AN UNEXPECTED PREFERRED CROWDED CONFORMATION IN 1-ARYL-2-(3-METHYL-1,2,4-TRIAZOL-4-YL)ETHANOL DERIVATIVES

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Abstract: A sterically crowded conformation in solution for 1-aryl-2-(3-methyl-1,2,4-triazol-4-yl)ethanol derivatives **3** is suggested from spectroscopic data. The X-ray difraction analysis of structures **3a** and **3d** confirms such preferred structural array giving the unexpected synclinal conformation in the solid state. Bond distances between the triazole methyl hydrogen atoms and the center of the aromatic ring are in good agreement with those previously reported in the literature to explain this type of structural arrangement.

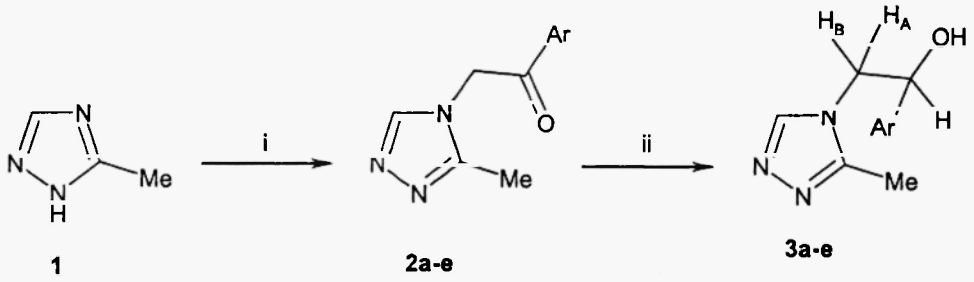
Introduction

Frequently, chemists assume that molecules should attain the most stable conformation with bulky substituents lying as far as possible from each other in space. However, exceptions to the general assumption are known. Sulphoxides adopt synclinal conformation between the 4-butyl group and the phenyl substituent.[1] Carter and coworkers have provided evidence that 1,3,5-trineopentylbenzene adopts a conformation with its three *t*-butyl groups on the same face of the aromatic ring.[2] It has been suggested that an attractive force between the aromatic ring and the C-H moiety may be operating. This controversial interaction has been derived from the ^{1}H NMR[3], X-ray diffraction[4,5] and theoretical studies.[6,7]

In this report we provide experimental data that are consistant with a sterically crowed conformation in 1-aryl-2-(3-methyl-1,2,4-triazol-4-yl)ethanol derivatives **3**. The 1,2,4-triazole system has been investigated previously in connection with several biological activities.[8,9]

Results and discussion

1-Aryl-2-(3-methyl-1,2,4-triazol-4-yl)ethanol derivatives **3** were prepared in good yields by the carbonyl reduction of phenacyl substituted triazoles **2** using lithium borohydride in dry dioxane. Ketones **2** in turn were prepared from 3-methyl-1,2,4-triazole **1**.[11]

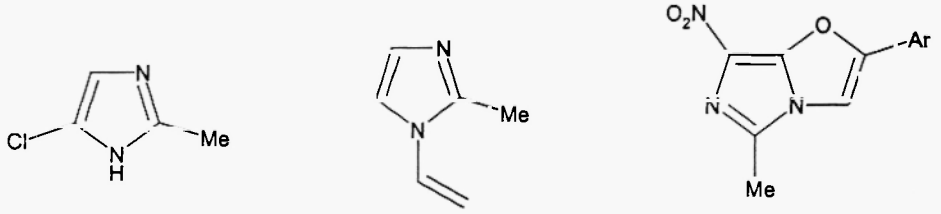


1 **2a-e** **3a-e**

i. $ArCOCH_2Br$, K_2CO_3, MeCN; ii $NaBH_4$, Li_2CO_3, dioxane, 60°C

a: Ar = 4-ClC_6H_4; b: Ar = 4-FC_6H_4; c: Ar = 4-MeC_6H_4; d: Ar = 4-$MeOC_6H_4$; e: Ar = C_6H_5

The position of the aryl substituent in compounds **3** was determined by both ^1H NMR and X ray diffraction studies.[11] The chemical shift (δ 2.52) for the methyl protons in 3-methyl-1,2,4-triazole **1** agrees well with that for similar compounds **4**, **5** or **6**.[12] The chemical shift comparison for compounds **4-6**, triazolylketones **2** and hydroxy derivatives **3** is given in Table 1. The data show that, in comparison to **1**, the methyl signal in products **2** is shifted upfield, probably due to an interaction of the methyl hydrogens with the phenyl electronic current which exerts a shielding effect according to Ban.[4] Carbonyl reduction of compounds **2** shifts the methyl signal in compounds **3** further upfield.



