ELSEVIER

Journal of Fluorine Chemistry 80 (1996) 31–34

JOURNAL OF FLUORINE CHEMISTRY

Formation of the *N*-oxides of heteroaromatic nitrogen compounds by perfluorinated oxaziridines

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Accepted 2 April 1996

Abstract

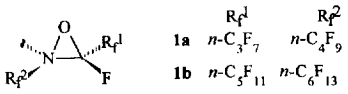
On treatment with perfluoro-*cis*-2,3-dialkyloxaziridines, mono-, bi-, and tricyclic nitrogen heteroaromatics afford the corresponding *N*-oxides under mild reaction conditions and in medium to high yields. The course of the reaction is not altered by the presence of various residues on the ring or in side chains and the *N*-oxides of polyfunctional, naturally occurring compounds have been prepared.

Keywords: Perfluorinated oxaziridines; *N*-Oxide; *N*-Imine; Oxidation; Heterocycle

1. Introduction

Perfluorinated oxaziridines undergo isomerization or cycloaddition reactions [1] and work as aminating [2] and oxygenating [3] agents. The type of reactivity depends on the nature of both the oxaziridine and the substrate. For instance, a fluoride anion attacks only the nitrogen of 2-trifluoromethyl-3,3-difluorooxaziridine [2a] while it is reactive at both nitrogen and carbon with 2-pentafluorothio-3,3-difluorooxaziridine [2b]. Furthermore, 2-trifluoromethyl-3,3-difluorooxaziridine affords 1,3-oxazolidines with fluorinated olefins (cycloaddition reaction) and epoxides with hydrocarbon olefins (epoxidation reaction).

Recently we have studied the reactivity of perfluoro-*cis*-2,3-dialkyloxaziridines **1a,b**. These compounds have been shown to oxidize secondary alcohols and ethers to the corresponding ketones, aliphatic and aromatic sulfides to sulfoxides and sulfones. More interestingly, they have been used for the regio-, diastereo-, and enantioselective oxyfunctionalization of unactivated tertiary hydrocarbon sites and of di- or trisubstituted silanes [4]. In this paper we describe how various pyridines and their benzo fused derivatives afford the corresponding *N*-oxides when reacted with oxaziridines **1**. In order to prove the general usefulness of the approach, the *N*-oxides of some polyfunctional and bioactive natural compounds have been prepared. Interest in the reaction described comes from the fact that the *N*-oxides of heteroaromatic nitrogen compounds are useful synthetic intermediates [5], naturally occurring alkaloids [6], and metabolic products of commonly employed drugs [7] (Scheme 1).



	R_f^1	R_f^2
1a	n-C_3F_7	n-C_4F_9
1b	n-C_5F_{11}	n-C_6F_{13}

Scheme 1. Formulae.

2. Results and discussion

When pyridine derivatives **2a–g** were treated with an equimolecular amount of the perfluoro-2-*n*-butyl-3-*n*-propyloxaziridine **1a**, at −60 °C and in halogenated solvent, the corresponding *N*-oxides **3a–g** have been obtained in medium to high yields (Scheme 2). Similarly to what has been observed in the oxidation of alcohols, olefins, and hydrocarbons [4a,b,d], azaalkene **4a** was formed as a 'coproduct'. No substantial difference was observed when the oxidation of **2a, d, h, r** was performed with the perfluoro-2-*n*-hexyl-3-*n*-pentyloxaziridine **1b**. Using the same experimental procedure, oxidation of bi- and tricyclic compounds **2h–l** with stoichiometric amounts of the oxaziridine **1a** afforded *N*-oxides **3h–l** in good yields (Scheme 3).

To further test the compatibility of functional groups in the formation of *N*-oxides of six-membered heteroaromatics, the reaction of some natural polyfunctional substrates has been studied. Pyridoxine **2m** is one of the vitamins of the B_6 complex and papaverine **2p** is a well known alkaloid endowed with pharmacologically useful smooth muscle relaxant prop-

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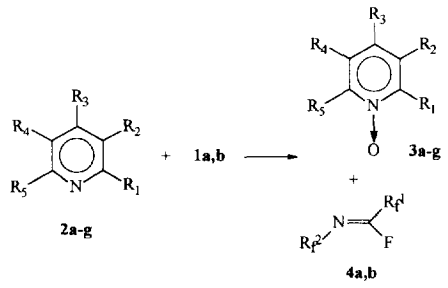
PII S0022-1139(96)03456-2



