Synthesis of 1,1-Bis(1,2,4-triazol-1-yl)-based Potential Aromatase Inhibitors

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Reactions of bis-(1,2,4-triazolyl) sulfoxide **2** with various carbonyl compounds **3** led to the formation of twelve corresponding 1,1-bis-(1,2,4-triazolyl) compounds, with structures resembling closely some previously prepared aromatase inhibitors.

In memory of the founder of the Journal of Heterocyclic Chemistry, Professor Raymond N. Castle, as a token of respect and friendship.

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Introduction.

Aromatase inhibitors play an important role in breast cancer treatment by blocking the terminal step in estrogen biosynthesis [1a,b]. Among various 1,2,4-triazol-1-yl based aromatase inhibitors, 1,1-bis(1,2,4-triazol-1-yl) compounds such as 1,2-dihydro-1,1-dimethyl-2-oxo-8-[di(1*H*-1,2,4-triazol-1-yl)methyl] naphtho[2,1-*b*]furan-7-carbonitriles (Figure 1) are claimed to be highly active with little cytotoxicity [2].

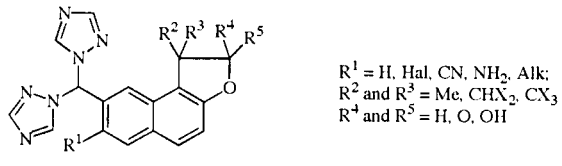
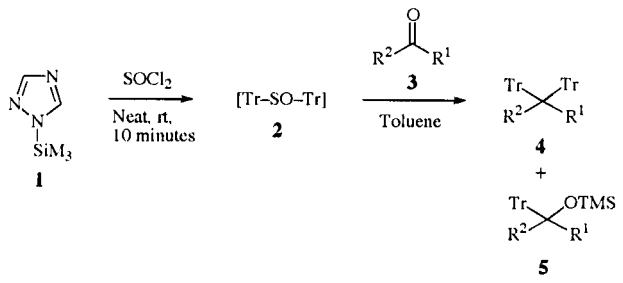


Figure 1

Known procedures for the construction of 1,1-bis(1,2,4-triazol-1-yl) moieties involve: (i) the nucleophilic displacement of dihalogenomethylenes by 1,2,4-triazole [2, 3a,b]; (ii) simultaneous formation of both triazole rings on various non-cyclic molecules [4a-d]; and (iii) modifications of molecules already containing two triazolyl rings [5a,b]. We now report a novel one step procedure to form 1,1-bis(1,2,4-triazol-1-yl) derivatives from the corresponding carbonyl compounds which offers some increase in generality and diversity of substituents as compared to existing methods.

Scheme 1



Results and Discussion.

Previously we detected 1,1-bis(1*H*-1,2,3-benzotriazol-1-yl) compounds as side products in reactions of *N*-acylbenzotriazoles with aldehydes [6]. Following up this result led to the route for 1,1-bis-(1,2,4-triazolyl) derivatives given in Scheme 1. In a standard procedure, 1 mmol of thionyl chloride was premixed with 2 mmol of 1-trimethylsilyl-1,2,4-triazole **1** [7] to give unstable bistriazolyl sulfoxide **2** which was characterized spectroscopically. The trimethylsilyl chloride by-product must be removed under vacuum to avoid formation of **5** [8]. Upon heating **2** in toluene with the carbonyl compound **3** the desired 1,1-bis(1,2,4-triazol-1-yl) derivatives **4** were obtained in 45-95% yields (Table 1). Heating neat, or in other solvents, produced inferior results. The products **4f,g** were obtained as pure compounds; **4a-e,h-l** were isolated by column chromatography. This procedure is applicable to both aliphatic aldehydes (to give **4a-c**) and aromatic aldehydes with a wide range of substituents to give 1,1-bis(1,2,4-triazol-1-yl) derivatives **4d-j**.

Table 1 [a]

Entry	Carbonyl Compound	Time (hours)	Yield (%)	mp
4a	Et-CHO [b]	0.5	61	100-102°
4b	*n*-Pr-CHO [b]	0.5	68	oil
4c	*i*-Pr-CHO [b]	0.5	53	oil
4d	C_6H_5-CHO	0.5	65	117-118°
4e	4-MeC_6H_4-CHO	0.5	74	111-112°
4f	4-$Me_2NC_6H_4$-CHO	0.5	95	110-112°
4g	4-ClC_6H_4-CHO	0.5	82	105-106°
4h	4-NCC_6H_4-CHO	0.5	79	oil
4i	4-$O_2NC_6H_4$-CHO	0.5	58	hygroscopic
4j	$Me_2CHCH_2CHC(C_6H_5)$-CHO	0.5	54 [c]	oil
4k	9-Fluorenone	20	68	222-223°
4l	4-*tert*-Butylcyclohexanone	2	45 [d]	151-152°

[a] All reactions, unless otherwise stated, were carried out at 90° in toluene. [b] Reaction carried out at room temperature. Minor amount of the corresponding enamine was observed in the reaction mixture after purification. [c] The 1,3-bis(1,2,4-triazol-1-yl) isomer **6j** was isolated in 16% yield. [d] The corresponding enamine **7l** was isolated in 49% yield.

