Deprotonation of 2-Substituted Pyrazole 1-Oxides

Inés Almena,[a] Mikael Begtrup[b,*] and Antonio de la Hoz[a]

[a] Universidad de Castilla-La Mancha, E-13071 Ciudad Real, Spain and [b] Department of Organic Chemistry, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark

Almena, I., Begtrup, M. and de la Hoz, A., 1992. Deprotonation of 2-Substituted Pyrazole 1-Oxides. – Acta Chem. Scand. 46: 1096–1100.

H-3 and H-5 are more acidic in 2-benzylpyrazole 1-oxide than in the parent 1-benzylpyrazole. Deprotonation followed by addition of dimethyl disulfide proceeds with low mono- and regio-selectivity to give a mixture of 3-methylthio-, 5-methylthio- and 3,5-bis(methylthio)-substituted products. With chloroform as the electrophile, addition takes place exclusively at the 5-position. The extensive deoxygenation taking place during these reactions is effected by hydrogen developed during the deprotonation.

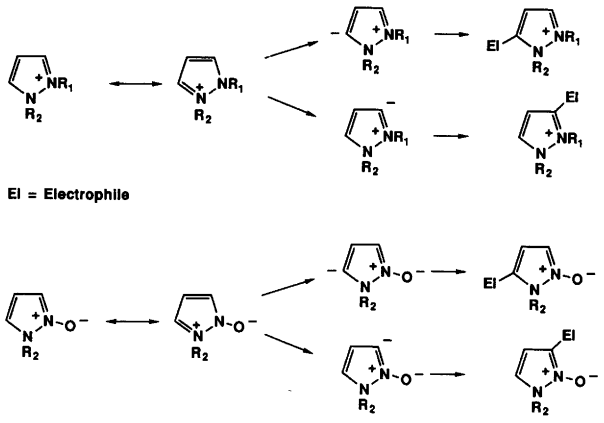
Introduction of a positive charge in an azole ring activates the ring positions adjacent to the positive nitrogen atoms towards deprotonation. The anion thus formed is susceptible to subsequent reaction with an electrophile. This activation is usually achieved by quaternization or by *N*-oxidation of the azole.[1]

In 1,2-alkyl-substituted pyrazolium ions the substituents at the nitrogen atoms are similar. Accordingly low mono- and regio-selectivity is observed in these species. The substituents at the nitrogen atoms are very different in the 2-alkylpyrazole *N*-oxides; they should therefore show greater selectivity in deprotonation reactions. An extended donor–acceptor analysis of azole *N*-oxides confirms this expectation indicating that the position adjacent to an oxygen-substituted nitrogen atom is less acidic than the position adjacent to an alkyl-substituted nitrogen atom.[2] Another advantage of *N*-oxides compared with azolium ions is that the *N*-oxygen can be removed under mild conditions. Therefore, selective introduction of substituents in otherwise inaccessible positions of the azole nucleus can be achieved effectively through a sequence of activation, deprotonation, reaction with an electrophile, and deoxygenation. This approach has been successfully used in the selective introduction of electrophiles in 3-substituted-1,2,3-triazole 1-oxides.[3,4]

Results and discussion

In 2-substituted pyrazole 1-oxides both C-3 and C-5 are adjacent to positive nitrogen atoms owing to mesomeric delocalization. Therefore, H-3 and H-5 are activated towards deprotonation. Accordingly, H-3 and H-5 are exchanged with deuterium in a solution of potassium deuteroxide in deuterium oxide. Contrary to the donor–acceptor analysis, H-5 is the more acidic, being exchanged 1.07 times faster than H-3 in 2-benzylpyrazole 1-oxide (**1**). H-4 is not exchanged even under forcing conditions.

In order to investigate the potential of deprotonation followed by reaction with an electrophile in synthesis, the deprotonation of 2-benzylpyrazole 1-oxide (**1**) was performed using different combinations of bases and solvents. In parallel experiments, deprotonation was followed by addition of methyl iodide and dimethyl disulfide as the electrophiles. These experiments, shown in Table 1 (entries 1–5, 11–19 and 25), indicate that the best results are obtained using sodium hydride, a strong and non-nucleophilic base, in dichloromethane at 70 °C. Blank experiments demonstrated that dichloromethane itself is not deprotonated under these conditions. The use of other strong bases, such as butyllithium, lithium diisopropylamide or lithium tetramethylpiperidide in tetrahydrofuran or potassium amide in ammonia, caused decomposition of the pyrazole *N*-oxide (entries 2–5). The decomposition may be due to nucleophilic attack at the pyrazole nucleus, known to be susceptible to addition of weaker nucleophiles like methoxide ion.[5] No reaction was observed under milder



Scheme 1.

