CSIRO PUBLISHING

www.publish.csiro.au/journals/ajc *Aust. J. Chem.* **2003**, *56*, 913–916

On the Thermally Induced Rearrangement of 2-Alkoxypyridines to *N*-alkylpyridones

Troy Lister,[A] *Rolf H. Prager*,[A,B] *Michael Tsaconas*[A] *and Kerry L. Wilkinson*[A]

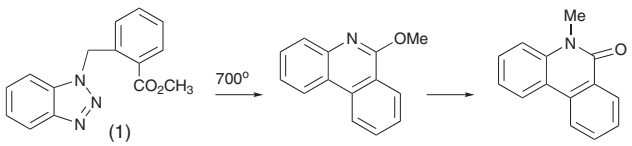
[A] School of Chemistry, Physics and Earth Sciences, Flinders University, Adelaide 5001, Australia.
[B] Author to whom correspondence should be addressed (e-mail: rolf.prager@flinders.edu.au).

Analogues of 2-methoxypyridine undergo rearrangement to *N*-methylpyridones under flash vacuum pyrolysis (FVP) conditions. Ethoxy derivatives undergo competitive ethyl migration and elimination of ethylene. Analogues of 4-methoxypyridine do not undergo rearrangement under FVP conditions, but demethylation on silica may occur. The ease of rearrangement follows the basicity of the alkoxyhetarene to some extent. The vapour-phase rearrangements have been contrasted to condensed-phase pyrolyses, and a four-centre transition state for the former is supported by computation. The rearrangement allows structural assignment to the two products from the reaction of 2,4-dichloroquinoline with pyrrolidine.

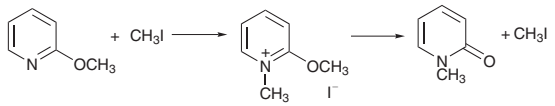
Manuscript received: 11 February 2003.
Final version: 1 May 2003.

Introduction

In a recent study of the flash vacuum pyrolysis of some *N*-benzylbenzotriazoles,[1] we reported the isolation of *N*-methylphenanthridone from the pyrolysis of 2-methoxycarbonylbenylbenzotriazole (1) (Scheme 1). It was postulated that the phenanthridone was formed by the thermal rearrangement of the presumed precursor, 6-methoxyphenanthridine, by a process involving migration of the *O*-methyl group to the nitrogen atom. Such transformations have not been widely observed in the vapour phase. The reaction is formally similar to the thermal rearrangement of alkyl imino-ethers into *N*-alkylamides, which has been found to be intermolecular,[2] but which is catalyzed by electrophilic reagents, such as alkyl halides,[2] or nucleophilic reagents, such as halides.[3] A number of transformations of 2- and 4-alkoxyhetarenes into *N*-alkyl amides have been observed in condensed phases. Haitinger and Lieben[4] reported partial rearrangement of 4-methoxypyridine to *N*-methyl-4-pyridone in 1885; Knorr[5] the rearrangement of 2-methoxy-4-methylquinoline to the *N*-methyl-2-quinolone; Conrad and Limpach[6] the rearrangement of 4-methoxy-2-methylquinoline to the *N*-methyl-4-quinolone; and Meyer[7,8] reported a number of instances of similar rearrangements, usually induced by bulk heating around 300°C. Lehmstedt[9] studied the reactions of molten 9-methoxyacridine at 200°, and noted that the hydrate formed mainly acridin-9(10*H*)-one, whereas the anhydrous material formed an 80 : 20 mixture of 10-methylacridin-9(10*H*)-one and acridin-9(10*H*)-one. Like the more recent reports of methyl group migrations reported by Martinez-Diaz[10] in the solid or liquid phase, these reactions are all likely to be bimolecular,[10] and probably occur by pathways



Scheme 1.



Scheme 2.

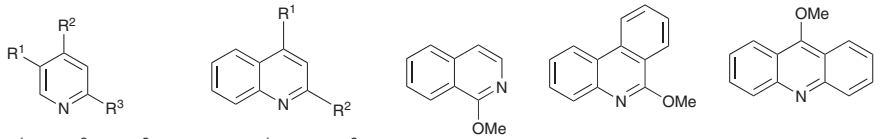
analogous to that shown in Scheme 2. The condensed-phase methyl migrations have been subjected to kinetic[11,12] and theoretical[11] studies at the restricted Hartree–Fock level with a 3–21G basis set, and it is concluded that a bimolecular, highly ordered mechanism applies.

