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A Methylene Bridge as Protecting Group. 1. Selective Preparation of 4-Alkyl-1,2,4-triazoles.

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Abstract. An efficient preparation of the title compounds is described. Easily accessible bis(1,2,4-triazol-1-yl)methane is transformed into double azolium salts which, by nucleophilic substitution, yield 4-substituted-1,2,4-triazoles. The method involves the use of a methylene moiety as a protecting group for the two azole units. © 1997, Elsevier Science Ltd. All rights reserved.

The ability of the azole nitrogen to coordinate the iron atom of cytochrome P-450 enzymes makes N-substituted azoles interesting synthetic targets.[1-3] The alkylation of azoles usually requires a deprotonation step followed by reaction with an electrophile (alkyl halide or tosylate).[4-6] Other methods such as the Mitsunobu reaction[7,8] or via 1-benzenesulfonylazoles[9] have been reported. When these methods are applied to 1,2,4-triazole 1-substituted derivatives are obtained, which in some cases countain minor quantities of 4-substituted 1,2,4-triazoles.[10-13] Two main methodologies for preparing 4-substituted 1,2,4-triazoles have been used: i) ring formation from substituted acyclic compounds[6], and ii) blocking the N-1 atom followed by quaternization and cleavage of the protective group. The low accessibility of the appropriate acyclic compounds makes the former method of little general applicability. The latter is more extensively used and trityl, benzyl, phenacyl and acyl groups have all been used as protective groups. However, a drawback of the method is the low selectivity and poor yields in the N-protection step[14] as well as the lability of the protecting group under quaternization conditions.[15] When acyl groups[11,16] are employed, forcing reaction conditions and expensive alkylating agents such as oxonium salts are required. Recently the 2-cyanoethyl group has been reported,[17] as an efficient protective group although the deprotection step had to be performed under strong basic conditions.

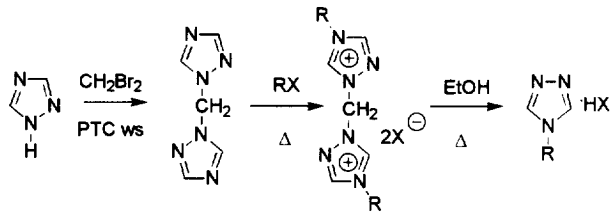
This paper describes a new way of exclusively preparing 4-substituted-1,2,4-triazoles. The method is based on the alkylation of bis(1,2,4-triazol-1-yl)methane, which can be envisaged as two 1,2,4-triazole rings protected by a methylene bridge.

This method of protecting a 1,2,4-triazole ring is compatible with strong basic conditions since alkaline hydroxides are used in the preparation of bis(1,2,4-triazol-1-yl)methane[18] and ring deprotonation with n-

butyllithium has been performed without affecting the methylene group.[19]

Results and Discussion

Starting from 1,2,4-triazole three reaction steps are required (Scheme). The initial step of synthesising the bis(1,2,4-triazol-1-yl)methane is efficiently performed under Phase Transfer Catalysis conditions without solvent (PTC ws) following a general method for the preparation of bis(azol-1-yl)methanes.[18]



Scheme

3, 6 X = TsO; **4, 7** X = I; **5, 8** X = Br

	a	**b**	**c**
R	methyl	ethyl	butyl
	d	**e**	**f**
R	octyl	hexadecyl	allyl
	g	**h**	**i**
R	propargyl	benzyl	isopropyl

The desired alkylation is then carried out by heating a mixture of bis(1,2,4-triazol-1-yl)methane **2** and a large excess of the appropriate alkylating agent (bromide, iodide or tosylate[20]) thus, affording the double azolium salts in high yield. (Table) The excess alkylating agent is recovered by direct distillation or by addition of a suitable solvent, followed by filtration and evaporation of solvent.