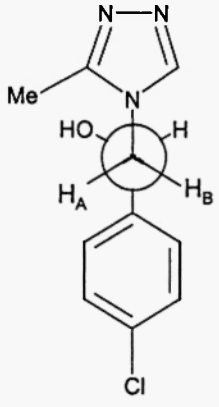
4 **5** **6**

It can suggested that for **3** either a conformer or a combination of conformers with the methyl sustituent directly shielded by the phenyl ring is preferred.

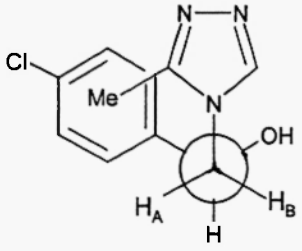
Table 1. ^1H NMR methyl chemical shifts of 1,2,4-triazol derivatives **1-6**

Compound	Methyl chemical shift	Compound	Methyl chemical shift	Compound	Methyl chemical shift
1	2.52	**2a**	2.26	**3a**	2.17
4	2.40	**2b**	2.42	**3b**	2.18
5	2.39	**2c**	2.31	**3c**	2.13
6	2.5	**2d**	2.43	**3d**	2.17
		2e	2.26	**3e**	2.14

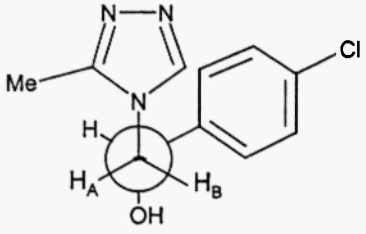
The efficiency of semiempirical methods to predict conformational preferences has been shown.[13] We decided to apply the AMI semiempirical method[14] to calculate the relative stability of conformers **3aA-3aC**. The following ΔH_f values were obtained: 39.1 Kcal/mol for structure **3aA**, 39.6 Kcal/mol for structure **3aB** and 39.9 Kcal/mole for **3aC**. The energy difference among these conformers is less than one Kcal/mole. This result implies that the three conformers enjoy a very close stability and suggests that the sum of all attractive forces in the synclinal arrangements overcome the possible sterical repulsion between bulky substituents.



3aA



3aB



3aC

A more conclusive evidence for a synclinal conformation was obtained from the X ray diffraction analysis. In the X-ray derived structure of alcohols **3a** and **3d**, it is evident that the methyl group of the triazole system lies very close to the aromatic ring (Figure 1). Consideration of the dihedral angles (H-8A-C8-C7-H-7A and H-8A-C8-C7-H-7B) in compound **3a** (-51.9° and 65.5° respectively) obtained from the X -ray diffraction data favors a synclinal conformer. The distances between the hydrogen atom of the methyl group and the center of the aromatic ring are 2.275Å and 2.742Å for alcohols 3a and **3d,** respectively. These distances are in good agreement with those reported for similar structural arrays.

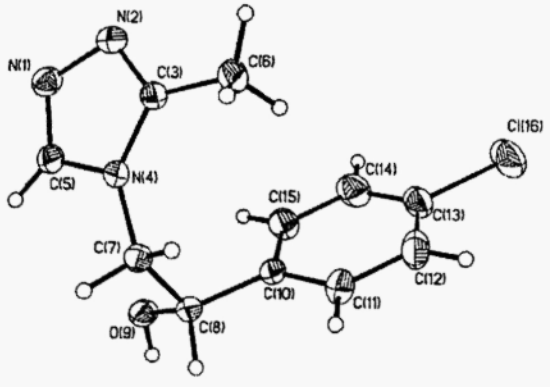


Figure 1. X-ray diffraction analysis of compound **3a**.

Experimental

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin Elmer FT 1600 infrared spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded obtained in DMSO-d_6 using a Bruker DPX spectrometer. Chemical shifts are given in ppm downfield from TMS. Mass spectra were obtained on a JEOL JMSAX505HA instrument. Column chromatography was carried out with silica gel (Merck 60, 70-230 mesh) as the adsorbent. X- Ray data were collected on a Siemens P4 diffractometer with graphite monochromated Mo-K radiation (λ = 0.71073).

General procedure for the synthesis of aryl 3-methyl-1,2,4-triazol-4-ylmethyl ketones 2a-e

3-Methyl-1,2,4-triazole (0.1g, 1.2 mmol) was dissolved in a stirred CH_3CN (10 mL) suspension of anhydrous K_2CO_3 (0.17g, 1.2 mmol). Reaction flask was heated at 50 °C and stirring was continued for 10 min. Then the corresponding phenacyl bromide (1.26 mmol) was slowly added and the mixture was refluxed for 6 h. The mixture was cooled, filtered through Celite, concentrated, and the residue was crystallized from water.

