On Triazoles XXXVII. [1,2]. The Correct Structure
of the Products Formed from 1,2,4-Triazolethiones
with α-Halogenated Acetophenones

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The reaction of 1,2,4-triazolethiones with α-halogenated acetophenones was re-investigated. It was proven that in contrast to the literature data the products obtained were S-alklylated derivatives.

Fluconazole [1,3-bis-(1H-1,2,4-triazol-1-yl)-2-(2,4-di-fluorophenyl)-2-propanol (**5**, Scheme 1)] was reported in 1990 as one of the most active water-soluble oral antifungal agents [3]. Its synthesis was described from α-(1H-1,2,4-triazol-1-yl)-2',4'-difluoroacetophenone (**1**) through its epoxydation with **2** (generated *in situ* from trimethylsulfoxonium iodide and a base) and ring opening of the epoxide **3** formed with 1,2,4-triazole (**4**) (Scheme 1) [4,5].
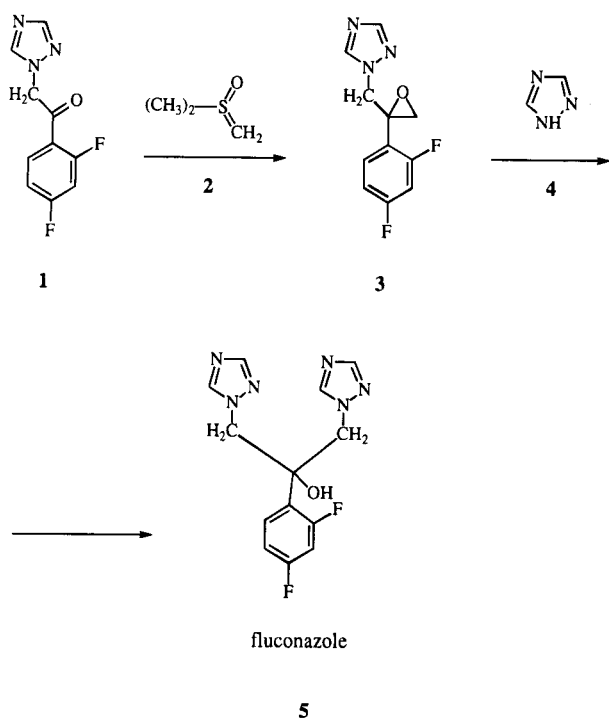
The synthesis of the intermediate **1** was performed either by direct alkylation of 1,2,4-triazole (**4**) with 2-chloro-2',4'-difluoroacetophenone (**6**) to yield after an extensive workup the required **1** in 40% yield (Scheme 2) [4], or by the alkylation of 4-amino-4H-1,2,4-triazole (**7**) with **6** to yield **8** that could be converted to **1** by diazotation and the loss of nitrous oxide in excellent yield [4,5].