Alkyl tosylates were used instead of alkyl halides where possible, to avoid the likelihood of nucleophilic attack by the counter ion. As bromide and iodide anions have been reported[21] to promote bridge cleavage in bis(pyrazol-1-yl)methane. With highly reactive bromides (benzyl, allyl and propargyl) however bridge cleavage is not observed and satisfactory yields are obtained. Butyl and octyl iodides likewise afford favourable yields although variable quantities of 1,4-dialkyl-1,2,4-triazolium iodide are also detected. Generally speaking it can be said that for the introduction of primary alkyl functions, tosylates are the best choice given the cleaner reactions and quantitative yields. In order to introduce secondary alkyl groups it is necessary to use iodides since tendency of the secondary tosylates to eliminate[22] under the reaction conditions. The reaction time must however be extended to 15 days to obtain satisfactory yields (65%). The deprotection step is simply and quantitatively accomplished by refluxing the bisazolium for 5 days. The quaternization enhances the azole ability to act as a leaving group[23] while the methylene bridge bearing two azolium salts is now a high reactive centre towards nucleophiles, even those as weak as alcohols. The deprotection time can be shortened to 5-12 hours using a higher boiling alcohol such as n-butanol. Alternatively a stronger nucleophile such as sodium

sulfide can be used although the deprotection is not as clear and the yield drop to ca. 60%.

Table. Preparation of 4,4'-disubstituted 1,1'-methylenebis(1,2,4-triazolium) salts.

product	mp (°C)	time (h)	T (°C)	yield (%)
3a	170-171	24	90	>99
3b	151-152	24	90	>99
3c	158-160	24	90	>99
4c	188-189	7	130	80
3d	168-169	48	90	72
		7	130	70
4d	219-220	7	130	70
3e	204-206 (d)	120	90	92
		5	140	90
5f	183-186 (d)	120	70	78
5g	211-212 (d)	120	90	71
5h	241-242 (d)	24	130	99
4i	>300	360	90	65

In conclusion an efficient preparation of 4-substituted 1,2,4-triazoles in high yields is reported. The method represents the use of a methylene moiety as a protecting group for two azole units. This methodology opens new possibilities for the preparation of the least common regioisomer in N-substituted heterocycles.

Experimental Section

Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 CHN microanalyzer. ^{1}H NMR spectra were recorded on a Varian Geminy 200 spectrometer operating at 199.975 MHz. ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer operating at 75.414 MHz. Chemical shifts are expressed in parts per million (d) relative to tetramethylsilane as internal standard in DMSO-d_6.

Synthesis of bis(1,2,4-triazol-1-yl)methane **2**.

In a 25 mL closed vessel 1,2,4-triazole (1.38 g, 20 mmol), finely ground potassium hydroxide (2.24 g, 40 mmol) and TBAB (193 mg, 0.6 mmol) and 0.15 mL of water were stirred for 1 hour. Then dibromomethane (5.22 g, 30 mmol) was added and the stirring was continued at room temperature for 48 hours. The reaction crude was extracted with dichloromethane (5 x 20 mL) and chromatographed on silica gel (13 g). Elution with ethyl acetate afforded the pure product (1.15 g, 77%). mp 142-143°C (toluene), lit.[24] 127°C. ^{1}H-NMR: δ 6.40 (s, 2H), 8.00 (s, 2H), 8.40, (s, 2H).

Synthesis of 4,4'-disubstituted 1,1'-methylenebis(1,2,4-triazolium) salts.

General Procedure. A mixture of bis(1,2,4-triazol-1-yl)methane **2** (1-4 mmol) and an excess of the appropriate electrophile (iodide, bromide or tosylate) was stirred and heated (70-140 °C) for the adequate time (5-120 h). Pure products were isolated following methods A or B.

Method A: After cooling, any remaining electrophile was recovered by extracting the mixture with the appropriate solvent and distilling under vacuum. The 1,1'-methylenebis(1,2,4-triazolium) salts were isolated by washing the remaining solid with the appropriate solvent.