4-(4'-Chlorophenacyl)-3-methyl-1,2,4-triazole (2a): Yield 48%; mp 138-140 °C; IR 1680, 1600 cm^{-1};^{1}H NMR δ 8.34 (s, 1H), 8.05 (dd J = 6.7 Hz J = 1.9 Hz, 2H), 7.6 (dd, J = 6.7 Hz, J = 1.9 Hz, 2H), 5.87 (s, 2H), 2.26 (s, 3H). Anal. Calcd for $C_{11}H_{10}N_3OCl$: C, 56.05; H, 4.24; N, 17.83. Found: C, 55.90; H, 4.34; N, 17.91.

4-(4'-Fluorophenacyl)-3-methyl-1,2,4-triazole (2b): Yield 75%; mp 152-153 °C; IR 1685, 1603 cm^{-1}; ^{1}H NMR δ 8.14 (s, 1H), 7.96 (dd J = 7.0 Hz, J = 2.2 Hz), 7.53 (dd, J = 7.0 Hz, J = 2.2 Hz), 5.56 (s, 2H), 2.42 (s, 3H). Anal. Calcd for $C_{11}H_{10}N_3OF$: C, 60.27; H, 4.56; N, 19.18. Found: C, 60.10; H, 4.40; N, 19.02.

3-Methyl-4-(4'-methylphenacyl)-1,2,4-triazole (2c): Yield 81%; mp 119-120 °C; IR 1679, 1605 cm^{-1}. ^{1}H NMR δ 8.36 (s, 1H), 7.97 (dd J = 7.8 Hz, J = 1.5 Hz, 2H), 7.40 (dd, J = 7.8 Hz, J = 1.5 Hz, 2H), 5.85 (s, 2H), 2.40 (s, 3H) 2.31 (s 3H). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.97; H, 6.04; N, 19.53. Found: C, 66.88; H, 5.91; N, 19.42.

4-(4'Methoxyphenacyl)-3-methyl-1,2,4-triazole (2d): Yield 55%; mp 125-126 °C; IR 1681, 1609 cm^{-1}. ^{1}H NMR δ 8.12 (s, 1H), 7.90 (dd J = 6.9 Hz, J = 2.0 Hz, 2H), 7.01 (dd, J = 6.9 Hz, J = 2.0 Hz, 2H), 5.54 (s, 2H), 3.90 (s 3H), 2.43 (s, 3H). Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.62; N, 18.18. Found: C, 62.25; H, 5.70; N, 18.07.

3-Methyl-4-phenacyl-1,2,4-triazole (2e): Yield 72%; mp 107-108 °C; ^{1}H NMR δ 8.36 (s, 1H, H-5), 7.27-7.38 (m, 5H),5.89 (s, 3H). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.47; N, 20.89. Found: C, 65.59; H, 5.54; N, 20.75.

General procedure for the synthesis of alcohols 3a - 3e

$NaBH_4$ (0.33 g, 8.65 mmol) was added to anhydrous dioxane (50 mL), and the mixture was stirred at room temperature for 1 h under nitrogen. Then Li_2CO_3 (0.64 g, 8.5 mmol) was added and the mixture was heated at 60°C.

At this temperature the corresponding aryl 3-methyl-1,2,4-triazolyl ketone (2.2 mmol) was slowly added and heating and stirring was continued for another 12 h under nitrogen. The reaction mixture was then allowed to cool to room temperature, filtered through Celite, concentrated and the residue was crystallized from water.

1-(4-Chlorophenyl)-2-(3-methyl-1,2,4-triazol-4-yl)ethanol (3a): Yield 83%; mp 200 – 202 °C; IR 3157, 1597 cm^{-1}; ^1H NMR δ 8.24 (s, 1H), 7.40 (dd, J = 8.6 Hz, J = 2.1 Hz, 2H), 7.34 (dd, J = 8.5 Hz, J = 2.1 Hz, 2H), 5.96 (d, J = 4.1 Hz, 1H), 4.86 (m, 1H), 4.11 (dd, J = 14.2 Hz, J = 4.0 Hz 1H), 3.99 (dd, J = 14.2 Hz, J = 7.6 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR δ 150.5, 144.3, 141.3, 132.1, 128.2, 128.0, 70.7, 50.6, 9.8; MS m/z 237 $(M)^+$.
Anal. Calcd for $C_{11}H_{12}N_3OCl$: C, 55.58; H, 5.02; N, 17.68. Found: C, 55.45; H, 5.16; N, 17.60.

