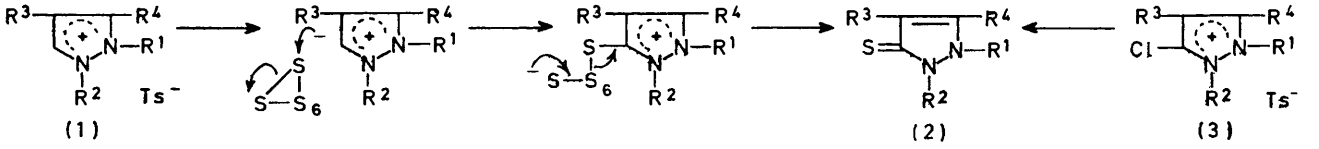
Reactions Between Azolium Anions and Electrophilic Reagents. Part II.[1] Direct Thiation of 1,2-Disubstituted Pyrazolium Anions with Sulphur

By **Mikael Begtrup**, Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Pyrazolium salts (1) afford Δ^3-pyrazoline-5-thiones (2) in good yields when treated with sulphur and sodium hydride in dimethylformamide. Pyrazolium salts (1a) with two different *N*-substituents produce two isomeric Δ^3-pyrazoline-5-thiones (2a and b) in a ratio reflected by the ratio between the deuterium exchange rates of H-3 and H-5 in the starting material (1a).

NN'-DISUBSTITUTED Δ^3-pyrazoline-5-thiones (2) have been prepared previously from *NN'*-disubstituted 3-chloropyrazolium salts (3) by substitution of chlorine with sulphide or thiosulphate ion.[2,3a,4] 5-Substituted their anions, with pyridine or triethylamine as the base, is formulated as an ionic process (Scheme 1).[10-13] This reaction is attractive since 5-unsubstituted or *NN'*-dialkylpyrazolium salts (1) in contrast to the



SCHEME 1

NN'-(alkyl,aryl)-3-chloropyrazolium salts are readily accessible [3b] whereas 5-unsubstituted or *NN'*-dialkyl-3-chloropyrazolium salts are not so.[5] Hence, there is a need for an alternative synthesis of 3-unsubstituted or *NN'*-dialkyl-Δ^3-pyrazoline-5-thiones.

Thiation of pyrazolium salts (1) with elemental sulphur analogous to the reported thiation of imidazolium,[6] thiazolium,[7] and 1,2,4-triazolium [8,9] salts *via* 3-chloro-derivatives (3), are readily available.[5,14] However, our attempts to thiate pyrazolium salts (1) did not affect the starting material. Presumably the initial abstraction of pyrazolium protons, known to be less acidic than imidazolium, thiazolium, or 1,2,4-triazolium protons,[5,15-17] requires a stronger base than pyridine or triethylamine. However, thiation of

[1] Part I, M. Begtrup, *Acta Chem. Scand.*, in the press.
[2] A. Michaelis, *Annalen*, (*a*) 1902, **320**, 1; (*b*) 1904, **331**, 197.
[3] T. L. Jacobs, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, London, 1957, vol. 5, (*a*) p. 158; (*b*) p. 101.
[4] R. Fusco, in 'Heterocyclic Compounds,' ed. A. Weissberger, Wiley, London, 1967, vol. 22, pp. 58 and 283.
[5] M. Begtrup, *Acta Chem. Scand.*, 1973, **27**, 2051.
[6] H.-J. Schönherr and H.-W. Wanzlick, *Annalen*, 1970, **731**, 176.
[7] H.-W. Wanzlick, H.-J. Kleiner, I. Lasch, H. U. Füldner, and H. Steinmaus, *Annalen*, 1967, **708**, 155.
[8] R. Walentowski and H.-W. Wanzlick, *Z. Naturforsch.*, 1970, **25b**, 1421.
[9] H. G. O. Becker, D. Nagel, and H. J. Timpe, *J. prakt. Chem.*, 1973, **315**, 97.
[10] N. A. Pryor, 'Mechanisms of Sulfur Reactions,' McGraw-Hill, New York, 1962, p. 7.
[11] H. Schumann, in 'Sulfur in Organic and Inorganic Chemistry,' ed. A. Senning, Marcel Dekker, New York, 1972, vol. 3, p. 1.
[12] O. Foss, in 'The Chemistry of Organic Sulfur Compounds,' eds. N. Kharasch and C. Y. Meyers, Pergamon, Oxford, 1961, vol. 1, p.83.
[13] R. Mayer, *Z. Chem.*, 1973, **13**, 321.
[14] A. N. Kost and I. I. Grandberg, *Adv. Heterocyclic Chem.*, 1966, **6**, 347.
[15] R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, 1964, **86**, 1865.
[16] M. Begtrup, *Acta Chem. Scand.*, 1970, **24**, 1819.
[17] M. A. Schroeder and R. C. Makino, *Tetrahedron*, 1973, **29** 3469.

