SELECTIVE ALKYLATIONS OF 1,2,4-TRIAZOLE AND BENZOTRIAZOLE IN THE ABSENCE OF SOLVENT

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Abstract- Alkylation of 1,2,4-triazole and benzotriazole has been performed either in basic media under solvent free phase transfer catalysis conditions or in the absence of base by conventional and microwave heating. Several parameters affecting the selectivity have been studied. In the case of triazole alkylation, microwave irradiation produces specific (non thermal) effects both on reactivity and selectivity.

INTRODUCTION

The alkylation of 1,2,4-triazole and benzotriazole has been performed in homogeneous media[1-6] and under solid-liquid or liquid-liquid Phase Transfer Catalysis (ptc).[7-10] However, in most cases, mixtures of the possible isomers have been obtained. In the alkylation of 1,2,4-triazole, in addition to N-1 and N-4 alkylations, quaternisation has also been detected.[11]

We describe here the alkylation of these substrates using solvent-free techniques. They concern either basic conditions under ptc without solvent[12,13] or non basic conditions, with microwave[14] or conventional heating. These techniques usually provided good yields and selectivities in addition to an easy work-up under mild and cheap conditions.

RESULTS AND DISCUSSION

Reactions in the presence of base

Results obtained in the alkylation of 1,2,4-triazole by ptc without solvent (Table 1) showed that only the strengh of the base, essentially due to cation effect (Entry 2 *vs* 6), and the nature of the alkyl group have some influence on the N-1/N-4 ratio. N-4 Alkylation is favoured with the more reactive halides (Entries 1 *vs* 12, 2 *vs* 13 and 11 *vs* 15), while LiOH and KF/Al_2O_3 as bases favour both N-4 alkylation and quaternisation (Entries 1 *vs* 3, 2 *vs* 6 and 7 *vs* 9). This results can be explained considering that the reaction may take place simultaneously with the free base and via the anion, as shown by experiments in the absence of base (see below).

In the alkylation of benzotriazole by ptc without solvent, no significant variation of the N-1/N-2 ratio has been observed with the studied factors. This result is in agreement with theoretical calculations[15] suggesting that position 1 is favoured both thermodynamically and kinetically.

The proportion of isomer N-2 is incrased with bulk of alkyl halides due to a steric interaction between H-7 and the alkyl group[6] (Table 2).

Alkylation under basic conditions is directed to in N-1 by the higher charge density and the coefficients of the HOMO on this site both in benzotriazole and 1,2,4-triazole that make difficult any change in the selectivity.

Reactions in the absence of base

We have performed the alkylation of these substrates in the absence of both solvent and base by conventional or microwave heating, using an oil bath in the first case and a domestic oven in the later. The use of microwaves has been successful with several substrates and can have a specific effect on the reaction.[14] Alkylation in the absence of base is controlled by tautomeric equilibrium.

Alkylation of 1,2,4-triazole in the absence of solvent under conventional heating produced increases in quaternized products when compared to PTC conditions using a base (Table 3, Entries 2 *vs* 1, 6 *vs* 4, 9 *vs* 8 and 12 *vs* 11)).

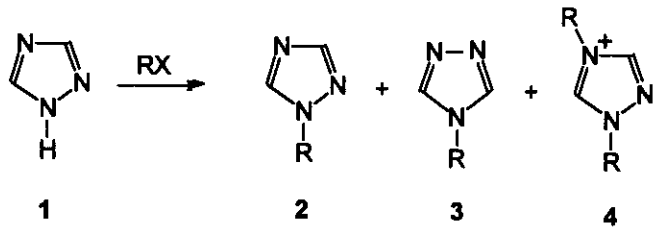

Table 1. Alkylation of 1,2,4-triazole (PTC conditions)

1:base:RX = 1:2.3:1.1 mole ratio; TBAB 2%[a] ; reaction time 24 h.

