1,2-BIS(AZOL-1-YL)ETHANES. DEPROTONATION AND SUBSEQUENT REACTION WITH ELECTROPHILES

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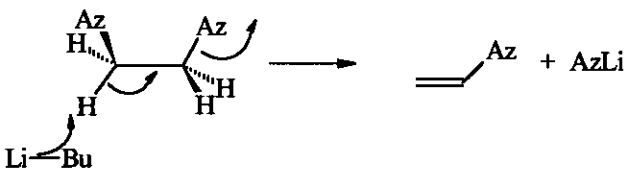
Abstract- Deprotonation of the title compounds and subsequent reaction with electrophiles have been performed. The main factor governing the reaction, substitution *vs* elimination, is the acidity of the ring hydrogen atoms.

Deprotonation of heterocyclic systems and subsequent reaction with electrophiles have been widely studied.[1,2] We have specially paid attention to bis(azol-1-yl)methanes[3] due to their ability as complexating agents[4] or their use as intermediates in synthesis.[5] Other heterocyclic systems, as thiophene[6] and pyrrole[7] derivatives, 1-benzylazoles,[8] 1-substituted benzotriazoles[9] and binuclear heteroaromatic systems[10] have been studied by other authors.

In the case of bis(azol-1-yl)methanes competition between deprotonation at the bridge and ring has been explained[3] considering the structure of the substrates, the HSAB principle and the nature of the electrophile. Bridge positions are activated by the presence of two adjacent nitrogen atoms. However in the case of 1,2-bis(azol-1-yl)ethanes, ring deprotonation must be favoured in relation to bridge deprotonation because bridge positions are only activated by one nitrogen atom towards α-lithiation and, considering β-lithiation, also one nitrogen atom can coordinate the base when pyrazole and 1,2,4-triazole derivatives are used. However, taking in to account the ability of azoles as good leaving groups,[11] deprotonation at methylene moieties may produce an irreversible β-elimination (Scheme 1). The aim of this work is the study of competition between these two reactions.

RESULTS

The substrates 1,2-bis(pyrazol-1-yl)ethane (**1**), 1,2-bis(imidazol-1-yl)ethane (**2**) and 1,2-bis(1,2,4-triazol-1-yl)ethane (**3**) represent a full set of different structural effects towards deprotonation at the ring position and methylene bridge. Table 1 summarizes the results when the 1,2-bis(azol-1-yl)ethanes (**1**)-(**3**) were allowed to react (THF, 0 °C) with n-butyllithium under nitrogen (60 min), followed by addition of the electrophile (room temperature, 14 hours).



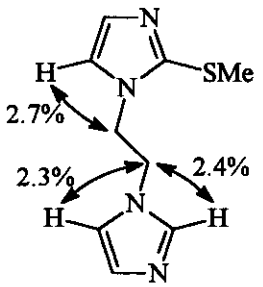
Scheme 1

Assignment of the ^{1}H and ^{13}C-nmr spectra of compounds was performed by their multiplicity and coupling constants and, when necessary, by NOE difference spectroscopy[12] and Heteronuclear Correlation Experiments.

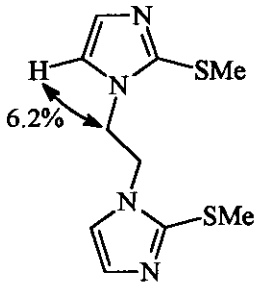
In compound (**1d**) H-5' signal was differentiated by its chemical shift, differentiation between H-4 and H-4' was performed by the multiplicity, H-4' is a triplet and H-4 is a doublet.

In imidazole derivatives (**2c**), (**2d**) and (**2e**) differentiation between H-4 and H-5 was performed by NOE difference spectroscopy. Irradiation at the substituent in position 1 produces an enhancement in the H-5 signals (Scheme 2). In compound (**2d, SMe**) the nmr of both rings were differentiated by the multiplicity, H-4 and H-5 are doublets and H-4' and H-5' triplets. Assignment of the ^{13}C signals was performed by Heteronuclear Correlation Spectroscopy.