Method B: After cooling, any remaining electrophile was recovered by distilling under vacuum at room temperature. The 1,1'-methylenebis(1,2,4-triazolium) salts left were washed with ethyl acetate and, when necessary, recrystallized.

4,4'-Dimethyl-1,1'-methylenebis(1,2,4-triazolium) ditosylate (3a). 600 mg (4 mmol) of **2** and 15 mL of methyl tosylate. Temperature, 90 °C. Reaction time, 24 h. Method A: Extraction of the electrophile with hexane-toluene 1:1. Product was washed with hexane. Yield 100%. mp 170-171 °C upon recrystallization from ethanol-ethyl acetate. ^{1}H NMR δ 2.31 (s, 6H), 3.97 (s, 6H), 7.14, (d, *J*=8.0 Hz, 4H), 7.19 (s, 2H), 7.49 (d, *J*=8.0 Hz, 4H), 9.30 (s, 2H), 10.42 (s, 2H); ^{13}C NMR δ 20.7, 34.5, 62.2, 125.4, 128.0, 137.5, 145.6, 146.3. Anal. Calcd for $C_{21}H_{26}N_6O_6S_2$: C, 48.26; H, 5.02; N, 16.09. Found: C, 48.72; H,5.21; N, 15.86.

4,4'-Diethyl-1,1'-methylenebis(1,2,4-triazolium) ditosylate (3b). 300 mg (2 mmol) of **2** and 15 mL of ethyl tosylate. Temperature, 90 °C. Reaction time, 24 h. Method A: Extraction of the electrophile with hexane-toluene 1:1. Product was washed with hexane. Yield 100%. mp 151-152 °C upon recrystallization from ethanol-ethyl acetate. ^{1}H NMR δ 1.41 (t, *J*=7.3 Hz, 6H), 2.29 (s, 6H), 4.34 (c, *J*=7.3 Hz, 4H), 7.11 (d, *J*=7.9, 4H), 7.12 (s, 2H), 7.47 (d, *J*=7.9, 4H), 9.41 (s, 2H), 10.50 (s, 2H); ^{13}C NMR δ 14.2, 20.8, 43.6, 62.4, 125.4, 128.1, 137.8, 145.1, 145.3, 145.4. Anal. Calcd for $C_{23}H_{30}N_6O_6S_2$: C, 50.17; H, 5.49; N, 15.26. Found: C, 50.23; H, 5.65; N, 14.99.

4,4'-Dibutyl-1,1'-methylenebis(1,2,4-triazolium) ditosylate (3c). 300 mg (2 mmol) of **2** and 15 mL of butyl tosylate. Temperature, 90 °C. Reaction time, 24 h. Method A: Extraction of the electrophile with hexane-toluene 1:1. Product was washed with hexane. Yield 100%. mp 159-160 °C upon recrystallization from chloroform-ethyl acetate. ^{1}H NMR δ 0.92 (t, *J*=7.2 Hz, 6H), 1.32 (sext., *J*=7.5 Hz, 4H), 1.82 (quint., *J*=7.5 Hz, 4H), 2.31 (s, 6H), 4.34 (t, *J*=7.3 Hz, 4H), 7.13 (s, 2H), 7.14 (d, *J*=7.7 Hz, 4H), 7.49 (d, *J*=7.7 Hz, 4H), 9.44 (s, 2H), 10.54 (s, 2H); ^{13}C NMR δ 13.2, 18.7, 20.8, 30.6, 47.7, 62.5, 125.4, 128.1, 137.8, 145.2, 145.3, 145.4. Anal. Calcd for $C_{27}H_{38}N_6O_6S_2$: C, 53.45; H, 6.31; N, 13.85. Found: C, 53.75; H, 5.97; N, 13.88.