* To whom correspondence should be addressed.

Table 1. Deprotonation of 2-benzylpyrazole 1-oxide (**1**) (1.0 mmol) followed by addition of an electrophile.

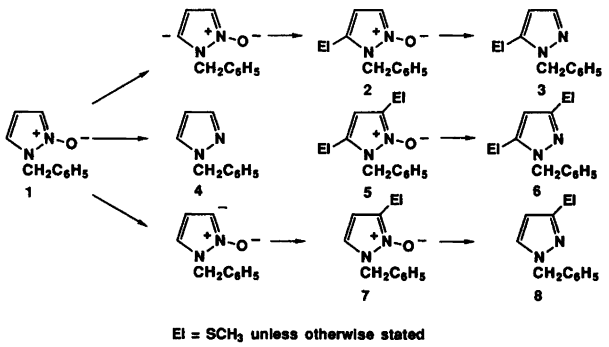
Entry	Base	Equiv.	Solvent	ml	Electrophile	Equiv.	*t*/h	*T*/°C	Product mixture	
									1-Benzylpyrazole (**4**) (%)[a]	2-Benzylpyrazole 1-oxide (**1**) (%)[a]
1	Bu^{t}OK	2.0	Bu^{t}OH	1.0	CH_3I	3.0	1+2[b]	60	0	100
2	KNH_2	2.0	NH_3	10.0	CH_3I	3.0	0.5+1[b]	−33	[c]	
3	LDA[d]	2.0	THF	1.0	CH_3I	3.0	1+2[b]	−78	[c]	
4	LiTMP[e]	6.0	THF	1.0	CH_3I	3.0	0.25+1[b]	−78	[c]	
5	Bu^{n}Li	3.0	THF	1.0	CH_3I	3.0	0.5	−78	[c]	
6	NaH	6.0	CH_2Cl_2	1.0	$Br(CH_2)_3Br$	3.0	48	70	100 (72)	0
7	NaH	6.0	CH_2Cl_2	3.0	C_6H_5NCO	3.0	48	70	0	100 (100)
8	NaH	6.0	CH_2Cl_2	1.0	CBr_4	1.0	48	70	82	18
9	NaH	6.0	CH_2Cl_2	1.0	CCl_4	3.0	48	70	0	100 (71)
10	NaH	6.0	CH_2Cl_2	1.0	CH_3CHO	3.0	48	70	49	51
11	NaH	3.0	THF	1.0	CH_3I	3.0	20	20	25	75
12	NaH	6.0	CH_2Cl_2	1.0	CH_3I	3.0	48	50	0	100
13	NaH	6.0	CH_2Cl_2	1.0	CH_3I	3.0	48	70	100 (25)	0
14	NaH	6.0	CH_2Cl_2	1.0	CH_3SSCH_3	3.0	48	70	32.1[f]	0 (5.5)[f]
15	NaH	6.0	$CHCl_3$	1.0	CH_3SSCH_3	3.0	48	70	26.8[g]	31.7[g]
16	NaH	6.0	$CHCl_3$	1.0	CH_3SSCH_3	3.0	72	70	24.9[h]	0[h]
17	NaH	6.0	DMF	1.0	CH_3SSCH_3	3.0	24	70	0	100
18	NaH	6.0	Pyridine	1.0	CH_3SSCH_3	3.0	48	70	0	100
19	NaH	4.4	THF	1.0	CH_3SSCH_3	3.0	24	50	0	100 (68)
20	NaH	6.0	$CHCl_3$	1.0	$CHCl_3$	–	48	70	19[i]	72.4[i]
21	NaH	6.0	CH_2Cl_2	1.0	CS_2	3.0	48	70	82	18
22	NaH	6.0	CH_2Cl_2	1.0	Cyclohexanone	3.0	48	70	24	76
23	NaH	6.0	CH_2Cl_2	1.0	Paraformaldehyde	3.0	48	70	100 (43)	0
24	NaH	6.0	CH_2Cl_2	1.0	S_8	3.0	48	70	100 (20)	0
25	NaOH	2.0	Toluene +H_2O	1.0 0.133	CH_3SSCH_3	2.0	48	Reflux	0	100

