Syntheses of 1-Substituted 1,2,4-Triazoles, Imidazoles and Benzimidazoles

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Substituted 2-phenethyl-1,2,4-triazoles, 1-phenethylimidazoles **3** and 1-phenethylbenzimidazoles **5** were synthesized from the reaction of compound **8** with tri-*n*-butyltin hydride in good yield. The reaction of substituted-2-phenethyl halide with 1*H*-1,2,4-triazoles, imidazoles and benzimidazoles gave a low yield. The yield was increased by the use of substituted-2-phenethyl *p*-toluensulfonate.

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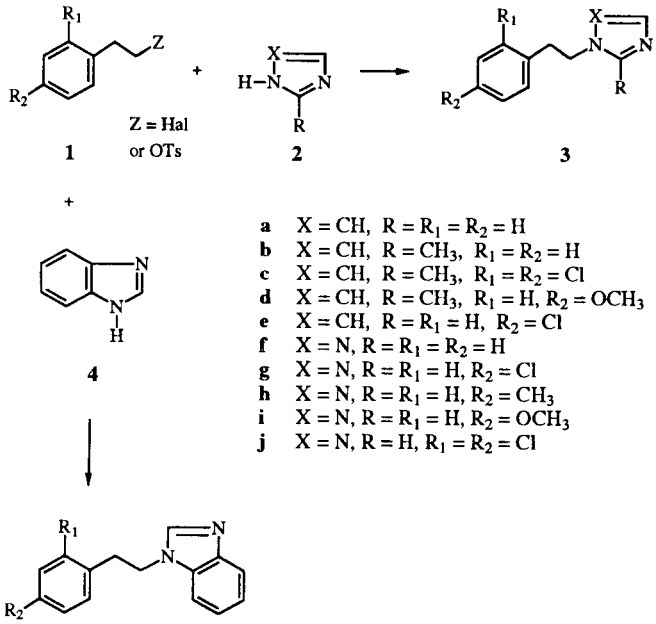
The considerable biological importance of imidazoles, benzimidazoles and triazoles has stimulated much work on these heterocycles [1-6]. We would like to report the syntheses of the title compounds as possible effective drugs in fertility regulation [7].

The most common method for the preparation of the title compounds is the reaction of an alkyl halide with the desired heterocycle [8]. The reaction of imidazole, triazole or benzimidazole in tetrahydrofuran with sodium hydride and a substituted 2-phenethyl halide afforded the desired compounds **3** or **5** in low yield. The yield was increased by using substituted 2-phenethyl *p*-toluensulfonate (Scheme 1).

Scheme 1

Method A:



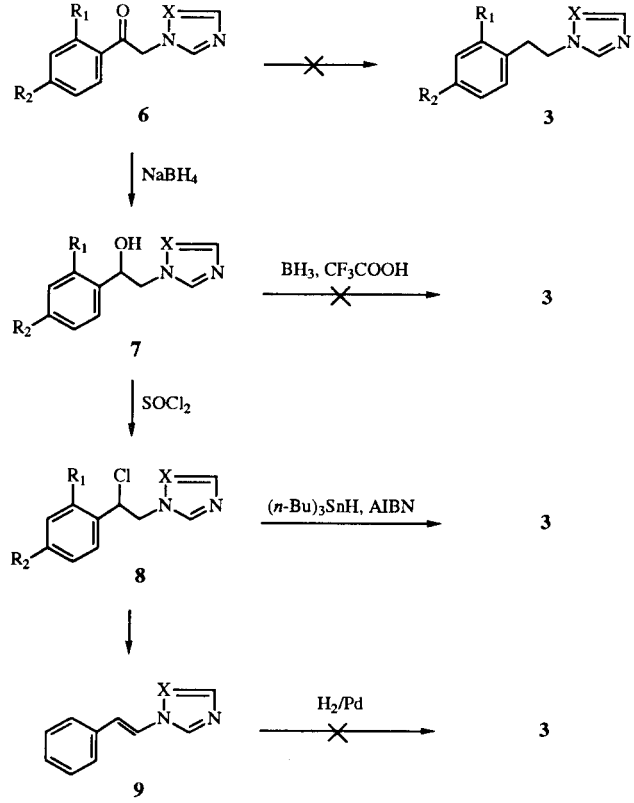
a X = CH, R = R_1 = R_2 = H
b X = CH, R = CH_3, R_1 = R_2 = H
c X = CH, R = CH_3, R_1 = R_2 = Cl
d X = CH, R = CH_3, R_1 = H, R_2 = OCH_3
e X = CH, R = R_1 = H, R_2 = Cl
f X = N, R = R_1 = R_2 = H
g X = N, R = R_1 = H, R_2 = Cl
h X = N, R = R_1 = H, R_2 = CH_3
i X = N, R = R_1 = H, R_2 = OCH_3
j X = N, R = H, R_1 = R_2 = Cl