4,4'-Dibutyl-1,1'-methylenebis(1,2,4-triazolium) diiodide (4c). 100 mg (0.67 mmol) of **2** and 15 mL of butyl iodide. Temperature, reflux (130 °C). Reaction time, 7 h. Method B: Yield 80%. mp 188-189 °C upon recrystallization from ethanol-ethyl acetate. ^{1}H NMR δ 0.92 (t, *J*=7.3 Hz, 6H), 1.32 (sext., *J*=7.3 Hz, 4H), 1.83 (quint., *J*=7.3 Hz, 4H), 4.35 (t, *J*=7.3 Hz, 4H), 7.11 (s, 2H), 9.43 (s, 2H), 10.49 (s, 2H); ^{13}C NMR δ 13.2, 18.7, 30.7, 47.8, 62.5, 145.0, 145.5. Anal. Calcd for $C_{13}H_{24}N_6I_2$: C, 30.13; H, 4.67; N, 16.22. Found: C, 30.46;

H, 4.48; N, 15.99.

4,4'-Dioctyl-1,1'-methylenebis(1,2,4-triazolium) ditosylate (3d). 407 mg (2.7 mmol) of **2** and 5.4 g (19 mmol) of octyl tosylate. Temperature, 90 °C. Reaction time, 48 h. Method A: Extraction of the electrophile with ethyl acetate. Product was washed with ethyl acetate. Yield 72%.

Alternatively, 18 mg (0.12 mmol) of **2** and 250 mg (0.88 mmol) of octyl tosylate. Temperature, 130 °C. Reaction time, 7 h. Method A: Extraction of the electrophile with ethyl acetate. Product was washed with ethyl acetate. Yield 70%. mp 168-169 °C upon recrystallization from acetone. ^{1}H NMR δ 0.86 (t, *J*=6.3 Hz, 6H), 1.15-1.35 (m, 20H), 1.70-1.90 (m, 4H), 2.29 (s, 6H), 4.30 (t, *J*=7.7 Hz, 4H), 7.11 (d, *J*=8.2 Hz, 4H), 7.12 (s, 2H), 7.47 (d, *J*=8.2 Hz, 4H), 9.41 (s, 2H), 10.52 (s, 2H); ^{13}C NMR δ 13.9, 20.7, 22.0, 25.4, 28.3, 28.4, 28.7, 31.1, 47.9, 62.5, 125.4, 128.0, 137.6, 145.2, 145.4, 145.5. Anal. Calcd for $C_{35}H_{54}N_6O_6S_2$: C, 58.47; H, 7.58; N, 11.70. Found: C, 58.65; H, 7.40; N, 11.56.

4,4'-Dioctyl-1,1'-methylenebis(1,2,4-triazolium) diiodide (4d). 100 mg (0.67 mmol) of **2** and 15 mL of octyl iodide. Temperature, 130 °C. Reaction time, 7 h. Method B: Recrystallization from ethanol-ethyl acetate. Yield 70%. mp 219-220 °C. ^{1}H NMR δ 0.86 (t, *J*=6.5 Hz, 6H), 1.15-1.40 (m, 20H), 1.75-1.95 (m, 4H), 4.33 (t, *J*=7.5 Hz, 4H), 7.11 (s, 2H), 9.42 (s, 2H), 10.48 (s, 2H); ^{13}C NMR δ 13.9, 22.0, 25.4, 28.3, 28.4, 28.8, 31.1, 48.0, 62.5, 145.0, 145.5. Anal. Calcd from $C_{21}H_{40}N_6I_2$: C, 40.01; H, 6.40; N, 13.33. Found: C, 40.07; H, 6.07; N, 13.08.

4,4'-Dihexadecyl-1,1'-methylenebis(1,2,4-triazolium) ditosylate (3e). 150 mg (1 mmol) of **2** and 2.78 g (7 mmol) of hexadecyl tosylate. Temperature, 90 °C. Reaction time, 120 h. Method A: Extraction of the electrophile with ethyl acetate. Product was washed with ethyl acetate. Yield 92%.

