An Improved Procedure for the Preparation of 1-Benzyl-1*H*-1,2,3-triazoles from Benzyl Azides.

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A procedure for the preparation of substituted 1-benzyl-1*H*-1,2,3-triazoles from benzyl azides under very mild conditions is described. The method provides improved yields and extends the scope of the Dimroth Reaction to other types of active methylene compound to those previously used. Benzyl azides react with active methylene compounds in dimethyl sulphoxide catalysed by potassium carbonate at 35-40° to give 1*H*-1,2,3-triazoles usually in good yield. Acetonitrile derivatives gave 5-amino-1*H*-1,2,3-triazoles whereas diethyl malonate gave 5-hydroxy-1*H*-1,2,3-triazoles. 1*H*-1,2,3-Triazole-4-carboxylate esters and 1*H*-1,2,3-triazole-4-ketones were obtained from ethyl acetoacetate and β-diketones respectively. Benzyl methyl ketone reacted to give a 5-methyl-4-phenyl-1*H*-1,2,3-triazole, but acetone and acetophenone failed to react. Other active methylene compounds which did not react under these reaction conditions included ethyl cyanoacetate, ethyl fluoroacetate and ethyl nitroacetate.

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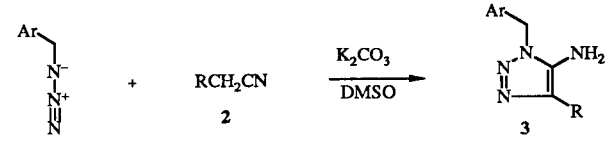
Substituted 5-amino-1-benzyl-1*H*-1,2,3-triazoles have recently been shown to be a new class of antiproliferative agents useful in the treatment of psoriasis, certain types of cancer and other diseases [1]. Although these compounds had been prepared previously for another application [2,3], in order to exploit this new discovery for the treatment of disease, a method suitable for large scale synthesis of 1-benzyl-1*H*-1,2,3-triazoles was required.

The preparation of 1-aryl-1*H*-1,2,3-triazoles by reaction between phenyl azide and active methylene compounds with sodium ethoxide in boiling ethanol was first described by Dimroth in 1902 [4,5]. However, the usefulness of the method is somewhat limited due to the lability of the triazole or active methylene compound under the vigorous reaction conditions employed. Thus, 1-substituted-5-amino-1*H*-1,2,3-triazoles are liable to undergo a Dimroth rearrangement to yield 4-substituted amino derivatives [6,8], and alkyl or benzyl azides with certain active methylene compounds give only moderate or poor yields of desired products [6,9-11]. Some success in improving yields had been achieved by the use of potassium t-butoxide as base at room temperature, which gave good yields of 5-amino-1*H*-1,2,3-triazoles from benzyl and *n*-hexyl azides with phenylacetonitrile [12], but with methyl ketones yields of product were variable due to dimerisation of the ketones and other side reactions [13,14].

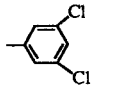
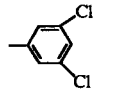
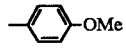
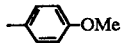
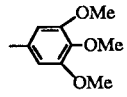
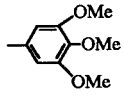
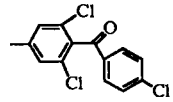
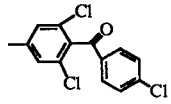
We now report a simple method for the preparation of benzyl-1*H*-1,2,3-triazoles from benzyl azides and active methylene compounds under mild conditions using anhydrous potassium carbonate as base in dimethyl sulphoxide. In many cases, at the end of the reaction period, the pure product may be isolated by dilution of the reaction mixture with water, followed by filtration.

The method is effective for the preparation of

Scheme 1



1 2 3

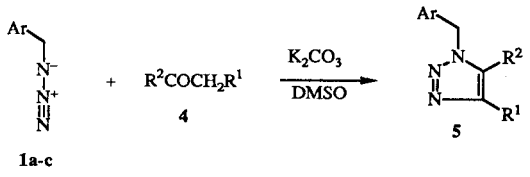
	Ar		Ar	R
1a	C_6H_5	3a	C_6H_5	$CONH_2$
1b		3b		$CONH_2$
1c		3c		$CONH_2$
1d		3d		$CONH_2$
1e		3e		$CONH_2$
		3f	C_6H_5	CN
		3g	C_6H_5	C_6H_5
		3h	C_6H_5	CO_2Et

	R
2a	$CONH_2$
2b	CN
2c	C_6H_5
2d	CO_2Et

5-amino-1*H*-1,2,3-triazoles **3** from cyanoacetamide, malonitrile and phenylacetonitrile in 48-94% yields (Table 1), but surprisingly no reaction occurred with ethyl cyanoacetate to give the ester **3h**.