pyrazolium salts (1) with sulphur was accomplished in good yield by using sodium hydride in dimethylformamide.* The usefulness of this experimentally simple process was demonstrated by the preparation of Δ^3-pyrazoline-5-thiones (2) with a variety of *N*- or *C*-substituents from readily accessible pyrazolium salts (1) in yields (Table 1) similar to those (Table 2) obtained by treatment of the relatively inaccessible chloropyrazolium salts (3) with sulphide or thiosulphate.

TABLE 1

Conversion of 1,2-disubstituted pyrazolium tosylates into 1,2-disubstituted Δ^3-pyrazoline-5-thiones

Starting material (1) [or (1a)]					Product(s) (2) [or (2a or b)]							% Found: % Required				
R^1	R^2	R^3	R^4	Ref.	R^1	R^2	R^3	R^4	Yield (%) †	Recryst. from	M.p. (°C)	C	H	N	S	Hal
Me	Me	H	H	16	Me	Me	H	H	67	$CHCl_3$–Et_2O	187—189	46·8	6·25	21·75	25·05	
												46·85	6·3	21·85	25·0	
Me	Me	Br	Me	16	Me	Me	Br	Me	55	$CHCl_3$–Et_2O	225—227 [b]	32·6	4·05	12·5	14·35	36·1
												32·6	4·1	12·65	14·5	36·15
CH_2Ph	CH_2Ph	H	H	*a*	CH_2Ph	CH_2Ph	H	H	80	$CHCl_3$–Et_2O	151—154	72·65	5·7	9·8	11·35	
												72·8	5·75	10·0	11·45	
Me	CH_2Ph	H	H	5	CH_2Ph	Me	H	H	15	$CHCl_3$–Et_2O	162—165	64·55	5·9	13·75	15·65	
												64·65	5·9	13·7	15·7	
					Me	CH_2Ph	H	H	19	$CHCl_3$–Et_2O	170—172	64·55	5·85	13·65	15·7	
												64·65	5·9	13·7	15·7	
Me	CH_2Ph	Cl	H	5	CH_2Ph	Me	Cl	H	20	EtOAc	158—159	55·1	4·7	11·8	13·25	14·65
												55·35	4·65	11·75	13·45	14·9
					Me	CH_2Ph	Cl	H	19	EtOAc	139—144	55·2	4·7	11·9		
												55·35	4·65	11·78		
Me	CH_2Ph	Br	H	5	CH_2Ph	Me	Br	H	22	EtOAc	167—168	46·7	3·95	10·0	11·25	
												46·55	3·9	9·9	11·3	
					Me	CH_2Ph	Br	H	24	EtOAc	157—158	46·55	4·05	9·8	11·2	28·4
												46·55	3·9	9·9	11·3	28·2
Me	Ph	H	H	5	Ph	Me	H	H	47	EtOAc	141—142	63·0	5·35	14·9	16·9	
												63·1	5·3	14·75	16·85	
					Me	Ph	H	H	38	EtOAc	155—158	63·15	5·25	14·6	16·9	
												63·1	5·3	14·75	16·85	
Me	Ph	Cl	H	5	Ph	Me	Cl	H	27	$CHCl_3$–Et_2O	205	53·25	3·95	12·6	14·3	15·6
												53·45	4·05	12·45	14·25	15·8
					Me	Ph	Cl	H	34	$CHCl_3$–Et_2O	178—180	53·4	4·0	12·55	14·2	15·65
												53·45	4·05	12·45	14·25	15·8
Me	Ph	Br	H	5	Ph	Me	Br	H	17	CH_2Cl_2–Et_2O	212—216	44·55	3·4	10·4	12·05	29·8
												44·6	3·35	10·4	11·9	29·6
					Me	Ph	Br	H	21	CH_2Cl_2–Et_2O	216—217	44·65	3·45	10·4	11·95	29·7
												44·6	3·35	10·4	11·9	29·6

[a] 1,2-Dibenzylpyrazolium bromide, m.p. 192°, was prepared (82%) by heating 1-benzylpyrazole (R. G. Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 3994) with benzyl bromide (1·2 equiv.) to 100° for 3 h. The mixture was then washed with ether and recrystallized from methanol–ether. [b] Another modification melts at *ca.* 186°.

