SELECTIVE ALLYLATION AND PROPARGYLATION OF AZOLES BY PHASE TRANSFER CATALYSIS IN THE ABSENCE OF SOLVENT

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Abstract- Phase transfer catalysis without solvent allows the selective preparation of *N*-allyl- and *N*-propargylazoles or *N*-(1-propenyl)- and *N*-(1,2-propadienyl)azoles by reaction of the parent azole with allyl or propargyl bromides. Small variations in the reaction conditions, base or temperature, afford the desired selectivity.

INTRODUCTION

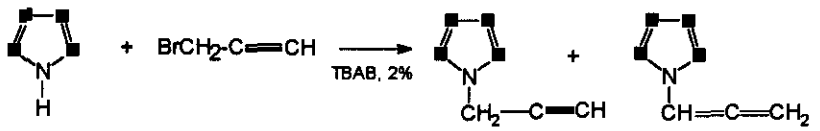
N-Vinylazoles are usually prepared by addition of the parent azole to activated triple bonds,[1] by elimination of *N*-2-haloethylazoles[2,3] or by base-catalyzed isomerisation of *N*-allylazoles.[2,3] In other respects, base-catalyzed isomerisation of *N*-propargylazoles has been used for the preparation of *N*-(1,2-propadienyl)azoles.[4]

However, in most cases, these compounds have been obtained as by-products in the alkylation of azoles with 1,2-dihaloethanes[5,6] or propargyl halides.[7]

Following our studies on alkylation of azoles under solvent-free conditions,[8] we have performed the reaction of pyrazole, imidazole, 1,2,4-triazole and benzotriazole with allyl and propargyl bromides under solid-liquid Phase transfer catalysis without solvent. We hope thus to obtain 1-allyl- and 1-propargylazoles or 1-(1-propenyl)- and 1-(1,2-propadienyl)azoles, the later resulting from alkylation

with subsequent isomerisation in one pot procedure. Solvent-free techniques have been shown to be useful and specially efficient in isomerisation[9] or in alkylation-isomerisation[10] of allyl and propargyl derivatives of carbocycles and heterocycles.

Alkylation with propargyl bromide



■ = N, CH or benzo

1 **2**

Table 1. Reactions with Propargyl Bromide

Entry	Azole	Base	molar ratio[a)]	T(°C)	t(h)	**1 / 2**	yield (%)
1	Pyrazole	K_2CO_3	1/2/1.5	room temperature	24	100 / 0	67
2	Pyrazole	KOH	1/2/1.5	40	24	0 / 100	37
3	Imidazole[10]	KOH/TiO_2[b)]	1/1/1	room temperature		99 / 1	74
4	Imidazole[10]	KOH[b)]	1/1/1	55		0 / 100	81
5	1,2,4-Triazole	K_2CO_3	1/2.3/1.7	room temperature	19	100 / 0	47
6	1,2,4-Triazole	KOH	1/2.3/1.7	room temperature	24	8 / 92	c)
7	Benzotriazole	K_2CO_3	1/2/2	room temperature	16	77 / 0 (N-1) 18 / 5 (N-2)	63 14
8	Benzotriazole	KOH	1/2/2	room temperature	24	0 / 100 (N-1)	30

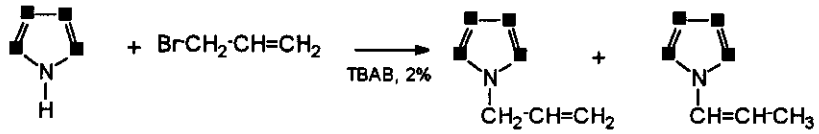
a) Azole / Base / Propargyl bromide. b) Aliquat 336, 5%, instead of TBAB (tetrabutylammonium bromide), 2%. c) Decompose on isolation.

Using a mild base, potassium carbonate, reactions with propargyl bromide (Table 1) afforded *N*-propargylazoles without isomerisation of the triple bond. Only benzotriazole afforded 5% of 2-(1,2-propadienyl)benzotriazole. This fact suggests that a benzylic hydrogen in the 2-position of benzotriazole is more acidic than in the 1-position, in accordance with the higher charge density of nitrogen-1.[11]

Alkylation followed by isomerisation (Table 1, Entries 2, 4, 6, 8) is achieved in similar conditions but using a stronger base, potassium hydroxide. With this base no alkylation or isomerisation in 2-position of benzotriazole is observed.

It is noticeable that no alkylation in position 4 of 1,2,4-triazole is observed.

Alkylations with allyl bromide



■ = N, CH or benzo

3 **4** (Z+E)

Table 2. Reactions with Allyl Bromide.