Since bimolecular reactions in the vapour phase at low pressures are highly unlikely, a cyclic, four-centre mechanism appears likely under these conditions, and accordingly we have investigated the possible vapour-phase rearrangement of a number of alkoxyhetarenes in order to clarify the processes involved.

Discussion

The alkoxyhetarenes (2)–(12), Scheme 3, were synthesized by reaction of the corresponding chloro compound with the sodium alkoxide. Each compound was subjected to FVP at 600°C, a temperature chosen because all compounds reacted

 10.1071/CH03044 0004-9425/03/090913



	R^1	R^2	R^3
(2)	H	H	OMe
(3)	NO_2	H	OMe
(4)	H	H	OEt
(5)	H	OMe	H

	R^1	R^2
(6)	H	OMe
(7)	Me	OMe
(8)	H	OEt
(9)	OMe	Me

(10) (11) (12)

Scheme 3.

Table 1. Products of flash vacuum pyrolysis of (2)–(11) at 600°C

Compound	% OR after FVP[A]	% NR after FVP[A]
2-methoxypyridine (2)	40	60
2-methoxy-5-nitropyridine (3)	90	10
2-ethoxypyridine (4)	40	60
4-methoxypyridine (5)	100	0
2-methoxyquinoline (6)	50	50
2-methoxy-4-methylquinoline (7)	65	35
2-ethoxyquinoline (8)	1	6[B]
4-methoxy-2-methylquinoline (9)	0	0[C]
1-methoxyisoquinoline (10)	30	70
6-methoxyphenanthridine (11)	70	30
9-methoxyacridine (12)	0	0[D]

[A] Percentage of pyrolysate, which was usually about 90% of that expected.
[B] 93% quinolin-2(1*H*)-one.
[C] 100% 2-methylquinolin-4(1*H*)-one.
[D] 100% acridone.

somewhat at this temperature, and the extent of reaction would allow some estimation of the relative ease of reaction. The results of the pyrolyses are collected in Table 1.

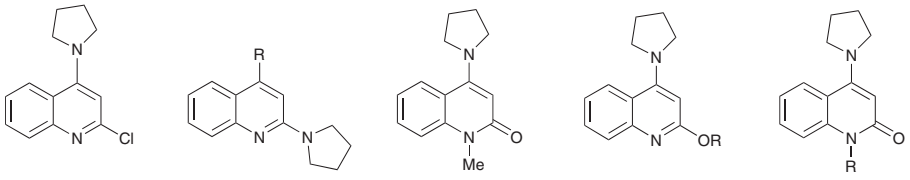
Each of the heterocycles with a methoxy group adjacent to the nitrogen atom underwent conversion to the corresponding *N*-methyl amide to some extent, consistent with our original hypothesis.[1] The 4-methoxyquinoline derivative (9) was totally demethylated, and 4-methoxypyridine (5) was recovered unchanged. 9-Methoxyacridine (12) was quantitatively demethylated to acridin-9(10*H*)-one, and careful GC-MS analysis failed to obtain any evidence for the presence of 10-methylacridone. In view of the evidence of Lehmstedt[9] of the lability of the 9-methoxyacridine towards acids, we assumed the demethylation was probably due to the presence of acidic sites on the silica tube or packing, but prior treatment of the tube with chlorotrimethylsilane failed to alter this observation in any way. Since the methoxyacridine was anhydrous,[9] we again conclude that the results observed by Lehmstedt are indicative of bimolecular reactions similar to Scheme 2. The failure to observe any *N*-methylated products from 4-methoxyhetarenes in the FVP experiments suggests the transformation of 2-methoxyhetarenes is intramolecular. Definite evidence to support this hypothesis was obtained by carrying out the FVP of a mixture of 2-ethoxypyridine and 2-methoxyisoquinoline. In this case, to avoid differential sublimation rates into the pyrolysis tube, the mixture was initially dissolved in chlorobenzene, and the solution dropped into the pyrolysis tube at 700°C. Careful GC-MS and NMR analysis of the products showed there was no crossover of alkyl groups, as might be expected in a bimolecular process. The 1-methoxyisoquinoline was 60% converted to *N*-methylisoquinolin-2-one, and 2-ethoxypyridine was 65% converted to *N*-ethylpyridin-2-one; no *N*-ethylisoquinolin-2-one or *N*-methylpyridin-2-one could be observed.

