Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9649–9653

TETRAHEDRON

Synthesis of benzothiopyrano[2,3-*b*]indol-11-one and benzopyrano[2,3-*b*]indol-11-one

Robert Engqvist[a,b] and Jan Bergman[a,b,*]

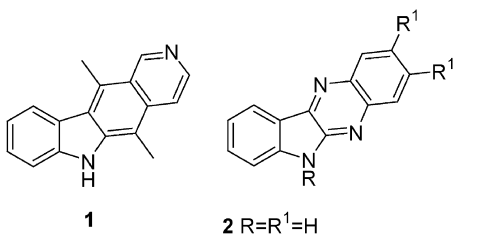
[a]*Unit for Organic Chemistry, CNT, Department of Biosciences at Novum, Karolinska Institute, Novum Research Park, SE-141 57 Huddinge, Sweden*
[b]*Södertörn University College, SE-141 04 Huddinge, Sweden*

Received 16 July 2003; revised 4 September 2003; accepted 25 September 2003

Abstract—The fused heterocycles benzothiopyrano[2,3-*b*]indol-11-one and benzopyrano[2,3-*b*]indol-11-one, have been prepared from methyl 3-indole carboxylate in two steps.

1. Introduction

Certain tetracyclic ring systems such as ellipticine (**1**) are powerful intercalators of DNA and derivatives of **1** have been used in cancer chemotherapy.[1] Unfortunately **1** is also very toxic. Therefore considerable efforts have been invested in attempts to develop active compounds with reduced toxicity. In this context we are interested in tetracyclic heterocycles containing indole cores such as indolo[2,3-*b*]quinoxaline (**2**). Unfortunately derivatives of **2** were inactive against most types of cancer except against Burkitt's lymfoma. Because of its viral relationship several derivatives of **2** were tested on a number of virus. In these tests e.g. the derivative **3** showed high activities against HSV-1, CMV and VZV. In contrast to **1** derivatives of **2** have low toxicity[2] (Fig. 1).



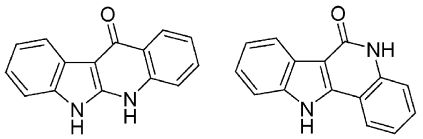
1

2 R=R^1=H
3 R=$C_2H_5N(CH_3)_2$, R^1=CH_3

Figure 1.

2. Results and discussion

Quinolino[2,3-*b*] indol-11-one (**4**) has recently been prepared for the first time,[3] whereas its angular isomer **5** has been known for a long time and a large number of syntheses are known[4] (Fig. 2).



4 **5**

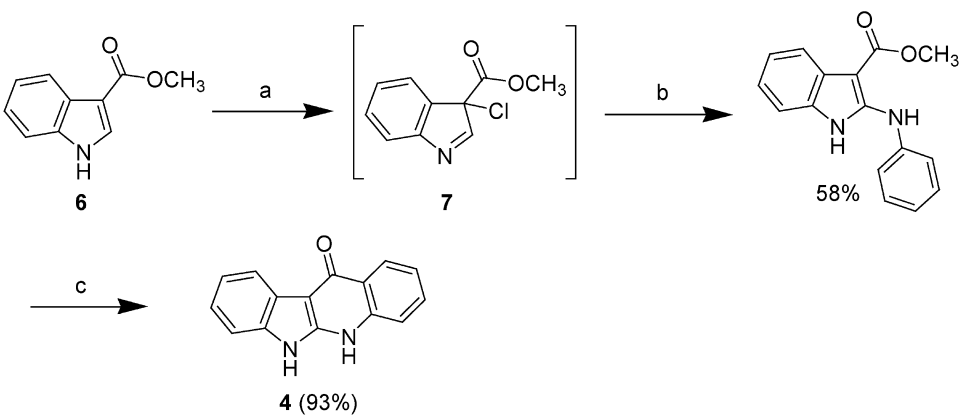
Figure 2.

