Syntheses of Substituted-1,2,4-triazoles

A. Shafiee*, F. Naghashian and N. Reghabi

Department of Chemistry, Faculty of Pharmacy,
The Medical Sciences University of Tehran,
Tehran, Iran

Received May 18, 1992

Starting from the readily available 3-phenylpropionitrile, 3-(or 5-)(2-phenethyl)-1,2,4-triazole **3** was prepared. Reaction of compounds **3** with diazomethane afforded 1-methyl-3-(2-phenethyl)-1,2,4-triazole (**4**) and 1-methyl-5-(2-phenethyl)-1,2,4-triazole (**5**). Reaction of compound **3** with methanesulfonyl chloride, benzenesulfonyl chloride or *p*-toluenesulfonyl chloride afforded only one of the expected isomer; namely compounds **6**, **7** and **8** respectively.

J. Heterocyclic Chem., **29**, 1863 (1992).

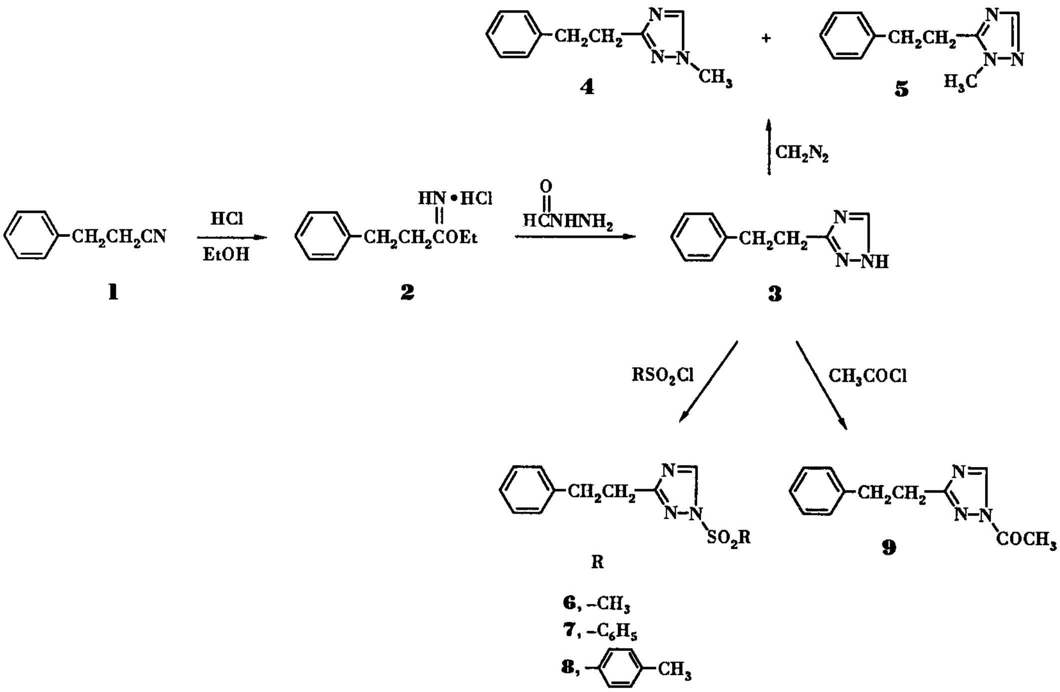
The considerable biological importance of triazoles has stimulated much work on this heterocycle [1-5]. We would like to report the syntheses of the title compounds as possible effective drugs in fertility regulation [6].

The synthesis of 3-(or 5-)(2-phenethyl)-1,2,4-triazole **3** was achieved according to Scheme 1.

Reaction of 3-phenylpropionitrile with ethanol and hydrochloric acid afforded ethyl 3-phenylpropionimidate hydrochloride (**2**). Reaction of formylhydrazine with **2** gave compound **3**. The reaction of diazomethane with compound **3** gave 1-methyl-3-(2-phenethyl)-1,2,4-triazole (**4**) and 1-methyl-5-(2-phenethyl)-1,2,4-triazole (**5**). The structures of compounds **4** and **5** were confirmed by C-13 nmr spectroscopy. In compound **4**, C_3 and C_5 of triazole appeared at 162 and 141.6 ppm respectively, while in compound **5**, C_3 and C_5 of triazole appeared at 149.6 ppm and 154 ppm respectively. The ^{1}H nmr and mass spectra of compounds **4** and **5** were also in agreement to the suggested structures (see Experimental). In addition the tlc of both compounds was instructive. Compound **5** because of steric hindrance of the substituents should move faster relative to compound **4**. In fact compounds **4** and **5** had $R_f = 0.41$ and $R_f = 0.49$ respectively.