Alternatively, 100 mg (0.67 mmol) of **2** and 1.85 g (4.67 mmol) of hexadecyl tosylate. Temperature, 140 °C. Reaction time, 5 h. Method A: Extraction of the electrophile with ethyl acetate. Product was washed with ethyl acetate. Yield 90%. mp 204-206 °C (decomposition) upon recrystallization from ethanol. ^{1}H NMR δ 0.85 (t, *J*=6.4 Hz, 6H), 1.15-1.35 (m, 26H), 1.70-1.90 (m, 4H), 2.29 (s, 6H), 4.31 (t, *J*=7.5 Hz, 4H), 7.10 (d, *J*=8.0, 4H), 7.11 (s, 2H), 7.47 (d, *J*=8.0, 4H), 9.41 (s, 2H), 10.49 (s, 2H); ^{13}C NMR δ 13.9, 20.7, 22.0, 25.4, 28.3, 28.6, 28.7, 28.9, 28.9, 29.0, 31.2, 48.0, 62.4, 121.4, 125.4, 137.5, 145.1, 145.5, 145.7. Anal. Calcd for $C_{51}H_{86}N_6O_6S_2$: C, 64.93; H, 9.20; N, 8.91. Found: C, 64.75; H, 8.88; N, 8.75.

4,4'-Diisopropyl-1,1'-methylenebis(1,2,4-triazolium) diiodide (4i). 100 mg (0.67 mmol) of **2** and 15 mL of isopropyl iodide. Temperature, reflux (90 °C). Reaction time, 15 days. Method B: Recrystallization from ethanol-ethyl acetate. Yield 65%. mp >300 °C. ^{1}H NMR δ 1.55 (d, *J*=6.6 Hz, 12H), 4.86 (sept. *J*=6.6 Hz, 2H), 7.05 (s, 2H), 9.56 (s, 2H), 10.57 (s, 2H); ^{13}C NMR δ 21.9, 52.6, 62.4, 144.2. Anal. Calcd for $C_{11}H_{20}N_6I_2$: C, 26.94; H, 4.11; N, 17.15. Found: C, 27.17; H, 3.93; N, 16.88.

4,4'-Diallyl-1,1'-methylenebis(1,2,4-triazolium) dibromide (5f). 150 mg (1 mmol) of **2** and 15 mL of allyl bromide. Temperature, reflux (70 °C). Reaction time, 120 h. Method B: Yield 78%. mp 183-186 °C (decomposition) upon recrystallization from ethanol. ^{1}H NMR δ 5.06 (d, *J*=6.18 Hz, 4H), 5.43-5.52 (m, 4H),

6.01-6.20 (m, 2H), 7.20 (s, 2H), 9.44 (s, 2H), 10.59 (s, 2H); ^{13}C NMR δ 49.9, 62.4, 121.8, 130.2, 145.2, 145.3. Anal. Calcd for $C_{11}H_{16}N_6Br_2$: C, 33.70; H, 4.11; N, 21.43. Found: C, 34.02; H, 4.06; N, 21.19.

4,4'-Dipropargyl-1,1'-methylenebis(1,2,4-triazolium) dibromide (5g). 150 mg (1 mmol) of **2** and 15 mL of propargyl bromide. Temperature, reflux (90 °C). Reaction time, 120 h. Method B: Recrystallization from methanol. Yield 71%. mp 211-212 °C (decomposition). ^{1}H NMR δ 4.07 (t, *J*=2.6 Hz 2H), 5.44 (d, *J*=2.6 Hz, 4H), 7.23 (s, 2H), 9.51 (s, 2H), 10.67 (s, 2H); ^{13}C NMR δ 38.9, 62.4, 74.7, 80.8, 145.0, 145.2. Anal. Calcd for $C_{11}H_{12}N_6Br_2$: C, 34.04; H, 3.12; N, 21.66. Found: C, 34.45; H, 3.17; N, 21.27.