[a]Determined by ^{1}H NMR spectroscopy, yield of isolated product is given in parentheses. [b]Before and after the addition of the electrophile. [c]The reaction led to decomposition. [d]LDA: Lithium diisopropylamide. [e]LiTMP: Lithium 2,2,6,6-tetramethylpiperidide. [f]In addition, 1-benzyl-5-methylthiopyrazole (**3**) (21.4 %), 1-benzyl-3-methylthiopyrazole (**8**) (14.3 %), 1-benzyl-3,5-bis(methylthio)pyrazole (**6**) (32.1 %), 2-benzyl-5-methylthiopyrazole 2-oxide (**7**) (3.0 %) were produced. [g]In addition, 1-benzyl-3-methylthiopyrazole (**8**) (17.1 %), 2-benzyl-5-methylthiopyrazole 1-oxide (**7**) (24.4 %) were produced. [h]In addition, 1-benzyl-5-methylthiopyrazole (**3**) (60.1 %), 1-benzyl-3-methylthiopyrazole (**8**) (12.5 %), and 1-benzyl-3-chloropyrazole (**8**; El=Cl) (2.5 %) were produced. [i]In addition, 8.6 % of 1-benzyl-3-chloropyrazole (**8**; El=Cl) was detected.

conditions. Thus the use of potassium *tert*-butoxide in *tert*-butyl alcohol, sodium hydride in dichloromethane at 50 °C, or sodium hydroxide in toluene–water were not successful (entries 1, 12 and 25).

In order to introduce substituents, deprotonation performed under the optimal conditions was followed by addition of different electrophiles. Preparatively useful reactions were only observed when dimethyl disulfide (entries 14–16) or chloroform (entry 20) were employed as electrophiles. It was necessary for the chloroform to be present in large excess (as the solvent). Chloroform, like tetrachloromethane and tetrabromomethane, may halogenate by an ionic or a radical mechanism.[6–10] The reason why tetrachloromethane and tetrabromomethane did not halogenate the *N*-oxide **1** may be that they could not be used in substantial excess since they did not dissolve **1**.

In the reactions with dimethyl disulfide and chloroform, deoxygenation of the starting material (**1**) was a competitive process and the products were only slowly deoxygenated. Hence yields of substituted pyrazole *N*-oxides are low. When chloroform was used as the electrophile, 1-benzyl-3-chloropyrazole was the sole substitution product. When dimethyl disulfide was used as the electrophile and chloroform as the solvent the regioselectivity was poor, a 1.43:1 mixture of 3- and 5-substituted methylthio compounds being formed (entries 15 and 16). When the solvent was changed to dichloromethane, mono-selectivity was also lost, 3-, 5-, and 3,5-disubstituted products being formed (entry 14).



Scheme 2.

Table 2. ^{1}H NMR data of 2-benzyl pyrazole 1-oxides and of 1-benzylpyrazoles in $CDCl_3$ with tetramethylsilane as an internal standard, when not otherwise stated.

	$\delta_{H\text{-}3}$	$\delta_{H\text{-}4}$	$\delta_{H\text{-}5}$	δ_{Ph}	δ_{CH_2} (δ_{CH_3})	$J_{3,4}$/Hz	$J_{4,5}$/Hz	$J_{3,5}$/Hz
2-Benzyl substituted pyrazole 1-oxide								
2		6.12	6.76	7.26–7.39	5.31 (2.49)		3.1	
1-Benzyl substituted pyrazole								
3		6.22	7.2	7.18–7.39	5.27 (2.50)		2.27	
6		6.24		7.19–7.32	5.36 (2.49; 2.27)			
8	7.2	6.32		7.18–7.29	5.41 (2.28)		1.6	

[a]With CD_3CN as the solvent.

The presence of 1-benzylpyrazole (**4**) and deoxygenated substitution products indicates that **4** may be the precursor of the substitution products. This possibility could be excluded since 1-benzylpyrazole (**4**) remained unchanged when treated with sodium hydride and dimethyl disulfide in a blank experiment. This proves that deprotonation takes place in the pyrazole *N*-oxide.

