SYNTHESIS OF TRIAZOLYLBENZOISOXAZOLE DERIVATIVES †

Özkan Sezer*, Kadir Dabak, Olcay Anaç, Ahmet Akar

Istanbul Technical University, Faculty of Sciences, Department of Chemistry, 80626 Maslak, Istanbul, Turkey.

Abstract: Seven 1*H*-1,2,3-triazole derivatives synthesized from α-diazo-β-oxoaldehydes were cyclized to yield new 3-(1-phenyl-1,2,3-triazole-4-yl)benzisoxazoles. The method consists of the cyclization of ortho substituted aromatic oximes.

Introduction:

Benzisoxazoles are important compounds in the pharmacological, agricultural and dye applications (1-3). Many patents can be found on their syntheses (3). The earliest and most generally used method for the synthesis of benzisoxazoles (indoxazenes) is the cyclization of ortho substituted aromatic oximes (1).

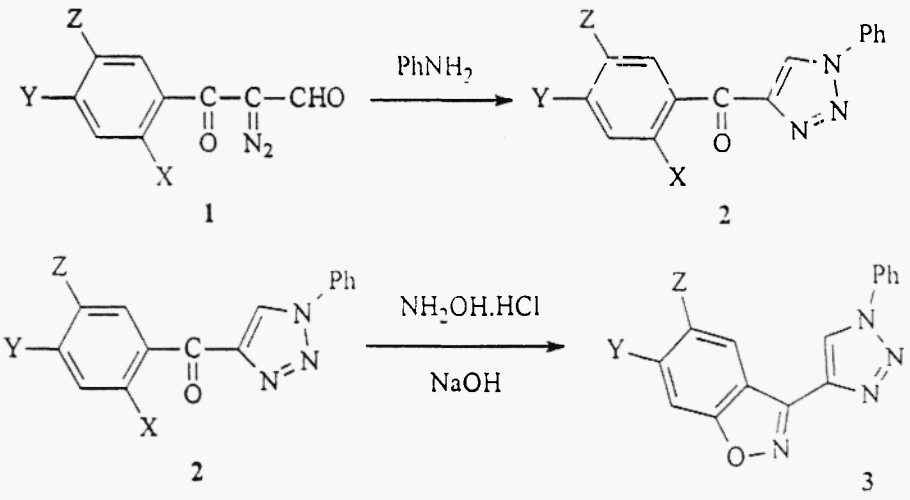
In 1994 we developed a novel diazo transfer method which allowed a fairly general synthetic route to α-diazo-β-oxoaldehydes **1** (4). We also re-investigated an existing method which also leads to these compounds (5). A successful and regiospesific conversion of these diazoaldehydes to v-triazoles was realized recently in our laboratory (6). In this paper we now report our attempts to synthesise 3-(1-phenyl-1,2,3-triazole-4-yl)benzisoxazole derivatives **3** utilizing these α-diazo-β-oxoaldehydes **1** (Scheme 1).

---

† Dedicated to the 225th aniversary of the Istanbul Technical University.

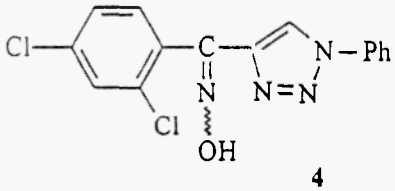
* Correspondance author; e-mail: oosezer@hidiv.cc.itu.edu.tr

Scheme 1.



Results and Discussion:

Compounds 1 (4,5) and 2 (6) were synthesised in moderate to good yields according to literature procedures (Scheme-1). Of the seven different triazoles **2a-2g** synthesised five are new compounds. The results are summarised in Table 1.



4

Conversion of the triazole keto functions to oximes with $NH_2OH.HCl$ in the presence of excess of NaOH and the cyclization of the new functions to the benzoisoxazoles were realised in a one-pot reaction (Scheme 1). In most of the reactions, after several hours of reflux, the compounds 3 precipitated by cooling of the reaction mixture to room temperature. The results are summarised in Table 2. The starting materials and products could be easily differentiated by the downfield shift of the H-C(6') signals of 2 (around δ 7.6-7.85) to H-C(4) signals of 3 (around δ 8.2-8.59 in ^{1}H NMR.