2a-g + 1a,b → 3a-g + 4a,b

2, 3a $R_1 = CH_3$; $R_2 = R_3 = R_4 = R_5 = H$

2, 3b $R_1 = CH_2CH_3$; $R_2 = R_3 = R_4 = R_5 = H$

2, 3c $R_1 = (CH_2)_2CH_3$; $R_2 = R_3 = R_4 = R_5 = H$

2, 3d $R_1 = (CH_2)_2CH{=}CHCH_3$; $R_2 = R_3 = R_4 = R_5 = H$

2, 3e R_1 = CO-2-pyridyl, $R_2 = R_3 = R_4 = R_5 = H$

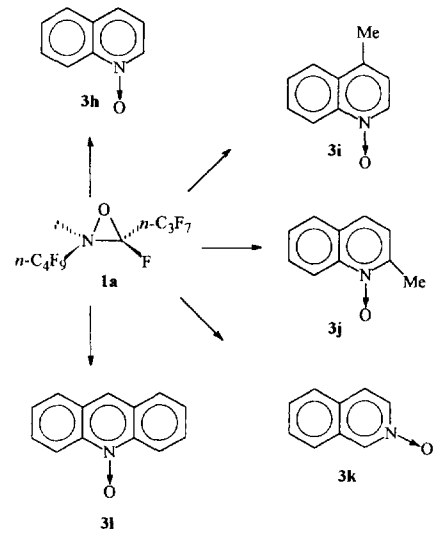
2, 3f $R_1 = CH_3$; $R_4 = COOCH_3$; $R_2 = R_3 = R_5 = H$

2, 3g $R_1 = R_3 = R_5 = CH_3$; $R_2 = R_4 = H$

1a, 4a $R_f^1 = n\text{-}C_3F_7$; $R_f^2 = n\text{-}C_4F_9$

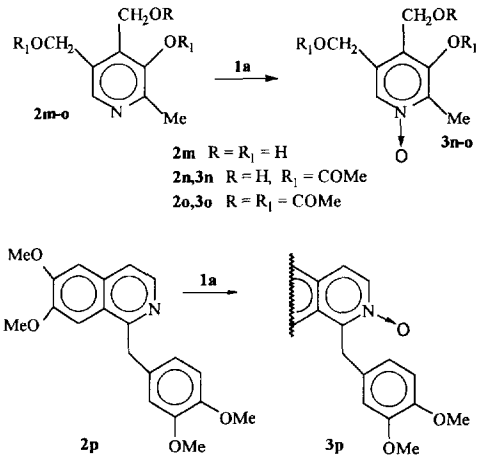
1b, 4b $R_f^1 = n\text{-}C_5F_{11}$; $R_f^2 = n\text{-}C_6F_{13}$

Scheme 2.



Scheme 3.

erties. When di-*O*-acetylpyridoxine (**2n**) and the tri-*O*-acetyl analogue (**2o**) have been treated with an equimolecular amount of the oxaziridine **1a** the corresponding *N*-oxides (**3n,o**) have been isolated in good yield and a similar selective formation of the *N*-oxide was obtained starting from papaverine (**2p**) (Scheme 4). Nikethamide (**2q**) is a central and respiratory stimulant commonly used for human therapy and on reaction with **1a** the corresponding *N*-oxide **3q** [7] was formed in medium yields (Scheme 5). It is interesting to observe that starting from nikethamide **2q** minor amounts of the pyridinium *N*-imine **5q** were also isolated (**3q**:**5q** ratio 3:1). The formation of both oxidation and amination products occurred also when 4-acetylpyridine **2r** was treated with **1a** or **1b**. The perfluorobutyryl- or perfluoro-*n*-hexanoyl-*N*-imines, **5r** and **5s**, respectively were in fact isolated along with the *N*-oxide **3r**.



2m-o → 3n-o (1a)

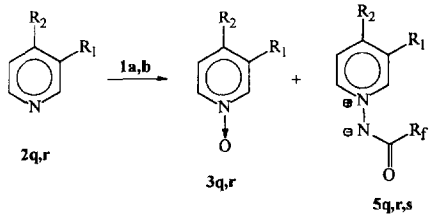
2m $R = R_1 = H$

2n,3n $R = H$, R_1 = COMe

2o,3o $R = R_1$ = COMe

2p → 3p (1a)

Scheme 4.