Attempts to extend this method to ketones gave mixed results. While 9-fluorenone gave the corresponding product **4k** in 68% yield, thioxanthen-9-one and 4-(dimethylamino)benzophenone failed to produce the desired product even under forcing conditions. Furthermore, enolizable ketones turned out to be prone to triazole elimination leading to the corresponding enamine derivative. Thus, the 4-*tert*-butylcyclohexanone afforded product **4l** was obtained only in 45% yield, while 5-hydroxy-1-tetralone and 1-indanone yielded only enamine products in 32% and 45% respectively.

In conclusion, a number of novel 1,1-bis(1,2,4-triazol-1-yl) based potential aromatase inhibitors were prepared by a new method in 45-95% yield. This method is complementary to those previously known and offers a short entry to compounds not readily accessible by other methods.

EXPERIMENTAL

All reactions were carried out under an atmosphere of argon, unless otherwise specified. Glassware was routinely oven-dried at 160° for a minimum of 4 hours and then connected to a vacuum line before assembling under dry argon stream. Anhydrous toluene was obtained by distillation over sodium immediately prior to use. Melting points were determined using a Thomas Hoover capillary Melting Point Apparatus and are not corrected. ^{1}H nmr (300 MHz) and ^{13}C nmr (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer using deuteriochloroform ($CDCl_3$) as solvent with TMS as the internal reference for ^{1}H nmr and the central line of $CDCl_3$ as the reference for ^{13}C nmr. The gc-ms instrument used in the optimization of the procedure was a Hewlett Packard 5890 Series II Gas Chromatograph coupled to a 5972 Mass Selective Detector. Elemental analyses were performed on a Carlo Erba-1106 instrument. Column chromatography was carried out on MCB silica gel (230-400 mesh).

General Procedure for the Preparation of 1,1-bis-(1,2,4-triazol-1-yl) compounds **4**.

1-(Trimethylsilyl)triazole (11 mmoles) **1** was weighted in a round-bottomed flask under Argon and thionyl chloride (6 mmoles) was added dropwise at room temperature. A yellow solid precipitated after the addition of the first drops. The mixture was stirred at room temperature under Argon for 15 minutes and the resulting solid **2** was dried under vacuum. Mp, 105-106°, ^{1}H nmr (deuteriochloroform): δ 8.82 (s, 2H), 8.17 (s, 2H); ^{13}C nmr (deuteriochloroform): δ 158.3, 143.5.

Dry toluene (10 ml) was added to **2** followed by addition of the corresponding aldehyde (5 mmoles), the resulting mixture was stirred at room temperature or heated at 90° depending on the reactive aldehyde. The solvent was removed under vacuum, yielding an oil which was purified by crystallization or chromatography in silica gel (hexanes /EtOAc).

1-[1-(1*H*-1,2,4-Triazol-1-yl)propyl]-1*H*-1,2,4-triazole (**4a**).

This compound was obtained as white microcrystals (61%), mp 100-102°; ^{1}H nmr (deuteriochloroform): δ 8.43 (s, 2H), 7.98 (s, 2H), 6.49 (t, J = 7.5 Hz, 1H), 2.67 (c, J = 7.4 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C nmr (deuteriochloroform): δ 152.3, 142.7, 73.1, 26.8, 9.5.

Anal. Calcd. for $C_7H_{10}N_6$ (178.20): C, 47.18; H, 5.67. Found: C, 46.88; H, 5.68.

1-[1-(1*H*-1,2,4-Triazol-1-yl)butyl]-1*H*-1,2,4-triazole (**4b**).

This compound was obtained as a colorless oil (68%); ^{1}H nmr (deuteriochloroform): δ 8.52 (s, 2H), 8.00 (s, 2H), 6.68 (t, J = 7.4 Hz, 1H), 2.62 (q, J = 7.2 Hz, 2H), 1.31 (q, J = 7.2 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C nmr (deuteriochloroform): δ 152.0, 142.7, 71.3, 34.8, 18.1, 12.8.