k R_1 = R_2 = H
l R_1 = H, R_2 = OCH_3
m R_1 = R_2 = Cl

Another method for the preparation of 1-substituted imidazoles is the reaction of the appropriate amine with chloroacetal to give the *N*-substituted aminoacetal which was allowed to react with thiocyanic acid to yield a 1-substituted 2-mercaptoimidazole. The latter compound was desulfurized with Raney nickel to produce a 1-substituted imidazole in moderate yield [9]. However, this method was not feasible in our case. Finally, we could obtain 1-substituted imidazoles and triazoles by the method shown in Scheme 2 (method B).

Scheme 2

Method B:



a X = CH, R_1 = R_2 = H
b X = CH, R_1 = H, R_2 = Cl
c X = N, R_1 = R_2 = H
d X = N, R_1 = H, R_2 = Cl
e X = N, R_1 = R_2 = Cl

The reaction of compound **6** [10] with hydrazine in alkaline medium (Wolff-Kishner reaction), borane-tetrahydrofuran in trifluoroacetic acid [11], sodium borohydride in trifluoroacetic acid [12], lithium aluminum hydride-aluminum chloride [13] and triethyl silane in trifluoroacetic acid [14] did not yield compound **3**. Moreover, the reaction of compound **7** [10] with borane-tetrahydrofuran in trifluoroacetic acid [11] and sodium borohydride in trifluoroacetic acid [12], as well as the reduction of 1-styryl-1,2,4-triazole **9** [15] with hydrogen in the presence of palladium-carbon did not give the desired compound **3**. However, compound **3** was obtained from the reaction of compound **8** [10] with tri-*n*-butyltin hydride [16,17] in the presence of azobisisobutyronitrile (AIBN) in good yield. The mp, yields and analytical data of the compounds prepared are summarized in Table 1.

Table 1

Mp, Yields and Analytical Data for Compounds **3a-j** and **5k-n**

Compound [a]	Mp,°C	Yield method A	Yield method B	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
3a	oil	52	82	$C_{11}H_{12}N_2$	76.74	76.89	6.98	6.79	16.28	16.12
3b	oil	55	- [e]	$C_{12}H_{14}N_2$	77.42	77.31	7.53	7.64	15.05	14.92
3c	oil	40	- [e]	$C_{12}H_{12}Cl_2N_2$	56.47	56.32	4.71	4.58	10.98	10.82
3d	oil	45	- [e]	$C_{13}H_{16}N_2O$	72.22	72.36	7.41	7.54	12.96	13.11
3e	oil	42	75	$C_{11}H_{11}ClN_2$	63.92	63.75	5.33	5.21	13.56	13.42
3f	146-148 [b]	47	80	$C_{10}H_{12}ClN_3$	57.28	57.09	5.73	5.61	20.05	20.22
3g	oil	45	92	$C_{10}H_{10}ClN_3$	57.83	57.94	4.82	4.95	20.24	20.09
3h	58-60 [c]	48	- [e]	$C_{11}H_{13}N_3$	70.59	70.43	6.95	6.84	22.46	22.63
3i	51-53 [c]	33	- [e]	$C_{11}H_{13}N_3O$	65.02	64.91	6.40	6.28	20.69	20.73
3j	173-175 [b]	31	84	$C_{10}H_{10}Cl_3N_3$	43.09	42.93	3.59	3.69	15.08	14.93
5k	139-140 [c]	73	- [e]	$C_{15}H_{14}N_2$	81.08	81.21	6.31	6.50	12.61	12.73
5l	174-175 [b]	68	- [e]	$C_{16}H_{17}ClN_2O$	66.55	66.63	5.89	5.95	9.71	9.84
5m	137-138 [d]	70	- [e]	$C_{15}H_{12}Cl_2N_2$	61.86	61.71	4.12	4.05	9.62	9.76