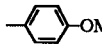
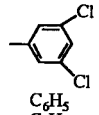
5-Hydroxy-1*H*-1,2,3-triazoles **5a-c** were obtained from diethyl malonate in 77-96% yield (Table 2), but ethyl phenylacetate only gave a poor yield (8%) of 1-benzyl-5-hydroxy-4-phenyl-1*H*-1,2,3-triazole **5d** after a prolonged reaction time. Attempts to obtain the novel fluoro **5e** or

Scheme 2



1a-c

	R^1	R^2
4a	CO_2Et	OEt
4b	C_6H_5	OEt
4c	F	OEt
4d	NO_2	OEt
4e	CO_2Et	Me
4f	C_6H_5	Me
4g	H	Me
4h	H	C_6H_5
4i	MeCO	Me
4j	C_6H_5CO	Me

	Ar	R^1	R^2
5a	C_6H_5	CO_2Et	OH
5b		CO_2Et	OH
5c		CO_2Et	OH
5d	C_6H_5	C_6H_5	OH
5e	C_6H_5	F	OH
5f	C_6H_5	NO_2	OH
5g	C_6H_5	CO_2Et	Me
5h		CO_2Et	Me
5i	C_6H_5	C_6H_5	Me
5j	C_6H_5	H	Me
5k	C_6H_5	H	C_6H_5
5l	C_6H_5	MeOH	Me
5m		MeOH	Me
5n	C_6H_5	MeOH	C_6H_5
5o	C_6H_5	C_6H_5CO	Me
5p		MeOH	C_6H_5
5q		C_6H_5CO	Me

nitro **5f** triazoles by reaction between benzyl azide and ethyl fluoroacetate or ethyl nitroacetate were unsuccessful. The procedure was also very effective for the preparation of ethyl 1*H*-1,2,3-triazole-4-carboxylate esters **5g** and **5h** from ethyl acetoacetate in 84 and 89% yields (Table 2).

Benzyl methyl ketone and benzyl azide reacted under these conditions to give 1-benzyl-5-methyl-4-phenyl-1*H*-1,2,3-triazole **5i** in 90% yield, but no reaction occurred with the simple methyl ketones, acetone or acetophenone, to give triazoles **5j** and **5k**. This suggested that 1,2,3-triazole-4-ketones would be stable under these reaction conditions, thus providing a simple route to acyltriazoles from β-diketones. Reports of the preparation of acyl-1,2,3-triazoles in the literature are rare. 4-Acetyl-1-phenyl-1*H*-1,2,3-triazole and the 5-methyl derivative were obtained from triazolecarboxylate esters by Claisen condensation with ethyl acetate followed by decarboethoxylation [15], and 5-benzoyl-1-phenyl-1*H*-1,2,3-triazole was obtained from the triazole acid chloride by Friedel-Crafts reaction with benzene [15]. Later reports describe more convenient procedures for the preparation of acyltriazoles by cycloaddition between azides and acetylenic ketones [16] or chlorovinyl ketones [17]. We now report that reaction between benzyl azides **1a** and **1b** and acetylacetone in dimethyl sulphoxide with potassium carbonate provided excellent yields (82 and 96%) of the triazole methyl ketones **5l** and **5m**. Benzoylacetone reacted with benzyl azides to give separable mixtures of the methyl ketones **5n** and **5p** with the phenyl ketones **5o** and **5q** in high yields (Table 2). This novel route to acyltriazoles thus demonstrates the wide scope of the Dimroth reaction under these mild conditions.