Anal. Calcd. for $C_8H_{12}N_6$ (192.23): C, 49.98; H, 6.30. Found: C, 49.74; H, 6.49.

1-[2-Methyl-1-(1*H*-1,2,4-triazol-1-yl)propyl]-1*H*-1,2,4-triazole (**4c**).

This compound was obtained as a colorless oil (53%); ^{1}H nmr (deuteriochloroform): δ 8.47 (s, 2H), 8.00 (s, 2H), 6.18 (d, J = 10.8 Hz, 1H), 3.20-3.00 (m, 1H), 0.92 (d, J = 7.5 Hz, 6H); ^{13}C nmr (deuteriochloroform): δ 152.2, 143.0, 77.6, 33.1, 18.4.

Anal. Calcd. for $C_8H_{12}N_6$ (192.23): C, 49.98; H, 6.30; N, 43.73. Found: C, 50.09; H, 6.68; N, 43.59.

1-[Phenyl(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-1,2,4-triazole (**4d**).

This compound was obtained as white microcrystals (65%), mp 117-118°; ^{1}H nmr (deuteriochloroform): δ 8.34 (s, 2H), 8.04 (s, 2H), 7.90 (s, 1H), 7.60-7.45 (m, 3H), 7.30-7.20 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 152.7, 143.9, 132.9, 130.3, 129.2, 126.9, 73.6.

Anal. Calcd. for $C_{11}H_{10}N_6$ (226.24): C, 58.39; H, 4.46; N, 37.16. Found: C, 58.11; H, 4.38; N, 36.76.

1-[(4-Methylphenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-1,2,4-triazole (**4e**).

This compound was obtained as white microcrystals (74%), mp 111-112°; ^{1}H nmr (deuteriochloroform): δ 8.31 (s, 2H), 8.03 (s, 2H), 7.84 (s, 1H), 7.25 (d, J = 7.7 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H), 2.38 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 152.6, 143.8, 140.6, 129.9, 129.7, 126.9, 73.7, 21.0.

Anal. Calcd. for $C_{12}H_{12}N_6$ (240.27): N, 34.99. Found: N, 34.68.

4-[Di(1*H*-1,2,4-triazol-1-yl)methyl]-*N,N*-dimethylaniline (**4f**).

This compound was obtained as yellow needles (95%), mp 110-112°; ^{1}H nmr (deuteriochloroform): δ 8.25 (s, 2H), 8.02 (s, 2H), 7.69 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 2.99 (s, 6H); ^{13}C nmr (deuteriochloroform): δ 152.6, 151.3, 143.6, 128.3, 119.0, 112.0, 74.1, 40.1.

Anal. Calcd. for $C_{13}H_{15}N_7$ (269.31): C, 57.97; H, 5.63; N, 36.42. Found: C, 57.60; H, 5.75; N, 36.11.

1-[(4-Chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-1,2,4-triazole (**4g**).

This compound was obtained as white microcrystals (82%), mp 105-106°; ^{1}H nmr (deuteriochloroform): δ 8.36 (s, 2H), 8.05 (s, 2H), 7.88 (s, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 152.8, 143.9, 136.5, 131.4, 129.5, 128.4, 73.0.

Anal. Calcd. for $C_{11}H_9ClN_6$ (260.69): C, 50.68; H, 3.49; N, 32.25. Found: C, 50.28; H, 3.50; N, 31.98.

4-[Di(1*H*-1,2,4-triazol-1-yl)methyl]benzonitrile (**4h**).

This compound was obtained as a brown oil (79%); ^{1}H nmr (deuteriochloroform): δ 8.42 (s, 2H), 8.09 (s, 2H), 7.95 (s, 1H),

7.75 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 153.1, 144.1, 138.0, 132.9, 127.8, 117.5, 114.4, 72.8.

HRMS Calcd. for $C_{12}H_9N_7$: 352.0996 (M^++1); observed: 252.0997.

1-[(4-Nitrophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-1,2,4-triazole (**4i**).

This compound was obtained as a hygroscopic yellow semi-solid (58%); ^{1}H nmr (deuteriochloroform): δ 8.46 (s, 2H), 8.29 (d, J = 8.6 Hz, 2H), 8.10 (s, 2H), 8.03 (s, 1H), 7.42 (d, J = 8.7 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 153.1, 144.1, 139.7, 128.3, 124.3, 124.2, 72.6.

Anal. Calcd. for $C_{11}H_9N_7O_2$ (271.24): C, 48.71; H, 3.35. Found: C, 48.93; H, 3.66.

1-[(*E*)-5-Methyl-2-phenyl-1-(1*H*-1,2,4-triazol-1-yl)-2-hexenyl]-1*H*-1,2,4-triazole (**4j**).