2q,r → 3q,r + 5q,r,s (1a,b)

2q, 3q R_1 = $CONEt_2$; $R_2 = H$

2r, 3r $R_1 = H$; R_2 = COMe

5q R_1 = $CONEt_2$; $R_2 = H$; $R_f = n\text{-}C_3F_7$

5r $R_1 = H$; R_2 = COMe; $R_f = n\text{-}C_3F_7$

5s $R_1 = H$; R_2 = COMe; $R_f = n\text{-}C_5F_{11}$

Scheme 5.

The structure of pyridinium *N*-imines **5** was established by spectroscopic and analytical data. In ^{19}F and ^1H-NMR spectra the signals of a perfluorinated chain and of an aromatic system were observed, respectively. A direct indication of the presence of a ylide-like moiety was that in **5r** the UV absorption occurring at 280 nm in methanol solution underwent a strong negative solvatochromism. This is consistent with an intramolecular charge transfer process and is typical for pyridinium *N*-imines [8]. A linear correlation between absorption wavelength and polarity of the solvent (Dimroth R_T parameter) was observed (Fig. 1) [9].

The results obtained deserve some general comments. Oxaziridines **1a,b** perform the oxygenation of mono-, bi-, and tricyclic nitrogen heteroaromatics to corresponding *N*-oxides and the presence of one to four substituents on the ring do not change the reaction course. While olefin and alcohol moieties are known to be oxidized by perfluorinated oxaziridines **1** [4a,d], these functionalities remain unaffected in substrates **2d** and **2n**, respectively. Under the reaction conditions adopted, a selective oxygenation at the nitrogen atom of pyridine substrates can therefore be realized in the presence of alkyl, alkenyl, hydroxy, and oxycarbonyl groups. The reaction conditions used are very mild and other reagents

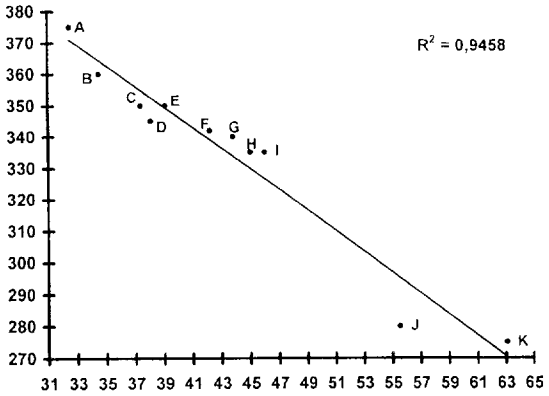


Fig. 1. Dependence of absorption wavelength of *N*-imine **5r** on the polarity of the solvent (Dimroth R_T parameter): A = carbon tetrachloride, B = benzene, C = tetrahydrofurane, D = ethyl acetate, E = chloroform, F = acetone, G = dimethyl formamide, H = dimethyl sulfoxide, I = acetonitrile, J = methanol, K = water.

commonly used to perform the same transformation either require more drastic conditions (hydrogen peroxide, peracids, hydroperoxides, sodium perborate) [10] or have a limited shelf life (dioxiranes) [11].

When no *ortho* substituents are present on the pyridine ring (compounds **2q,r**), oxaziridines **1** behave as both oxygenating and aminating reagents. In this respect it is interesting to remember that hydrocarbon oxaziridines can also either oxygenate or aminate a nitrogen atom [12], the former process being favoured by the presence of bulky or electron withdrawing substituents on the nitrogen of the three-membered ring [13]. Perfluorinated residues are both sterically demanding and electron withdrawing groups; these characteristics can therefore explain the good oxidizing properties of perfluorinated oxaziridines **1**. Furthermore, moving from the observation that oxygenation of a given substrate is favoured with respect to its amination by the presence of bulky residues on the oxaziridine, it becomes reasonable that the increase of steric hindrance on the heteroaromatic substrate through the presence of substituents on the *ortho* position(s) also favours the oxidative abilities of a given oxaziridine.

3. Experimental

NMR spectra were recorded on a Bruker AC 250 spectrometer in $CDCl_3$ solution with TMS as internal standard for ^1H and $CFCl_3$ for ^{19}F, *J* are in Hz. Mass spectra were recorded with a VG-70EQ apparatus; IR spectra with Perkin Elmer 2000 FT-IR and UV spectra with Jasco Uvidec-510. Flash chromatographies were performed with silica gel 60 (60–200 μm, Merck). Microanalyses were performed by Redox Snc, Cologno Monzese, Milano, Italy.