The benzyl azides were prepared from benzyl alcohols

Table 1
Preparation and Properties of 5-Amino-1-benzyl-1,2,3-trizoles **3**

Compound	Azide	Actve methyline compound	Reaction time (hours)	Yield [a] (%)	m.p. [b] (°C)	Molecular Formula	EIMS Base Peak, M^+	Analysis % Calcd./Found		
3a	**1a**	**2a**	5	84 (81) [9]	236-238 (233-235)	$C_{10}H_{11}N_5O$	91,217 (76%)			
3b	**1b**	**2a**	1	94	230-232	$C_{10}H_9Cl_2N_5O$	28,285 (62%)	41.98 42.02	3.17 3.21	24.48 24.57
3c	**1c**	**2a**	60	75	205-208	$C_{11}H_{13}N_5O_2$	121,247 (12%)	53.44 53.32	5.30 5.32	28.32 28.32
3d	**1d**	**2a**	24	91	195-196	$C_{13}H_{17}N_3O_4$	181,307 (37%)	50.81 50.86	5.58 5.61	22.79 22.76
3e	**1e**	**2a**	2	90 (41) [2]	200-202 (198-200)	$C_{17}H_{12}Cl_3N_5O_2$	139,423 (51%)			
3f	**1a**	**2b**	18	48 (17) [9]	181-182 (175-176)	$C_{10}H_9N_5$	91,199 (28%)			
3g	**1a**	**2c**	24	84 (78) [12]	157-158 (156-157)	$C_{15}H_{14}N_4$	131,250 (36%)			
3h	**1a**	**2d**	48	No reaction						

[a] Yield of isolated product. In brackets, reported yield. [b] In brackets, literature mp.

Table 2

Preparation and Propterties of 1-Benzyl-1*H*-1,2,3-triazoles **5**

Compound	Azide	Active Methylene compound	Reaction time (hours)	Yield [a] (%)	mp [b] (°C)	Molecular Formula	EIMS Base Peak, M+	Analysis Calcd./Found C	H	N
5a	**1a**	**4a**	44	77 (48) [9]	95-96 (111-112)	$C_{12}H_{13}N_3O_3$	91, 247 (24%)			
5b	**1b**	**4a**	72	96	101-102	$C_{12}H_{11}Cl_2N_3O_3$	174, 315 (10%)	45.59 45.50	3.51 3.52	13.29 13.25
5c	**1c**	**4a**	72	92 (67) [19]	109 (117)	$C_{13}H_{15}N_3O_4$	176, 277 (17%)			
5d	**1a**	**4b**	96	8	195	$C_{15}H_{13}N_3O$	132, 251 (35%)	71.70 71.61	5.21 5.31	16.72 16.75
5e	**1a**	**4c**	48	No reaction						
5f	**1a**	**4d**	48	No reaction						
5g	**1a**	**4e**	44	84	76-78	$C_{13}H_{15}N_3O_2$	91, 245 (16%)	63.66 63.51	6.61 6.18	17.13 17.17
5h	**1b**	**4e**	18	89	111-112	$C_{13}H_{13}Cl_2N_3O_2$	216 (M+1)	49.70 49.69	4.17 4.20	13.37 13.27
5i	**1a**	**4f**	24	90 (85) [14]	93-94 (93-94)	$C_{16}H_{15}N_3$	130, 249 (12%)			
5j	**1a**	**4g**	48	No reaction						
5k	**1a**	**4h**	48	No reaction						
5l	**1a**	**4i**	48	82	oil	$C_{12}H_{13}N_3O$	91, 215 (42%)	66.96 66.82	6.09 6.19	19.52 19.58
5m	**1b**	**4i**	18	96	oil	$C_{12}H_{11}Cl_2N_3O$	159, 283 (39%)	50.73 50.79	3.90 3.96	14.79 14.72
5n	**1a**	**4j**	48	25	oil [c]	$C_{17}H_{15}N_3O$	278 (M+1)	73.63 73.63	5.45 5.53	15.15 15.12
5o				42	oil [c]	$C_{17}H_{15}N_3O$	278 (M+1)	73.63 73.61	5.45 5.54	15.15 15.12
5p	**1c**	**4j**	18	36	oil [d]	$C_{17}H_{13}Cl_2N_3O$	105,345 (33%)	58.98 59.39	3.78 3.99	12.14 11.93
5q				54	oil [d]	$C_{17}H_{13}Cl_2N_3O$	105,345 (27%)	58.98 59.05	3.78 3.87	12.14 12.08

[a] Yield of isolated product. In brackets, reported yield. [b] In brackets, literature mp. [c] Combined yield 67%, separated by chromatography. [d] Combined yield 90%, separated by chromatograghy.

in dimethylformamide by reaction with thionyl chloride followed by treatment with sodium azide at room temperature in a 'one-pot' process, which avoided the isolation of the lachrymatory intermediate benzyl chlorides.