4,4'-Dibenzyl-1,1'-methylenebis(1,2,4-triazolium) dibromide (5h). 150 mg (1 mmol) of **2** and 15 mL of benzyl bromide. Temperature, 130 °C. Reaction time, 24 h. Method A: Extraction of the electrophile with methylene chloride. Product was washed with methylene chloride. Yield 99%. mp 241-242 °C (decomposition) upon recrystallization from methanol. ^{1}H NMR δ 5.68 (s, 4H), 7.16 (s, 4H), 7.45-7.60 (m, 10H), 9.59 (s, 2H), 10.71 (s, 2H); ^{13}C NMR δ 50.8, 62.5, 128.9, 129.0, 129.1, 133.1, 145.1, 145.3. Anal. Calcd for $C_{19}H_{20}N_6Br_2$: C, 46.36; H, 4.10; N, 17.07. Found: C, 46.61; H, 4.18; N, 16.92.

Deprotection step

General procedure. Method A: A mixture of the appropriate amount of 4,4'-disubstituted 1,1'-methylenebis(1,2,4-triazolium) salt and 15 mL of ethanol was stirred at reflux for five days. The solvent was evaporated under vacuum and an hygroscopic oil that crystallized after some hours was obtained. The product was dried under vacuum at 60 °C. In all cases quantitative yields were obtained.

Method B: A mixture of the appropriate amount of 4,4'-disubstituted 1,1'-methylenebis(1,2,4-triazolium) salt and 15 mL of butanol was stirred and refluxed for the adequate time. The solvent was evaporated and the product was washed with carbon tetrachloride and dried under vacuum at 60 °C.

4-Methyl-1,2,4-triazolium tosylate (6a). Method A or Method B (5 h, 90%). mp 145-146 °C (ethanol-diethyl ether). ^{1}H NMR δ 2.31 (s, 3H), 3.89 (s, 3H), 7.14 (d, *J*=7.7 Hz, 2H), 7.50 (d, *J*=8.0 Hz, 2H), 9.45 (s, 2H); ^{13}C NMR δ 20.8, 33.3, 125.4, 128.1, 137.8, 144.2, 145.4. Anal. Calcd for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46. Found: C, 47.02; H, 5.35; N, 16.66.

4-Ethyl-1,2,4-triazolium tosylate (6b). Method A. mp 99-100 °C (ethanol-diethyl ether). ^{1}H NMR δ 1.46 (t, *J*=7.4 Hz, 3H), 2.31 (s, 3H), 4.25 (c, *J*=7.4 Hz, 2H), 7.13 (d, *J*=8.1 Hz, 2H), 7.49 (d, *J*=8.1 Hz, 2H), 9.44 (s, 2H); ^{13}C NMR δ 14.7, 20.8, 42.4, 125.5, 128.1, 137.9, 143.4, 145.3. Anal. Calcd for $C_{11}H_{15}N_3O_3S$: C, 49.06; H, 5.61; N, 15.60. Found: C, 49.32; H, 5.90; N, 15.89.

4-Butyl-1,2,4-triazolium tosylate (6c). Method A. mp 68-70 °C (ethanol-diethyl ether). ^{1}H NMR δ 0.92 (t, *J*=7.4 Hz, 3H), 1.29 (sext., *J*=7.4 Hz, 2H), 1.81 (quint., *J*=7.4 Hz, 2H), 2.31 (s, 3H), 4.23 (t, *J*=7.4 Hz, 2H), 7.13 (d, *J*=7.9 Hz, 2H), 7.48 (d, *J*=7.9 Hz, 2H), 9.50 (s, 2H); ^{13}C NMR δ 13.3, 18.8, 20.8, 32.0, 46.6, 125.5, 128.1, 137.8, 143.6, 145.4. Anal. Calcd for $C_{13}H_{19}N_3O_3S$: C, 52.51; H, 6.44; N, 14.13. Found: C, 52.13; H, 6.72; N, 14.02.