In a search for more active antifungal agents Ertan and

Scheme 1
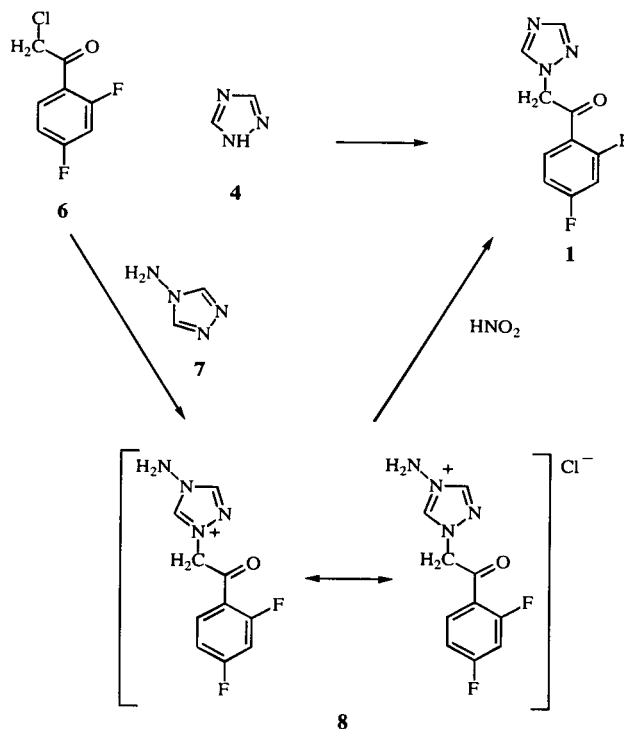
Scheme 2

coworkers [6] reacted different 3-mercapto-5-R-1,2-tria-zoles **9** with α-halogenated acetophenones **10** (R[1] = Ar) and claimed to prepare 3-mercapto-5-R-1,2,4-triazol-2-yl)acetophenones **11** (R = H, alkyl, R[1] = aryl; Scheme 3; compounds are depicted in incorrect tautomeric forms given by the authors). In the above work the authors also took in account the possibility of the formation of the corresponding **12** type *S*-alkylated derivatives (Scheme 4), but on the basis of the chemical shifts of the COCH$_2$ protons appearing at rather lower field (between 4.6 and 4.87 ppm) being thought to be caused by the deshielding effect of the corresponding triazole nitrogen atoms they excluded the possibility of their formation. The authors also described the ir, uv and ms (in both, EI and CI modes) spectral data of the derivatives obtained.

As the *N*-substituted thiouras **13** and their cyclic ana-
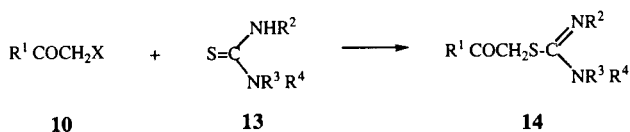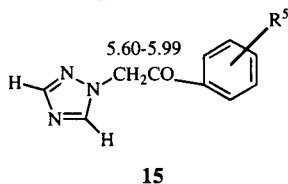
Scheme 3
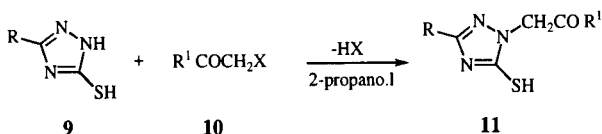
Scheme 4
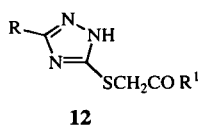
logues **13** (R^2 + R^3 = alkylene) were reported to be *S*-alkylated by α-bromoketones **10** (X = Br) to yield acyl-methyl isothioureas **14** (Scheme 5) [7] and some *N*-benzo-ylmethylated triazoles **15** (Scheme 6) were reported to have the chemical shifts of the COCH$_2$ moieties between 5.60 and 5.99 ppm [8] the structure **11** (Scheme 3) of the products obtained by Ertan *et al.* [6] seemed to be highly improbable.

Thus we repeated two of their experiments, namely the reaction of 2,3-dihydro-1,2,4-triazole-3(1*H*)-one **9a** (R =

Scheme 5

Scheme 6

H) and 2,3-dihydro-5-methyl-1,2,4-triazole-3(1*H*)-one **9b** (R = methyl) with 2,4'-dichloroacetophenone **10** (R' = 4-chlorophenyl, X = chloro) (Scheme 7) in 2-propanol using exactly the same reaction conditions as described [6]. However, as could be expected the products that crystallized from the reaction mixtures were the corresponding hydrochlorides **12a.HCl** and **12b.HCl**, respectively, and the bases **12a** and **12b** had to be liberated from them. It should be noted that while **12a** was stable enough to be liberated from **12a.HCl** by sodium ethoxide in ethanol **12b** was extremely sensitive to strong bases (sodium methoxide, sodium ethoxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, *etc.*) thus its liberation from **12b.HCl** was possible only with triethylamine in dry chloroform at room temperature.

The melting points of both, the hydrochlorides **12a.HCl** and **12b.HCl** (183-185° and 199-202°, respectively) and the corresponding bases **12a** and **12b** (116-117° and

Scheme 7
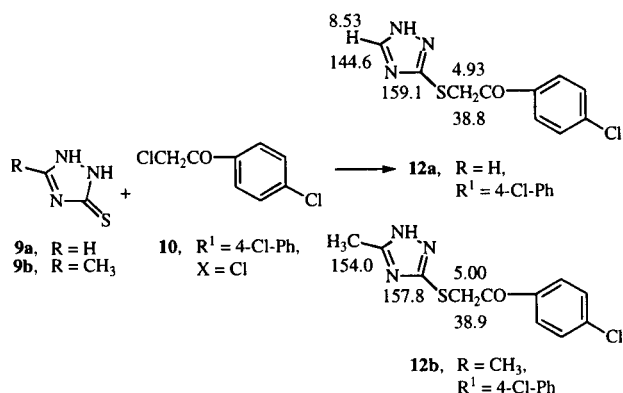
190-192°, respectively) were very different from those given by Ertan *et al.* [6] (236° and 228°, respectively).