Entry	RX	base	T (°C)	**2 / 3 / 4** [b]
1	BuBr	KOH	RT	91 / 9 / 0
2	BuBr	KOH	80	92 / 8 / 0
3	BuBr	K_2CO_3	RT	83 / 17 / 0
4	BuBr	K_2CO_3	80	85 / 15 / 0
5[c]	BuBr	KOBu^t	RT	82 / 18 / 0
6	BuBr	LiOH [d]	80	74 / 14 / 12
7[e]	BuBr	KF/Al_2O_3 (1:2)	RT	74 / 0 / 26
8[e]	BuBr	KF/Al_2O_3 (1:4)	RT	88 / 0 / 12
9[e]	BuBr	KF/Al_2O_3 (1:6)	RT	93 / 7 / 0
10	BuCl	KOH	RT	90 / 10 / 0
11	BuOTs	KOH	80	96 / 4 / 0
12	BnCl	KOH	RT	84 / 16 / 0
13	BnCl	KOH	80	87 / 13 / 0
14	BnCl	K_2CO_3	80	84 / 16 / 0
15	BnOTs	KOH	80	87 / 13 / 0

a) tetrabutylammonium bromide; no reaction in the absence of catalyst; b) determined by gc and ^{1}H-nmr. c) mole ratio 1:1.2:1.1; d) H_2O 10%; e) mole ratio 1:1.7:1.1.

Table 2. Alkylation of benzotriazole. Effect of the alkylating agent.

Mole ratio Benzotriazole / KOH / RX= 1 / 2.4 / 2; TBAB 2%, room temperature.

RX	$C_{16}H_{33}Br$	$C_8H_{17}Br$	C_4H_9Br	CH_3I	$PhCH_2Br$
N1 / N2	53 / 47	53 / 47	56 / 44	72 / 28	78 / 22

Table 3. Alkylation of 1,2,4-triazole under the solvent-free conditions.

Mole ratio **1**: RX= 1: 1.1

Entry	RX	**ptc**[a] t(h), T(°C)	**Conventional Heating** t(h), T(°C)	**Microwave Irradiation** W, t(min), T(°C)[d]	**2 / 3 / 4** [b]	Yield[c] (%)
1	$C_{16}H_{33}Br$	36, 80			96 / 4 / 0	83
2	$C_{16}H_{33}Br$		24, 120		0 / 0 / 100	33
3	$C_{16}H_{33}Br$			780, 3, 137	no reaction	0
4	$C_8H_{17}Br$	24, 80			93 / 7 / 0	84
5	$C_8H_{17}Br$		1.5 min, 130		no reaction	0
6	$C_8H_{17}Br$		1, 120		42 / 28 / 30	--
7	$C_8H_{17}Br$			780, 1.5, 130	75 / 0 / 25	44
8	C_4H_9Br	24, 80			92 / 8 / 0	83
9	C_4H_9Br		1, 120		43 / 37 / 20	--
10	C_4H_9Br			780, 5, 90	no reaction	0
11	$PhCH_2Cl$	24, 80			87 / 13 / 0	74
12	$PhCH_2Cl$		5 min, 165		0 / 0 / 100[e]	13
13	$PhCH_2Cl$		1, 120		decomposition	--
14	$PhCH_2Cl$			450, 5, 165	100 / 0 / 0	70

a) **1**:Base; 1:2.3 mole ratio. b) determined by ^{1}H-nmr and gc c) related to azole d) Final temperature.

e) together with decomposition.

Microwave irradiation produced here two kinds of specific (non thermal) effects as compared with classical heating under the same conditions of time and temperature:

- an enhancement in reactivity, as it provokes the reaction in one case (Entry 7 *vs* 5).
- a change in selectivity in the reaction with benzyl chloride, as quaternisation is obtained by classical heating and N-1 alkylation with microwave irradiation (Entry 12 *vs* 14).

To the best of our knowledge this specific effect of microwave irradiation on selectivity is one of the first observed in synthetic organic chemistry. Under the quasi-stoechiometric conditions used here, the formation of quaternized product (**4**) under classical heating may be significant of a slow first alkylation of N-1 followed by rapid alkylation at N-4. Under microwave, the only product (**2**) (N-1 alkylation) was observed. Consequently, the specific microwave effect may be due essentially to the acceleration of the previous N-1 alkylation leading thus to total consumption of benzyl chloride and therefore to suppresion of quaternisation.

Alkylation of benzotriazole (Table 4) in the absence of base led to some quaternisation and an increase of the N-1 alkylated isomer (quaternisation must be considered as N-1 alkylation) when compared with the ptc conditions using a base. This effect is specially important with bulky alkyl halides and a minor extent with benzyl bromide, because in the free base N-1 is still more nucleophilic than N-2.[16] In this heterocycle no specific effect in the selectivity was observed using microwave irradiation, i.e. the selectivity remains the same with that under classical or microwave heating.

Table 5 shows the best results obtained with various alkyl halides together with the appropriate technique and a comparison with classical methods.

Considering these results, the most important factor controlling the selectivity is the technique involved. However, none of the three methods studied can be considered, in a general manner, superior to the others.