In one reaction (2a→3a) the oxime intermediate was also isolated: Acidification of the mother solution of the reaction with dilute HCl gave compound 4. In the reaction 2→3, the ease of elimination of the hydrogen halide is influenced by the configuration of the oxime (7). It is reported that, *syn* form of the oxime, produces benzisoxazole easier than the *anti* form. In our study, we did not work on the configuration of the oxime. In the reaction of 2f, we observed a substitution in the 5-position of the benzoyl group and the compound 3f (Y=F, Z=OC_2H_5) was obtained instead of the expected compound (Y=F, Z=F).

Table-1: Triazole products 2.

Product	X	Y	Z	Yield (%)	M.p. (°C)
2a	Cl	Cl	H	80[a]	134-5[c]
2b	Br	Br	H	82[b]	150-2[d]
2c	F	H	H	74	95-6
2d	Cl	H	H	68	92-4
2e	Cl	H	Cl	78	171-5
2f	F	F	F	90	140-2
2g	OCH_3	OCH_3	H	85	134-5[e]

[a] 87 (5). [b] 80 (5). [c] 135-136.5° (5). [d] 151-2 (5). [e] Softens around 120°

Table-2: Benzoisoxazole products 3.

Product	Y	Z	Yield (%)	M.p. (°C)
3a	Cl	H	17	210
3b	Br	H	22	208-9
3c	H	H	32	159-160
3f	OC_2H_5	F	20	190[a,b]

[a] Decomposition. [b] Softens around 186°

In the reactions of **2d** and **2g** with NH_2OH, only the starting materials and their impure oxime derivatives were obtained. In the reaction of **2e** a third substance was obtained the structure of which was left unidentified.

Conclusion:

The advantage of this reaction is that it yields a very interesting structure, which has two different potentially biologically active structures – triazole and benzoisoxazole structures – on the same compound. The biological activities of these new compounds, especially with respect to their tuberculosis inhibitory activity will be investigated.

Acknowledgement:

This work was supported by a grant from the I. T. Ü. Research Foundation.

Experimental:

Melting points on an Electrothermal glass-bath apparatus in capillary tubes. IR (KBr, cm^{-1}): Jasco FT-IR, model 5300. NMR (δ [ppm], $CDCl_3$): 200 MHz Bruker and 270 MHz JEOL JNM EX270 instruments, TMS as internal standard; coupling constants J given in Hz. ^{13}C-NMR: at 50 MHz on the Bruker and at 67.8 MHz on the Jeol instruments. EI-MS: on a VG-Zabspec double-focusing spectrometer at 70 eV and on a Kratos model MS25 magnetic sector mass spectrometer at 70 eV. All diazo compounds **1** were prepared as described in the literature (4,5) and used without purification. Syntheses of the triazole compounds **2** were described in the literature (6).

Syntheses of compounds 3a-3f. $NH_2OH.HCl$ (7.3 mmol) was dissolved in a mixture of ethanol and water (10/70 v/v). NaOH (46 mmol) and **2** (4.6 mmol) were added to this solution. The reaction mixture was refluxed for 8 hr, then cooled to room temperature. The precipitated compound was filtered and compounds **3** were obtained in almost pure form. Recrystallized from ethanol effected further purification. The filtrate from the reaction of **2a** was acidified and oxime derivative **4** was obtained. The yields and m.p. are given in Table 2.

4-(2'-Fluorobenzoyl)-1-phenyl-1H-1,2,3-triazole (2c): IR: 3121, 3065, 1666, 1520, 1487, 1280, 1255, 910, 752. ^{1}H-NMR (270 MHz): 8.64 (s, H-C(5)); 7.51-7.92 (m, 9 arom. H). ^{13}C-NMR (67.8 MHz): 116.74, 120.88, 124.16, 125.39, 126.16, 129.63, 130.00, 131.37, 132.02, 133.94, 134.07, 137.10, 140.07, 148.95, 152.83. EI-MS: 267 (12, M^+), 239 (13), 198 (12), 144 (15), 123 (100), 95 (29), 77 (39), 51 (19), 32 (7).

4-(2'-Chlorobenzoyl)-1-phenyl-1H-1,2,3-triazole (2d): IR: 3126, 1665, 1591, 1522, 1241, 902, 745, 693. ^{1}H-NMR (200 MHz): 8.64 (s, H-C(5)); 7.36-7.88 (m, 9 arom. H). ^{13}C-NMR (50 MHz): 120.88, 125.54, 126.60, 129.65, 129.99, 130.21, 130.49, 132.01. EI-MS: 283 (11, M^+), 254 (36), 248 (23), 227 (33), 220 (69), 214 (52), 165 (21), 144 (43), 139 (100), 111 (60), 77 (79).