The synthesis of **4** available is out-lined in Scheme 1.[3] The crucial intermediate **7** was generated from **6** and *N*-chlorosuccinimide (NCS) in the presence of *N*,*N*-dimethylpiperazine and (without isolation) reacted with aniline giving the corresponding 2,3-disubstituted indole, which were subsequently easily cyclized to **4** in hot diphenyl ether in a high yield (Scheme 1).

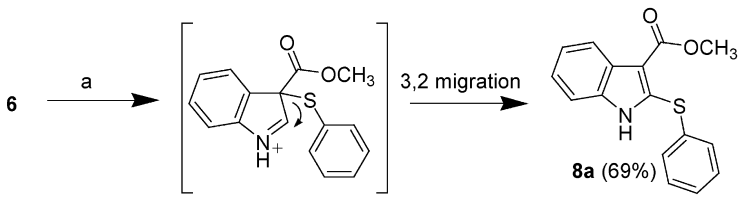
By using thiophenol and phenol as partners to **7** it is possible to introduce sulfur and oxygen functionalities in the 2-position of the indole, thus yielding **8a** and **8b**, respectively. Unfortunately, diphenyl disulfide was formed as a side product in the reaction with thiophenol decreasing the yield of **8a**. Attempts to increase the yield by additional equivalents of thiophenol failed. However, **8a** could be made in 69% yield by reacting **6** with phenylsulfenyl chloride (**9**). This was done easily by adding sulfuryl chloride to a mixture of diphenyl disulfide and **6** in chloroform, thereby generating the sulfenyl chloride **9** in situ. A plausible mechanism is that **9** reacts at the 3-position

Keywords: indoles; benzopyranones; benzothiopyranones.
* Corresponding author. Tel.: +46-8-6089204; fax: +46-8-6081501; e-mail: jabe@cnt.ki.se

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.084



Scheme 1. (a) NCS, 1,4-dimethylpiperazine, CH_2Cl_2, 0°C, 2 h. (b) Trichloroacetic acid, aniline, room temperature, 2 h. (c) Diphenyl ether, reflux, 30 min to 3 h 30 min.



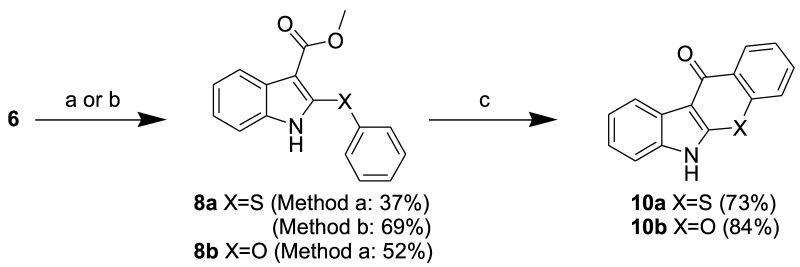
Scheme 2. (a) SCl (**9**), $CHCl_3$, room temperature, 3 h 30 min.

of **6** and thereafter migrates to the 2-position (Scheme 2). Hamel has discussed similar mechanisms in the formation of 2,3-bisphenylthioindoles from 3-phenylthioindole.[5]

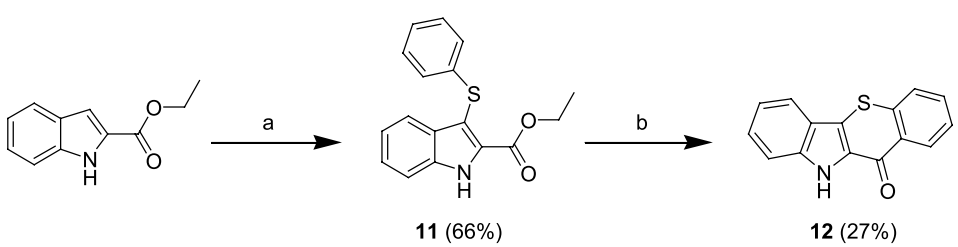
It was not possible to cyclize either **8a**, or **8b** by heating in diphenyl ether as it was in the case of **4** (Scheme 1). Instead compounds **8a**–**b** were cyclized in hot polyphosphoric acid (PPA) to benzothiopyrano[2,3-*b*]indol-11-one (**10a**) and benzopyrano[2,3-*b*]indol-11-one (**10b**) in good yields (Scheme 3).