The reaction of compound **3** with methanesulfonyl chloride afforded only 1-methanesulfonyl-3-(2-phenethyl)-1,2,4-triazole (**6**). Similar results were observed in the reaction of compound **3** with benzenesulfonyl chloride and *p*-toluenesulfonyl chloride. In the former compound **7** and in the latter compound **8** were isolated. The structures of compounds **6**, **7** and **8** were established by ^{1}H nmr spectra. In the nmr of all of these compounds CH_2CH_2 of 2-phenethyl, similar to its starting material, appeared as a singlet. In addition, H_5 of triazole ring appeared at lower field relative to the starting material. These data indicate that the

Scheme 1



product ratio is governed by the steric effect of the phenethyl group at the 3 position and the reaction of alkyl (or aryl)sulfonyl chloride occurred preferentially at the N-1 atom because it is sterically less hindered than N-2 atom. Similar results were observed in the methylation of 1,2,4-triazoles [7].

Acetylation of compound **3** with acetyl chloride afforded 1-acetyl-3-(2-phenethyl)-1,2,4-triazole (**9**). The nmr of the crude product was in agreement with structure **9**. The CH_2-CH_2 of 2-phenethyl group appeared as a singlet at 3.08 and H_5 of triazole ring at 8.78 ppm. Compound **9** was unstable and decomposed upon purification.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded using a Perkin-Elmer Model 550 SE. The ir spectra were obtained using a Perkin-Elmer 781 spectrograph (potassium bromide disks). The ^1H nmr spectra were recorded on a Bruker FT-80 spectra and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 eV.

Ethyl 3-Phenylpropionimidate Hydrochloride (**2**).

To a solution of 3-phenylpropionitrile (5.24 g, 0.04 mole) in absolute ethanol (5 ml) and diethyl ether (10 ml) hydrogen chloride gas was bubbled for 1 hour. The precipitate was filtered and washed with ether to give 7.68 g (90%) of compound **2**, mp 128-130°; ^1H nmr (deuteriochloroform): 7.12 (s, 5H, aromatic), 4.18 (q, 2H, CH_2O), 2.80 (m, 4H, CH_2), 1.30 ppm (t, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.83; H, 7.49; N, 6.56. Found: C, 61.73; H, 7.58; N, 6.48.

3-(or 5-)(2-Phenethyl)-1,2,4-triazole (**3**).

To a solution of compound **2** (8.54 g, 0.04 mole) in ethanol (60 ml) and triethylamine (5 ml) a solution of formylhydrazine (2.4 g, 0.04 mole) in ethanol (15 ml) was added. The mixture was stirred for 2 hours at room temperature and then refluxed for 1 hour. The solvent was evaporated. To the residue water (10 ml) was added and extracted with ethyl acetate (3 x 50 ml). The organic layer was dried (sodium sulfate), filtered and evaporated. To a solution of the residue in ethyl acetate a solution of hydrochloric acid in ether was added. The precipitate was filtered and washed with ethyl acetate. The precipitate was dissolved in water, sodium bicarbonate was added and the solution was extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered and evaporated. The residue was crystallized from ether-petroleum ether to give 3.11 g (45%) of **3**, mp 62-64°; uv (methanol): λ max 212 nm (ϵ = 2050); ir (potassium bromide): ν 3490 cm^{-1} (NH); ^1H nmr (deuteriochloroform): 8.0 (s, 1H, triazole), 7.2 (m, 5H, phenyl) and 3.15 ppm (s, 4H, CH_2); ms: m/z (%) 173 (M^+, 100), 146 (12), 105 (12), 97 (35), 92 (96), 66 (17) and 33 (21).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.36; H, 6.36; N, 24.28. Found: C, 69.52; H, 6.21; N, 24.36.