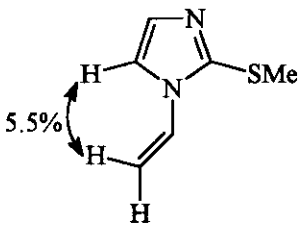
In 1-(5-methylthio-1,2,4-triazol-1-yl)-2-(1,2,4-triazol-1-yl)ethane (**3d**) differentiation between the methylene protons was performed by NOE difference spectroscopy. Irradiation on the middle of the multiplet at 4.65-4.69 produces an enhancement of the signal at 7.79 (H-5') (Scheme 2). Differentiation between C-3 and C-3' was performed by their multiplicity, C-3 is a doublet and C-3' is a double-doublet. H-3, H-3' and other ^{13}C-nmr signals were assigned by Heteronuclear Correlation Experiments.



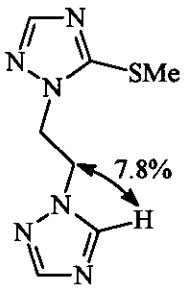
2d



2e



2c



3d

Scheme 2

DISCUSSION

The following differences between these three substrates are obseved:

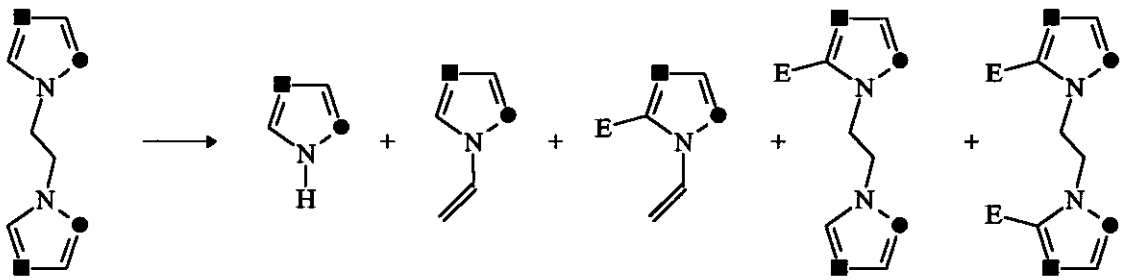
i) in the case of 1,2-bis(pyrazol-1-yl)ethane (**1**), elimination products are almost exclusively formed (Entries 1 and 2).

ii) substitution at C-2 is the main reaction when 1,2-bis(imidazol-1-yl)ethane (**2**) is used (Entries 3-6).

iii) substitution at C-5 is the only reaction when 1,2-bis(1,2,4-triazol-1-yl)ethane (**3**) is used (Entries 7 and 8).

In these substrates the deprotonation could take place at the ring or at the bridge. Our own results[3] and the other bibliographical data[2] indicate that deprotonation might occur by two different mechanisms: acid-

base or coordinative. An acid-base mechanism produces ring substitution while a coordinative mechanism yields elimination products. So, the acidity of the ring hydrogen atoms of **1**, **2** and **3** (positions 5, 2 and 5 respectively) and the existence of coordination positions (N-2 in pyrazole, N-2 in 1,2,4-triazole or sulfur atoms in methylthio derivatives) must be the factors to consider.



1, ●=N, ■=CH **a** **b** **c** **d** **e**
2, ●=CH, ■=N
3, ●=N, ■=N

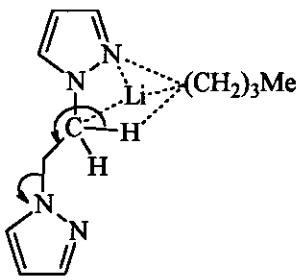
Table 1. Yields of elimination and/or substitution products

Entry	Azole	Mole Ratio[a)]	E[b)]	**a**	**b**	**c**	**d**	**e**
1	**1**	1:1:1	SMe	30	30	0	0	0
2	**1**	1:2.1:2.1	SMe	62	c)	12	2	0
3	**2**	1:1:1	SMe	22[d)]	0	22	16	21
4	**2**	1:2.1:2.1	SMe	12[d)]	0	12	9	54
5	**2**	1:1:0.5	Me	0	0	0	45	0
6	**2**	1:2.1:1.1	Me	0	0	0	16	29
7	**3**	1:1:1	SMe	0	0	0	48	2
8	**3**	1:2.1:2.1	SMe	0	0	0	21	47

a) Substrate:base:electrophile. b) E = SMe, electrophile = dimethyl disulfide; E = Me, electrophile = dimethyl sulfate. c) Detected in the reaction crude by ^{1}H-nmr, yield not determined. d) Detected in the reaction crude by ^{1}H-nmr.