In spite of the very different melting points the ir carbonyl bands of the bases **12a** and **12b** (ν C=O = 1687 and 1691 cm^{-1}, respectively) differed only slightly from those given in [2] (ν C=O = 1700 and 1700 cm^{-1}, respectively), and their pmr data were practically equivalent with those given in [6] {compare: **12a**: δ, ppm 4.77 (s, 2H), 7.61 (dt, 2H), 8.04 (dt, 2H), 8.53 (s, 1*H*), 14.1 (b, 1H) with lit [6]: δ, ppm 4.84, 7.62, 8.03 and 8.5; and **12b**: δ, ppm 2.30 (s, 3H), 4.72 (s, 2H), 7.60 (dt, 2H), 8.03 (dt, 2H), 13.6 (b, 1H) with lit [6]: δ, ppm 2.32, 4.8, 7.58 and 8.00; all spectra recorded in DMSO-d$_6$}.

Also the uv spectra - even in [6] neither the solvents nor the intensities were given - were comparable with those reported {compare: **12a**: (ethanol): λ max [nm] (ε. 10^{-3}) 253.5 (15.2), 202.5 (21.3); (acetonitrile): λ max [nm] (ε. 10^{-3}) 252.5 (12.6), 215.5 (15.2); with lit [6]: λ max [nm] 251 and 210; and **12b**: (ethanol): λ max [nm] (ε. 10^{-3}) 254.5 (18.4), 203.0 (25.6); (acetonitrile): λ max [nm] (ε. 10^{-3}) 253.5 (17.3) with lit [6]: λ max [nm] 255 and 209}.

The ms spectra of **12a** and **12b** showed besides the moecular ions very analogous fragmentation pattern to that given in [6]. However, the intensities of the individual fragments could not be compared as they were not reported in [6].

Altogether, on the basis of the spectral data it can be stated that the products obtained by us are equivalent with those obtained by Ertan *et al.* [6]. However, their structure should be **12a** and **12b** as proved by their cmr spectra, where the SCH_2CO carbon atoms appeared at 38.8 and 38.9 ppm, respectively (compare with the NCH_2CO carbon atom of **16** (Scheme 8) appearing at 55.3 ppm, prepared as a model compound and recorded under the same conditions). Structures **12a** and **12b**, are also in agreement with our INEPT measurements made with the corresponding hydrochlorides (see Experimental).

After being sure that **12a** and **12b** are *S*-alkylated derivatives it remained to answer the question what is their tautomeric structure as they could exist in 1*H*-, 2*H*- and 4*H*-tautomeric forms. For this purpose we proved first by
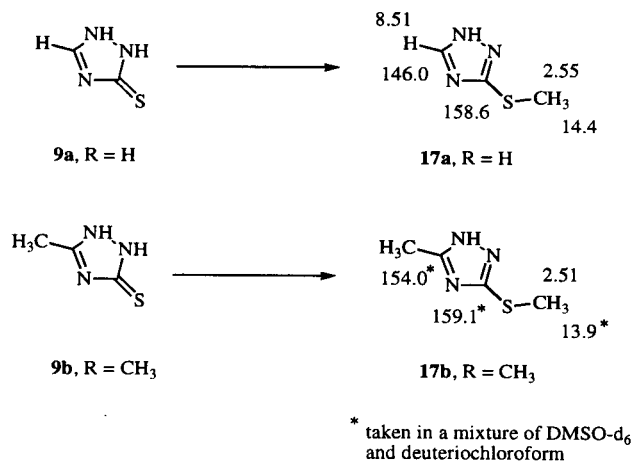
Scheme 8

16
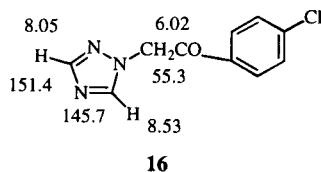
INEPT that in **16** (Scheme 8) the triazole carbon atom appearing at 145.7 ppm corresponded to the carbon atom 5 and that of appearing at 151.4 ppm corresponded to the carbon atom 3 of the 1*H*-tautomeric structure. However, as a consequence of the equivalent substituents (hydrogen atoms) of the triazole carbon atoms this model compound could also be understood as a 2*H*-tautomeric form, in which the carbon atom 3 appeared at 145.7 ppm and that of carbon atom 5 appeared at 151.4 ppm.