† Of single, crude pyrazolinethione.

TABLE 2

Conversion of 1,2-disubstituted 3-chloropyrazolium salts into 1,2-disubstituted Δ^3-pyrazoline-5-thiones

Starting material [a] (3)	Product (2)	With sodium thiosulphate			With potassium sulphide	
R^1	R^2	Method of prep.	Yield (%) †	M.p.[b] (°C)	Yield (%) †	M.p. (°C)
Me	Me	A	30	187—189	52	183—186
CH_2Ph	Me	B	72	161—163	58	160—161
Me	Ph	A	84	159	100	156—159
Ph	Me	B	46	141—142	66	133—134

† Of crude product.

[a] Prepared as described in ref. 5. [b] Recrystallization media given in Table 1.

Pyrazolium salts (1a) with two different *N*-substituents gave rise to pairs of isomeric Δ^3-pyrazoline-5-thiones (2a and b). Provided that the reaction is kinetically controlled and that the deprotonation is rate-limiting, the relative stability of the anions (4) and (5) should determine the ratio between the products (2a and b). The relative stability of the anions (4) and (5), in turn, is reflected by the ratio between the rates of the base-catalysed exchange of H-3 and H-5 in the starting material (1a) with deuterium. H-3 is exchanged 1·12—1·16 times faster than H-5 in 1-methyl-2-benzylpyrazolium tosylates (1a; R^1 = Me, R^2 = CH_2Ph).[5] Accordingly, 1-methyl-2-benzylpyrazolium tosylate (1a; R^1 = Me, R^2 = CH_2Ph, R^3 = H) and its 4-chloro- (R^3 = Cl) and 4-bromo- (R^3 = Br) derivatives produce the isomeric pyrazolinethiones (2a and b; R^1 = Me, R^2 = CH_2Ph, R^3 = H, Cl, or Br) in the ratio 1·03—1·04 : 1 (Table 1).

1-Methyl-2-phenylpyrazolium tosylate (1a; R^1 = Me, R^2 = Ph, R^3 = H) and its 4-chloro- (R^3 = Cl) and 4-bromo- (R^3 = Br) derivatives produce the isomeric pyrazolinethiones (2a and b; R^1 = Me, R^2 = Ph, R^3 = H, Cl, or Br) in the ratio 1·1—1·6 (Table 1). This is in reasonable agreement with the ratio of 1·2—

* Sodium hydride in dimethylformamide was found to be preferable to other combinations of sodium hydride or potassium hydride, t-butoxide, or amide (as the base) and dimethylformamide, triethylamine, dimethyl sulphoxide, *N*-methylaniline, hexamethylphosphoramide, or ammonia (as the solvent).

1·4 : 1 between the exchange rates of H-3 and H-5 in the corresponding starting materials.[5]

These results confirm the proposed ionic mechanism and indicate that the distribution between isomeric pyrazolinethiones (2a and b) in general may be predicted from the deuterium exchange rates of H-3 and H-5 in the starting material (1a).

All compounds were identified on the basis of elemental analysis and n.m.r. spectra. The structure of 2-benzyl-1-methyl-Δ^3-pyrazoline-5-thione (2b; R^1 = Me, R^2 = CH_2Ph, R^3 = H) is apparent from its formation from 1-benzyl-3-chloro-2-methylpyrazolium tosylate (3; R^1 = CH_2Ph, R^2 = Me, R^3 = R^4 = H) on treatment with sulphide or thiosulphate (Table 2). 2-Benzyl-1-methyl-Δ^3-pyrazoline-5-thione (2b; R^1 = Me, R^2 = CH_2Ph, R^3 = H) gives rise to a phenyl group multiplet in the ^1H n.m.r. spectrum whereas the isomeric compound (2a) shows a phenyl group singlet.* The ^1H n.m.r. spectra of the two isomeric methylbenzylchloro- and methylbenzylbromo-Δ^3-pyrazoline-5-thiones show a corresponding difference on which the structural assignments of the single isomers were based (Table 3).†