In the case of **1**, a competence between both mechanisms, due to the low H-5 acidity and the existence of N-2 atom, was observed. Considering the exclusive elimination when a 1:1:1 molar ratio is used, a predominance of the coordinative mechanism could be inferred (Scheme 3). Imidazole derivative (**2**) does not have any atom in adequate position to permit a coordinative mechanism, substitution products were

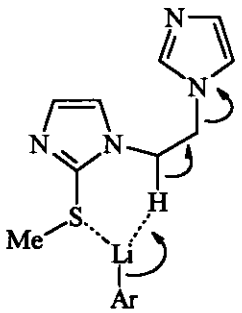
obtained; only when a methylthio was incorporated elimination products were obtained. In the case of **3**, no elimination products were obtained, a coordinative mechanism is not present, even when a methylthio was incorporated. This fact indicates the high acidity of H-5, but it is not clear why the elimination on **3d** and **3e** do not occur as in **2d (SMe)**.



Scheme 3

Consumption of *n*-BuLi in the deprotonation process (before the addition of dimethyl disulfide) could explain this result. In order to verify this possibility two different experiments were performed. In one hand, the treatment of any reaction (**3** + *n*-BuLi + MeSSMe) crude with one equivalent of *n*-BuLi caused elimination, in the other hand, after deprotonation with *n*-BuLi, one equivalent of benzyl bromide was added but n-pentylbenzene or 1,2-diphenylethane was not detected (a blank experiment, *n*-BuLi + $PhCH_2Br$ afforded these products). Then, we can conclud that the absence of the elimination when **3** is used is justified by the consumption of the base in the deprotonation process. Similar results were obtained when this set of experiments was repeated with bis(imidazol-1-yl)ethane (**2**), giving rise to a new question: considering that *n*-BuLi has been consumed in the deprotonation process, what is the base that causes the elimination on **2d (SMe)**? The only possibility is that the anion of bis(imidazol-1-yl)ethane acts as base. This fact was confirmed by the treatment of 1-(2-methylthioimidazol-1-yl)-2-(imidazol-1-yl)ethane (**2d**) with the anion of **2**. Now the elimination products were obtained by a coordinative mechanism (Scheme 4). Reactions with 1,2,4-triazole derivatives (**3d**) and (**3e**) with the anion of **3** did not afford elimination

products. So, it could be confirmed that the anion of bis(imidazol-1-yl)ethane is more basic than that of bis(1,2,4-triazol-1-yl)ethane.



ArH = bis(imidazol-1-yl)ethane

Scheme 4

In conclusion deprotonation of bis(azol-1-yl)ethanes is controlled by the acidity of the ring hydrogen atoms. 1,2-Bis(pyrazol-1-yl)ethane (**1**) yields always elimination products. Substitution at the heterocyclic ring is observed with 1,2-bis(imidazol-1-yl)ethane (**2**) and 1,2-bis(1,2,4-triazol-1-yl)ethane (**3**). Introduction of a good coordinating substituent directs the reaction towards elimination by deprotonation at the methylene bridge.

EXPERIMENTAL

Mps were determined with a Gallenkamp capillary apparatus and are uncorrected. Microanalyses were performed in a Perkin-Elmer 2400 CHN microanalyzer. Ir spectra were recorded in liquid film except otherwise stated, using a Philips PU 9500 spectrophotometer. ^{1}H and ^{13}C-nmr spectra were recorded in deuterochloroform (TMS) solution except otherwise stated, using a Varian Unity 300 (300 MHz) spectrometer. *J* values are given in Hz. Signal assignments have been performed by 1D NOE and HETCOR experiments when required. NOE experiments were performed by recording the FID with irradiation at the methylene signals followed by subtraction of the FID recorded with an off resonance frequency of 3000 Hz for the decoupler (decoupler power 20 dB except for **2c (SMe)** and **3d**; in these

cases 5 dB and 2 dB, respectively, were used). Silica gel 60 (70-230 mesh) (Merck) was used in column chromatography.