The triazole carbon atom of **12a** (Scheme 7) attached to the triazole hydrogen atom appeared at 144.6 ppm, consequently derivative **12a** should be in 1*H*-tautomeric form in DMSO-d_6 solution. This is also in agreement with the chemical shift of the triazole carbon atom 3 of **12a** appearing at 159.1 ppm being in good agreement with the chemical shift of the carbon atom 3 of a definitely *S*-alkylated derivative **17a** (R = H, Scheme 9) (see its SCH_3 group appearing at 14.4 ppm) prepared again as a model compound. The chemical shift of 159.1 ppm excludes also the possibility of the 4*H*-tautomeric form where the carbon atom was expected at about 146 ppm [9].

The situation was very similar in case of derivative **12b**, too, (Scheme 7) the carbon atom 3 of which appeared with the chemical shift of 157.8 ppm (compare with **16b**: δ C-3 = 159.1 ppm, Scheme 9) and as a consequence of the methyl group attached the carbon atom 5 appeared at

154.0 ppm (compare with **17b**: δ C-5 = 154.0 ppm, Scheme 9) proving again unequivocally its 1*H*-tautomeric structure in DMSO-d_6 solution.

Scheme 9

9a, R = H   **17a**, R = H

9b, R = CH_3 **17b**, R = CH_3

* taken in a mixture of DMSO-d_6 and deuteriochloroform

EXPERIMENTAL

Melting points were determined on a Koffler-Boetius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The ultraviolet spectra were obtained with a Pye Unicam SP 8-150 instrument. The pmr and cmr measurements were performed using a Varian VXR-400 instrument at 400 and 101 MHz, respectively.

3-(4-Chlorobenzoylmethylthio)-1*H*-1,2,4-triazole Hydrochloride (12a.HCl, R = H) - Reproduction of Ertan's Experiment.

To a hot solution of 6.06 g (0.06 mole) 2,3-dihydro-1,2,4-triazole-3(1*H*)-thione (**9a**, R = H) [10] in 60 ml of 2-propanol 11.34 g (0.06 mole) of 2,4'-dichloroacetophenone (**10**, R^1 = 4-Cl-Ph, X = Cl; Aldrich) was added in one portion and refluxed with stirring for 5 minutes. The reaction mixture crystallized while hot shortly after the addition of 2,4'-dichloroacetophenone. After cooling the crystals were filtered off and washed with 2-propanol to yield 16.8 g (96%) of 3-(4-chlorobenzoylmethylthio)-1*H*-1,2,4-triazole hydrochloride (**12a.HCl**, R = H) that after recrystallization from dimethylformamide melted at 183-185°; ir: ν C=O = 1671 cm^{-1}; pmr (DMSO-d_6): δ, ppm 4.93 (s, 2H, $COCH_2$), 7.61 (dt (J = 8.6 and 2.4 Hz), 2H, PhH-3' and 5'], 8.03 [dt (J = 8.6 and 2.4 Hz), 2H, PhH-2' and 6'], 8.77 (s, 1H, CH), 10.7 (b, 2H, NH); cmr (DMSO-d_6): 40.0 ($COCH_2$), 129.2 (PhC-2' and 6'), 130.6 (PhC-3' and 5'), 134.3 (PhC-1'), 138.9 (PhC-4'), 145.6 (C-5), 155.3 (C-3), 192.8 (C=O); sel. irr. at 4.93 ppm INEPT at 155.3 and 192.8 ppm; sel. irr. at 8.77 ppm INEPT at 155.3 ppm; uv (ethanol): λ max [nm] (ε. 10^{-3}) 254 (15.0) and 202.5 (20.3); uv (acetonitrile): λ max [nm] (ε. 10^{-3}) 251.5 (13.1) and 213.5 (9.8); ms: (EI) m/z (relative intensity %): 253 (M$^+$, 4), 235 (1), 225 (2), 211 (2), 152 (2), 139 (100), 125 (5), 114 (4), 111 (22), 75 (12), 36 (30). lit [6] 253 (M$^+$), 235, 225, 211, 153, 139, 114, 77.