1-Methyl-3-(2-phenethyl)-1,2,4-triazole (**4**) and 1-Methyl-5-(2-phenethyl)-1,2,4-triazole (**5**).

To a stirring solution of compound **3** (1.73 g, 0.1 mole) in methanol (20 ml) a solution of diazomethane in ether was added. After one hour the reaction was complete. The solvent was evaporated. The residue was purified by preparative tlc on silica gel using ethyl acetate-methanol (90:10) as the eluent. The fast moving fraction (R_f = 0.49) was compound **5** (an oil, 0.69 g, 37%); ^1H nmr (deuteriochloroform): 7.76 (s, 1H, H_3-triazole), 7.18 (m, 5H, aromatic), 3.45 (s, 3H, methyl) and 3.01 ppm (s, 4H, CH_2); ^{13}C nmr (deuteriochloroform): 154 (C_5-triazole), 149.6 (C_3-triazole), 139.7 (C_1-phenyl), 128.2 (C_2-phenyl), 127.9 (C_3-phenyl), 126.1 (C_4-phenyl), 34.2 (-C-ph), 33.5 (-C-triazole) and 27.5 ppm (methyl); ms: m/z (%) 187 (M^+, 89), 172 (26), 158 (19), 134 (24), 110 (100), 91 (99), 65 (58) and 39 (22); compound **5** as the hydrochloride had mp 65-68°.

Anal. Calcd. for $C_{11}H_{14}ClN_3$: C, 59.06; H, 6.26; N, 18.79. Found: C, 58.94; H, 6.39; N, 18.87.

The slow moving fraction (R_f = 0.41) was compound **4** (an oil, 0.8 g, 43%); ^1H nmr (deuteriochloroform): 7.84 (s, 1H, H_5-triazole), 7.2 (m, 5H, phenyl), 3.72 (s, 3H, CH_3) and 3.03 ppm (s, 4H, CH_2); ^{13}C nmr (deuteriochloroform): 162 (C_3-triazole), 141.6 (C_5-triazole), 139.3 (C_1-phenyl), 126.5 (C_2-phenyl), 126.25 (C_3-phenyl), 123.9 (C_4-phenyl), 33.6 (-C-phenyl), 32.3 (-C-triazole) and 28 ppm (methyl); ms: m/z (%) 187 (M^+, 76), 172 (22), 146 (51), 131 (20), 110 (82), 91 (100), 65 (44) and 42 (29).

Compound **4** as hydrochloride had mp 135-138°.

Anal. Calcd. for $C_{11}H_{14}ClN_3$: C, 59.06; H, 6.26; N, 18.79. Found: C, 59.21; H, 6.34; N, 18.63.

1-Methanesulfonyl-3-(2-phenethyl)-1,2,4-triazole (**6**).

To a stirring solution of compound **3** (1.73 g, 0.01 mole) in triethylamine (25 ml) methanesulfonyl chloride (1.26 g, 0.011 mole) was added dropwise. After 30 minutes the reaction was complete (tlc). The solvent was evaporated. To the residue water (25 ml) was added and extracted with ether. The solvent was evaporated and the residue was purified by tlc on silica gel using chloroform-ethyl acetate (90:10) as eluent to give 1.13 g (45%) of compound **6**, mp 67-68° (ether-petroleum ether); ir (potassium bromide): ν 3160 (H-C_5 triazole), 3020 (phenyl), 1360 and 1110 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): 8.56 (s, 1H, H_5-triazole), 7.2 (s, 5H, phenyl), 3.30 (s, 3H, CH_3) and 3.1 ppm (s, 4H, CH_2); ^{13}C nmr (deuteriochloroform): 167 (C_3-triazole), 144.8 (C_5-triazole), 140.5 (C_1-phenyl), 128.4 (C_2-phenyl), 128.35 (C_3-phenyl), 126.2 (C_4-phenyl), 41.6 (-C-phenyl), 33.6 (-C-triazole) and 3.01 ppm (methyl).

1-Benzensulfonyl-3-(2-phenethyl)-1,2,4-triazole (**7**).