[a] Unless otherwise mentioned the compounds were prepared similar to example 1 (see experimental). [b] As hydrochloride salts, crystallized from ethanol. [c] Crystallized from ethanol-ether. [d] Crystallized from methanol. [e] The preparation of this compound by method B was not attempted.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded on a Perkin Elmer 550 SE spectrophotometer. The ir spectra were obtained on a Perkin Elmer 267 spectrophotometer (potassium bromide disks). The nmr spectra were recorded on a Bruker FT-80 spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. The mass spectra were run on Varian Model MAT MS-311 spectrometer at 70 ev.

1-(2-Phenethyl)benzimidazole (**5k**).

Method A.

Example 1: To a stirred solution of benzimidazole (2.36 g, 0.02 mole) in dry tetrahydrofuran (40 ml) was added sodium hydride (0.6 g, 0.025 mole). After 15 minutes this mixture was added dropwise to a stirring solution of 2-phenethyl *p*-toluensulfonate (5.52 g, 0.02 mole) in tetrahydrofuran (30 ml). The progress of the reaction was followed by tlc (silica gel, chloroform). When the reaction was complete, the mixture was filtered and the solvent was evaporated. The residue was acidified with 5% hydrochloric acid (30 ml) and extracted with ethyl acetate (2 x 50 ml). The aqueous solution was neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 30 ml). The organic layer was dried with sodium sulfate. The solvent was evaporated and the residue was crystallized from ether-petoleum ether to give compound (**5k**) (3.24 g, 73%) mp 139-140°C [ref 18, mp 74-75°]; mp as the hydrochloride 218-220°; uv (water as the hydrochloride): λ_{max} 267 (log ε =3.9) and 243 nm (log ε = 3.89); ^{1}H-nmr (deuteriochloroform, as free base): 8.14 (s, 1H, H_2 benzimidazole), 7.55 (m, 2H, aromatic), 7.17 (m, 7H, aromatic), 3.80 (t, 2H, CH_2N) and 3.01 (t, 2H, CH_2); ms: m/z (%) 222 (M^+, 14), 118 (100), 91 (96), 54 (12) and 44 (20).

Compounds (**3a-3j**), **5l** and **5m** were prepared similarly (Table 1).

1-[2-(2,4-Dichlorophenyl)ethyl]-1,2,4-triazole (**3j**).

Example 2:

To a stirred solution of sodium (2.3 g, 0.1 mole) in ethanol (80 ml), 1*H*-1,2,4-triazole (6.9 g, 0.1 mole) was added. After 30 minutes, 2-(2,4-dichlorophenyl)ethyl bromide (25.4 g, 0.1 mole) in ethanol (60 ml) was added dropwise.

The mixture was refluxed overnight. After cooling, ether (60 ml) was added, the precipitate was filtered and the solvent was evaporated. To the residue 5% hydrochloric acid (40 ml) was added and extracted with ethyl acetate (2 x 50 ml). The aqueous layer was neutralized with sodium bicarbonate and extracted with ethyl acetate (2 x 50 ml). The organic layer was dried with sodium sulfate, the solvent was evaporated and the residue was crystallized from ethyl acetate-ether to give **3j** (1.22 g, 5%), mp 111-113° (mp of hydrochloride 173-175°); uv (methanol): λ_{max} 220 nm (log ε = 4.23); ir (potassium bromide): ν 2050, 865 and 825 cm^{-1} (aromatic); ^{1}H-nmr (deuteriochloroform); 8.03 (s, 2H, triazole), 7.42 (d, 1H, H_3 of phenyl, $J_{3,5}$ = 2 Hz), 7.17 (dd, 1H,

H5 of phenyl, $J_{3,5}$ = 2 Hz, $J_{5,6}$ = 8.2 Hz), 6.91 (d, 1H, H_6 of phenyl, $J_{5,6}$ = 8.2 Hz), 4.31 (t, 2H, CH_2N) and 3.19 (t, 2H, CH_2), ms: m/z (%) 241 (M^+, 4), 206 (81), 161 (98), 159 (100), 137 (29), 125 (60), 102 (94), 101 (94), 99 (91), 89 (94), 75 (94), 73 (87), 63 (92), 51 (92) and 39 (61).