In a similar manner to **8a**, the 2,3-disubstituted indole **11** was prepared in good yield, but the cyclization in PPA at 160°C gave a mixture of benzothiopyrano[3,2-*b*]indol-11-one (**12**) and ethyl indole-2-carboxylate. When the reaction was performed at 205°C only **12** was obtained in a moderate yield (27%) (Scheme 4).

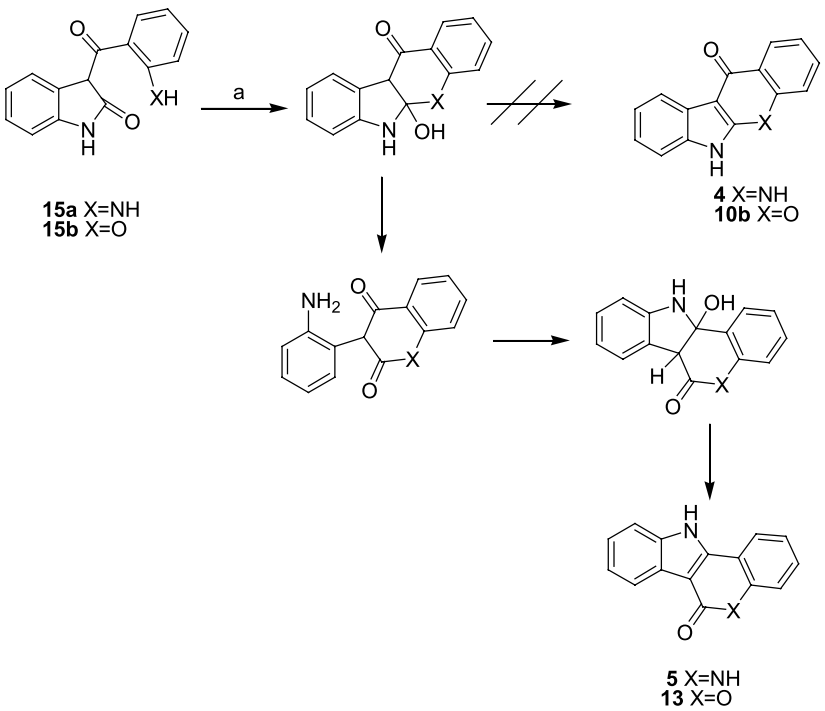
Compound **10a** has been described in the literature and was first synthesized by Hamel from indole and *o*-carbomethoxybenzenesulfenyl chloride in three steps giving a mixture of **10a** and **12**.[6] We have recently shown that a molecule originally published as having the linear structure **4**, is in fact the angular isomer **5**,[3] which was prepared as outlined



Scheme 3. (a) (i) NCS, *N*,*N*-dimethylpiperazine, CH_2Cl_2, 0°C, 2 h; (ii) trichloroacetic acid, phenol or thiophenol, 25°C, 2–2.5 h; (b) diphenyl disulfide, SO_2Cl_2, 0–25°C, 4 h; (c) PPA, 160°C, 2 h.



Scheme 4. (a) **9**, $CHCl_3$, room temperature, 2 h; (b) PPA, 205°C, 1 h.

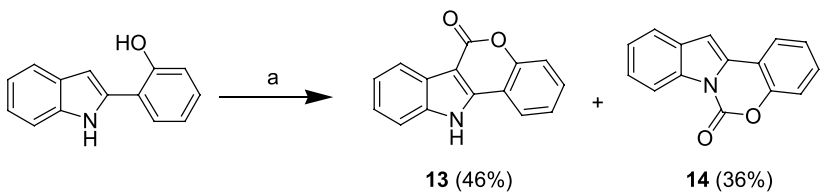


Scheme 5. (a) HCl, methanol, reflux, 15 h.[8]