1-(4-Fluorophenyl)-2-(3-methyl-1,2,4-triazol-4-yl)ethanol (3b): Yield 76%; mp 210 – 211 °C; IR 3323, 1600 cm^{-1}; ^1H NMR δ 8.25 (s, 1H), 7.39 (dd, J = 8.63 Hz, J = 2.1 Hz, 2H-), 7.35 (dd, J = 8.4 Hz, J =2.1 Hz, 2H), 5.93 (d, J = 4.4 Hz, 1H), 4.87 (m, 1H), 4.12 (dd, J = 14.3 Hz, J = 4.0 Hz, 1H), 3.99 (dd, J = 14.3 Hz, J = 7.5 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR δ 150.6, 144.3, 141.1, 132.0, 128.1, 127.9, 70.6, 50.5, 9.7; MS m/z 221 $(M)^+$.
Anal. Calcd for $C_{11}H_{12}N_3OF$: C, 59.72; H, 5.43; N, 19.00. Found: C, 59.60; H, 5.52; N, 18.86.

1-(4-Tolyl)-2-(3-methyl-1,2,4-triazol-4-yl)ethanol (3c): Yield 64%; mp 174 - 175 °C; IR 3371, 1606 cm^{-1}; ^1H NMR δ 8.22 (s, 1H), 7.17 (dd J = 8.6 Hz J = 2.1 Hz, 2H), 7.12 (dd, J = 8.2 Hz, J = 2.1 Hz, 2H), 5.75 (d, J = 4.3 Hz, 1H), 4.78 (m, 1H), 4.06 (dd, J = 14.9 Hz, J = 4.1 Hz, 1H), 3.96 (dd, J = 14.9 Hz, J = 7.6 Hz, 1H), 2.27 (s, 3H), 2.13 (s, 3H); ^{13}C NMR δ 150.5, 144.2, 139.0, 132.6, 128.6, 125.9, 71.1, 50.8, 26.6, 9.6; MS m/z 217 $(M)^+$.
Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.36; H, 6.92; N, 19.35. Found: C, 66.29; H, 6.83; N, 19.29.

1-(4-Anisyl)-2-(3-methyl-1,2,4-triazol-4-yl)ethanol (3d): Yield 75%; mp 180 - 182 °C; IR 3168, 1611 cm^{-1}; ^1H NMR δ 8.27 (s, 1H), 7.24 (dd J = 8.6 Hz, 2.1 Hz, 2H), 6.91 (dd, J = 8.6 Hz, 2.1 Hz, 2H), 4.82 (dd, J = 7.3 Hz, 3.9 Hz, 1H, H-8), 4.10 (dd, J = 14.2 Hz, 3.9 Hz 1H), 4.01 (dd, J = 14.2 Hz, 7.3 Hz, 1H), 3.74 (s, 3H), 2.17 (s, 3H); ^{13}C NMR δ 158.8, 150.6, 144.3, 134.0, 127.2, 113.6, 70.9, 55.1, 50.9, 9.6; MS m/z 233 $(M)^+$.
Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.43; N, 18.02. Found: C, 61.73; H, 6.36; N, 17.76.

1-Phenyl-2-(3-methyl-1,2,4-triazol-4-yl)ethanol (3e):Yield 70%; mp 164 - 166°C; IR 3223, 1608 cm^{-1}; ^1H NMR δ 8.26 (s, 1H), 7.26-7.37 (m, 3H), 5.84 (d, J = 2.9 Hz, 1H), 4.85 (m, 1H), 4.11 (dd, J = 14.2 Hz, 4.0 Hz, 1H), 4.0 (dd, J = 14.2 Hz, 7.5Hz, 1H), 2.14 (s, 3H);
^{13}C NMR δ 150.6, 144.4, 142.1, 128.2, 127.6, 126.0, 71.3, 50.8, 9.6; MS m/z 203 $(M)^+$.
Anal. Calcd for $C_{12}H_{13}N_3O$: C, 65.02; H, 6.40; N, 20.68. Found: C, 64.96; H,6.50; N, 20.60.

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11. **X-Ray crystal data of 3a**. $C_{11}H_{12}N_3OCl$: crystal dimension 0.4 X 0.4 X 0.5, triclinic, space group P1, a = 5.6188 (5),b = 7.3633 (5), c = 14.9867 (9), V = 568.48 (7)^3 , Z = 2. D_{calcd} = 1.389 mgm^{-3}, R = 0.0548, R_w = 0.1258. **X-Ray crystal data of 3d**. $C_{12}H_{15}N_3O_2$: crystal dimension 0.1 X 0.5 X 0.6 triclinic, space group P1,a = 5.6952 (6), b = 7.3054 (6), c = 15.875 (2), V= 599.46 (11)^3 , Z = 2. D_{calcd} = 1.292 mgm^{-3}, R = 0.0682, R_w = 0.1299
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Received on September 15, 2002