Entry	Azole	Base	Molar ratio[a]	T(°C)	t(h)	**3 / 4**	**4**; *Z* / *E*	Yield(%)
1	Pyrazole	KOH	1 / 2 / 1	room temperature	48	100 / 0	--	83
2	Pyrazole	KOH	1 / 2 / 1	80	24	0 / 100	67 / 33	65
3	Imidazole	^{t}BuOK	1 / 1.1 / 1	0	5	85 / 15	--	
4	Imidazole	^{t}BuOK	1 / 2 / 1	0	5	15 / 85	51 / 49	33
5	1,2,4-Triazole	KOH	1 / 2.3 / 1.1	room temperature	16	92 / 0 (N-1) 8 / 0 (N-4)	--	53[b]
6	1,2,4-Triazole	NaOH	1 / 2.3 / 1	80	24	0 / 100 (N-	76 / 24	44
7	Benzotriazole	K_2CO_3	1 / 2 / 1	room temperature	24	70 / 0 (N-1) 30 / 0 (N-2)	--	61 24
8	Benzotriazole	NaOH	1 / 2 / 1	80	24	0 / 86 (N-1) 0 / 14 (N-2)	54 / 46 8 / 92	75 12

a) Azole / Base / Allyl bromide. b) N-1 isomer.

Reactions with allyl bromide are also selective (Table 2). Alkylation and isomerisation are now controlled mainly by the temperature. Reactions at room temperature afforded *N*-allylazoles even with strong bases (Entries 1, 3 and 5) while at 80ºC *N*-(1-propenyl)azoles were obtained (Entries 2, 6 and 8).

However, reactions with imidazole (Entries 3 and 4) have been performed at 0ºC and using potassium *tert*-butoxide, because under the standard conditions and specially at 80ºC quaternisation is favoured.[12] Isomerization has been now controlled by varying the proportion of base (Table 2, Entries 3 and 4).

In comparison with propargyl halide, isomerisation of 2-allylbenzotriazole is achieved again easily than in the 1-substituted isomer. In the reaction with 1,2,4-triazole, the 4-substituted isomer is observed.

The *Z*/*E* observed ratio in *N*-(1-propenyl)azoles is strongly dependent on the azole. There is specifically an important difference between 1-(1-propenyl)benzotriazole, *Z*/*E* ratio 54/46, and 2-(1-propenyl)benzotriazole, *Z*/*E* ratio 8/92; and in most cases the most hindered *Z* isomer is the major component.

Ratios and differences observed do not agree with previous results on the isomerisation of *N*-allylazoles. Katritzky has recently reported[2] the isomerisation of 1- and 2-allylbenzotriazole with potassium *tert*-butoxide in *tert*-butanol (Table 4). Similar results are observed with 1-allyl- and 2-allylbenzotriazole, the less hindered *E* isomer being the major component.

In order to check if these differences are a consequence of the reaction (alkylation and subsequent isomerisation *versus* isomerisation) or a result of the technique involved (basic isomerisation in solvent-free conditions *versus* in *tert*-butanol solution) or the nature of the base we have performed a series of the reactions involving Katritzky's or solvent-free conditions (Tables 3 and 4).

The results show that alkylation with subsequent isomerisation is strongly dependent on the azole and the base. Thus in the case of 1-allylpyrazole, using KOH in all conditions a *Z*/*E* ratio around 60/40 is obtained and, using ^{t}BuOK, this ratio arises 15/85. However in the case of benzotriazole, in solvent-free conditions, a *Z*/*E* ratio around 40/60 is obtained, using KOH, or 33/67, using ^{t}BuOK, in 1-substituted derivative, whereas, a 10/90 *Z*/*E* ratio is obtained in all conditions in the case of 2-allylbenzotriazole. This result is consistent with the higher acidity of the methylene in position-2. Even isomerisation has been performed using potassium carbonate in solvent-free conditions (*Z*/*E*

ratio, 20/80). The use of a stronger base in the absence of solvent provide mixtures of isomers of 3-(2-benzotriazolyl)hexadiene. The formation of these products could be explained considering the good leaving group nature of benzotriazole.[13]

Table 3. Allylation followed by isomerisation (*Z*/*E* ratio)

azole	solvent free (KOH)	solvent free (^{t}BuOK)	^{t}BuOK/^{t}BuOH
1-Allylbenzotriazole	43 / 57	33 / 67	37 / 63 (24 h) 57 / 43 (3 h)
2-Allylbenzotriazole	2 / 98	13 / 87	9 / 91
1-Allylpyrazole	67 / 33	13 / 87	15 / 85

Table 4. Isomerisation (*Z*/*E* ratio)

azole	solvent free (KOH)	solvent free (^{t}BuOK)	^{t}BuOK/^{t}BuOH
1-Allylbenzotriazole	20 / 80	22 / 78	16 / 84[c)]
2-Allylbenzotriazole	a) b)	--	20 / 80
1-Allylpyrazole	57 / 43	18 / 82	10 / 90[c)]

a) mixtures of isomers of 3-(2-Benzotriazolyl)hexadiene were obtained.

b) 20 / 80 using potassium carbonate (3 h, 80°C). c) ref. 2.