The structure of 2-methyl-1-phenyl-Δ^3-pyrazoline-5-thione (2a; R^1 = Me, R^2 = Ph, R^3 = H) is apparent from its formation from 3-chloro-1-methyl-2-phenylpyrazolium tosylate (3; R^1 = Me,R^2 = Ph, R^3 = R^4 = H). Similarly, the structure of the isomer (2b) is apparent from its preparation from (3; R^1 = Ph, R^2 = Me, R^3 = R^4 = H). The methyl group of the pyrazolinethione (2a) resonates at higher field and exhibits a larger positive benzene solvent shift than that of the isomer (2b) (Table 3).†

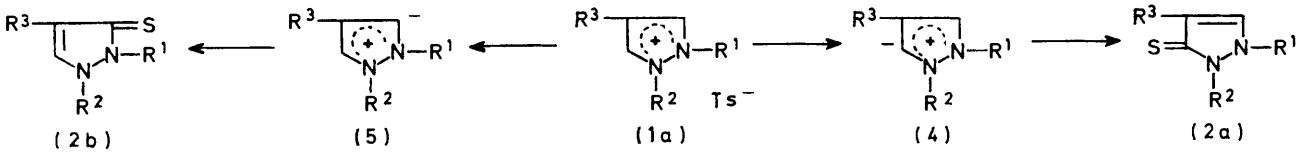
These characteristics were used to assign the structure of the methylphenylchloro- and methylphenylbromo-Δ^3-pyrazoline-5-thiones obtained as single isomers. The assignments were confirmed by ^{13}C n.m.r. spectra (Table 4).† 2-Methyl-1-phenyl-Δ^3-pyrazoline-5-thione (2a; R^1 = Me, R^2 = Ph, R^3 = H) can be distinguished from its isomer (2b) by the increased ^{13}C chemical shifts of the *ortho*-phenyl and the methyl carbon atoms.[18] The chloro- and bromo-derivatives showed similar characteristics.

EXPERIMENTAL

Column chromatography and preparative t.l.c. were carried out as described previously.[5] The purity of all compounds was checked by t.l.c.

Preparation of 1,2-Disubstituted Δ^3-Pyrazoline-5-thiones (2) by Thiation of 1,2-Disubstituted Pyrazolium Salts (1).—The procedure described previously [1] was employed; 1·1 equiv. of sodium hydride were used with halogen-substituted starting material [with the exception of (1; R^1 = R^2 = R^4 = Me, R^3 = Br)], 3 equiv. in all other cases. When an n.m.r. spectrum of the crude product proved that only one pyrazolinethione was present, purification was effected by recrystallization (Table 1). When the n.m.r. spectrum indicated that the crude product contained two isomers, separation was achieved by chromatography as described below.

(*a*) 1-Methyl-2-benzylpyrazolium tosylate (1a; R^1 = Me, R^2 = CH_2Ph, R^3 = H) gave a mixture of isomers



SCHEME 2

(2a and b; R^1 = Me, R^2 = CH_2Ph, R^3 = H) in the ratio 1·03 : 1 as indicated by an n.m.r. spectrum. Preparative t.l.c. [3 elutions with ethyl acetate–chloroform (1 : 1)] afforded *2-benzyl-1-methyl-Δ^3-pyrazoline-5-thione* (R_F 0·25) and *1-benzyl-2-methyl-Δ^3-pyrazoline-5-thione* (R_F 0·12).

(*b*) 2-Benzyl-4-chloro-1-methylpyrazolium tosylate (1a; R^1 = Me, R^2 = CH_2Ph, R^3 = Cl) gave the two isomers (2a and b; R^1 = Me, R^2 = CH_2Ph, R^3 = Cl) in the ratio 1·01 : 1 as shown by an n.m.r. spectrum. Preparative t.l.c. [ethyl acetate–chloroform (1 : 1); three elutions] produced *1-benzyl-4-chloro-2-methyl-Δ^3-pyrazoline-5-thione* (R_F 0·62) and *2-benzyl-4-chloro-1-methyl-Δ^3-pyrazoline-5-thione* (R_F 0·50).

