solvents were obtained from *Fluka* (CH-Buchs) and used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: recorded at 500.1 and 125.7 MHz, resp., on a *Bruker DRX 500-AVANCE* instrument; in $CDCl_3$; δ in ppm rel. to Me_4Si (= 0 ppm), *J* in Hz. EI-MS (70 eV): *Finnigan MAT-8430* mass spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

Scheme 2



General Procedure for the Preparation of Compounds **2** (exemplified for **2a**). To a magnetically stirred soln. of phenyl isocyanate (**1a**; 0.12 g, 1 mmol) and diisopropyl azodicarboxylate (0.20 g, 1 mmol) in anh. CH_2Cl_2 (5 ml) was added dropwise a soln. of Ph_3P (0.26 g, 1 mmol) in CH_2Cl_2 (3 ml) at r.t. over 10 min. The mixture was stirred for 1 h. The solvent was removed under reduced pressure, and the residue was separated by CC (SiO_2, *Merck* 230–240 mesh) with hexane/AcOEt mixtures as eluent.

*1-Methylethyl 4,5-Dihydro-3-(1-methylethoxy)-5-oxo-4-phenyl-1*H*-1,2,4-triazole-1-carboxylate* (**2a**). Yield: 299 mg (98%). Colorless crystals. M.p. 88–90°. IR (KBr): 1780 (NCON); 1741 (NCO_2^iPr); 1621 (C=N); 1367, 1306 (C–O). ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.36 (*d*, *J* = 6.2, 6 H); 1.39 (*d*, *J* = 6.2, 6 H); 5.19 (*sept.*, *J* = 6.2, 1 H); 5.24 (*sept.*, *J* = 6.2, 1 H); 7.35–7.44 (*m*, 5 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 21.08; 21.13; 71.65; 74.37; 125.19; 127.83; 128.50; 130.35; 148.12; 148.44; 149.86. EI-MS: 307 (24, $[M+2]^+$), 306 (100, $[M+1]^+$), 305 (27, M^+), 262 (10), 220 (100), 177 (100), 120 (48), 93 (35), 43 (100). Anal. calc. for $C_{15}H_{19}N_3O_4$ (305.33): C 59.01, H 6.27, N 13.76; found: C 59.05, H 6.34, N 13.72.

*1-Methylethyl 4,5-Dihydro-3-(1-methylethoxy)4-(3-methylphenyl)-5-oxo-1*H*-1,2,4-triazole-1-carboxylate* (**2b**). Yield: 312 mg (98%). Colorless crystals. M.p. 81–83°. IR (KBr): 1776 (NCON); 1745 (NCO_2^iPr); 1612 (C=N); 1365, 1308 (C–O). ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.29 (*d*, *J* = 6.2, 6 H); 1.33 (*d*, *J* = 6.2, 6 H); 2.28 (*s*, 3 H); 5.12 (*sept.*, *J* = 6.2, 1 H); 5.17 (*sept.*, *J* = 6.2, 1 H); 7.06 (*d*, *J* = 7.8, 1 H); 7.10 (*d*, *J* = 7.6, 1 H); 7.13 (*s*, 1 H); 7.24 (*t*, *J* = 7.8, 1 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 20.57; 21.00; 21.06; 71.49; 74.23; 122.27; 125.81; 128.22; 128.26; 130.15; 138.48; 148.06; 148.44; 149.90. EI-MS: 321 (54, $[M+2]^+$), 320 (100, $[M+1]^+$), 319 (38, M^+), 276 (19), 234 (100), 191 (100), 134 (33), 107 (19), 91 (10), 43 (50). Anal. calc. for $C_{16}H_{21}N_3O_4$ (319.36): C 60.18, H 6.63, N 13.16; found: C 60.09, H 6.68, N 13.12.

*1-Methylethyl 4-Benzyl-4,5-dihydro-3-(1-methylethoxy)-5-oxo-1*H*-1,2,4-triazole-1-carboxylate* (**2c**). Yield: 255 mg (80%). Colorless oil. IR (KBr): 1780 (NCON); 1742 ($NCO_2{}^i$Pr); 1616 (C=N); 1365, 1314 (C–O). ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.36 (*d*, *J* = 6.1, 6 H); 1.39 (*d*, *J* = 6.2, 6 H); 4.67 (*s*, 2 H); 5.16 (*sept.*, *J* = 6.2, 1 H); 5.19 (*sept.*, *J* = 6.2, 1 H); 7.35–7.44 (*m*, 5 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 21.54; 21.56; 43.63; 71.94; 74.51; 128.19; 128.36; 128.49; 134.89; 148.55; 149.76; 151.14. EI-MS: 321 (34, $[M+2]^+$), 320 (75, $[M+1]^+$), 319 (10, M^+), 276 (6), 234 (50), 191 (85), 91 (100), 43 (73). Anal. calc. for $C_{16}H_{21}N_3O_4$ (319.35): C 60.18, H 6.63, N 13.16; found: C 60.11, H 6.68, N 13.12.