EXPERIMENTAL

Melting points were determined with a Buchi apparatus and are uncorrected. Infra red (ir) spectra were recorded on a Perkin Elmer 781 spectrophotometer as nujol mulls (solids) or liquid films (oils). A Bruker FT (250 MHz) spectrometer was used to determine nuclear magnetic resonance (nmr) spectra, with tetramethylsilane (TMS) as internal reference and deuterioacetone as solvent (unless otherwise stated). High pressure liquid chromatography (hplc) using a Waters chromatograph with a uv detector (λ = 239 nm) and Hypersil 5 microns ODS, 25 cm x 4.5 mm column was used to measure the purity of compounds with the following solvent system 40% acetonitrile: 60% 0.0025M phosphoric acid, flow 1.5 ml min^{-1}. Mass spectra were recorded on a Finnegan Mat TSQ70 spectrometer. Chemical ionisation mass spectra were recorded using methane as the ionising gas.

3,5-Dichlorobenzyl Azide (**1b**).

A solution of 3,5-dichlorobenzyl alcohol (10.0 g, 57 mmoles) in DMF (20 ml) was treated with thionyl chloride (4.4 ml, 60 mmoles), added over 15 minutes and maintaining a temperature of 20-30° by cooling in a water bath. The solution of the benzyl chloride (hplc Rt 8.0 minutes) was neutralised by the addition of potassium carbonate (15.8 g, 0.11 mole) and the mixture stirred for 30 minutes. DMSO (50 ml) was added, followed by sodium azide (5.6 g, 86 mmoles) and stirring continued at Rt for 1.5 hours, when hplc showed complete reaction to form the azide, Rt 8.5 minutes. The reaction mixture was partitioned between water (200 ml) and ethyl acetate (100 ml). The organic phase was washed with water, dried (sodium sulfate) and evaporated under reduced pressure at $<30°$ to give 11.0 g (95%) of the azide **1b** as an oil; ir: 2100 cm^{-1} (N_3); ^1H nmr: δ 4.55 (s, CH_2, 2H), 7.4-7.5 (m, ArH's, 3H); ms: base peak 159, $M^{+\cdot}$ 201 (25%).

Anal. Calcd. for $C_7H_5Cl_2N_3$: C, 41.62; H, 2.50; N, 20.79. Found: C, 41.80; H, 2.62; N, 20.56.

3,4,5-Trimethoxybenzyl Azide (**1d**).

Thionyl chloride (2.5 ml, 34 mmoles) was added over 15 minutes to a solution of 3,4,5-trimethoxybenzyl alcohol (5.0 g, 25

mmoles) in DMF (10 ml) maintaining a temperature of 20-30° by cooling in a water bath. The solution of the benzyl chloride was diluted with DMSO (50 ml), the *p*H adjusted to 8 ±0.2 by addition of aqueous ammonium hydroxide (20*N*) and then sodium azide (2.95 g, 45 mmoles) added. The mixture was stirred at room temperature for 18 hours and then partitioned between water (400 ml) and hexane (100 ml). The organic phase was washed with water, dried (sodium sulfate) and evaporated under reduced pressure to give 4.2 g (75%) of the azide **1d** as an oil, hplc, Rt 12.9 minutes; ir: 2140 cm^{-1} (N_3); ^1H nmr: δ 3.74 (s, OMe, 3H), 3.84 (s, $(OMe)_2$, 6H), 4.36 (s, CH_2, 2H), 7.30 (s, ArH's, 2H).

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 54.01; H, 5.94; N, 18.67.

Benzyl azide **1a** [18], 4-methoxybenzyl azide **1c** [19] and 4-(4-chlorobenzoyl)-3,5-dichlorobenzyl azide **1e** [2] were prepared similarly.