Reaction with other electrophiles under optimum conditions for deprotonation gave only mixtures of 1-benzylpyrazole (**4**) and 2-benzylpyrazole 1-oxide (**1**) (entries 13 and 21–24). The extent of deoxygenation depends on the electrophile used. For example, paraformaldehyde gave only 1-benzylpyrazole (**4**) (entry 23) while tetrachloromethane left the 2-benzylpyrazole 1-oxide (**1**) unchanged (entry 9). Acetaldehyde produced a 1:1 mixture of 1-benzylpyrazole and 2-benzylpyrazole 1-oxide (entry 10).

Deoxygenation takes place even in the absence of an electrophile to give a 4.0:1 mixture of 1-benzylpyrazole (**4**) and 2-benzylpyrazole 1-oxide (**1**) under standard conditions. Reductive properties of sodium hydride have been reported under similar reaction conditions, e.g., in attempts to alkylate 4-hydroxyadamantane in tetrahydrofuran or norcamphor in glyme with methyl iodide.[11,12] Three mechanisms for the reduction can be envisaged: (i) addition of a hydrogen radical (ii) nucleophilic addition of hydride ion, or (iii) hydrogenolysis effected by hydrogen evolved during the deprotonation. Hydrogen radicals have been reported to add to heterocyclic salts,[11] but seem not to be involved in the reduction of the pyrazole 1-oxide (**1**) since addition of benzophenone as a radical trap does not influence the reduction. Examples of nucleophilic addition of sodium hydride are rare.[12] On the other hand pyrazole 1-oxides are very susceptible to attack by other nucleophiles.[5] Nucleophilic addition of hydride ions seems not to be involved in the reduction of the pyrazole 1-oxide (**1**) since the yield of 1-benzylpyrazole (**4**) drops from 81 to 5 % when sodium hydride was replaced with sodium borohydride, an efficient hydride donor. Hydrogenolysis seems to account for the reaction as supported by the fact that the pyrazole 1-oxide (**1**) underwent 27 % reduction when heated with 6 equivalents of hydrogen under standard conditions. In the absence of hydrogen the pyrazole 1-oxide (**1**) remained unchanged.

The hydrogenolysis mechanism is also supported by the fact that in the original experiments, reduction is only observed under conditions where deprotonation produces the required hydrogen. Thus, neither deprotonation nor reduction is observed when the reaction temperature is reduced from 70 to 50 °C.

Table 3. ^{13}C NMR data of 2-benzyl pyrazole 1-oxides and of 1-benzylpyrazoles in $CDCl_3$ with the solvent signal (δ 76.90) as an internal standard, when not otherwise stated.

	$\delta_{C\text{-}3}$ ($\delta_{C\text{-}1'}$)	$\delta_{C\text{-}4}$ ($\delta_{C\text{-}2'}$)	$\delta_{C\text{-}5}$ ($\delta_{C\text{-}3'}$)	δ_{CH_2} δ_{CH_3} ($\delta_{C\text{-}4'}$)
2-Benzyl substituted pyrazole 1-oxide				
2	– (138.1)	103.5 (128.7)	117.5 (129.1)	49.5 15.2 (128.7)
1-Benzyl substituted pyrazole				
6	146.7 (136.7)	109.0 (127.2)	137.8 (126.5)	53.1 16.3 16.6 (127.6)

Conclusions. *N*-Oxidation of pyrazoles activates positions adjacent to the nitrogen atoms (position 3 and 5) towards deprotonation. The anions formed react with dimethyl disulfide or chloroform as the electrophile giving rise to methylthio- and chloro-substituted pyrazole 1-oxides. However, competitive deoxygenation of the pyrazole

1-oxide through deprotonation followed by hydrogenolysis is the prevailing reaction.

Experimental

General. Liquid reagents were distilled before use; solid reagents were dried over phosphorus pentaoxide. Filtration through silica gel was performed using silica gel Merck 60 (70–230 mesh). Ammonia was distilled from potassium. Dichloromethane was dried over sodium hydride. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride. Toluene was distilled from calcium hydride. *tert*-butyl alcohol and pyridine were dried over sodium hydride. *N,N*-Dimethylformamide (DMF) was dried as described in Ref. 13. Methyl iodide, dimethyl disulfide, and carbon disulfide were distilled from sodium hydride. All reactions were performed using syringe techniques and screw-cap-sealed reaction vessels[14] in an atmosphere of nitrogen dried over phosphorus pentaoxide. The identity of all products was affirmed by comparison with authentic samples.[5] ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. NMR data are shown in Tables 2 and 3.