In conclusion, solvent-free techniques are useful tools for the alkylation of 1,2,4-triazole and benzotriazole:

- Yields are at least comparable with those obtained by classical methods.
- The selectivity can be selected by using the appropriate technique.- Microwave irradiation has a specific effect on the alkylation of 1,2,4-triazole producing higher selectivity and yields as compared with conventional heating under the same conditions.

This constitues one of the first examples of such a change in the selectivity due to microwave irradiation.

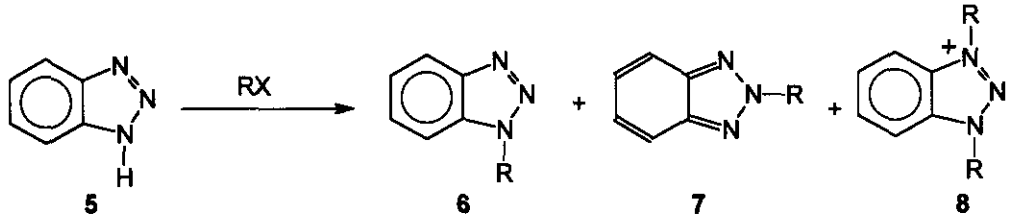

Table 4. Alkylation of benzotriazole in solvent-free conditions [a]

Entry	RX	**ptc**[b] t(h), T(°C)	**Conventional Heating** t(h), T(°C)	**Microwave irradiation** W, t(min), T(°C)[c]	**6 / 7 / 8** [d]	Total Yield (%)
1	$C_{16}H_{33}Br$	24, RT			53 / 47 / 0	20
2	$C_{16}H_{33}Br$		24, 120		88 / 12 / 0	51
3	$C_{16}H_{33}Br$			750, 5, 218	85 / 15 / 0	65
4	$C_8H_{17}Br$	18, RT			53 / 47 / 0	92
5	$C_8H_{17}Br$		18, 120		82 / 18 / 0	67
6	$C_8H_{17}Br$			750, 4, 200	85 / 15 / 0	80
7	C_4H_9Br	18, RT			56 / 44 / 0	88
8	C_4H_9Br		18, 120		55 / 3 / 42	99
9	C_4H_9Br			780, 1, 125	86 / 10 / 4	21
10	$PhCH_2Br$	2, RT			78/ 22 / 0	90
11	$PhCH_2Br$		1, 120		72 / 0 / 28	74
12	$PhCH_2Br$			450, 3, 183	56/22 / 22	69

a) **5**:RX=1:2 mole ratio. b) **5**:Base= 1:2.3 mole ratio. c) Final temperature. d) determined by gc and ^1H nmr.

Table 5. Selected conditions for the alkylation of **1** and **5**.

Entry	Substrate	RX	Technique[a]	**2 / 3 / 4**	Yield [b]	**2 / 3** lit.,[6]	Yield[6] (%)
1	1,2,4-triazole	$C_{16}H_{33}Br$	PTC	96 / 4 / 0	83	--	--
2	"	$C_8H_{17}Br$	PTC	93 / 7 / 0	84	100 / 0[c]	89[c]
3	"	$C_8H_{17}Br$	MW	75 / 0 / 25	44	--	--
4	"	C_4H_9Br	PTC	92 / 8 / 0	83	100 / 0	55
5	"	CH_3I	PTC	85 / 15 / 0	not isolated		
6	"	$PhCH_2Cl$	MW	100 / 0 / 0	70	94 / 6	85
				6 / 7 / 8		**6 / 7** lit.,[6]	
7	benzotriazole	$C_{16}H_{33}Br$	MW	85 / 15 / 0	65	--	--
8	"	$C_8H_{17}Br$	MW	85 / 15 / 0	80	--	--
9	"	C_4H_9Br	PTC	56 / 44 / 0	85	53 / 47	86
10	"	CH_3I	PTC	72 / 28 / 0	89	63 / 37	95
11	"	$PhCH_2Br$	CH	72 / 0 / 28	100	75 / 25	99
12	"	$PhCH_2Br$	PTC	78 / 22 / 0	90	--	--

a) PTC: Phase Transfer Catalysis, MW: microwave heating, CH: conventional heating (oil bath).

b) Total yield.c) Using polyethyleneglycol as phase transfer agent.

EXPERIMENTAL

Starting compounds were of commercial quality. Melting points were determined on a Gallenkamp MFB-595 and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 883. ^{1}H-Nmr spectra were recorded on a Bruker AW-80 (80 MHz), using TMS as internal standard. Gas chromatographic analyses were performed on a Carlo Erba G.C.-6000 equipped with flame-ionization detector. Silica gel (70-230 mesh) was used in column chromatography.

