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Synthesis, crystal structures and spectral characterization of chiral 4-R-1,2,4-triazoles

Il'ya A. Gural'skiy [a, *], Viktor A. Reshetnikov [a], Irina V. Omelchenko [b], Agnieszka Szebesczyk [c], Elzbieta Gumienna-Kontecka [c], Igor O. Fritsky [a]

[a] Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska 64/13, 01601 Kyiv, Ukraine
[b] STC, Institute for Single Crystals, National Academy of Science of Ukraine, Lenin Ave. 60, 61001 Kharkov, Ukraine
[c] Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, Wroclaw 50383, Poland

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ABSTRACT

1,2,4-triazoles attract attention as actively used medications and ligands for constructing coordination architectures. In this paper we describe four optically active 4-substituted 1,2,4-triazoles that have been prepared by Bayer's synthesis from the corresponding aliphatic chiral amines. This approach tends to be universal towards different triazoles and permits to conserve a homochirality of substrates. Novel asymmetric molecules have been characterized by spectroscopic techniques and their structures have been retrieved from the single crystal X-ray analysis. Chiro-optical studies of these heterocycles have been made by means of circular dichroism spectroscopy.

1. Introduction

Derivatives of 1,2,4-triazole have become a matter of many synthetic developments in regards to their medical and material applications. Biological activity of these heterocyclic systems is brightly represented by the antifungal medications, such as fluconazole, itraconazole, voriconazole, posaconazole etc. [1–3]. Some triazoles were confirmed to have a promising antitubercular activity [4]. Certain pesticides, weedicides, fungicides based upon 1,2,4-triazole fragment were proposed. In material chemistry, a special attention towards 4-substituted 1,2,4-triazoles is related to their coordination chemistry. 1D iron(II) polymeric complexes with 4R-1,2,4-triazoles are known for their spin crossover behaviour [5], which is one of the most spectacular phenomenon of molecular bistability [6].

Elaboration of homochiral pharmaceutically important molecules is frequently a crucial step towards their medical applications. On the other hand, the synthesis of chiral ligands constitutes an important challenge to the synthetic chemistry in regards of their use for the stereoselective catalysis [7] and for the construction of advanced materials [8]. To the best of our knowledge, no chiral 4-substituted 1,2,4-triazoles have been reported to date.

2. Experimental

2.1. Synthesis

Freshly prepared monoformylhydrazide was refluxed for 3.5 h with a 20% excess of triethyl orthoformate in water-free methanol. After cooling to 40 °C, the n-primary amine (1 equiv.) was added and the mixture refluxed for 6–7 h. In order to get rid of excess of the amine, the resulting mixture was heated under vacuum at 220 °C. The solid triazoles **1**–**3** were recrystallized from i-PrOH.

(2S)-2-(4H-1,2,4-triazol-4-yl)propan-1-ol (1). Yield: 2.02 g (53.5%); white solid; mp 98 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.45 (d, 3H), 3.58 (m, 2H), 4.37 (m, 1H), 5.02 (s, 1H), 8.38 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 142.12, 64.75, 53.88, 17.14. Anal. Calcd for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.05. Found: C, 47.32; H, 7.02; N, 33.03. *m/z* = 128.1 $[M+H]^+$. IR (KBr): 3164, 3100, 2854, 1527, 1462, 1372, 1198, 985, 650 cm^{-1}.

(2S)-3-methyl-2-(4H-1,2,4-triazol-4-yl)butan-1-ol (2). Yield: 2.52 g (54.4%); white solid; mp 106 °C.

* Corresponding author.
E-mail address: illia.guralskyi@univ.kiev.ua (I.A. Gural'skiy).

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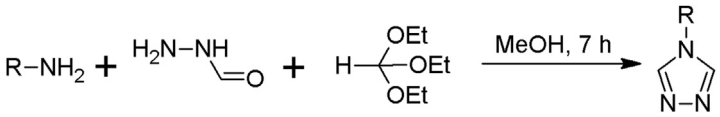
Table 1
Crystal data and structure refinement for **1**–**4**.

Identification code	**1**	**2**	**3**	**4**
Empirical formula	$C_5H_9N_3O$	$C_7H_{13}N_3O$	$C_8H_{15}N_3$	$C_{10}H_{17}N_3$
Formula weight	127.15	155.20	153.23	179.26
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Triclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P1$
a/Å	4.9153 (2)	6.6618 (6)	7.8453 (4)	11.423 (3)
b/Å	6.8128 (4)	7.5779 (6)	10.5984 (6)	12.5029 (17)
c/Å	19.1627(10)	16.6766 (16)	11.2101 (5)	13.6295 (17)
α/°	90.00	90.00	90.00	114.301 (13)
β/°	90.00	90.00	90.00	101.892 (17)
γ/°	90.00	90.00	90.00	100.953 (16)
Volume/Å^3	641.70 (6)	841.88 (13)	932.09 (8)	1651.6 (6)
Z	4	4	4	6
ρ_{calc}g/cm^3	1.316	1.225	1.092	1.081
μ/mm^{-1}	0.096	0.085	0.069	0.067
F (000)	272.0	336.0	336.0	588.0
Crystal size/mm^3	0.5 × 0.5 × 0.3	0.6 × 0.3 × 0.3	0.4 × 0.3 × 0.2	0.2 × 0.05 × 0.05
2Θ range for data collection/°	6.34 to 55.12	6.58 to 55	7.28 to 60	5.922 to 51.998
Reflections collected	2596	4366	6210	17793
Independent reflections	R_{int} = 0.0131, R_{sigma} = 0.0260	R_{int} = 0.0227, R_{sigma} = 0.0519	R_{int} = 0.0267, R_{sigma} = 0.0449	R_{int} = 0.0803, R_{sigma} = 0.2861
Data/restraints/parameters	1478/0/118	2639/0/103	2713/0/104	11925/288/806
Goodness-of-fit on F^2	1.070	1.040	0.948	0.747
Final R indexes [I ≥ 2σ (I)]	R_1 = 0.0370, wR_2 = 0.0813	R_1 = 0.0493, wR_2 = 0.0878	R_1 = 0.0514, wR_2 = 0.0958	R_1 = 0.0649, wR_2 = 0.0666
Final R indexes [all data]	R_1 = 0.0499, wR_2 = 0.0897	R_1 = 0.0939, wR_2 = 0.1086	R_1 = 0.1115, wR_2 = 0.1105	R_1 = 0.3527, wR_2 = 0.1139
Largest diff. peak/hole/e Å^{-3}	0.10/−0.16	0.12/−0.17	0.10/−0.11	0.14/−0.11