This compound was obtained as a colorless oil (54%); ^{1}H nmr (deuteriochloroform): δ 8.35 (s, 2H), 8.00 (s, 2H), 7.52 (s, 1H), 7.30-7.25 (m, 3H), 7.10-7.00 (m, 2H), 5.46 (t, J = 7.3 Hz, 1H), 1.89 (t, J = 7.1 Hz, 2H), 1.59 (hp, J = 6.6 Hz, 1H), 0.78 (d, J = 6.6 Hz, 6H); ^{13}C nmr (deuteriochloroform): δ 152.3, 143.8, 135.1, 134.4, 133.9, 128.6, 128.5, 128.1, 75.4, 37.4, 28.2, 22.1.

Anal. Calcd. for $C_{17}H_{20}N_6$ (308.39): C, 66.21; H, 6.55. Found: C, 66.27; H, 6.92.

1-[(*E*)-5-Methyl-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)-1-hexenyl]-1*H*-1,2,4-triazole (**6j**).

This compound was obtained as a colorless oil (16%); ^{1}H nmr (deuteriochloroform): δ 8.00 (s, 1H), 7.88 (s, 1H), 7.86 (s, 1H), 7.40-7.35 (m, 3H), 7.30 (s, 1H), 7.21 (s, 1H), 6.85-6.75 (m, 2H), 5.25 (t, J = 7.4 Hz, 1H), 2.25-2.05 (m, 1H), 2.00-1.80 (m, 1H), 1.58 (hp, J = 6.5 Hz, 1H), 0.98 (d, J = 6.5 Hz, 6H); ^{13}C nmr (deuteriochloroform): δ 151.9, 151.0, 142.4, 133.6, 131.7, 129.7, 129.3, 127.9, 124.8, 63.1, 40.1, 24.5, 22.4, 22.0.

Anal. Calcd. for $C_{17}H_{20}N_6$ (308.39): C, 66.21; H, 6.55; N, 27.26. Found: C, 65.97; H, 6.85; N, 26.99.

1-[9-(1*H*-1,2,4-Triazol-1-yl)-9*H*-fluoren-9-yl]-1*H*-1,2,4-triazole (**4k**).

This compound was obtained as white microcrystals (54%), mp 222-223°; ^{1}H nmr (deuteriochloroform): δ 8.20 (s, 2H), 8.09 (d, J = 7.6 Hz, 2H), 8.03 (s, 2H), 7.77 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 153.2, 142.8, 139.8, 138.6, 131.8, 128.8, 127.0, 121.0, 82.2.

Anal. Calcd. for $C_{17}H_{12}N_6$ (300.33): C, 67.98; H, 4.04; N, 27.99. Found: C, 67.96; H, 4.10; N, 27.93.

1-[4-(*tert*-Butyl)-1-(1*H*-1,2,4-triazol-1-yl)cyclohexyl]-1*H*-1,2,4-triazole (**4l**).

This compound was obtained as white microcrystals (45%), mp 151-152°; ^{1}H nmr (deuteriochloroform): δ 8.52 (s, 1H), 8.14 (s,1H), 7.99 (s, 1H), 7.88 (s,1H), 3.45 (d, J = 12.9 Hz, 2H), 2.34 (t, J = 13.2 Hz, 2H), 1.98 (d, J = 12.7 Hz, 2H), 1.40-1.00 (m, 3H), 0.82 (s, 9H); ^{13}C nmr (deuteriochloroform): δ 152.2, 151.7, 142.7, 140.5, 76.6, 46.4, 35.1, 32.2, 27.3, 22.8.

HRMS Calcd. for $C_{14}H_{22}N_6$: 275.1967 (M^++1); observed: 275.1984.

1-[4-(*tert*-Butyl)-1-cyclohexen-1-yl]-1*H*-1,2,4-triazole (**7l**).

This compound was obtained as colorless microcrystals (49%), mp 69-70°; ^{1}H nmr (deuteriochloroform): δ 8.24 (s, 1H), 7.96 (s, 1H), 6.30-6.20 (m, 1H), 2.80-2.60 (m, 1H), 2.60-2.40 (m, 1H), 2.35-2.20 (m, 1H), 2.10-1.90 (m, 2H), 1.50-1.30 (m, 2H), 0.93 (s, 9H); ^{13}C nmr (deuteriochloroform): δ 151.4, 139.7, 133.6, 117.1, 43.3, 31.9, 27.0, 26.9, 25.3, 23.3.

Anal. Calcd. for $C_{12}H_{19}N_3$ (205.31): N, 20.47. Found: N, 20.76.

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