Determination of the relative acidity of the ring-protons. 2-Benzylpyrazole 1-oxide (**1**) (39 mg), potassium hydroxide (28 mg), deuterium oxide (0.5 ml) and tetradeuteriomethanol (0.1 ml) were heated to 50 °C for 35 min. Extraction with dichloromethane (5 × 3 ml), drying ($MgSO_4$) and removal of the dichloromethane gave 39 mg (100 %) of compound **1** in which H-5 and H-3 had been exchanged with deuterium to an extent of 59 % and 55 %, respectively.

Deprotonation followed by addition of electrophiles. (a) With sodium hydride as the base. Under nitrogen, a 55 % suspension of sodium hydride in mineral oil (262 mg) was washed with dry hexane (2 × 2 ml). A solution of 2-benzylpyrazole 1-oxide (**1**) (174 mg) and 6 equivalents of the appropriate electrophile in dry dichloromethane, THF, DMF, pyridine, or chloroform (1 ml) were added at 20 °C and the mixture was stirred at 70 °C for 48 h. When sulfur, dimethyl disulfide, or carbon disulfide were used, the mixture was stirred with methyl iodide (0.19 ml) at 20 °C for 15 h. Centrifugation and washing of the residue with dry dichloromethane (10 ml) left the crude product. When dimethyl disulfide was used, the crude product was purified by preparative TLC (hexane–ethyl acetate [9:1]) to give 27.6 mg (22 %) of 1-benzyl-3,5-bis(methylthio)pyrazole (**6**) and 55 mg of a 2.0:3.6:1 mixture of 1-benzylpyrazole (**4**), 1-benzyl-5-methylthiopyrazole (**3**), and 1-benzyl-3-methylthiopyrazole (**8**).

(b) With butyllithium, lithium diisopropylamide or lithium tetramethylpiperidide as the base. Lithium diisopropylamide (LDA) and lithium tetramethylpiperidide (LiTMP) were prepared by treatment of the corresponding amines with a 1.55 M solution of butyllithium in hexane at 20 °C for 0.5 h. The hexane was removed *in vacuo* prior to the addition of THF and the electrophile and the mixture was heated as described in Table 1. Dichloromethane (10 ml) was then added and the mixture evaporated to dryness. The content of the residue as found by ^{1}H NMR spectroscopy is given in Table 1.

(c) With potassium amide in ammonia as the base. A solution of potassium amide was prepared by addition of potassium (39 mg) and iron(III) nitrate hexahydrate as a catalyst to dry ammonia (4 ml). 2-Benzylpyrazole 1-oxide (**1**) (87 mg) was added and the mixture was stirred under reflux for 0.5 h. Methyl iodide (0.16 ml) was added and stirring under reflux was continued for 1 h. Addition of ammonium chloride, evaporation of the solvent, addition of dichloromethane (5 ml), washing with water (2 ml), drying (magnesium sulfate) and removal of the solvent afforded 73.4 mg of a crude product which was analyzed by ^{1}H NMR spectroscopy. Results are given in Table 1.

(d) With potassium tert-*butoxide in* tert-*butyl alcohol as the base.* A solution of 2-benzylpyrazole 1-oxide (**1**) (87 mg) and potassium *tert*-butoxide (112 mg) in *tert*-butyl alcohol (0.5 ml) was stirred at 60 °C for 1 h. Methyl iodide (0.16 ml) was added and the mixture was stirred at 60 °C for 2 h. Addition of dichloromethane (5 ml), washing with water (2 ml), drying (magnesium sulfate) and removal of the solvent afforded 75.6 mg of crude product which was analyzed by ^{1}H NMR spectroscopy. Results are given in Table 1.

(e) With sodium hydroxide as the base in the presence of a phase transfer catalyst. A 60 % suspension of sodium hydroxide in water (0.133 ml), was added to a solution of 2-benzylpyrazole 1-oxide (**1**) (174 mg), tetrabutylammonium bromide (97 mg), and dimethyl disulfide (0.18 ml) in toluene (1 ml). Heating to reflux for 48 h, decantation, extraction with dichloromethane (3 × 15 ml), drying (magnesium sulfate) and removal of the solvent afforded the crude product which was analyzed by ^{1}H NMR spectroscopy. Results are given in Table 1.

