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An investigation into the alkylation of 1,2,4-triazole

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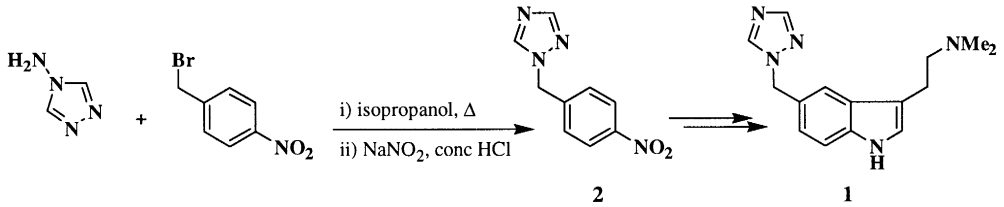
Abstract

The alkylation of 1,2,4-triazole with 4-nitrobenzyl halides and a variety of bases afforded the 1- and 4-alkylated isomers with a consistent regioselectivity of 90:10. Previously reported regiospecific alkylations of 1,2,4-triazole were re-examined and the quoted isomer ratios were shown to depend on the isolation procedure. The use of DBU as base in the alkylation of 1,2,4-triazole allows for a convenient and high yielding synthesis of 1-substituted-1,2,4-triazoles. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: 1,2,4-triazole; DBU; regioselective alkylation; rizatriptan.

Fused and pendant 1,2,4-triazoles are a ubiquitous feature of many pharmaceutical and agrochemical products.[1] The 1-substituted-1,2,4-triazole nucleus is particularly common and examples can be found in marketed drugs such as fluconazole,[2] terconazole[3] and rizatriptan (**1**).[4] An alkylation reaction would be an obvious method of introducing this triazole unit. However, the controlled, regioselective alkylation of 1,2,4-triazole can be problematic, with mixtures of isomers produced and over-alkylation leading to salt formation possible. While such problems have been noted,[5] there are also several contrasting reports of regiospecific alkylation reactions.[6] We recently required the efficient synthesis of 1-alkyl-1,2,4-triazole derivatives and now report our findings on this apparently trivial reaction. We also disclose a mild and convenient method for the alkylation of 1,2,4-triazole, which uses the weakly nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).



Scheme 1.

Rizatriptan (**1**) is a recently marketed 5-$HT_{1B/1D}$ receptor agonist which is prescribed for the acute treatment of migraine.[4] Two syntheses of this compound have been reported, both of which proceed

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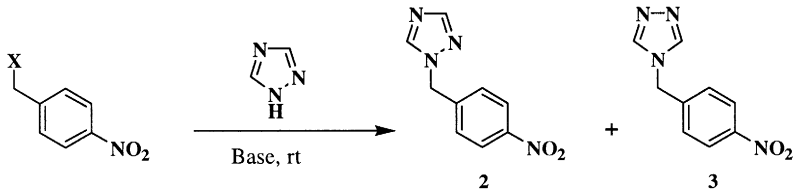
via 4-nitrobenzyl triazole (**2**) with either a Fisher indole reaction[4] or a Pd-mediated cyclisation[7] used to construct the indole heterocycle (Scheme 1).

The Process Chemistry route to compound **2** utilised a two-step alkylation of 4-aminotriazole with 4-nitrobenzyl bromide followed by sodium nitrite deamination with evolution of nitrous oxide.[8] This was an efficient sequence affording an overall yield of >90% from 4-aminotriazole. An attractive alternative is the alkylation of 1,2,4-triazole with a 4-nitrobenzyl halide, as this is one synthetic step shorter and would allow the use of cheaper reagents (triazole and 4-nitrobenzyl chloride versus 4-aminotriazole and 4-nitrobenzyl bromide). However, the reported yield of alkylated product by this method was moderate (52%) but, of relevance to the present study, the authors observed that the alkylation gave "as expected, a single isomer".[4]

As part of our ongoing research, the alkylation route to compound **2** was re-examined. Following the described procedure (NaH, 4-nitrobenzyl bromide, DMF, rt), we obtained a 90:10 mixture of the 1- and 4-isomers, **2** and **3**, respectively (Scheme 2). When this reaction was repeated with a range of conditions, on each occasion, a surprisingly consistent ratio of alkylated 1,2,4-triazoles was obtained. At no stage could we significantly alter this ratio, either by changing the base used (NaH, K_2CO_3, Cs_2CO_3, DBU, LiOH, NaOH, tetramethylguanidine); changing the electrophile (X=Cl, Br) or changing the solvent (MeOH, THF, toluene, CH_3CN, DMF). This could imply alkyl group isomerisation, however, literature precedent for such an equilibration is only reported at high temperatures.[9] The isomer ratios were also constant (±2%) from the first analysis point of 5 min up to 3 days, apparently indicating that the ratios do not result from an equilibration.