Compounds **3f, 3g, 3h** and **3i** were prepared similarly. The yields were 21%, 25%, 6% and 5% respectively.

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

Method B.

A mixture of compound **8c** [10] (1.25 g, 6 mmoles) in dry toluene (50 ml) was added dropwise over 30 minutes to a stirred refluxing solution of tributylstannane (2.7 g, 9.3 mmoles) and azobisisobutyronitrile (20 mg, 0.12 mmole) in toluene (200 ml) under nitrogen. The solution was refluxed for an additional 4 hours. The solvent was evaporated under the reduced pressure and 5% hydrochloric acid (40 ml) was added. The mixture was extracted with ethyl acetate (2 x 50 ml). The aqueous layer was neutralized with sodium bicarbonate and extracted with ethyl acetate (2 x 50 ml). The organic layer was dried with sodium sulfate and the solvent was evaporated. The residue was dissolved in dry ether and hydrogen chloride gas was bubbled through it to give compound **3f** as the hydrochloride (1.58 g, 80%). The salt was recrystallized from ethanol, mp 146-148°; ^{1}H-nmr (deuteriochloroform, as a free base): 7.9 (s, 1H, triazole), 7.74 (s, 1H, triazole), 7.12 (m, 5H, C_6H_5), 4.31 (t, 2H, CH_2N) and 3.09 (t, 2H, CH_2), ms: m/z (%) 173 (M^+, 96), 172 (43), 145 (25), 118 (30), 105 (95), 104 (100), 103 (92), 91 (99), 77 (93), 65 (95), 51 (92) and 39 (93). Compounds **3a, 3e, 3g** and **3j** were prepared similarly (Table 1).

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REFERENCES AND NOTES

[1] A. Shafiee, F. Naghashian and N. Reghabi, *J. Heterocyclic Chem.*, **29**, 1859 (1992) and references cited therein.

[2] W. O. Foye, Principles of Medicinal Chemistry, Lea & Febiger, Philadelphia, 1989 p. 728.

[3] H. Timmler, W. Kraemer, K. H. Buechel, W. Brandes, P. E. Frohberger, and B. Homeyer, German Offen., 2,628,420 (1978); *Chem. Abstr.*, **88**, 15261m (1978).

[4] K. A. M. Walker, European Patent Appl. EP 64,244 (1982); *Chem. Abstr.*, **98**, 143420w (1983).

[5] B. H. Vickery, S. Anik and R. E. Jones, European Patent Appl. EP 65,385 (1982); *Chem. Abstr.* **98**, 732321p (1983).

[6] K. A. M. Walker, D. R. Hirschfeld and M. Marx, *J. Med. Chem.*, **21**, 1335 (1978).

[7] R. Maybury, *Chem. Eng News*, August 12, p 28 (1991).

[8] C. Ainsworth, N. R. Eastorn, M. Livezey, D. E. Morrison and W. R. Gibson, *J. Med. Chem.* **5**, 383 (1962).

[9] W. N. Cannon, C. E. Powell and R. G. Jones, *J. Org. Chem.*, **22**, 1323 (1957).

[10] H. Timmler, K. H. Buechel, W. Brandes and P. E. Frohberger, *Ger.man Offen.* 2,547,954 (1977), *Chem. Abstr* , **87**, 53317m (1977).

[11] B. E. Maryanoff, D. F. McComsey, and S. O. Nortey, *J. Org. Chem.* **46**, 355 (1981).

[12] G. W. Gribble, R. M. Leese and B. E. Evans, *Synthesis*, 172 (1977).

[13] R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

[14] C. T. West, S. J. Donnelly, D. A. Kooistra and M. P. Doyle, *J. Org. Chem.*, **38**, 2675 (1973).

[15] F. Linhart, B. Zeeh and H. Adolphi, *German Offen.* 2,833,194 (1980), *Chem. Abstr.*, **92**, 215449p (1980).

[16] W. P. Neumann, Synthesis, 665 (1987).

[17] H. G. Kuivila, *Synthesis*, 499 (1970).

[18] H. Matrick and A. R. Day, *J. Org. Chem.*, **26**, 1646 (1961).