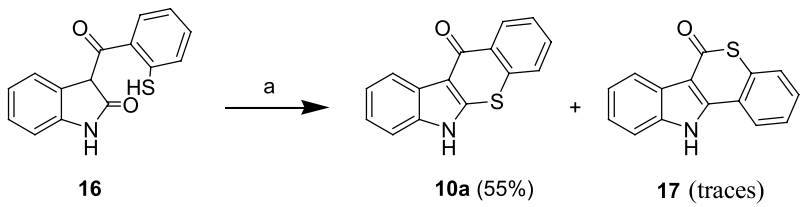
in Scheme 5. The corresponding chromone derivative was similarly prepared and assigned a linear structure **10b** by Eiden et al.,[7,8] which has now also been shown to be incorrect. As indicated in Scheme 5, ring opening of the intermediate, probably after protonation of the anilinic nitrogen atom in the tetrahedral intermediate, takes preference over elimination of water.

The angular regioisomeric product (**13**) obtained from 3-(2-hydroxybenzoyl)-oxindole according to Scheme 5 is in fact identical with a product previously prepared by Stadlbauer and Kappe from 4-amino-3-phenylbenzopyran-2-one.[4c–e] The angular isomer could also be prepared from 2-(2-hydroxyphenyl)indole and triphosgene, a reaction that also yielded the isomer **14** as a minor product (Scheme 6). Base-induced cyclization of **15a** and **15b** invariably produced the angular products **5** and **13**, respectively. In contrast, cyclization of the thiol **16** mainly gave the linear isomer (**10a**).[8] Only traces of the angular isomer (**17**) could be detected (Scheme 7). This may occur because the C–S bondlength is longer than both the C–N and the C–O and hence would favour elimination of water from the tetrahedral intermediate because of the more flexible ring.

In summary, the 2,3-disubstituted indoles **8a–b** were readily formed from methyl indole-3-carboxylate and subsequently easily cyclized in hot PPA to benzothiopyrano-[2,3-*b*]indol-11-one (**10a**) and benzopyrano[2,3-*b*]indol-11-one (**10b**), respectively. We could thereby conclude that the molecule previously reported[7,8] as benzopyrano[2,3-*b*]-indol-11-one is in fact the angular regioisomeric structure i.e. benzopyrano[3,2-*c*]indol-6-one (**13**).



Scheme 6. (a) Triphosgene, acetic acid, reflux, 1 h.



Scheme 7. (a) HCl, methanol, reflux, 15 h.[8]

3. Experimental

3.1. General

NMR spectra were recorded in DMSO-d_6 solutions at room temperature and using the signal from DMSO-d_6 (^{1}H: δ=2.50 ppm; ^{13}C: δ=39.5 ppm) as internal standard, on a Bruker DPX 300 (300 MHz) spectrometer. J values are given in Hz and δ values are given in ppm. IR spectra are recorded on a Perkin–Elmer 1600 FTIR. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. Chromatography was performed on Merck silica gel 60, TLC analyses were run on Merck silica gel F_{254} plates. The elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Solvents were of analytical grade and were used as received.

3.1.1. Methyl 2-phenylthio indole-3-carboxylate (8a). *Method A*. A suspension of methyl indole-3-carboxylate (0.52 g; 3.0 mmol) in dichloromethane (20 mL) was cooled to 0°C under argon and treated sequentially with *N*,*N*-dimethylpiperazine (0.23 g; 2.0 mmol) and *N*-chlorosuccinimide (0.44 g; 3.3 mmol) in one portion. The resulting solution was stirred for 2 h at 0°C whereupon a solution of thiophenol (0.70 g; 6.4 mmol) and trichloroacetic acid (0.12 g; 0.73 mmol) in dichloromethane (10 mL) was added and the solution stirred at room temperature for 2.5 h. The reaction mixture was washed with aq. $NaHCO_3$ (10%), aq. HCl (1 M) and water. The organic layer was dried with $MgSO_4$. The product was isolated by chromatography (20% ethyl acetate in *n*-hexane). Yield: 0.31 g (37%).