Procedures for alkylation in the absence of solvent.

Method A (PTC): Substrate (**1** or **5**) (10 mmol) and the required proportions (23 mmol) of a finely ground base and a phase transfer agent (2 mmol) were mixed and submerged in an ultrasonic

cleaning bath (50 w, 200 MHz) for 15 min. The halide (11 mmol) was added at 0°C and the mixture was stirred at the temperature and during the time indicated in Tables.

Method B (Classical heating): A mixture of substrate (**1** or **5**) (10 mmol) and the appropiate halide (11 mmol) was heated in an oil bath at 120 ° C for the time indicated in Tables.

Method C (Microwave heating): A mixture of substrate (**1** or **5**) (10 mmol) and the appropriate halide (11 mmol) was placed into a pyrex flask and introduced in a domestic microwave oven (Whirpool Philips 5964) and irradiated at the temperature and for the time indicated in Tables. Crude products were extracted with dichloromethane (2x25 ml). Removal of the solvent and column chromatography on silica gel afforded the pure products.

1-Methyl-1,2,4-triazole. Not isolated. ^{1}H Nmr ($CDCl_3$) δ(ppm) : 3.9 (s, 3H), 7.9 (s, 1H), 8.1 (s, 1H).

1-Butyl-1,2,4-triazole. Method A. Isolated by column chromatography (ethyl acetate) 76%, bp 75°C/4 mm (lit.,[17] 118-120°C/15 mm). *1-Octyl-1,2,4-triazole*. Method A. Column chromatography (ethyl acetate) 78%. Method C, 44%, bp 90°C/0.1mm. (lit.,[5] bp 151-152°C/16 mm). ν_{max} (neat)/cm^{-1} 1501, 1465, 1272. ^{1}H-Nmr ($CDCl_3$) δ(ppm): 0.8-1.8 (m, 15H), 1.9 (q, *J*=7, 2H), 4.1 (t, *J*=7, 2H), 7.8 (s, 1H), 8.0 (s, 1H). *1-Hexadecyl-1,2,4-triazole*. Method A. Column chromatography (ethyl acetate) 80%, mp 68-70°C (methanol). ν_{max}(KBr)/cm^{-1} 1510, 1462, 1271, 724. ^{1}H Nmr ($CDCl_3$) δ(ppm): 0.9-1.8 (m, 31H), 4.1 (t, *J*=7, 2H), 7.9 (s, 1H), 8.0 (s, 1H). Anal.Calcd for $C_{18}H_{35}N_3$:C 73.72, H 11.94, N 14.33. Found: C 73.63, H 12.18, N14.03. *1-Benzyl-1,2,4-triazole*. Method C. 70%, bp. 110°C/0.001mm (lit.,[5] mp 53-54°C). *1-Methylbenzotriazole*. Method A. Isolated by literature procedure[18] 64%, mp 63-64°C (hexane) (lit.,[5] 64-66°C). *2-Methylbenzotriazole*. Method A. Isolated by literature procedure[18] 25%, bp 110°C/20mm (lit.,[4] 103-104°C/15mm). *1-Butylbenzotriazole*. Method A. Column chromatography (hexane:ethyl acetate, 9:1) 49%. Method C. 19%, bp 111-114°C/0.2mm (lit.,[3] 112-115°C/0.2mm).

2-Butylbenzotriazole. Method A. Column chromatography (hexane:ethyl acetate, 9:1) 36%, bp 65-68°C/0.2mm (lit.,[3] 65-70°C/0.2mm). *1-Octylbenzotriazole*. Method C. Column chromatography (hexane:ethyl acetate, 9:1) 68%, bp 135°C/0.05mm. ν_{max} (neat)/cm^{-1} 1494, 1453, 744. ^{1}H Nmr ($CDCl_3$) δ(ppm): 0.9-2.0 (m, 15H), 4.6 (t, *J*=7, 2H), 7.2-7.6 (m, 3H), 7.9-8.2 (m, 1H). Anal. Calcd for $C_{14}H_{21}N_3$:C 72.69, H 9.15, N 18.16. Found: C 73.12, H 8.78, N 18.07. *2-Octylbenzotriazole*. Method C. Column chromatography (hexane:ethyl acetate, 9:1) 12%, bp 110°C/0.01mm. ν_{max} (neat)/cm^{-1} 1565, 1465, 745. ^{1}H Nmr ($CDCl_3$) δ(ppm): 0.8-2.1 (m, 15H), 4.6 (t, *J*=7, 2H), 7.2-7.5 and