4-Octyl-1,2,4-triazolium tosylate (6d). Method A or Method B (5 h, 95%). mp 87-88 °C (ethanol-diethyl ether). ^{1}H NMR δ 0.87 (t, *J*=6.6 Hz, 3H), 1.15-1.35 (m, 10 H), 1.70-1.90 (m, 2H), 2.30 (s, 3H), 4.22 (t, *J*=7.3 Hz, 2H), 7.12 (d, *J*=8.1 Hz, 2H), 7.50 (d, *J*=8.1 Hz, 2H), 9.51 (s, 2H); ^{13}C NMR δ 13.9, 20.7, 22.0, 25.5, 28.3, 28.4, 29.1, 31.1, 46.5, 125.4, 128.0, 137.6, 143.5, 145.6. Anal. Calcd for $C_{17}H_{27}N_3O_3S$: C, 57.76; H, 7.70; N, 11.89. Found: C, 57.63; H, 7.82; N, 11.84.

4-Hexadecyl-1,2,4-triazolium tosylate (6e). Method A. mp 169-171 °C (ethanol-diethyl ether). ^{1}H NMR δ 0.83 (t, *J*=6.2 Hz, 3H), 1.15-1.35 (m, 26H), 1.70-1.90 (m, 2H), 2.27 (s, 3H), 4.16 (t, *J*=7.2 Hz, 2H), 7.09 (d, 8.0 Hz, 2H), 7.45 (d, 8.0 Hz, 2H), 9.35 (s, 2H); ^{13}C NMR δ 13.9, 20.7, 22.0, 25.5, 28.3, 28.6, 28.8, 28.9, 29.0, 29.1, 31.2, 46.4, 125.4, 127.9, 137.5, 143.4, 145.7. Anal. Calcd for $C_{25}H_{43}N_3O_3S$: C, 64.48; H, 9.31; N, 9.02. Found: C, 64.80; H, 9.70; N, 9.22.

4-Allyl-1,2,4-triazolium bromide (8f). Method A. mp 137-139 °C (ethanol-diethyl ether). ^{1}H NMR δ 4.91 (dt, *J*=6.0, 1.4 Hz, 2H), 5.31 (ddt, *J*=17.1, 1.4, 1.3 Hz, 1H), 5.38 (ddt, *J*=10.4, 1.4, 1.3 Hz, 1H), 6.09 (ddt, *J*=17.1, 10.4, 6.0 Hz, 1H), 9.42 (s, 2H); ^{13}C NMR δ 48.6, 120.5, 131.3, 143.5. Anal. Calcd for $C_5H_8N_3Br$: C, 31.60; H, 4.24; N, 22.11. Found: C, 31.52; H, 4.38; N, 22.01.

4-Propargyl-1,2,4-triazolium bromide (8g). Method A. mp 211-212 °C (ethanol-diethyl ether). ^{1}H NMR δ 3.75 (t, *J*=2.6 Hz, 1H), 5.14 (d, *J*=2.6 Hz, 2H), 9.05 (s, 2H); ^{13}C NMR δ 35.0, 76.9, 77.8, 143.1. Anal. Calcd for $C_5H_6N_3Br$: C, 31.94; H, 3.22; N, 22.35. Found: C, 32.32; H, 3.47; N, 22.70.

4-Benzyl-1,2,4-triazolium bromide (8h). Method A. mp 168-170 °C (ethanol-diethyl ether). ^{1}H NMR δ 5.47 (s, 2H), 7.43 (m, 5H), 9.41 (s, 2H); ^{13}C NMR δ 49.5, 128.5, 128.7, 129.0, 134.6, 143.5. Anal. Calcd for $C_9H_{10}N_3Br$: C, 45.02; H, 4.20; N, 17.50. Found: C, 45.02; H, 3.99; N, 17.52.