3.1. General procedure. Preparation of 2-(3-pentenyl)-pyridine N-oxide (3d) with perfluoro-cis-2-n-butyl-3-n-propyloxaziridine (1a)

To a solution of 2-(3-pentenyl)pyridine ((*E*)/(*Z*) mixture, **2d**) (100 mg, 0.68 mmol) in $CHCl_3$ (0.3 ml) was added a solution of the oxaziridine **1a** (368 mg, 0.82 mmol) in $CFCl_3$ (0.3 ml) at −60 °C. After stirring for 30 min at the same temperature, the reaction was quenched by the addition of perfluoro-tributylamine. The mixture was stirred, then allowed to warm to room temperature. The perfluorinated layer was extracted with $CHCl_3$ and combined organics were evaporated under reduced pressure. The residue was flash chromatographed (AcOEt/MeOH, 9:1) to give 2-(3-pentenyl)pyridine *N*-oxide in pure form ((*E*)/(*Z*) mixture **3d**, 85 mg, 77% yield): ^1H NMR ($CDCl_3$) δ: 1.57 and 1.64 (d each, 3H, CH_3); 2.43 (m, 2H, CH_2); 3.0 (t, 2H, CH_2); 5.47 (m, 2H, CH=CH); 7.19 (m, 3H, H-3, H-4, H-5); 8.27 (m, 1H, H-6) ppm. IR (neat) (cm^{-1}): 1230 (N–O str.). MS (EI) *m/z*: 163 (M^+); 147 [$(M-O)^+$].

A similar procedure was employed when perfluoro-*cis*-2-*n*-hexyl-3-*n*-pentyloxaziridine (**1b**) was used and **3d** was isolated in 80% yield.

Di-(2-pyridyl)ketone *N*-oxide (**3e**, 50% yield): ^1H NMR ($CDCl_3$) δ: 7.40–7.50 (m, 4H, H-3, H-3', H-4', H-5'); 7.92 (m, 1H, H-4); 8.11 (d, 1H, H-5); 8.19 (t, 1H, H-2'); 8.60 (d, 1H, H-2). IR (KBr) (cm^{-1}): 1689 (C=O str.); 1257 (N–O str.). MS (CI isobutane) *m/z*: 201 [$(M+1)]^+$].

Methyl 6-methylnicotinate *N*-oxide (**3f**, 71% yield): ^1H NMR ($CDCl_3$) δ: 2.6 (s, 3H, CH_3); 3.96 (s, 3H, OCH_3); 7.35 (d, 1H, $J=6$ Hz, H-3); 7.78 (d, 1H, $J=6$ Hz, H-4); 8.85 (s, 1H, H-6) ppm. IR (KBr) (cm^{-1}): 1720 (C=O str.); 1305 (C–O str.); 1240 (N–O str.). MS (EI) *m/z*: 167 (M^+); 150 [$(M-OH)^+$].

Di-*O*-acetylpyridoxol *N*-oxide (**3n**, 60% yield): ^1H NMR ($CDCl_3$) δ: 2.03 (s, 3H, CH_3); 2.32 (s, 3H, CH_3CO); 2.39 (s, 3H, CH_3CO); 4.78 (s, 2H, CH_2OH); 5.08 (s, 2H, CH_2OAc); 8.3 (s, 1H, H-6). IR (KBr) (cm^{-1}): 1775 and 1739 (C=O str.); 1112 (N–O str.). MS (EI) *m/z*: 269 (M^+); 209 [$(M-CH_3COOH)^+$].

Papaverine *N*-oxide (**3p**, 82% yield): ^1H NMR ($CDCl_3$) δ: 3.82 (s, 6H, 2 OCH_3); 3.97 (s, 3H, OCH_3); 4.01 (s, 3H, OCH_3); 4.77 (s, 2H, CH_2); 6.76 (s, 1H, ring C proton); 6.79 (d, 1H, ring C proton, $J=2$ Hz); 7.02 (d, 1H, ring C proton, $J=2$ Hz); 7.05 (s, 1H, H-5); 7.22 (s, 1H, H-8); 7.43 (d, 1H, H-4, $J=7$ Hz); 8.18 (d, 1H, H-3, $J=7$ Hz). MS (EI) *m/z*: 355 (M^+); 338 [$(M-OH)^+$].