7.7-8.0 (AA'BB' system, 4H). Anal. Calcd for $C_{14}H_{21}N_3$ C 72.69, H 9.15, N 18.16. Found:C 72.51, H 8.81, N 17.83. *1-Hexadecylbenzotriazole.* Method C. Column chromatography (hexane:ethyl acetate, 95:5) 55%, mp 115-118°C. ν_{max}(KBr)/cm^{-1} 1493, 1467, 736. ^{1}H-Nmr ($CDCl_3$) δ(ppm): 0.9-2.0 (m, 31H), 4.6 (t,*J*=7, 2H), 7.2-7.6 (m, 3H), 7.9-8.2 (m, 1H). Anal. Calcd for $C_{22}H_{37}N_3$ C 76.96, H 10.78, N 12.24.Found: C 76.69, H 10.79, N 11.80. *2-Hexadecylbenzotriazole.* Method C. Column chromatography (hexane:ethyl acetate, 95:5) 10%, bp 120°C/0.01mm. ν_{max} (neat)/cm^{-1} 1565, 1465, 744. ^{1}H Nmr ($CDCl_3$) δ(ppm): 0.9-2.1 (m, 31H), 4.7 (t, *J*=7, 2H), 7.2-7.5 and 7.7-8.0 (AA'BB' system, 4H). Anal. Calcd for $C_{22}H_{37}N_3$:C 76.96, H 10.78, N 12.24. Found C 76.66, H 10.39, N 12.04.

1-Benzylbenzotriazole. Method B. 74%, m p 115-118°C (lit.,[6] 115-117°C). *2-Benzylbenzotriazole.* Method A. 20%, bp 120°C/0.01mm (lit.,[6] oil).

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REFERENCES

1. F. Krollpfeifer, A. Rosenberg, and C. Mulhausen, *Liebigs Ann.Chem.*, 1935, **515**, 113.
2. F. Krollpfeifer, H. Potz, and A. Rosenberg, *Ber.,* 1938, **71B**, 596.
3. M.R. Atkinson and J.B. Polya, *J.Chem.Soc.*, 1954, 141.
4. R.A. Olofson and R.V. Kendall, *J.Org.Chem.*, 1970, **35**, 2246.
5. F. Separatore, M.I. LaRotonda, G. Paglietti, E. Ramaundo, C. Silipo, and A. Vittoria, *Farmaco*, 1978, **33**, 901.
6. A.R. Katritzky, W. Kuzmierkiewicz, and J.V. Greenhill, *Recl.Trav.Chim. Pays-Bas*, 1991, **110**, 369.
7. R. Böhm, *Pharmazie*, 1978, **33**, 83.
8. R. Claramunt, J. Elguero, and R. Garceran, *Heterocycles*, 1985, **23**, 2895.
9. H. Zhang, L. Liao, and Q. Guo, *Youji Huaxue*, 1986, 108 (*Chem.Abstr.,*1986, **105**, 226456).
10. H. Zhang, L. Liao, and Q. Guo, *Xiamen Daxve Xuebao, Ziran Wexueban*, 1987, **26**, 341 (*Chem.Abstr.,*1988, **108**, 75308).
11. K. Yamaguchi and M. Kinoshita, *J.Chem.Soc., Perkin Trans.I*, 1973, 2506.

12. G. Bram, A. Loupy, and J. Sansoulet, *Isr.J.Chem.*, 1985, **23**, 2895.

13. G. Bram, A. Loupy, and J. Sansoulet, *New J.Chem.*, 1992, **16**, 233.

14. G. Bram, A. Loupy, and D. Villemin; "Microwave activation of Reactions on Organic and Inorganic Solid Supports", in "Solid Supports and Catalysts in Organic Synthesis"; H. Smith Ed. Ellis Horwood, 1992.

15. F. Tomás, J.M. Abboud, J. Laynez, R. Notario, L. Santos, S.O. Nilsson, J. Catalán, R. Claramunt, and J. Elguero, *J.Am.Chem.Soc.*, 1989, **111**, 7348.

16. H. Warmhoff; Comprehensive Heterocyclic Chemistry; Vol. 5, 669 ed. by A.R. Katritzky Pergamon Press, 1984.

17. R. Gassend, J.C. Maire, and J.C. Pommier, *J.Organometal.Chem.*, 1977, **133**, 169.

18. J.Bergman and P. Sand, *Tetrahedron Lett.*, 1984, **25**, 1957.

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