4-Isopropyl-1,2,4-triazolium iodide (7i). Method A. mp 134-135 °C (ethanol-diethyl ether). ^{1}H NMR δ 1.49 (d, *J*=6.7 Hz, 6H); 4.67 (sept., *J*=6.7 Hz, 1H); 9.41 (s, 2H); ^{13}C NMR δ 22.4, 50.1, 142.1. Anal. Calcd for $C_5H_{10}N_3I$: C, 25.12; H, 4.22; N, 17.58. Found: C, 25.26; H, 4.44; N, 17.76.

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REFERENCES AND NOTES

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1. Mason, J. Y., *Biochem. Soc. Trans.*, **1993**, *21*, 1057
2. Testa B., Jenner P., *Drug. Metab. Rev.*, **1981**, *12*, 1
3. Vanden Bossche H., In *Sterol Biosynthesis Inhibitors, Pharmaceutical and Agrochemical Aspects*; D. Berg, M. Plempel, Eds.; Ellis Horword: Chicester, England, **1988**.

4. Elguero J., In *Comprehensive Heterocyclic Chemistry*; Katritzky A. R., Rees C. W., Eds.; Pergamon: Oxford, **1984**; vol. 5
5. Grimmett M. R., In *Comprehensive Heterocyclic Chemistry*; Katritzky A. R., Rees C. W., Eds. Pergamon: Oxford, **1984**; vol. 5
6. Polya J. B., In *Comprehensive Heterocyclic Chemistry*; Katritzky A. R., Rees C. W., Eds. Pergamon: Oxford, **1984**; vol. 5
7. Botta M., Summa V., Trapassi G., Monteagudo E., Corelli F., *Tetrahedron Asymmetry*, **1994**, *5*, 181
8. Corelli F., Summa V., Brogi A., Monteagudo E., Botta M., *J. Org. Chem.*, **1995**, *60*, 2008
9. Katritzky A. R., Zhang G., Pernak J., Fan W., *Heterocycles*, **1993**, *36*, 1253
10. Atkinson M. R., Polya J. B., *J. Chem. Soc.*, **1954**, 141
11. Olofson R. A., Kendall R. V., *J. Org. Chem.*, **1970**, *35*, 2246
12. Katritzky A. R., Kuzmierkiewicz W., Greenhill J. V., *Recl. Trav. Chim. Pays-Bas*, **1991**, *110*, 369
13. Balasubramanian M., Keay J. G., Scriven E. F. V., Shobana, N., *Heterocycles*, **1994**, *37*, 1951
14. du Vigneaud V., Behrens O. K., *J. Biol. Chem.* **1937**, *117*, 27
15. Lauth de Viguerie N., Sergueeva N., Damiot M., Mawlawi H., Riviere M., Lattes A., *Heterocycles*, **1994**, *37*, 1561
16. Kashima C., Harada Y., Hosomi A., *Heterocycles*, **1993**, *35*, 433
17. Horváth A., *Synthesis*, **1995**, 1183
18. Díez-Barra E., de la Hoz A., Sánchez-Migallón A., Tejeda J., *Heterocycles*, **1992**, *34*, 1365
19. Díez-Barra E., de la Hoz A., Sánchez-Migallón A., Tejeda J., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1079
20. Tosylates were prepared following literature procedures. Szeja W., *Synthesis*, **1979**, 822
21. Claramunt R. M., Hernández H., Elguero J., Juliá S., *Bull. Soc. Chim. Fr.*, **1983**, II-5
22. March J., in "Advanced Organic Chemistry", 4th edition. John Wiley Ed. **1992**, New York, p. 1015
23. The ability of azoles to act as leaving groups has been well demonstrated by Katritzky. See for example Katritzky A. R., Xie L., Fan W-Q., *J. Org. Chem.*, **1993**, *58*, 4376
24. Juliá S., Sala P., del Mazo J., Sancho M., Ochoa C., Elguero J., Fayet J. P., Vertut, M.C., *J. Heterocycl. Chem.*, **1982**, *19*, 1141

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