General procedure.- In a Schlenk tube, the appropriate 1,2-bis(azol-1-yl)ethane (2 mmol) was dissolved in dry tetrahydrofurane (THF) (35 ml) and the solution was cooled to 0 °C. Under nitrogen, a 1,6 M solution of n-butyllithium in hexane was added dropwise during 5 min and the solution was stirred for 1h. The electrophile was added and the mixture was stirred at room temperature for 14 h. The reaction was quenched with ammonium chloride. After removal of solvents, the crude residue was extracted with chloroform (3x25 ml). Work-up was performed as indicated.

1,2-Bis(pyrazol-1-yl)ethane (**1**). *Reaction with dimethyl disulfide.* Flash chromatography using light petroleum (bp 40-60°C)-ethyl acetate (15:1), afforded 5-methylthio-1-vinylpyrazole (**1c**) (yellow oil). ^{1}H-Nmr (δ ppm): 2.40 (3H, s, SC*H*$_3$); 4.92 (1H, d, *J* 9.0, =C*H*$_2$); 5.77 (1H, d, *J* 15.5, =C*H*$_2$); 6.35 (1H, d, *J* 1.8, *H*-4); 7.32 (1H, dd, *J* 15.5, 9.0, C*H*=); 7.61 (1H, d, *J* 1.8, *H*-3), ^{13}C-nmr (δ ppm): 19.10 (S*C*H$_3$); 101.54 (=*C*H$_2$); 110.35 (*C*-4); 129.31 (*C*H=); 136.35 (*C*-5); 140.78 (*C*-3). Subsequent elution with light petroleum-ethyl acetate (2:1), gave a mixture of pyrazole (**1a**) and 1-(5-methylthiopyrazol-1-yl)-2-pyrazol-1-ylethane (**1d**). ^{1}H-Nmr (δ ppm) 2.14 (3H, s, SC*H*$_3$); 4.58-4.63 (4H, m, C*H*$_2$-C*H*$_2$); 6.12 (1H, t, *J* 2.1, *H*-4'); 6.23 (1H, d, *J* 1.8, *H*-4); 6.92 (1H, d, *J* 2.1, *H*-5'); 7.52 (1H, d, *J* 1.9) and 7.55 (1H, d, *J* 2.0) *H*-3 and *H*-3'.

1,2-Bis(imidazol-1-yl)ethane (**2**). *(a) Reaction with dimethyl disulfide.* Flash chromatography using chloroform-ethanol (15:1) gave 2-methylthio-1-vinylimidazole (**2c, Sme**) (yellow oil) that decomposes during purification. ^{1}H-Nmr (δ ppm): 2.60 (3H, s, SC*H*$_3$); 4.89 (1H, dd, *J* 9.0, 1.6, =C*H*$_2$); 5.20 (1H, dd, *J* 15.7, 1.6, =C*H*$_2$); 7.20 (1H, dd, *J* 15.7, 9.1, C*H*=); 7.07 (1H, d, *J* 1.5, *H*-4); 7.22 (1H, d, *J*1.5, *H*-5), ^{13}C-nmr (δ ppm): 16.03 (S*C*H$_3$); 101.82 (=*C*H$_2$); 116.78 (*C*-5); 128.45 (*C*H=); 130.14 (*C*-4); 143.14 (*C*-2), and 1,2-bis(2-methylthioimidazol-1-yl)ethane (**2e, SMe**). bp 250 °C (10^{-4} mbar). Ir (ν cm^{-1}): 1506, 1427. ^{1}H-Nmr (δ ppm): 2.56 (6H, s, SC*H*$_3$); 4.22 (4H, s, C*H*$_2$); 6.64 (2H, d, *J* 1.2, *H*-5 and *H*-5'); 7.02 (2H, d, *J* 1.2, *H*-4 and *H*-4'), ^{13}C-nmr (δ ppm): 16.37 (S*C*H$_3$); 46.23 (*C*H$_2$); 120.72 (*C*-5 and *C*-5'); 129.75 (*C*-4 and