4-(2',5'-Dichlorobenzoyl)-1-phenyl-1H-1,2,3-triazole (2e): IR: 3129, 1668, 1619, 1522, 1459, 1231, 1105, 922, 756, 687. ^{1}H-NMR (200 MHz): 8.66 (s, H-C(5)); 7.44-7.81 (m, 8 arom.H). ^{13}C-NMR (50 MHz): 120.89, 125.52, 129.78, 130.03, 131.60, 131.90. EI-MS: 317 (11, M^+), 288 (23), 282 (60), 254 (73), 248 (33), 199 (14), 173 (100), 144 (78), 104 (35), 77 (98), 63 (17).

4-(2',4',5'-Trifluorobenzoyl)-1-phenyl-1H-1,2,3-triazole (2f): IR: 3113, 3069, 1670, 1602, 1509, 1415, 1329, 1200, 880, 752, 677. ^{1}H-NMR (270 MHz): 8.67 (s, H-C(5)); 7.84-7.94 (m, 1H, H-C(6')); 7.78-7.81 (m, 2H); 7.50-7.63 (m, 3H); 7.04-7.13 (m, 1H, H-C(3')). ^{13}C-NMR (67.8 MHz): 120.88, 125.62, 129.81, 130.06, 134.77, 143.50. EI-MS: 303 (10, M^{+}), 275 (10), 234 (5), 159 (61), 131 (15), 104 (11), 91 (100), 43 (25).

4-(2',4'-Dimethoxybenzoyl)-1-phenyl-1H-1,2,3-triazole (2g): IR: 3112, 1650, 1605, 1505, 1470, 1269, 1215, 1030, 895, 763. ^{1}H-NMR (270 MHz): 8.56 (s, H-C(5)); 7.77-7.84 (m, 3H, phenyl); 7.46-7.59 (m, 2H (phenyl)+1H (H-C(6'))); 6.60 (dd, 1H, J=2.15 and 8.71, H-C(5')); 6.48 (d, 1H, J=2.11, H-C(3')); 3.88 (s, Me); 3.82 (s, Me). ^{13}C-NMR (67.8 MHz): 55.54, 55.86, 99.15, 104.69, 120.71, 125.03, 129.29, 129.90, 133.36, 136.55, 149.36, 160.64, 164.22, 185.96. EI-MS: 309 (2, M^{+}), 260 (8), 197 (10), 165 (92), 121 (23), 91 (33), 43 (100).

3-(1'-Phenyl-1H-1,2,3-triazole-4'-yl)-6-chlorobenzoisoxazole (3a): IR: 3115, 3050, 1607, 1500, 1490, 1395, 1243, 1070, 820, 745, 680. ^{1}H-NMR (200 MHz): 8.66 (s, 1H (triazole)); 8.49 (d, J=8.42, H-C(4)); 7.41-7.85 (m, 7H). ^{13}C-NMR (50 MHz): 110.09, 120.76, 124.89, 125.43, 129.44, 129.99, 136.57, 137.13, 163.73. EI-MS: 296 (27, M^{+}), 268 (79), 239 (38), 205 (52), 191 (20), 178 (18), 137 (49), 132 (75), 116 (75), 89 (68), 77 (100), 63 (48).

3-(1'-Phenyl-1H-1,2,3-triazole-4'-yl)-6-bromobenzoisoxazole (3b): IR: 3110, 3050, 1600, 1500, 1445, 1260, 1075, 905, 755. ^{1}H-NMR (200 MHz): 8.66 (s, 1H (triazole)); 8.44 (d, J=8.46, H-C(4)); 7.81-7.84 (m, 3H); 7.47-7.63 (m, 4H). ^{13}C-NMR (50 MHz): 113.15, 120.60, 125.18, 128.11, 129.49, 130.04. EI-MS: 342 (26, M^{+}), 314 (64), 285 (28), 205 (48), 132 (69), 116 (100), 89 (48), 77 (89), 63 (38).