Method B. Sulfuryl chloride (0.71 g; 5.25 mmol) was added to a solution of methyl indole-3-carboxylate (0.88 g; 5 mmol) and diphenyl disulfide (1.10 g; 5 mmol) in dry chloroform (25 mL) at 0°C under argon. The solution was stirred at 0°C for 30 min and thereafter at room temperature for 3.5 h. The reaction mixture was washed with aq. $NaHCO_3$ (10%) and brine. The organic layer was dried with $MgSO_4$. The product was isolated as a white solid by chromatography (15% ethyl acetate in *n*-hexane). Yield: 0.98 g (69%).

Mp: 133–134°C; IR ν_{max}: 3280, 1667, 1496, 1465, 1439, 1194, 1067, 750; ^{1}H NMR δ: 11.58 (1H, s, N*H*), 7.92 (1H, m, Ar*H*), 7.47–7.34 (6H, m, Ar*H*), 7.18–7.14 (2H, m, Ar*H*), 3.83 (3H, s, O*CH*$_3$); ^{13}C NMR δ: 164.3 (s), 137.9 (s), 136.5 (s), 131.7 (d, 2C), 131.5 (s), 129.9 (d, 2C), 128.5 (d), 126.5 (s), 122.5 (d), 121.5 (d), 120.2 (d), 111.7 (d), 105.9 (s), 50.8 (t). Anal. calcd for $C_{16}H_{13}NO_2S$ C, 67.82; H, 4.62; N, 4.94. Found C, 67.94; H, 4.55; N, 4.83.

3.1.2. Methyl 2-phenoxy indole-3-carboxylate (8b). A suspension of methyl indole-3-carboxylate (2.08 g; 11.9 mmol) in dichloromethane (50 mL) was cooled to 0°C under argon and treated sequentially with *N*,*N*-dimethylpiperazine (0.75 g; 6.6 mmol) and *N*-chlorosuccinimide (1.75 g; 13.1 mmol) in one portion. The resulting solution was stirred for 2 h at 0°C and then a solution of phenol (2.30 g; 24.5 mmol) and trichloroacetic acid (0.50 g; 3.1 mmol) in dichloromethane (50 mL) was added and the solution stirred at room temperature for 2 h. The reaction mixture was washed with aq. $NaHCO_3$ (10%), aq. HCl (1 M) and water. The organic layer was dried with $MgSO_4$. The product was isolated as a white solid by chromatography (20% ethyl acetate in *n*-hexane). Yield: 1.67 g (52%). Mp: 161–162°C; IR ν_{max}: 3196, 1679, 1666, 1473, 1371, 1211, 1095, 736; ^{1}H NMR δ: 12.27 (1H, s, N*H*), 8.00 (1H, m, Ar*H*), 7.42–7.34 (3H, m, Ar*H*), 7.21–7.05 (5H, m, Ar*H*), 3.68 (3H, s, O*CH*$_3$); ^{13}C NMR δ: 163.4 (s), 156.9 (s), 151.3 (s), 130.7 (s), 130.0 (d, 2C), 125.3 (s), 123.7 (d), 122.1 (d), 121.5 (d), 120.4 (d), 116.6 (d, 2C), 111.6 (d), 91.7 (s), 50.4 (t). Anal. calcd for $C_{16}H_{13}NO_3$ C, 71.90; H, 4.90; N, 5.24. Found C, 72.06; H, 4.88; N, 5.20.

3.1.3. Ethyl 3-phenylthio indole-2-carboxylate (11). Sulfuryl chloride (0.68 g; 5.0 mmol) was added to a solution diphenyl disulfide (1.10 g; 5.0 mmol) in chloroform (10 mL) at 0°C under argon and the reaction was stirred at room temperature for 30 min. This solution was added to ethyl indole-2-carboxylate (0.94 g; 5.0 mmol) in chloroform (10 mL) at 0°C and the reaction mixture was stirred in room temperature for 2 h 30 min. The reaction mixture was washed aq. $NaHCO_3$ (sat.) and water. The organic layer was dried with $MgSO_4$. The product was isolated by chromatography (10% acetone in *n*-hexane). Yield: 0.98 g (66%). Mp: 135–136°C [Lit.,[9] mp: 135°C]; The spectral data were in agreement with those published.[9]