We also attempted to observe the rearrangement of a number of *O*-methyl imidates to the corresponding *N*-methyl amides in solution or in the molten state by heating solutions in diphenylmethane at 255°C for 5 h (compounds (3), (6), and (10)), or neat in evacuated sealed tubes at 255°C for 2 h (compounds (2), (6), and (10)). In no instance could any of the *N*-methyl amide be observed by ^{1}H NMR spectroscopy. However, 1-methoxyisoquinoline (10) and 2-methoxy-4-methylquinoline (7) did undergo isomerization when heated in a sealed tube to 320°C for 8 h (90% and 10% conversion, respectively); 2-methoxyquinoline (6) and 6-methoxyphenanthridine (11) did not react under these conditions.

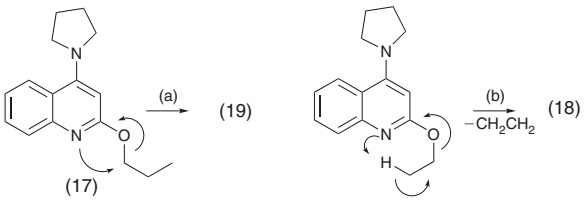
Since the above experiments clearly showed that under FVP conditions at 600°C, suitable heterocyclic *O*-methyl ethers could be partially rearranged to the *N*-methyl amide isomers by an intramolecular reaction, it remained to clarify why none of the hypothetical precursor, 6-methoxyphenanthridine, had been observed in the pyrolysis depicted in Scheme 1. When the pyrolysis temperature for 6-methoxyphenanthridine was increased to 700°C, the conversion of 6-methoxyphenanthridine to *N*-methylphenanthridone increased to 70%. It is possible that the failure to observe the former in the pyrolysis of (1) at this temperature[1] is due to chemical activation in this case: the decomposition of the triazole gives a diradical which rearranges in a highly exothermic process.*

We have been able to put this rearrangement to good use in some related work. The treatment of 2,4-dichloroquinoline with one equivalent of pyrrolidine in ethanol gave an almost equal mixture of compounds (13) and (14), Scheme 4. In view of the reports by Mekheimer[13,14] and Brown,[15] that the 4-chloro group is much more rapidly displaced by amines than the 2-chloro, these results were unexpected, although the solvents used were different. While the structures could be tentatively assigned by the observation that H3 in (13) resonated at higher field (δ 6.40) than H3 in (14) (δ 6.83),

* The authors are grateful to a referee for this suggestion.



Scheme 4.



Scheme 5.

Table 2. Predicted bond orders and bond lengths for the transition state

Bond[A]	Length [Å]	Order
1–2	1.345	1.339
2–3	1.398	1.456
3–4	1.410	1.367
4–5	1.380	1.548
5–6	1.430	1.161
6–1	1.375	1.188
6–7	1.286	1.405
7–8	2.068	0.374
1–8	2.100	0.322

[A] Bond numbering follows Diagram 1.

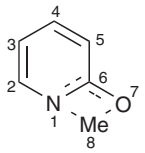


Diagram 1.

as expected on the basis of more efficient electron release from the pyrrolidino group into C3 in (13) than in (14); this was confirmed by treating (13) with sodium methoxide to give (15), which underwent rearrangement to the *N*-methylquinolone (16) on FVP at 600°C. Initially (13) was converted to the ethoxy derivative (17), which underwent FVP essentially exclusively to the quinolone (18) at 600°C; the *N*-ethylquinolone (19) was not present. Compound (20), prepared from (14) and sodium methoxide, failed to give any *N*-methylated material on FVP, and mainly decomposed at 600°C.

The pyrolysis products from (8) and (17) indicate that the presumed four-centre pathway (a), Scheme 5, has a higher activation energy than pathway (b), consistent with the facile elimination of ethylene by a six-membered cyclic mechanism.[16] While such a four-centre mechanism has been postulated previously for the condensed phase rearrangement of pseudosaccharin ethers and their mass spectral rearrangement,[17] we have obtained supporting evidence for the transition state in the vapour phase by semi-empirical calculations (Spartan, AM1), as summarized in Table 2. The transition state is essentially planar (Me─N─C_6─O dihedral angle 0.003°, see Diagram 1), and the reaction has an activation enthalpy of 323 kJ mol^{-1}, consistent with the high rearrangement temperature required.