Reaction of 1-benzylpyrazole (**4**) *with dimethyl disulfide.* 1-Benzylpyrazole (118 mg) was reacted according to procedure *(b)* to give 118 mg of unchanged starting material.

Reactions of 2-benzylpyrazole 1-oxide (**1**). 2-Benzylpyrazole 1-oxide (**1**) was treated with sodium hydride according to procedure *(a)* omitting the addition of the electrophile. This gave a 4.3:1 mixture (^{1}H NMR) of 1-benzylpyrazole (**4**) and 2-benzylpyrazole 1-oxide (**1**).

2-Benzylpyrazole 1-oxide (**1**) (87 mg), sodium borohydride (38 mg) and dry dichloromethane (0.5 ml) were stirred at 70 °C for 15 h. Filtration and removal of the solvent afforded 79 mg of a 1:19 mixture of 1-benzylpyrazole (**4**) and 2-benzylpyrazole 1-oxide (**1**).

2-Benzylpyrazole 1-oxide, dimethyl disulfide, benzophenone (273 mg), and dry dichloromethane were reacted according to *(b)* to give a mixture of 1-benzylpyrazole (**4**), 1-benzyl-5-methylthiopyrazole (**3**), 1-benzyl-3-methylthiopyrazole (**8**), and 1-benzyl-3,5-bis(methylthio)pyrazole (**6**).

2-Benzylpyrazole 1-oxide (87 mg), sodium (69 mg), dichloromethane (0.5 ml) and water (0.054 ml) were stirred at 70 °C for 48 h. Filtration, washing of the residue with dry dichloromethane (5 ml) and removal of the solvent afforded a 1:2.8 mixture of 1-benzylpyrazole (**4**) and 2-benzylpyrazole 1-oxide (**1**).

Separation of 1-benzylpyrazole (**4**) *and 2-benzylpyrazole 1-oxide* (**1**). This was performed by filtration of a 10 % solution of the mixture in dichloromethane through silica gel (4 g per gram of mixture). Elution with ethyl acetate–hexane (1:1) afforded 1-benzylpyrazole (**4**). Subsequent elution with ethyl acetate–methanol (1:1) afforded 2-benzylpyrazole 1-oxide (**1**).

Acknowledgements. This work was supported by the Danish Council for Technical and Scientific Research. The NMR spectrometer is a gift from the Velux Foundation of 1981, The Danish Council for Technical and Scientific Research, The Ib Henriksen Foundation, and the Torkil Steenbeck Foundation. Microanalyses were performed by LEO Pharmaceutical Products. Thanks are due to Dr. J. Øgaard Madsen for the mass spectra.

References

1. Begtrup, M. *Bull. Soc. Chim. Belg. 97* (1988) 573.
2. Begtrup, M. *Heterocycles 33* (1992) 1129.
3. Begtrup, M. and de la Hoz, A. *Unpublished results.*
4. Begtrup, M. and Johnsson, G. *Acta Chem. Scand., Ser. B 41* (1987) 724.
5. Begtrup, M., Larsen, P. and Vedsø, P. *To be published.*
6. Meyers, C. Y., Malte, A. M. and Matthews, W. S. *J. Am. Chem. Soc. 91* (1969) 7510.
7. Kattenberg, J., de Waard, E. R. and Huisman, H. O. *Tetrahedron 29* (1973) 4149.
8. Gronowitz, S., Hörnfeldt, A.-B. and Pettersson, K. *Synth. Commun. 3* (1973) 213.
9. Arnold, R. T. and Kulenovic, S. T. *J. Org. Chem. 43* (1978) 3687.
10. Regis, R. R. and Doweyko, A. M. *Tetrahedron Lett. 23* (1982) 2539.
11. Duddeck, H., Feverhelm, H. and Snatzke, G. *Tetrahedron Lett. 20* (1979) 829.
12. McConaghy, J. S. and Bloomfield, J. J. *J. Org. Chem. 33* (1968) 2425.
13. Burfield, D. R. and Smithers, R. H. *J. Org. Chem. 43* (1978) 3966.
14. Begtrup, M. *J. Chem. Educ. 64* (1987) 974.

Received March 9, 1992.