Isomer *Z* is the kinetic product, that in adequate conditions isomerises to *E* isomer, as the results obtained when a mixture of 1-propenylpyrazole isomers are treated with KOH or ^{t}BuOK indicate [a 66/34 (*Z*/*E*) mixture remains identical after 24 hours at 80°C, with KOH; whereas only *E* isomer remains when ^{t}BuOK was used]. The major amount of *E* isomer in alkylation followed by isomerisation respect to isomerisation is probably due to the longer reaction time.

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) and on a Varian-Unity (300 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.

General procedures for alkylation.

Solvent-free conditions.- Azole (10 mmol) and the required proportions of finely ground base (Tables 1 and 2) and the phase transfer agent (0.5 mmol) were mixed and submerged in an ultrasonic cleaning bath (50w, 200 MHz) for 15 min. The required proportion of halide (Tables 1 and 2) was added at 0°C and the reaction was stirred at the temperature and during the time indicated in Tables. Crudes were extracted with dichloromethane (2x25 ml). Removal of solvent and column chromatography on silica gel or ball-to-ball distillation afforded the pure products.

With solvent.- Azole (10 mmol), ^{t}BuOK (20 mmol), Bu_4NBr (0.5 mmol) and allyl bromide (pyrazole/allyl bromide, 1/1; benzotriazole/allyl bromide, 1/2) were disolved in ^{t}BuOH (5 ml) and placed in a round-bottom flask. The reaction was stirred at 80°C during 24 h. Crudes were extracted with dichloromethane and, after removal of solvent, *Z/E* ratio was determined by ^{1}H-nmr.

General procedure for isomerisations (with or without solvent).

Allylazole, base (molar ratio 1/1.5) and phase transfer agent (5%) were mixed and heated at 80°C during 24 h. Crudes were extracted with dichloromethane and, after solvent removal, *Z/E* ratio was determined by ^{1}H-nmr.

1-Allylpyrazole. 83%. bp 65°C /8 mm (lit.,[14] 61-63°C/12 mm). *1-(1-Propenyl)pyrazole*. 65%. *E* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.82 (dd, *J* = 7.1 and 1.7, 3H), 6.05 (dq, *J* = 14.2 and 7.1, 1H), 6.35 (dd, *J* = 2.4 and 1.2, 1H), 6.85 (dq, *J* = 14.2 and 1.7, 1H), 7.50 (d, *J* = 2 4, 1H), 7.55 (d, *J* = 1.2, 1H). *Z* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.96 (dd, *J* = 7.4 and 2, 3H), 5.35 (m, *J* = 9.3 and 7.4, 1H), 6.30 (dd, *J* = 2.4 and 1.2, 1H), 6.80 (dq, *J* = 9.3 and 2, 1H), 7.55 (d, *J* = 2.4, 1H), 7.60 (d, *J* = 1.2, 1H). *1-Allyl-1,2,4-triazole*. 53%. bp 75°C /3 mm (lit.,[14] 102-103°C/16 mm). *1-(1-Propenyl)-1,2,4-triazole*. 44%. Column chromatography (ethyl acetate). *E* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.85 (dd, *J* = 7.2 and 1.2, 3H), 6.27 (dq, *J* = 14.4 and 7.2, 1H), 6.90 (dq, *J* = 14.4 and 1.2, 1H), 7.95 (s, 1H), 8.15 (s, 1H). *Z* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.95 (dd, *J* = 7.2 and 2.1, 3H), 5.65 (dq, *J* = 9.0 and 7.2, 1H), 6.80 (dq, *J* = 9.0 and 2.1, 1H), 8.05 (s, 1H), 8.25 (s,1H). *1-Allylbenzotriazole*. 61%. Column chromatography (hexane / ethyl acetate, 95/5) bp 85°C /0.01 mm (lit.,[15] 161-162°C/15 mm). *2-Allylbenzotriazole*. 24%. Column chromatography (hexane / ethyl acetate, 95/5) bp 65°C /0.01 mm (lit.,[15] 127-128°C/15