5-Amino-1-(3,5-dichlorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (**3b**).

3,5-Dichlorobenzyl azide **1b** (11.0 g, 54.5 mmoles) and cyanoacetamide (5.8 g, 70 mmoles) were added to a suspension of milled potassium carbonate (31.5 g, 0.23 mole) in DMSO (70 ml). The mixture was stirred at room temperature for 1 hour, during which time a mild exotherm increased the temperature to 40°. Hplc indicated that no azide remained and that the solution contained a single product Rt 3.0 minutes. The mixture was added to water (1.5 l) over 30 minutes with stirring. The solid was collected by filtration, washed well with water and dried to give 15.3 g (96%) of the amino triazole **3b**, mp 230-232°, ir: 3420, 3280 and 3160 cm^{-1} (NH_2), 1650 cm^{-1} (C=O); ^1H nmr: δ 5.52 (s, CH_2, 2H), 7.32 (broad s, 2-, 6-H, 2H), 7.45 (broad s, 4-H, 1H).

The compounds in Table 1 were prepared similarly from cyanoacetamide, malonitrile or phenylacetonitrile.

Ethyl 5-Hydroxy-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole-4-carboxylate (**5b**).

4-Methoxybenzyl azide (3.0 g, 18.6 mmoles) and diethylmalonate (4.3 g, 25.7 mmoles) were added to a suspension of milled potassium carbonate (10.3 g, 74 mmoles) in DMSO (20 ml) and the mixture stirred at 40° for 72 hours. Hplc indicated complete reaction with a single product Rt 2.8 minutes. Aqueous hydrochloric acid (50 ml, 5*N*) was added over 30 minutes and the suspension cooled to 20°. The solid was collected by filtration, washed with water and then with hexane. The crystalline solid was dried *in vacuo* to give 4.8 g (92%) of the hydroxytriazole **5b**, mp 109° (lit [19] mp 117°); ir: 3350 cm^{-1} (OH), 1700 cm^{-1} (C=O); ^1H nmr: δ 1.30 (t, CH_3, 3H, J = 7 Hz), 4.28 (q, OCH_2, 2H, J = 7 Hz), 5.30 (s, CH_2, 2H), 6.90 (d, 2-, 6-H, 2H, J = 8.5 Hz) 7.25 (d, 3-, 5-H, 2H, J = 8.5 Hz).

Triazoles **5a** and **5c** Table 2 were prepared similarly, except in the latter case due to incomplete reaction, chromatography was used to isolate the product.

4-Acetyl-1-benzyl-5-phenyl-1*H*-1,2,3-triazole (**5m**) and 4-Benzoyl-1-benzyl-5-methyl-1*H*-1,2,3-triazole (**5n**).

Benzyl azide (3.0 g, 22.6 mmoles) and benzoylacetone (5.5 g, 34 mmoles) were added to a suspension of milled potassium carbonate (12.4 g, 90.4 mmoles) in DMSO (21 ml) and the mixture stirred at 35° for 48 hours. Hplc showed the formation of two products Rt 17.6 and 20.1 minutes. The mixture was diluted with water (100 ml) and extracted with ether (2 x 80 ml). The extract was washed with water, dried (sodium sulfate) and evaporated under reduced pressure to an oil. The oil was chromatographed on silica with toluene:diethyl ether (15:1) to give 2.7 g (42%) of the less polar benzoyltriazole **5n** as an oil; ir: 1645 cm^{-1} (C=O); ^1H nmr: δ 2.57 (s, CH_3, 3H), 5.70 (s, CH_2, 2H), 7.2-8.4 (m, Ph, 5H). Later fractions gave 1.5 g (25%) of the more polar acetyltriazole **5m** as an oil; ir: 1690 cm^{-1} (C=O); ^1H nmr: δ 2.55 (s, CH_3, 3H), 5.50 (s, CH_2, 2H), 6.9-7.5 (m, Ph, 5H).

The triazoles **5h**, **5o** and **5p** in Table 2 were prepared similarly from benzyl methyl ketone and benzoylacetone. Triazoles **5f**, **5g**, **5k** and **5l** were prepared similarly from ethyl acetoacetate and acetylacetone, except that chromatography to isolate pure products was unnecessary.

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