Scheme 2.

The optimum synthetic conditions we found were the use of DBU (1.2 equiv.), 4-nitrobenzyl chloride (1.0 equiv.), triazole (1.1 equiv.) and THF whereby a 93% yield of adducts in a 90:10 ratio was obtained.[10] Interestingly, successive aqueous washes increased the isomer ratio of **2**:**3** to 98:2. This preferential partition of the minor isomer to the aqueous layer may account for the earlier report of the alkylation reaction proceeding to give a single isomer.[4]

We were intrigued to see whether this simple partitioning of 4-alkyl-1,2,4-triazoles to an aqueous layer on work-up might explain some previously reported regiospecific alkylation reactions. Katritzky et al. have disclosed an improved method for the alkylation of 1,2,4-triazole and they give five examples of isomer ratios of 100:0 using a DMF/NaOH system.[6a] The experimental procedure for these reactions included an aqueous work-up and it was thought that the isomer ratio might not have been determined on the crude reaction mixtures. Table 1 illustrates our results following this procedure. Indeed, excellent isomer ratios were observed after work-up, however, the isomer ratios of the crude mixtures before work-up were only ca. 90:10.

In a related project, we required the synthesis of 1-ethyl-1,2,4-triazole. The use of NaOH/DMF was not practical, however, due to the difficulties in separation of the water soluble and volatile 1-ethyl-1,2,4-triazole from DMF. Instead, using DBU as base and THF as solvent, we obtained an 88% yield of products as a 90:10 mixture of isomers, again favouring the 1-isomer. An advantage of this method was that DBU·HX precipitated from the reaction and was easily removed by filtration. Concentration of the resulting liquors then gave the crude product which was easily purified by distillation to afford pure 1-ethyl-1,2,4-triazole (78% yield).

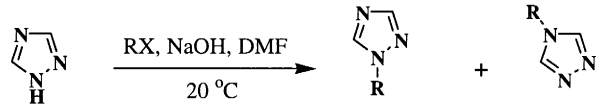


Table 1

RX	Reported Isomer Ratio[6a]	Ratio after Work-up **4**:**5**	Ratio of Crude Mixture **4**:**5**[a,b]
PrI	100:0	>99:1	88:12
BuBr	100:0	98:2	91:9
EtMeCHBr	100:0	96:4	90:10
EtO_2CCH_2Cl[c]	100:0	-----	-----
$PhCOCH_2Br$	100:0	98:2	94:6

(a) Isomer ratio based on ^1H NMR analysis of the product mixture. (b) All reactions were conducted at 20°C under an atmosphere of nitrogen. (c) We were unable to observe the expected product from this reaction, even at 0°C, due to competing hydrolysis of the ester.

Compared to previously reported alkylation methods,[1a–c] the use of DBU as base is a synthetically simple and mild method for the alkylation of 1,2,4-triazole.[11] Hence, we applied these conditions to a range of alkylating agents and obtained good yields for all substrates with the regioselectivity of the reactions varying from 86:14 up to 94:6 (Table 2).

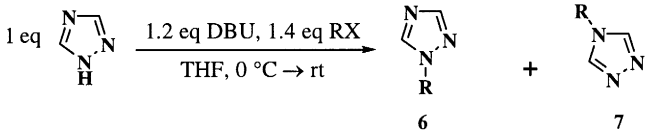


Table 2

Entry	RX	Isomer Ratio **6**:**7**[a]	Isolated Yield of **6**[b]
1	MeI	90:10	76%
2	EtI	90:10	78%
3	EtBr	92:8	75%
4	PrI	92:8	80%
5	Me_2CHI	89:11	77%
6	BuBr	89:11	85%
7	EtMeCHBr	90:10	55%
8	CH_2=$CHCH_2Br$	88:12	81%
9	EtO_2CCH_2Cl	91:9	69%
10	$EtO_2CC_2H_4Br$	90:10	78%[c]
11	$EtO_2CC_3H_6Br$	94:6	88%
12	$EtO_2CC_4H_8Br$	91:9	83%
13	BnCl	86:14	77%
14	$PhCOCH_2Br$	89:11	82%[d]
15	Ph_3CCl	92:8	100%[e]