N,N-Diethylnicotinamide *N*-oxide (**3q**, 29% yield): ^1H NMR ($CDCl_3$) δ: 1.21 (m, 3H, CH_3); 1.29 (m, 3H, CH_3); 3.28 (m, 2H, NCH_2); 3.52 (m, 2H, NCH_2); 7.25 (d, 1H); 7.35 (m, 1H); 8.24 (s, 2H, H-2, H-6) ppm. IR (neat) (cm^{-1}): 1635 (C=O str.); 1250 (N–O str.). MS (EI) *m/z*: 194 (M^+); 178 [$(M-O)^+$]; 177 [$(M-OH)^+$].

3-(*N,N*-Diethylcarbamoyl)pyridinium-*N*-perfluorobutyryl-imine (**5q**, 11% yield): Analysis: Calcd. for $C_{14}H_{14}F_7N_3O_2$ (389.26): C, 43.20; H, 3.62; F, 34.16; N, 10.80; O, 8.22%. Found: C, 43.32; H, 3.80; F, 34.09; N, 10.53; O, 8.23%. ^1H NMR ($CDCl_3$) δ: 1.14 (m, 3H, CH_3); 1.24 (m, 3H, CH_3); 3.24 (m, 2H, NCH_2); 3.55 (m, 2H, NCH_2); 7.8 (t, 1H, H-5); 8.06 (dd, 1H, H-4); 8.68 (dd, 1H, H-6); 8.82 (s, 1H, H-2) ppm. ^{19}F NMR ($CDCl_3$) δ: −81.89

(t, 3F, CF_3, $J=9$ Hz); −120.03 (q, 2F, CF_2, $J=9$ Hz); −128.01 (br s, 2F, CF_2) ppm. MS (EI) m/z: 389 (M^+).

4-Acetylpyridinium-*N*-perfluoro-butyryl-imine (**5r**, 30% yield): Analysis: Calcd. for $C_{11}H_7F_7N_2O_2$ (332.18): C, 39.77; H, 2.12; F, 40.03; N, 8.43; O, 9.63%. Found: C, 39.88; H, 2.20; F, 39.62; N, 8.27; O, 9.50%. ^{1}H NMR ($CDCl_3$) δ: 2.74 (s, 3H, $COCH_3$); 8.2 (d, 2H, $J=6$ Hz, H-3, H-5); 9.0 (d, 2H, $J=6$ Hz, H-2, H-6) ppm. ^{19}F NMR ($CDCl_3$) δ: −81.9 (t, 3F, CF_3); −120 (q, 2F, CF_2); −128 (s, 2F, CF_2) ppm. IR (KBr) (cm^{-1}): 1705 (MeC=O str.); 1640 (NC=O str.). MS (CI isobutane) m/z: 333 [(M+1)]$^+$].

4-Acetylpyridinium-*N*-perfluoro-*n*-hexanoyl-imine (**5s**, 22% yield): Analysis: Calcd. for $C_{13}H_7F_{11}N_2O_2$ (432.18): C, 36.13; H, 1.63; F, 48.35; N, 6.48; O, 7.40%. Found: C, 36.30; H, 1.50; F, 48.23; N, 6.61; O, 7.25%. ^{1}H NMR ($CDCl_3$) δ: 2.73 (s, 3H, $COCH_3$); 8.17 (d, 2H, $J=7$ Hz, H-3, H-5); 9.02 (d, 2H, $J=7$ Hz, H-2, H-6) ppm. ^{19}F NMR ($CDCl_3$) δ: −82.1 (t, 3F, $J=8$ Hz, CF_3); −119 (t, 2F, $J=12$ Hz, CF_2); −124 (m, 4F, 2 CF_2); −127.4 (m, 2F, CF_2) ppm. IR (KBr) (cm^{-1}): 1705 (MeC=O str.); 1642 (NC=O str.). MS (EI) m/z: 432 (M^+).

2-Picoline *N*-oxide (**3a**, 70% yield with **1a**, 75% yield with **1b**), quinoline *N*-oxide (**3h**, 82% yield with **1a**, 85% yield with **1b**), and isoquinoline *N*-oxide (**3k**, 65% yield) were identified by comparison of isolated products with authentic samples (purchased from Aldrich).

2-Ethylpyridine *N*-oxide (**3b**, 74% yield with **1a**, 70% yield with **1b**) [14], 2-propylpyridine *N*-oxide (**3c**, 68% yield) [14], collidine *N*-oxide (**3g**, 84% yield) [15], lepidine *N*-oxide (**3i**, 71% yield) [16], quinaldine *N*-oxide (**3j**, 76% yield) [16], acridine *N*-oxide (**3l**, 63% yield) [17], 4-acetylpyridine *N*-oxide (**3r**, 73% yield with **1a**, 76% yield with **1b**) [18], tri-*O*-acetylpiridoxol *N*-oxide (**3o**, 81% yield) [19] showed spectral and analytical data identical to those reported in the literature.