*1-Methylethyl 4-Butyl-4,5-dihydro-3-(1-methylethoxy)-5-oxo-1*H*-1,2,4-triazole-1-carboxylate* (**2d**). Yield: 199 mg (70%). Colorless wax. M.p. 38–40°. IR (KBr): 1781 (NCON); 1743 ($NCO_2{}^i$Pr); 1616 (C=N); 1366, 1313 (C–O). ^{1}H-NMR (500.1 MHz, $CDCl_3$): 0.86 (*t*, *J* = 7.2, 3 H); 1.27 (*quint.*, *J* = 7.3, 2 H); 1.34 (*d*, *J* = 6.1, 12 H); 1.55 (*quint.*, *J* = 7.2, 2 H); 3.47 (*t*, *J* = 6.9, 2 H); 5.13 (*sept.*, *J* = 6.2, 1 H); 5.16 (*sept.*, *J* = 6.2, 1 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 13.51; 19.63; 21.79; 21.83; 30.17; 40.01; 72.10; 74.42; 148.88; 150.19; 151.77. EI-MS: 287 (52, $[M+2]^+$), 286 (100, $[M+1]^+$), 285 (10, M^+), 242 (7), 200 (75), 157 (80), 140 (33), 100 (64), 43 (60). Anal. calc. for $C_{13}H_{23}N_3O_4$ (285.34): C 54.72, H 8.12, N 14.73; found: C 54.64, H 8.18, N 14.70.

*1-Methylethyl 4,5-Dihydro-3-(1-methylethoxy)-4-phenyl-5-thioxo-1*H*-1,2,4-triazole-1-carboxylate* (**2e**). Yield: 305 mg (95%). Colorless crystals. M.p. 121–123°. IR (KBr): 1746 ($NCO_2{}^i$Pr); 1612 (C=N); 1331, 1295 (C–O); 1215 (C=S). ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.32 (*d*, *J* = 6.2, 6 H); 1.43 (*d*, *J* = 6.2, 6 H); 5.18 (*sept.*, *J* = 6.2, 1 H); 5.23 (*sept.*, *J* = 6.2, 1 H); 7.29 (*d*, *J* = 7.4, 2 H); 7.44 (*t*, *J* = 7.3, 1 H); 7.47 (*t*, *J* = 6.9, 2 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 21.43; 21.55; 73.17; 76.46; 127.78; 129.12; 129.45; 131.88; 148.48; 153.56; 169.23. EI-MS: 323 (42, $[M+2]^+$), 322 (100, $[M+1]^+$), 321 (81, M^+), 278 (6), 235 (50), 193 (100), 136 (20), 43 (60). Anal. calc. for $C_{15}H_{19}N_3O_3S$ (321.39): C 56.06, H 5.96, N 13.07; found: C 56.00, H 5.91, N 12.95.

*1-Methylethyl 4,5-Dihydro-3-(1-methylethoxy)-4-methyl-5-thioxo-1*H*-1,2,4-triazole-1-carboxylate* (**2f**). Yield: 199 mg (77%). Colorless crystals. M.p. 67–70°. IR (KBr): 1740 ($NCO_2{}^i$Pr); 1616 (C=N); 1361, 1319 (C–O); 1211 (C=S). ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.39 (*d*, *J* = 6.2, 6 H); 1.40 (*d*, *J* = 6.2, 6 H); 3.32 (*s*, 3 H); 5.16 (*sept.*, *J* = 6.1, 1 H); 5.17 (*sept.*, *J* = 6.1, 1 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 21.48; 21.54; 28.99; 72.97; 76.17; 148.32; 154.06; 168.69. EI-MS: 261 (32, $[M+2]^+$), 260 (100, $[M+1]^+$), 259 (80, M^+), 216 (7), 173 (60), 131 (100), 74 (18), 43 (82). Anal. calc. for $C_{10}H_{17}N_3O_3S$ (259.32): C 46.32, H 6.61, N 16.20; found: C 46.25, H 6.54, N 16.12.

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