This compound was made from compound **3** and benzensulfonyl chloride similar to **6** in 55% yield, mp 85-86°; uv (ethanol): λ max 230 (ϵ = 11768), 270 nm (ϵ = 89661); ir (potassium bromide): ν 3120 (H-C_5 triazole), 3015 (phenyl), 1390 and 1115 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): 8.60 (s, 1H, H_5 triazole), 8.0 (dd, 2H, ph-SO_2, Jo = 8 Hz, Jm = 2.2 Hz), 7.65 (m, 3H, ph-SO_2), 7.2 (m, 5H, ph) and 3.0 ppm (s, 4H, CH_2); ^{13}C nmr (deuteriochloroform): 167.33 (C_3-triazole), 145 (C_5-triazole), 140.5, 136, 135.15, 129.6, 128.46, 128.34, 128.28 and 126.1 (C of phenyl), 33.6 (-C-ph) and 30.17 ppm (-C-triazole); ms: m/z (%) 313 (M^+, 14), 180 (16), 173 (42), 172 (100), 105 (15), 97 (18), 91 (44), 85 (14), 77 (42), 71 (20), 57 (31), 43 (22) and 40 (71).

Anal. Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.34; H, 4.79; N, 13.42. Found: C, 61.17; H, 4.65; N, 13.31.

1-*p*-Toluenesulfonyl-3-(2-phenethyl)-1,2,4-triazole (**8**).

This compound was made from compound **3** and *p*-toluenesulfonyl chloride similar to **6** in 50% yield, mp 98-99°; uv (ethanol): λ max 239 (ϵ = 14500), 269 nm (ϵ = 6860); ir (potassium bromide): ν 3120 (H-C_5 triazole), 3015 (phenyl), 1390 and 1115 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): 8.6 (s, 1H, H_5 triazole), 7.90 (d, 2H, ph-SO_2, J = 8 Hz), 7.45 (d, 2H, Ph-SO_2, J = 8 Hz), 7.20 (m, 5H, phenyl), 3.01 (s, 4H, CH_2) and 2.46 ppm (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 167.1 (C_3-triazole), 144.9 (C_5-triazole), 146, 140.5, 133.25, 130.2, 128.6, 128.3, 126.4 and 126.1 (C of phenyl), 33.65 (-C-ph), 30.17 (-C-triazole) and 21.8 ppm (methyl); ms: m/z (%) 327 (M^+, 3), 172 (100), 91 (77) and 65 (14).

Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.39; H, 5.20; N, 12.84. Found: C, 62.45; H, 5.36; N, 12.71.

Reaction of Acetyl Chloride with Compound **3**.

To a stirring solution of compound **3** (1.73 g, 0.01 mole) in triethylamine (25 ml) acetyl chloride (0.86 g, 0.011 mole) was added dropwise. The reaction mixture was worked up similar to **6** to give compound **9** as an oil; ^1H nmr (deuteriochloroform): 8.78 (s, 1H, H_5), 7.24 (m, 5H, phenyl), 3.08 (s, 4H, CH_2) and 2.65 ppm (s, 3H, CH_3). The compound was decomposed under tlc purification.

Acknowledgement.

This work was supported by a grant from International Organization of Chemical Sciences in Development (IOCD).

REFERENCES AND NOTES

[1] J. Heeres, R. Hendrickx and J. Van Custem, *J. Med. Chem.*, **26**, 611 (1983).

[2] J. Heeres, L. J. J. Backx and J. Van Custem, *J. Med. Chem.*, **27**, 894 (1984).

[3] K. Richadson and P. J. Whittle, *European Patent Appl. EP* 126, 581 (1984); *Chem. Abstr.*, **102**, 149271w (1985).

[4] F. T. Boyle, *European Patent Appl. EP* 122, 693 (1984); *Chem. Abstr.*, **102**, 149273y (1985).

[5] W. Meiser, K. H. Buechel, W. Kraemer and F. Grewe, *German Offen.* 2,201,063 (1973); *Chem. Abstr.*, **79**, 105257 (1973).

[6] R. Maybury, *C. & E. N.*, August 12, 28 (1991).

[7] M. Uda, Y. Hisazumi, K. Sato and S. Kubota, *Chem. Pharm. Bull.*, **24**, 3101 (1976).