3-(1'-Phenyl-1H-1,2,3-triazole-4'-yl)benzoisoxazole (3c): IR: 3140, 3055, 1615, 1597, 1503, 1467, 1250, 1038, 895, 882, 812, 757, 690. ^{1}H-NMR (270 MHz): 8.66 (s, 1H (triazole)); 8.55 (d, J=7.92, H-C(4)); 7.80-7.84 (m, 2H); 7.41-7.63 (m, 6H). ^{13}C-NMR (67.8 MHz): 109.65, 120.18, 120.70, 120.75, 124.22, 124.27, 129.38, 129.99, 130.38, 136.65, 138.88, 149.97, 163.59. EI-MS: 262 (23, M^{+}), 234 (53), 205 (24), 179 (5), 157 (4), 132 (31), 116 (100), 77 (82), 51 (47), 32 (17).

3-(1'-Phenyl-1H-1,2,3-triazole-4'-yl)-5-fluoro-6-ethoxybenzoisoxazole (3f): IR: 3114, 3055, 1610, 1503, 1472, 1255, 1040, 932, 882, 755. ^{1}H-NMR (270 MHz): 8.64 (s, 1H (triazole)); 8.19 (d, J=10.1, H-C(4)); 7.83 (m, 2H, phenyl); 7.51-7.62 (m, 3H, phenyl); 7.13 (d, H-C(7), J=7.2);

4.21 (q, OCH_2, J=6.9); 1.54 (t, OCH_2CH_3, J=6.9); ^{13}C-NMR (67.8 MHz): 14.44, 65.21, 93.78, 120.48, 120.77, 129.39, 129.99. EI-MS: 324 (2, M^+), 239 (2), 219 (2), 149 (15), 125 (11), 111 (22), 97 (36), 71 (58), 69 (55), 57 (100), 41 (61).

4-[(2',4'-Dichlorobenzoyl)(hydroxyimino)methyl]-1-phenyl-1H-1,2,3-triazole (4): IR: 3177, 1593, 1502, 1479, 1377, 1284, 1045, 931, 760, 690. ^{1}H-NMR (200 MHz): 9.25 (s, broad, oxime OH); 8.86 (s,1H (triazole)); 7.76-7.80 (m, 2H); 7.32-7.62 (m, 6H). ^{13}C-NMR (50 MHz): 110.11, 120.81, 124.94, 125.48, 125.94, 127.14, 129.19, 129.45, 129.84, 132.35, 135.16, 135.91, 136.67, 138.59, 147.65. EI-MS: 332 (70, M^+), 287 (63), 274 (100), 252 (84), 234 (41), 212 (56), 185 (65), 172 (23), 149 (36), 116 (56), 104 (54), 93 (45), 77 (96), 57 (27).

REFERENCES:

(1) A. Quilico *in* Heterocyclic Compounds, Vol. 17, Wiley-Interscience 1962, Chapter 4, pp. 153-176.

(2) (a) S. N. Kulkarni, S. V. Kamath, S. V. Devasthale, M. Hooper, Indian Drugs, 25, 464 (1988); (b) K. A. Thakar, A. B. Dumir, B. M. Dhawal, Curr. Sci., 49, 889 (1980); (c) L. Davis, R. C. Effland, J. Klein, R. W. Dunn, H. M. Geyer III, W. m. Petko, Drug Des. Discovery, 8, 225 (1992); (d) K. A. Thakar, B. M. Bhawal, J. Indian Chem. Soc., 54, 875 (1977).

(3) (a) A. E. Siegrist, J. P. Pauchard, B. De Sousa, Ger. Offen. 2,750,577 (Chem. Abstr., 90, 24794w (1979)); (b) L. A. Jackson, S. K. Malhotra, U.S. 4,888,041 (Chem. Abstr., 112, 212485t (1990)); (c) M. Nagano, J. Sakai, T. Kobayashi, M. Kozuka, N. Iwata, Y. Kubo, Eur. Pat. 456,519 (Chem. Abstr., 116, 83660c (1992)); (d) G. M. Shutske, L. L. Setescak, R. C. Allen, Eur. Pat. 2666 (US Pat. Appl. 853,313) (Chem. Abstr., 92, 94378d (1980)).

(4) Ö. Sezer, O. Anaç, Helv. Chim. Acta, 77, 2323 (1994).

(5) Ö. Sezer, K. Dabak, O. Anaç, A. Akar, Helv. Chim. Acta, 80, 960 (1997).

(6) Ö. Sezer, K. Dabak, O. Anaç, A. Akar, Helv. Chim. Acta, 79, 449 (1996).

(7) J. Meisenheimer, P. Zimmermann, U. v. Kummer, Liebigs Ann. Chem., 446, 205 (1925).

Received on October 30, 1998