Anal. Calcd. for $C_{10}H_9Cl_2N_3OS$ (M.W. 290.17): C, 41.39; H, 3.13; Cl, 24.44, N, 14.48; S, 11.05. Found: C, 41.52; H, 2.94; Cl, 24.60; N, 14.27; S, 11.20.

3-(4-Chlorobenzoylmethylthio)-1H-1,2,4-triazole (12a, R = H).

To a solution of sodium ethoxide [prepared from 5 ml of ethanol and 0.23 g (0.01 mole) of metallic sodium] 2.90 g (0.01 mole) of 3-(4-chlorobenzoylmethylthio)-1H-1,2,4-triazole hydrochloride (12a.HCl, R = H) was added and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* to dryness and the residue chromatographed on a silica gel column (eluent a 50:2 mixture of chloroform and ethanol) to yield 0.7 g (28%) of 3-(4-chlorobenzoylmethylthio)-1H-1,2,4-triazole (12a, R = H) that after recrystallization from 2-propanol melted 116-117°; ir: ν C=O = 1687 cm^{-1}; pmr (DMSO-d$_6$): δ, ppm 4.77 (s, 2H, COCH$_2$), 7.61 [dt (J = 8.6 and 2.4 Hz), 2H, PhH-3' and 5'], 8.04 [dt (J = 8.6 and 2.4 Hz), 2H, PhH-2' and 6'], 8.53 (s, 1H, CH), 14.1 (bs, 1H, NH); cmr (DMSO-d$_6$): δ, ppm 38.8 (COCH$_2$), 128.8 (PhC-2' and 6'), 130.2 (PhC-3' and 5'), 134.3 (PhC-1'), 138.4 (PhC-4'), 144.6 (C-5), 159.1 (C-3), 192.9 (C=O); uv (ethanol): λ max [nm] (ε. 10^{-3}) 253.5 (15.2) and 202.5 (21.3); uv (acetonitriles): λ max [nm] (ε. 10^{-3}) 252 (12.6) and 215 (9.7); lit [6] λ max [nm] 251 and 210.

Anal. Calcd. for $C_{10}H_8ClN_3OS$ (M.W. 253.71): C, 47.34; H, 3.18; Cl, 13.97; N, 16.56; S, 12.64. Found: C, 47.28; H, 3.20; Cl, 14.01; N, 16.62; S, 12.55.

3-(4-Chlorobenzoylmethylthio)-5-methyl-1H-1,2,4-triazole Hydrochloride (12b.HCl, R = CH$_3$) - Reproduction of Ertan's Experiment.

To a hot solution of 3.45 g (0.03 mole) of 2,3-dihydro-5-methyl-1,2,4-triazole-3(1H)-thione (9b, R = CH$_3$) [11] in 30 ml of 2-propanol 5.67 g (0.03 mole) was added 2,4'-dichloroacetophenone (10, R^1 = 4-Cl-Ph, X = Cl; Aldrich) in one portion and refluxed with stirring for 5 minutes. The reaction mixture crystallized while hot shortly after the addition of 2,4'-dichloroacetophenone. After cooling the crystals were filtered off and washed with 2-propanol to yield 7.70 g (84%) of 3-(4-chlorobenzoylmethylthio)-5-methyl-1H-1,2,4-triazole hydrochloride (12b.HCl, R = CH$_3$) that after recrystallization from methanol melted at 199-202°; ir: ν C=O = 1669 cm^{-1}; pmr (DMSO-d$_6$, 25°): δ, ppm 2.37 (s, 3H, CCH$_3$), 4.88 (s, 2H, COCH$_2$), 7.62 [dt (J = 8.6 and 2.3 Hz), 2H, PhH-3' and 5'], 8.02 [dt (J = 8.6 and 2.3 Hz), 2H, PhH-2' and 6'], 9.5 (b, 2H, NH); sel. irr. at 4.88 ppm INEPT at 8.02 ppm, pmr (DMSO-d$_6$, 70°): δ, ppm 2.46 (s, 3H, CCH$_3$), 5.00 (s, 2H, COCH$_2$), 7.63 [dt (J = 8.6 and 2.3 Hz), 2H, PhH-3' and 5'], 8.05 [dt (J = 8.6 and 2.3 Hz), 2H, PhH-2' and 6'], 11.5 (b, 2H, NH); cmr (DMSO-d$_6$): δ, ppm 10.8 (CH$_3$), 39.8 (COCH$_2$), 128.9 (PhC-2' and 6'), 130.3 (PhC-3' and 5'), 133.9 (PhC-1'), 138.7 (PhC-4'), 153.6 (C-3 and C-5), 192.2 (C=O); cmr (DMSO-d$_6$ + C$_6$D$_6$): δ, ppm 10.5 (CH$_3$), 40.2 (COCH$_2$), 128.6 (PhC-2' and 6'), 130.1 (PhC-3' and 5'), 133.8 (PhC-1'), 138.8 (PhC-4'), 153.5 (C-5), 153.8 (C-3), 191.9 (C=O); sel. irr. at 5.06 ppm INEPT at 153.8 and 191.8 ppm; sel. irr. at 2.46 ppm INEPT at 153.5 ppm; uv (ethanol): λ max [nm] (ε. 10^{-3}) 254 (14.9) and 203.5 (18.8); uv (acetonitrile): λ max [nm] (ε. 10^{-3}) 251.5 (13.2) and 213.5 (11.0); ms (EI) m/z (relative intensity %): 267 (M$^+$, 5), 249 (1), 239 (5), 225 (4), 152 (2), 139 (100), 128 (10), 125 (5), 111 (20), 75 (10), 36 (8); lit [6]: 267 (M$^+$), 249, 239, 225, 153, 139, 114, 77.