(*c*) 2-Benzyl-4-bromo-1-methylpyrazolium tosylate (1a; R^1 = Me, R^2 = CH_2Ph, R^3 = Br) produced the two isomers (2a and b; R^1 = Me, R^2 = CH_2Ph, R^3 = Br) in the ratio 1·04 : 1 (n.m.r. spectrum). Preparative t.l.c. [ethyl acetate–chloroform (1 : 1); three elutions] gave *1-benzyl-4-bromo-2-methyl-Δ^3-pyrazoline-5-thione* (R_F 0·66) and *2-benzyl-4-bromo-1-methylpyrazoline-5-thione* (R_F 0·54).

(*d*) 1-Methyl-2-phenylpyrazolium tosylate (1a; R^1 = Me, R^2 = Ph, R^3 = H) afforded a 1 : 1·68 mixture of isomers (2a and b; R^1 = Me, R^2 = Ph, R^3 = H) (n.m.r. spectrum). Column chromatography on silica gel (20 g per g of starting material) with ethyl acetate as eluant first gave *1-methyl-2-phenyl-Δ^3-pyrazoline-5-thione*. The column was then eluted with ethyl acetate–methanol (1 : 1) to give *2-methyl-1-phenyl-Δ^3-pyrazoline-5-thione*.

(*e*) 4-Chloro-1-methyl-2-phenylpyrazolium tosylate (1a; R^1 = Me, R^2 = Ph, R^3 = Cl) gave a 1 : 1·08 mixture of isomers (2a and b; R^1 = Me, R^2 = Ph, R^3 = Cl) (n.m.r. spectrum). Column chromatography (50 g of silica gel per g of starting material; ethyl acetate) first gave *4-chloro-1-methyl-2-phenyl-Δ^3-pyrazoline-5-thione*, then *4-chloro-2-methyl-1-phenyl-Δ^3-pyrazoline-5-thione*.

(*f*) 4-Bromo-1-methyl-2-phenylpyrazolium tosylate (1a; R^1 = Me, R^2 = Ph, R^3 = Br) gave the two isomers (2a and b; R^1 = Me, R^2 = Ph, R^3 = Br); ratio 1 : 1·63 (n.m.r. spectrum). Column chromatography (50 g of

* The same difference has been observed with the corresponding Δ^3-pyrazolin-5-ones.[5]

† Tables 3 (^1H n.m.r. data) and 4 (^{13}C n.m.r. data) are available as Supplementary Publication No. SUP 21243 (4 pp.). For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

[18] M. Begtrup, *Acta Chem. Scand.*, 1974, **B28**, 61.

silica gel per g of starting material: ethyl acetate) first yielded *4-bromo-1-methyl-2-phenyl-Δ^3-pyrazoline-5-thione*, then *4-bromo-2-methyl-1-phenylpyrazoline-5-thione*.

Preparation of 1,2-Disubstituted Δ^3-Pyrazoline-5-thiones (2) from 1,2-Disubstituted 3-Chloropyrazolium Tosylates (3) and Sodium Thiosulphate.[2b]—(*A*) The 1,2-disubstituted 3-chloropyrazolium tosylate (3) was heated to reflux for 8 h with aqueous 5% sodium thiosulphate (2 equiv.). The solution was then filtered and the residue washed with a small amount of water. The combined aqueous solutions were evaporated to dryness and the residue was extracted 6 times with boiling ethyl acetate (10 ml per g of starting material). Evaporation of the extract left the crude product (Table 2).

(*B*) The reaction was carried out as in (*A*). The mixture was then filtered and washed with water. The residue was extracted 5 times with methanol (10 ml per g of starting material). The methanol was removed and the mixture was extracted 6 times with boiling ethyl acetate (10 ml per g of starting material). Evaporation of the extract left the crude product (Table 2).

Preparation of 1,2-Disubstituted Δ^3-Pyrazoline-5-thiones (2) from 1,2-Disubstituted 3-Chloropyrazolium Tosylates (3) and Potassium Sulphide.[2a]—The 1,2-disubstituted 3-chloropyrazolium tosylate (3) was heated to reflux for 6 h with 1·2 equiv. of potassium sulphide and methanol (20 ml per g of starting material). The solution was then filtered and the residue was extracted 5 times with methanol (10 ml per g of starting material). The solution was filtered through activated carbon, the methanol was removed, and the residue was extracted 6 times with boiling ethyl acetate (10 ml per g of starting material). Evaporation of the extract afforded the crude product (Table 2).

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