C-4'); 142.90 (*C*-2 and *C*-2'). Anal. Calcd for $C_{10}H_{14}N_4S_2$: C, 47.2; H, 5.6; N, 22.0; S, 25.2. Found: C, 47.6; H, 5.6; N, 21.8; S, 25.5. Subsequent elution with chloroform-ethanol (7:2) afforded 1-(2-methylthioimidazol-1-yl)-2-(imidazol-1-yl)ethane (**2d, SMe**). bp 250 °C (10^{-4} mbar). Ir (ν cm^{-1}): 1505, 1429. ^{1}H-Nmr (δ ppm): 2.57 (3H, s, S*CH*$_3$); 4.25 (4H, s, *CH*$_2$); 6.62 (1H, d, *J* 1.4, *H*-5); 6.71 (1H, t, 1.2, *H*-5'); 7.04 (1H, d, *J* 1.4, *H*-4): 7.05 (1H, t, *J* 1.2, *H*-4'); 7.29 (1H, br s, *H*-2'), ^{13}C-nmr (δ ppm): 16.29 (q, *J* 142.2, S*CH*$_3$); 46.84 (t, *J* 141.3, *CH*$_2$-1'); 47.09 (t, *J* 141.6, *CH*$_2$-1); 118.69 (ddd, *J* 188.4, 16.1, 3.2, *C*-5'); 120.59 (dd, *J* 189.5, 15.8, *C*-5); 129.91 (dd, *J* 190.9, 9.1, *C*-4); 130.03 (dt, *J* 189.8, 10.5, *C*-4'); 137.01 (d, *J* 206.9, *C*-2'); 142.73 (s, *C*-2). Anal. Calcd for $C_9H_{12}N_4S$: C, 51.9; H, 5.8; N, 26.9; S, 15.4. Found: C, 52.4; H, 6.1; N, 26.4; S, 15.2.

(b) Reaction with dimethyl sulfate: Neutralization with potassium hydrogen carbonate and flash chromatography with chloroform-ethanol (1:1) gave a mixture of 1,2-bis(2-methylimidazol-1-yl)ethane (**2e, Me**). ^{1}H-Nmr (DMSO-d_6, δ ppm): 2.35 (6H, s, C*H*$_3$); 4.28 (4H, s, C*H*$_2$); 6.94 (2H, d, *J* 1.6, *H*-5 and *H*-5'); 6.88 (2H, d, *J* 1.6, *H*-4 and *H*-4') and 1-(2-methylimidazol-1-yl)-2-(imidazol-1-yl)ethane (**2d, Me**). ^{1}H-Nmr (DMSO-d_6, δ ppm): 2.35 (3H, s, C*H*$_3$); 4.15-4.40 (4H, m, C*H*$_2$); 6.77-7.23 (4H, m, *H*-4, *H*-5, *H*-4' and *H*-5'); 7.52 (1H, br s, *H*-2').

1,2-Bis(1,2,4-triazol-1-yl)ethane (3). Reaction with dimethyl disulfide: Flash chromatography with acetone, afforded 1,2-bis(5-methylthio-1,2,4-triazol-1-yl)ethane (**3e**). mp 121-122 °C (ethyl acetate). Ir (KBr, ν cm^{-1}): 1484, 1438. ^{1}H-Nmr (δ ppm): 2.60 (6H, s, S*CH*$_3$); 4.47 (4H, s, C*H*$_2$); 7.86 (2H, s, *H*-3 and *H*-3'), ^{13}C-nmr ($CDCl_3$) δ ppm 15.65 (S*CH*$_3$); 47.48 (*CH*$_2$); 151.90 (*C*-3 and *C*-3'); 153.85 (*C*-5 and *C*-5'. Anal. Calcd for $C_8H_{12}N_6S_2$: C, 37.5; H, 4.7; N, 32.8; S, 24.9. Found: C, 37.9; H, 4.9; N, 32.5; S, 25.0; and 1-(5-methylthio-1,2,4-triazol-1-yl)-2-(triazol-1-yl)ethane (**3d**). bp 250 °C (10^{-4} mbar). Ir (ν cm^{-1}):1506, 1423. ^{1}H-Nmr (δ ppm): 2.57 (3H, s, S*CH*$_3$); 4.47-4.51 (2H, AA'BB' system, *J* 4.6 and 6.4, *CH*$_2$-1); 4.65-4.69 (2H, AA'BB' system, *J* 4.6 and 6.4, *CH*$_2$-1'); 7.79 (1H, s, *H*-5'); 7.87 (1H, s, *H*-3); 7.96 (1H, s, *H*-3'), ^{13}C-nmr (δ ppm): 15.39 (q, *J* 143.5, S*CH*$_3$); 47.43 (td, *J* 143.5, 5.1, *CH*$_2$-1); 48.01 (t, *J* 143.6, *CH*$_2$-1'); 143.56 (dd, *J* 210, 7.7, *C*-5'); 151.90 (d, *J* 208, *C*-3); 152.44 (dd, *J* 208, 11.6, *C*-3'); 154.03 (*C*-

5). Anal. Calcd for $C_7H_{10}N_6S$: C, 40.0; H, 4.8; N, 40.0; S, 15.3. Found: C, 40.0 H, 4.6 N, 40.3; S, 15.1.