Anal. Calcd. for $C_{11}H_{11}Cl_2N_3OS$ (M.W. 304.20): C, 43.43; H, 3.64; Cl, 23.31; N, 13.81; S, 10.54. Found: C, 43.64; H, 3.71; Cl, 23.48; N, 13.54; S, 10.79.

3-(4-Chlorobenzoylmethylthio)-5-methyl-1H-1,2,4-triazole (12b, R = CH$_3$).

To a mixture of 3.04 g (0.01 mole) of 3-(4-chlorobenzoylmethylthio)-5-methyl-1H-1,2,4-triazole hydrochloride (12b.HCl, R = CH$_3$) in 20 ml of dry chloroform 1.53 ml (1.12 g, 0.011 mole) of triethylamine was added in one portion with stirring at room temperature. The mixture obtained was stirred at room temperature for 1 hour, the crystals were filtered off and washed with chloroform to yield 2.33 g (87%) of white crystals, mp 190-192°; ir: ν C=O = 1691 cm^{-1}; pmr (DMSO-d$_6$): δ, ppm 2.30 (s, 3H, CH$_3$), 4.72 (s, 2H, CH$_2$), 7.60 [dt (J = 8.6 and 2.2 Hz), 2H, PhH-3' and 5'], 8.03 [dt (J = 8.6 and 2.2 Hz), 2H, PhH-2' and 6'], 13.6 (bs, 1H, NH); cmr (DMSO-d$_6$): δ, ppm 11.7 (CCH$_3$), 38.9 (CH$_2$), 129.0 (PhC-2' and 6'), 130.4 (PhC-3' and 5'), 134.5 (PhC-1'), 138.6 (PhC-4'), 154.0 (C-5), 157.8 (C-3), 193.2 (C=O); uv (ethanol): λ max [nm] (ε. 10^{-3}) 254.5 (18.4) and 203.0 (25.6); uv (acetonitrile): λ max [nm] (ε. 10^{-3}) 253.5 (17.3); lit [6] λ max [nm] 255, 209.

Anal. Calcd. for $C_{11}H_{10}ClN_3OS$ (M.W. 267.74): C, 49.35; H, 3.76; Cl, 13.24; N, 15.69; S, 11.98. Found: C, 49.30; H, 3.80; Cl, 13.32; N, 15.66; S, 12.02.

1-(4-Chlorobenzoylmethyl)-1H-1,2,4-triazole (16).