mm). *1-(1-Propenyl)benzotriazole.* 75%. Column chromatography (hexane / ethyl acetate, 95/5). *E* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 2.00 (dd, *J* = 7.0 and 1.6, 3H), 6.50 (dq, *J* = 14.3 and 7.0, 1H), 7.30 (dq, *J* = 14.3 and 1.6, 1H), 7.30-7.70 (m, 3H), 8.00-8.10 (m, 1H). *Z* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 2.00 (dd, *J* = 7.3 and 1.8, 3H), 5.90 (dq, *J* = 8.6 and 7.3, 1H), 7.00 (dq, *J* = 8.6 and 1.8, 1H), 7.30-7.70 (m, 3H), 8.00-8.10 (m, 1H). *2-(1-Propenyl)benzotriazole.* 12%. Column chromatography (hexane / ethyl acetate, 95/5). *E* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 2.00 (dd, *J* = 7.1 and 1.6, 3H), 6.95 (dq, *J* = 14.1 and 7.1, 1H), 7.38 and 7.85 (AA'BB' system, *J* = 6.6 and 3.0, 4H), 7.39 (dq, *J* = 14.1 and 1.6, 1H). *Z* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 2.30 (dd, *J* = 7.1 and 1.5, 3H), 5.90 (dq, *J* = 8.6 and 7.1, 1H), 7.30-7.70 and 8.00-8.10 (AA'BB' system, 5H). *1-Allylimidazole.* 37%. Column chromatography (ethyl acetate) bp 90°C /1 mm (lit.,[14] 116°C /16 mm). *1-(1-Propenyl)imidazole.* 25%. Column chromatography (ethyl acetate/ ethanol, 9/1). *E* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.82 (dd, *J* = 6.8 and 1.7, 3H), 5.83 (dq, *J* = 14.1 and 6.8, 1H), 6.70 (dq, *J* = 14.1 and 1.7, 1H), 7.05 (s, 1H), 7.10 (s, 1H), 7.60 (s, 1H). *Z* isomer ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.82 (dd, *J* = 7.1 and 1.7, 3H), 5.53 (dq, *J* = 8.8 and 7.1, 1H), 6.62 (dq, *J* = 8.8 and 1.7, 1H), 7.00 (s, 1H), 7.10 (s, 1H), 7.60 (s, 1H). *1-Propargylpyrazole.* 67%. Column chromatography (dichloromethane) bp 85°C /4 mm (lit.,[16] 34°C /2 mm). *1-(1,2-Propadienyl)pyrazole.* 37%. Column chromatography (dichloromethane) bp 75°C /1 mm (lit.,[16] 60°C /1 mm). *1-Propargyl-1,2,4-triazole.* 47%. Column chromatography (ethyl acetate) bp 125-130°C /10 mm. ^{1}H-Nmr ($CDCl_3$) δ (ppm): 2.60 (t, *J* = 3.0, 1H), 5.00 (d, *J* = 3.0, 2H), 8.00 (s, 1H), 8.30 (s, 1H). *1-(1,2-Propadienyl)-1,2,4-triazole.* ^{1}H-Nmr ($CDCl_3$) δ (ppm): 5.70 (d, *J* = 6.6, 2H), 7.20 (t, *J* = 6.6, 1H), 8.00 (s, 1H), 8.20 (s, 1H). *1-Propargylbenzotriazole.* 63%. Column chromatography (hexane/ethyl acetate, 9/1) bp 95°C /0.01 mm (lit.,[2] m.p. 57-58°C). *1-(1,2-Propadienyl)benzotriazole.* 30%. Column chromatography (dichloromethane). ^{1}H-nmr ($CDCl_3$) δ (ppm): 5.80 (d, *J* = 6.6, 2H), 7.30-7.60 (m, 2H), 7.80-7.90 (m, 2H), 8.10 (m, 1H). *2-Propargylbenzotriazole.* 14% Column chromatography (hexane/ethyl acetate, 9/1) bp 75°C /0.01 mm. ^{1}H-Nmr ($CDCl_3$) δ (ppm). 2.60 (t, *J* = 2.7, 1H), 5.55 (d, *J* = 2.7, 2H), 7.40 and 7.89 (AA'BB' system, *J* = 6.6 and 3.1, 4H). *2-(1,2-Propadienyl)benzotriazole.* Column chromatography (hexane/ethyl acetate, 9/1). mp 91-93°C (ethyl acetate:ligth petroleum). ^{1}H-Nmr ($CDCl_3$) δ (ppm): 5.86 (d, *J* = 6.5, 2H), 7.68 (t, *J* = 6.5, 1H), 7.39 and 7.86 (AA'BB' system, *J* = 6.6 and 3.2, 4H).

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