Finally, we believe the elimination of ethylene from the 2-ethoxyquinoline derivatives (8) and (17), but not from 2-ethoxypyridine (4), may be a consequence of the greater volatility of the latter, and hence its shorter residence time in the pyrolysis tube. It is also possible that rearrangement must precede elimination of ethylene, but such considerations are beyond the scope of this study.

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini spectrometer at 300 and 75.5 MHz, respectively, in $CDCl_3$ unless otherwise stated. High-resolution mass spectra were recorded on a Kratos MS25RF spectrometer or at Monash University, Melbourne. Melting points were determined on a Reichert hot-stage apparatus and remain uncorrected. Radial chromatography was performed with silica gel 60 PF_{254} coated glass rotors using a Chromatotron (model 7924T). GC-MS analysis was performed on a Varian Saturn 4D instrument, using a 5% phenylmethyl polysiloxane column (30 m × 0.25 mm ID × 0.25 mm). Flash vacuum pyrolysis was carried out by slowly subliming the substrate through a silica tube (400 mm ×25 mm, packed with silica chips and heated to the quoted temperature) under reduced pressure (0.01 mmHg). The products were collected in a liquid nitrogen cold trap, and analyzed by means of GC-MS and NMR spectroscopy, followed by chromatographic isolation.

Alkoxy Heterocycles

The commercially available chloro compound (1 g) was refluxed in a solution of sodium methoxide (from 0.8 g Na) in methanol (8 mL) for 6 h. The solvent was removed, water (20 mL) added, and the product extracted with ether. The product was then purified by distillation or chromatography on silica. The identity of all compounds was confirmed by ^{1}H and ^{13}C NMR spectroscopy, by GC-MS, and by comparison with literature data. Ethoxy compounds were prepared analogously, substituting ethanol for methanol.

Relevant NMR chemical shifts: δ_H (2) 3.88 (OMe), 3.56 (NMe); (3) 4.08 (OMe), 3.69 (NMe); (4) 3.80 (OEt), 3.42 (NEt); (5) 3.92 (NMe), 3.82 (OMe); (6) 3.98 (OMe), 3.59 (NMe); (7) 4.04 (OMe), 3.67 (NMe); (8) 4.55 (OEt), 4.30 (NEt); (9) 4.01 (OMe), 3.72 (NMe); (10) 4.11 (OMe), 3.54 (NMe); (11) 4.22 (OMe), 3.75 (NMe); (12) 4.25 (OMe), 3.90 (NMe).

Thermolyses in Condensed Phase

(a) A sample of the methyl ether (ca. 100 mg) was heated in diphenylmethane (0.5 mL) under nitrogen at 255°C for 5 h. The product was analyzed directly by means of GC-MS. (b) The methyl ether (ca. 100 mg) was melted and heated in the absence of any solvent at 255°C in an evacuated sealed tube for 5 h, and the reaction mixture analyzed by means of ^{1}H NMR spectroscopy and by GC-MS. (c) A sample of the

methyl ether (ca. 100 mg) was heated in an evacuated sealed tube at 320°C for 8 h and analyzed by means of ^{1}H NMR spectroscopy and by GC-MS.

'Crossover' Reaction

A solution of 1-methoxyisoquinoline (100 mg) and 2-ethoxypyridine (100 mg) in chlorobenzene (600 μL) was dropped slowly, over 10 min, into the vertical silica packed column, used above (0.01 mm, 700°C). The total contents of the trap and column washings were analyzed by means of GC-MS.

Pyrolysis of 2-Ethoxyquinoline

2-Ethoxyquinoline (100 mg, 5.78 mmol) was pyrolyzed under FVP conditions (600°C, 130°C, 0.1 mm Hg). NMR spectrometry was used to analyze the mixture of products obtained from the pyrolysis tube. The major product (92%) was identified as quinolin-2-one. δ_H 8.30–7.30 (5 H, m), 6.30 (1 H, d, *J* 7.5). The second product (8%) was identified as *N*-ethylquinolin-2-one. δ_H 7.80–7.10 (5 H, m), 6.72 (1 H, d, *J* 9), 4.37 (2 H, q, *J* 7), 1.38 (3 H, t, *J* 7.2). δ_C 166.7, 141.0, 139.0, 138.6, 130.6, 127.7, 122.7, 121.3, 37.3, 12.7.