Acknowledgements

This research has been supported by the European Economic Community (INTAS-93-799). Prof. Tullio Caronna is gratefully acknowledged for discussions on UV spectra.

References

[1] (a) B.A. O'Brien, W.Y. Lam and D.D. DesMarteau, *J. Org. Chem., 51* (1986) 4466; (b) V.A. Petrov and D.D. DesMarteau, *J. Chem. Soc., Perkin Trans. 1*, (1993) 505; (c) D.P. Del'tsova, N.P. Gambaryan and E.P. Lur'e, *Izv. Akad. Nauk. SSSR, Ser. Khim., 8* (1979) 1788.

[2] (a) A. Sekiya and D.D. DesMarteau, *J. Org. Chem., 44* (1979) 1131; (b) A. Sekiya and D.D. DesMarteau, *Inorg. Chem., 19* (1980) 1330.

[3] L. Bragante and D.D. DesMarteau, *J. Fluorine Chem., 53* (1991) 181.

[4] (a) D.D. DesMarteau, V.A. Petrov, V. Montanari, M. Pregnolato and G. Resnati, *Tetrahedron Lett., 33* (1992) 7245; (b) D.D. DesMarteau, A. Donadelli, V. Montanari, V.A. Petrov and G. Resnati, *J. Am. Chem. Soc., 115* (1993) 4897; (c) M. Cavicchioli, V. Montanari and G. Resnati, *Tetrahedron Lett., 35* (1994) 6329; (d) M. Cavicchioli, A. Mele, V. Montanari and G. Resnati, *J. Chem. Soc., Chem. Commun.*, (1995) 901; (e) D.D. DesMarteau, V.A. Petrov, V. Montanari, M. Pregnolato and G. Resnati, *J. Org. Chem., 59* (1994) 2762; (f) M. Terreni, M. Pregnolato, G. Resnati and E. Benfenati, *Tetrahedron, 51* (1995) 7981.

[5] A.R. Katritzky and J.N. Lam, *Heterocycles, 33* (1992) 1011.

[6] A. Albini, *Heterocycles, 34* (1992) 1973.

[7] P. Chambon, R. Chambon-Mougenot and R. Guilluy, *C.R. Acad. Sci., Ser. D*, (1969) 523.

[8] J. Streith, *Heterocycles, 6* (1977) 2021.

[9] F.W. Fowler, A.R. Katritzky and R.J.D. Rutherford, *J. Chem. Soc. (B)*, (1971) 460.

[10] T.L. Gilchrist, in B.M. Trost and I. Fleming (eds.), *Comprehensive Organic Synthesis*, Vol. 7, Pergamon Press, Oxford, 1991, p. 749.

[11] R.W. Murray and R. Jeyaraman, *J. Org. Chem., 50* (1985) 2847.

[12] Y. Hata and M. Watanabe, *J. Am. Chem. Soc., 101* (1979) 6671; E. Schmitz, in A.R. Katrizky and C.W. Rees (eds.), *Comprehensive Heterocyclic Chemistry*, Vol. 7, Pergamon Press, Oxford, 1984, p. 204; S. Andreae and E. Schmitz, *Synthesis*, (1991) 327.

[13] W.W. Zajac Jr., T.R. Walters and M.G. Darcy, *J. Org. Chem., 53* (1988) 5856; F.A. Davis and A.C. Sheppard, *Tetrahedron, 45* (1989) 5703.

[14] A. Ohta, Y. Akita and C. Takagai, *Heterocycles, 6* (1977) 1881.

[15] G.A. Olah, K. Dunne, D.P. Kelly and Y.K. Mo, *J. Am. Chem. Soc., 94* (1972) 7438.

[16] K. Tori, M. Ogata and H. Kano, *Chem. Pharm. Bull., 11* (1963) 681.

[17] P. Hamm and W.V. Philipsborn, *Helv. Chim. Acta, 54* (1971) 2363.

[18] A.R. Katritzky and J.M. Lagowsky, *J. Chem. Soc.*, (1961) 43.

[19] G.R. Underwood, B. Paul and M.A. Becker, *J. Heterocyclic Chem., 13* (1976) 1229.