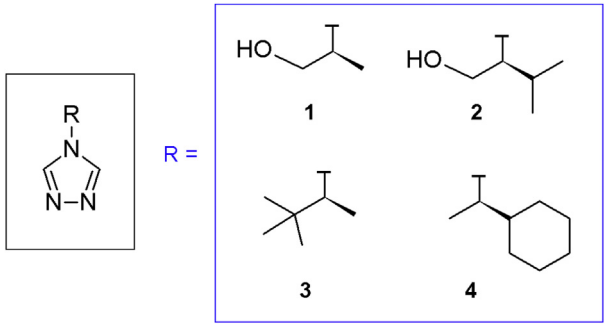


Scheme 1. Synthetic scheme for the preparative preparation of chiral 4-substituted 1,2,4-triazoles by Bayer's synthesis.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.71 (d, 3H), 0.99 (d, 3H), 2.14 (m, 1H), 3.67 (1H), 3.77 (1H), 3.89 (1H), 4.93 (s, 1H), 8.33 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 141.16, 64.34, 61.16, 29.14, 18.83. Anal. Calcd for $C_7H_{13}N_3O$: C, 54.17; H, 8.44; N, 27.08. Found: C, 53.56; H, 8.61; N, 26.39. m/z = 156.2 [M+H]$^+$. IR (KBr): 3196, 3087, 2971, 1527, 1198, 1024, 662 cm^{-1}.

4-[(2S)-3,3-dimethylbutan-2-yl]-4H-1,2,4-triazole (3). Yield: 2.80 g (61.7%); white solid; mp 135 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.89 (s, 9H), 1.46 (d, 3H), 4.17 (m, 1H), 8.34 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 142.75, 60,53, 34,36, 26.08, 15.48. Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.42. Found: C, 62.85; H, 9.73; N, 27.31. m/z = 154.2 [M+H]$^+$. IR (KBr): 3100, 2971, 1701, 1514, 1455, 1368, 1179, 1062, 656 cm^{-1}.

4-[(1S)-1-cyclohexylethyl]-4H-1,2,4-triazole (4). Yield: 4.02 g (75.4%); yellowish oil; bp 220 °C (1 atm.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.1 (m, 11H), 1.45 (d, 3H), 4.13 (m, 1H), 8.35 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 141.09, 57.39, 43.52, 28.93, 28.52, 25.14, 17.32. Anal. Calcd for $C_{10}H_{17}N_3$: C, 67.00; H, 9.56; N, 23.44. Found: C, 66.88; H, 9.46; N, 23.31. m/z = 180.1 [M+H]$^+$. IR (KBr): 3106, 2932, 2848, 1669, 1520, 1449, 1179, 663 cm^{-1}.



Scheme 2. Homochiral substituents in 1,2,4-triazolic ring of compounds **1**–**4**.

2.2. X-ray diffraction

Crystals of **1**–**3** suitable for the X-ray diffraction analysis were obtained by recrystallization from i-PrOH. Crystals of **4** were obtained by slow freezing of oil to 0 °C.

X-Ray diffraction studies of **1**–**4** were performed on an "Xcalibur 3" diffractometer (graphite-monochromated MoKα radiation (λ = 0.71073), CCD detector, ω-scans) at room temperature (295–303 K). Structures were solved by direct method and refined against F^2 within anisotropic approximation for all non-hydrogen atoms using OLEX2 program package [9] with SHELXS and SHELXL modules [10]. In **2**–**4**, all H atoms were placed in idealized positions and constrained to ride on their parent atoms with U_{iso} = nU_{eq} (n = 1.5 for OH and CH_3 groups and n = 1.2 for all other H atoms). OH and CH_3 groups were refined as rotating groups except structure **4**. In **1**, all H atoms were located from difference electronic map and refined isotropically.

In **4**, there are six molecules per independent part of the unit cell, and two of them carry structurally disordered cyclohexane rings (relative refined occupancy factors 0.5/0.5 for "D" molecule and 0.6/0.4 for "E" molecule). Similar bonds in disordered groups were restrained to be of similar lengths within an effective standard deviation of 0.01 Å. Also, the high thermal disordering of all six molecules requires rather strict restraints, namely: (a) all C–C bonds in cyclohexane rings were restrained to have fixed values of 1.54 Å to within 0.01 Å; (b) all N–N bonds were restrained to have approximately same values to within 0.01 Å; (c) anisotropic thermal parameters of all C atoms in cyclohexane rings were restrained