Reaction of 2,4-Dichloroquinoline with Pyrrolidine

Pyrrolidine (0.75 mL, 9.0 mmol) was added to a solution of 2,4-dichloroquinoline (1.4 g, 7.07 mmol) in ethanol (5 mL), and the mixture refluxed for 2 h. The solvent was evaporated and saturated sodium carbonate (40 mL) added to the residue which was extracted with dichloromethane (2 × 40 mL). The extract was dried and evaporated. NMR analysis indicated the presence of equal quantities of the two mono-substitution products. The product was purified by radial chromatography, eluting with ether/light petroleum (50 : 50). The first fraction (10%) was unreacted starting material. The second fraction (567 mg, 35%) was *4-chloro-2-pyrrolidinoquinoline*, pale yellow crystals, mp 76–79°. (Found: M^+ 232.0770. $C_{13}H_{13}N_2Cl$ requires M^+ 232.0767). δ_H 7.97 (1 H, dd, *J* 8.1, 1.5), 7.69 (1 H, d, *J* 8.9), 7.55 (1 H, dd, *J* 6.9, 1.5), 7.24 (1 H, dd, *J* 6.9, 1.5), 6.84 (1 H, s), 3.59 (4 H, m), 2.04 (4 H, m). δ_C 155.0, 148.9, 142.7, 130.3, 126.4, 124.0, 121.9, 120.6, 109.9, 46.9, 25.4. The third fraction (326 mg, 20%) was *2-chloro-4-pyrrolidinoquinoline*, colourless needles, mp 99–101°. (Found: M^+ 232.0768. $C_{13}H_{13}N_2Cl$ requires M^+ 232.0767). δ_H 8.19 (1 H, d, *J* 8.7), 7.88 (1 H, dd, *J* 8.4, 1.5), 7.58 (1 H, dd, *J* 6.9, 1.5), 7.33 (1 H, dd, *J* 6.9, 1.5), 6.42 (1 H, s), 3.71 (4 H, m), 2.06 (4 H, m). δ_C154.0, 151.2, 149.3, 129.3, 128.7, 124.9, 123.3, 119.9, 101.7, 52.1, 25.8. Mass spectrum *m*/*z* 232 (M^+, 100%), 203 (28), 189 (12), 162 (11), 140 (6), 128 (11), 101 (18), 75 (11), 43 (8).

2-Ethoxy-4-pyrrolidinoquinoline

2-Chloro-4-pyrrolidinoquinoline (100 mg) was reacted with sodium ethoxide as above at 80°C for 16 h. The solvent was evaporated, and the residue was extracted with ethyl acetate, and the extract washed with water, dried and evaporated to give the *title compound* (100 mg, 95%), which was used directly in the next experiment. (Found: M^+ 242.1419. $C_{15}H_{18}N_2O$ requires M^+ 242.1419). δ_H 8.10–7.10 (4 H, m), 5.97 (1 H, s), 4.45 (2 H, q, *J* 7.0), 3.59 (4 H, t, *J* 6.9), 2.02 (4 H, t, *J* 6.9), 1.42 (3 H, t, *J* 7.0). Mass spectrum *m*/*z* 242 (M, 73%), 227 (100), 214 (59), 198 (36), 185 (32), 171 (13), 145 (11), 116 (17), 84 (25), 70 (11), 51 (8).

Pyrolysis of 2-ethoxy-4-pyrrolidinoquinoline

2-Ethoxy-4-pyrrolidinoquinoline (100 mg, 0.41 mmol) was pyrolyzed under FVP conditions (750°C, 130°C, 0.1 mm Hg) and the only product, *4-pyrrolidinoquinolin-2(1H)-one*, a white solid, mp 199–201°, was collected from the pyrolysis tube. (Found: M^+ 214.1110. $C_{13}H_{14}N_2O$ requires M^+ 214.1106). δ_H 8.10–7.00 (4 H, m), 6.4 (1 H, s), 3.74 (4 H, t), 2.05 (4 H, t).