(a) Isomer ratio based on ^1H NMR analysis of the product mixture. (b) Yield refers to adduct **6** isolated after distillation. (c) Ethyl acrylate was formed in this reaction and may be the alkylating species. (d) Yield after silica gel chromatography. (e) This compound was isolated as a 92:8 mixture of isomers.

Notable examples include the reaction of alkyl esters (entries 9–12), which proceeded without competing hydrolysis, and secondary alkyl halides (entries 5 and 7), where competing dehydrohalogenation of the alkylating agent by DBU was not a serious competing problem.

Purification of the isomeric mixtures of triazoles was achieved by distillation (except entries 14 and 15). In this manner, pure 1-alkyl-1,2,4-triazoles were obtained (**6**:**7**≥99:1) without any attempt at fractionation. In each case, the 1-isomer had the lower boiling point as indicated by an examination of the distillation residue, which showed the presence of the 4-alkyl isomer. This highlights the difference in physical properties[12] of the two triazole isomers and the care needed in reporting regiospecific alkylation reactions, as distillation of a mixture invariably leads to the isolation of a single adduct.

In conclusion, DBU is a mild and convenient base for the alkylation of 1,2,4-triazole. Some literature reports of regiospecific alkylations of 1,2,4-triazole have been re-examined and in each case, the 1-isomer is accompanied by formation of the 4-isomer. However, such are the differing volatilities and polarities of these isomers, they are readily separable by distillation, recrystallisation or silica gel chromatography. Hence, in alkylation reactions of 1,2,4-triazoles which produce isomeric mixtures, the 4-isomer often goes undetected and thus unreported.

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10. Compounds **2** and **3**: To a mechanically stirred suspension of 1,2,4-triazole (10.0 g, 0.145 mol) and 4-nitrobenzyl chloride (22.4 g, 0.130 mol) in THF (100 mL) was added DBU (24.2 g, 0.159 mol) in THF (20 mL) via syringe pump over 1 h. The solution was stirred at room temperature for 16 h, filtered and the cake washed with THF (100 mL). The filtrate was concentrated to residue and partitioned between water (250 mL) and EtOAc (500 mL and 100 mL). The combined organic layers were concentrated to afford **2** and **3** (24.7 g, 93%) as a 94:6 mixture. Purification by silica gel chromatography (eluent EtOAc→EtOAc:MeOH, 85:15), yielded in elution order: 1-[(4-nitrophenyl)methyl]-1,2,4-triazole, **2** (19.0 g, 73%): mp 100–101°C (ref.[13]: mp 95–100°C); R_f (EtOAc:MeOH, 9:1) 0.71; ^{1}H NMR (250 MHz, d_6-DMSO): δ 8.61 (1H, s), 8.12–8.09 (2H, m), 7.92 (1H, s), 7.39–7.36 (2H, m), 5.49 (2H, s); ^{13}C NMR (62.5 MHz, d_6-DMSO): δ 153.0, 148.0, 145.6, 144.7, 129.8, 124.7, 52.1. Anal. calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44; O, 15.67. Found: C, 53.01; H, 3.84; N, 27.30; O, 15.68. 4-[(4-Nitrophenyl)methyl]-1,2,4-triazole, **3** (1.1 g, 4%): mp 143–145°C; R_f (EtOAc:MeOH, 9:1) 0.41; ^{1}H

NMR (250 MHz, d_6-DMSO): δ 8.54 (2H, s), 8.14–8.10 (2H, m), 7.42–7.38 (2H, m), 5.35 (2H, s); ^{13}C NMR (62.5 MHz, d_6-DMSO): δ 148.0, 145.0, 144.3, 129.6, 124.9, 47.6. Anal. calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44; O, 15.67. Found: C, 53.03; H, 3.85; N, 27.42; O, 15.70.

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