To a solution of 0.83 g (0.0112 mole) of 1,2,4-triazole (4, Fluka) in 6 ml of 2-propanol 1.7 g (0.09 mole) of 2,4'-dichloroacetophenone (10, R^1 = 4-Ch-Ph, X = Cl; Aldrich) and 1 ml of triethylamine were added and the mixture was refluxed with stirring for 2 hours. After cooling 10 ml of water was added to the reaction mixture, the crystals that precipitated were filtered off and washed with water. The dried crystals were chromatographed on a silica-gel column (eluent chloroform) to yield 0.88 g (50%) of 1-(4-chlorobenzoylmethyl)-1H-1,2,4-triazole (16), mp 137-139° (2-propanol); ir: ν C=O = 1697 cm^{-1}; pmr (DMSO-d$_6$): δ, ppm 6.02 (s, 2H, CH$_2$), 7.67 [dt (J = 8.6 and 2.4 Hz), 2H, PhH-3' and 5'], 8.05 (s, 1H, CH-3), 8.07 [dt (J = 8.6 and 2.4 Hz), 2H, PhH-2' and 6'], 8.53 (s, 1H, CH-5); cmr (DMSO-d$_6$): δ, ppm 55.3 (CH$_2$), 129.2 (PhC-2' and 6'), 130.1 (PhC-3' and 5'), 133.0 (PhC-1'), 139.2 (PhC-4'), 145.7 (C-5), 151.4 (C-3), 191.8 (C=O); sel. irr. at 6.00 ppm, INEPT at 133.0, 145.7 and 191.8 ppm.

Anal. Calcd. for $C_{10}H_8ClN_3O$ (M.W. 221.65): C, 54.19; H, 3.64; Cl, 16.00; N, 18.96. Found: C, 53.99; H, 3.66; Cl, 16.05; N, 19.03.

3-Methylthio-1H-1,2,4-triazole (17a, R = H).

To a solution of 0.8 g (0.02 mole) of sodium hydroxide in 10 ml of methanol 2.02 g (0.02 mole) of 2,3-dihydro-1,2,4-triazole-3(1H)-thione (9a, R = H) [10] was added at room temperature. After it was dissolved 1.31 ml (2.98 g, 0.021 mole) of methyl iodide was added to the reaction mixture and it was stirred at room temperature for 1 hour. The solution thus obtained was evaporated *in vacuo* to dryness and the crystalline residue was recrystallized from acetonitrile (charcoal) to yield 1.8 g (78%) of 3-methylthio-1H-1,2,4-triazole (17a, R = H), mp 83-85° pmr (DMSO-d$_6$ + deuteriochloroform + deuteriobenzene): δ, ppm 2.56 (s, 3H, SCH$_3$), 8.22 (bs, 1H, CH), 13.9 (bs, 1H, NH); cmr (DMSO-d$_6$ + deuteriochloroform, 36°): δ, ppm

14.2 (SCH$_3$), 144.4 (C-5, 1*H* and 2*H* forms), 151.4 (C-3, 2*H* form), 159.8 (C-3, 1*H* form); cmr (DMSO-d$_6$ + deuteriochloroform, 70°): δ, ppm 14.2 (SCH$_3$), 145.8 (C-5, 1*H* form), 157.1 (C-3, 1*H* form);

Anal. Calcd. for C$_3$H$_5$N$_3$S (M.W. 115.16): C, 31.29; H, 4.38; N, 36.49; S, 27.84. Found: C, 31.16; H, 4.45; N, 36.39; S, 27.80.

5-Methyl-3-methylthio-1*H*-1,2,4-triazole (**17b**, R = CH$_3$).

To a solution of 0.8 g (0.02 mole) of sodium hydroxide in 10 ml of methanol 2.30 g (0.02 mole) of 2,3-dihydro-5-methyl-1,2,4-triazole-3(1*H*)-thione (**9b**, R = CH$_3$) [11] was added at room temperature. After it was dissolved 2.62 ml (5.92 g, 0.042 mole) of methyl iodide was added to the reaction mixture and it was stirred at room temperature for 4 hours. The reaction mixture was made alkaline with concentrated ammonium hydroxide, evaporated *in vacuo* to dryness and the residue was recrystallized from benzene (charcoal) to yield 2.58 g (100%) of crude 5-methyl-3-methylthio-1*H*-1,2,4-triazole (**17b**, R = CH$_3$) that after recrystallization from acetonitrile melted at 99-101°; pmr (DMSO-d$_6$ + deuteriochloroform + deuteriobenzene): δ, ppm 2.06 (s, 3H, CCH$_3$), 2.51 (s, 3H, SCH$_3$), 13.5 (bs, 1H, NH); cmr (DMSO-d$_6$ + deuteriochloroform): δ, ppm 11.8 (CCH$_3$), 13.9 (SCH$_3$), 154.0 (C-5), 159.1 (C-3).

Anal. Calcd. for C$_4$H$_7$N$_3$S (M.W. 129.18): C, 37.19; H, 5.46; N, 32.53; S, 24.82. Found: C, 37.23; H, 5.45; N, 32.60; S, 24.78.

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