2-Methoxy-4-pyrrolidinoquinoline

A concentrated solution of sodium methoxide was prepared by dissolving solid sodium (1.0 g) in methanol (10 mL). To this was added a solution of 2-chloro-4-pyrrolidinoquinoline (250 mg, 1.08 mmol) in methanol (5 mL), and the mixture refluxed for 3 h. The solvent was evaporated and the residue shaken with water (30 mL) and extracted with ether (2 × 25 mL). The extract was dried and evaporated to give the *title compound* (160 mg, 65%) as a pale yellow oil. (Found: M^+ 227.1202. $C_{14}H_{16}N_2O$ requires M^+ 228.1263). δ_H 8.11 (1 H, dd, *J* 8.7, 1.5), 7.77 (1 H, dd, *J* 8.1, 1.5), 7.51 (1 H, dd, *J* 6.9, 1.5), 7.21 (1 H, dd, *J* 6.9, 1.5), 6.00 (1 H, s), 4.03 (1 H, s), 3.62 (4 H, m), 2.01 (4 H, m). δ_C 164.6, 155.1, 148.5, 128.6, 127.8, 124.9, 121.4, 119.9, 91.9, 53.0, 52.0, 25.9, Mass spectrum *m*/*z* 227 (M^+, 100%), 199 (29), 185 (10), 169 (7), 128 (15), 115 (17), 84 (40), 75 (9), 41 (12).

Pyrolysis of 2-methoxy-4-pyrrolidinoquinoline

2-Methoxy-4-pyrrolidinoquinoline (100 mg, 0.44 mmol) was pyrolyzed under FVP conditions (600°C, 130°C, 0.1 mm Hg). ^{1}H NMR analysis of the combined pyrolysate showed the presence of the starting material (60%) and a single product (30%). *N-Methyl-4-pyrrolidino-2-quinolone* was purified by column chromatography as a pale pink oil. (Found: M^+ 227.1240. $C_{14}H_{16}N_2O$ requires M^+ 228.1263). δ_H 7.99 (1 H, dd, *J* 8.9, 1.5), 7.51 (1 H, dd, *J* 7.2, 1.5), 7.33 (1 H, dd, *J* 8.9, 1.7), 7.14 (1 H, dd, *J* 7.2, 1.5), 5.86 (1 H, s), 3.65 (3 H, s), 3.59 (4 H, m), 1.99 (4 H, m). δ_C 163.4, 155.2, 154.3, 129.9, 126.2, 120.2, 117.5, 114.6, 97.6, 52.1, 25.8, 25.7.

Acknowledgments

The authors are grateful for support of this project by the Australian Research Council.

References

[1] J. Khalafy, R. H. Prager, *Aust. J. Chem.* **1998**, *51*, 925.
[2] C. G. McCarty, L. A. Garner, in *Amides and Imidates* (Ed. S. Patai) **1975**, ch. 4 (Wiley: New York, NY).
[3] G. T. Reynolds, C. J. M. Nagel, P. A. Larson, *J. Chem. Res. Synop.* **1982**, 310.
[4] C. Haitinger, F. Lieben, *Monatsh. Chemie* **1885**, *6*, 279.
[5] K. Knorr, *Liebigs Ann. Chem.* **1886**, *236*, 107.
[6] M. Conrad, L. Limpach, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 948.
[7] H. Meyer, R. Beer, *Monatsh. Chemie* **1906**, *27*, 259. H. Meyer, R. Beer, *Monatsh. Chemie* **1907**, *28*, 47.
[8] H. Meyer, R. Beer, *Monatsh. Chemie* **1913**, *34*, 1137.
[9] K. Lehmstedt, *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 1455.
[10] V. M. Martinez-Diaz, S. Rodriguez-Morgade, W. Schafer, T. Torres, *Tetrahedron* **1993**, *49*, 2261.
[11] M. Dessolin, O. Eisenstein, M. Golfier, T. Prange, P. Sautet, *J. Chem. Soc., Chem. Commun.* **1992**, 132.
[12] D. J. Brown, R. V. Foster, *J. Chem. Soc.* **1965**, 4911.
[13] R. Mekheimer, *J. Chem. Soc., Perkin Trans 1* **1999**, 2183.
[14] R. Mekheimer, *Synthesis* **2000**, 2078.
[15] R. Brown, R. Harcourt, *J. Chem. Soc.* **1959**, 3431.
[16] H. Hettler, H. Neygenfind, *Tetrahedron Lett.* **1966**, 6031.
[17] H. Hettler, *Tetrahedron Lett.* **1968**, 1793.