A mixture of **3d** and **3e** (prepared by the general procedure, Entry 8) was cooled to 0 °C, and before quenching, 1.6 ml (2.56 mmol) of a 1.6 M solution of n-butyllithium in hexane was added dropwise during 5 min. The solution was stirred at room temperature for 14 h. Following the general procedure and subsequent chromatography using light petroleum-ethyl acetate (5:1) afforded 2-methylthio-1-vinyl-1,2,4-triazole (**3c**) (22%). ^{1}H-Nmr (CD_3OD, δ ppm): 2.67 (3H, s, SC*H*$_3$); 5.10 (1H, dd, *J* 8.8, 1.0, =C*H*$_2$); 5.75 (1H, dd, *J* 15.2, 1.0, =C*H*$_2$); 7.11 (1H, dd, *J* 15.2, 8.8, C*H*=); 7.96 (1H, s, *H*-3), ^{13}C-nmr (CD_3OD, δ ppm): 15.28 (S*C*H$_3$); 104.24 (=*C*H$_2$); 127.48 (*C*H=); 151.46 (*C*-3); 151.60 (*C*-5), 2-methylthio-1,2,4-triazole (20%). ^{1}H-Nmr (δ ppm): 2.65 (3H, s, SC*H*$_3$); 8.19 (1H, s, *H*-3); 10.73 (1H, br s, NH), ^{13}C-nmr (δ ppm): 14.94 (S*C*H$_3$); 147.05 (*C*-3); 158.13 (*C*-5) and 1,2-bis(5-methylthio-1,2,4-triazol-1-yl)ethane (**3e**) (26%).

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REFERENCES

1. "Comprehensive Heterocyclic Chemistry", Vol 5, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984.
2. H. W. Gschwend and H. R. Rodriguez, "Organic reactions", Vol. 26, ed by W. G. Dauben, Robert E. Krieger Publishing Company, Malabar, Florida, 1984, pp. 1-360.
3. E. Díez-Barra, A. de la Hoz, A. Sánchez-Migallón, and J. Tejeda, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1079 and references cited.
4. S. Trofimenko; "Progress in Inorganic Chemistry", Vol. 34, ed. by S. J. Lippard, John Wiley and Sons, Inc. 1986, pp. 115-237.
5. A. R. Katritzky, H. Lang, and X. Lan, *Tetrahedron*, 1993, **49**, 2829 and references cited.

6. T. Kawase, T. Enomoto, C. Wei, and M. Oda, *Tetrahedron Lett.*, 1993, **34,** 8143.

7. F. Faigl and M. Schlosser, *Tetrahedron,* 1993, **49,** 10271.

8. a) M. Moreno-Mañas, J. Bassa, N. Lladó, and R. Pleixats, *J. Heterocycl. Chem.*, 1990, **27,** 673. b) D. K. Anderson, J. A. Sikorski, D. B. Reitz, and L. T. Pilla, *J. Heterocycl. Chem.*, 1986, **23,** 1257. c) A. R. Katritzky, A. E. Abdel-Rahman, D. E. Leahy, and O. A. Schwarz, *Tetrahedron,* 1983, **39,** 4133.

9. a) A. R. Katritzky, J. Wu, W. Kuzmierkiewicz, and S. Rachwal, *Liebigs Ann. Chem.*, 1994, 1. b) A. R. Katritzky, J. Wu, W. Kuzmierkiewicz, S. Rachwal, M. Balasubramanian, and P. J. Steel, *Liebigs Ann. Chem.*, 1994, 7.

10. B. L Finkelstein, *J. Org. Chem.*, 1992, **57,** 5538.

11. Katritzky widely showed this behaviour. See for example A. R. Katritzky, L. Xie, and W-Q. Fan, *J. Org. Chem.*, 1993, **58,** 4376.

12. W. Holzer, *Tetrahedron,* 1991, **47,** 1393 and 5471.

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