3.1.4. Benzothiopyrano[2,3-*b*]indol-11-one (10a). Compound **8a** (0.100 g; 0.35 mmol) was heated in PPA (1 g) at 160°C for 2 h. The reaction mixture was allowed to cool to 80°C and water (80 mL) was added. The solid thus formed was isolated by filtration, washed with water and dried. The product was purified by chromatography with 40% acetone in *n*-hexane giving **10a** as a white solid. Yield: 65 mg (73%). Mp: 330–337°C (decomp.) [Lit.,[6] mp: >300°C]; The spectral data were in agreement with those published.[6]

3.1.5. Benzopyrano[2,3-*b*]indol-11-one (10b). Compound **8b** (0.200 g; 0.75 mmol) was heated in PPA (2 g) at 160°C for 2 h. The reaction mixture was allowed to cool to 80°C and water (80 mL) was added. The solid thus formed was isolated by filtration, washed with water and dried. The product was purified by chromatography with 40% acetone in *n*-hexane giving **10b** as a white solid. Yield: 147 mg (84%). Mp: 344–349°C (decomp.); IR ν_{max}: 3018, 2740, 1624, 1604, 1519, 1198, 749; ^{1}H NMR δ: 12.87 (1H, s, N*H*), 8.25 (1H, dd, 7.8, 1.4, Ar*H*), 8.11 (1H, m, Ar*H*), 7.80–7.70 (2H, m, Ar*H*), 7.55–7.48 (2H, m, Ar*H*), 7.34–7.28 (2H, m, Ar*H*); ^{13}C NMR δ: 171.6 (s), 155.8 (s), 153.5 (s), 132.8 (d), 131.9 (s), 125.6 (d), 125.0 (d), 123.6 (d), 123.5 (s), 122.0 (d), 121.9 (s), 120.4 (d), 117.7 (d), 111.8 (d), 98.8 (s). Anal. calcd for $C_{15}H_9NO_2$ C, 76.59; H, 3.86; N, 5.95. Found C, 76.69; H, 3.88; N, 5.92.

3.1.6. Benzothiopyrano[3,2-*b*]indol-11-one (12). Ethyl 3-thiophenyl indole-2-carboxylate (0.150 g; 0.505 mmol) was heated in PPA (1.5 g) at 205°C for 50 min. The reaction mixture was allowed to cool to room temperature and water was added. The solid thus formed was isolated by filtration, washed with water and dried. The blackish solid was purified by sublimation (200°C, 0.35 mbar) to give a white solid. Yield: 34 mg (27%). Mp: 300–325°C (decomp.)

[Lit.,[6] mp: >300°C]; The spectral data were in agreement with those published.[6]

3.1.7. Reaction of 2-(2-hydroxyphenyl)indole and triphosgene. Triphosgene (0.99 g; 3.33 mmol) was added to a solution of 2-(2-hydroxyphenyl) indole[9] in acetic acid (10 mL). The reaction mixture was heated to reflux for 1 h and thereafter filtrated while it was hot and washed with acetic acid and ethanol to give benzopyrano[4,3-*b*]indol-6-one (**10b**). Yield: 0.55 g (46%). Mp: >360°C [Lit.,[4e] mp: 315°C]; The spectral data were in agreement with those published.[4e]

The mother liquor was poured into water and the solid thus formed was isolated by filtration and washed with water to give **14**. An analytical sample was recrystallized from 2-propanol. Yield: 0.42 g (36%). Mp: 153–154°C; IR ν_{max}: 1756, 1468, 1447, 1354, 1340, 1216, 1202, 1132, 997, 748; ^{1}H NMR δ: 8.34 (1H, m, Ar*H*), 8.14 (1H, m, Ar*H*), 7.77 (1H, m, Ar*H*), 7.53–7.40 (6H, m, Ar*H*); ^{13}C NMR δ: 148.1 (s), 143.5 (s), 133.7 (s), 132.1 (s), 130.2 (d), 130.0 (s), 125.5 (d), 124.5 (d), 124.5 (d), 123.8 (d), 120.9 (d), 116.5 (d), 115.0 (d), 113.9 (s), 101.0 (d); Anal. calcd for $C_{15}H_9NO_2$ C, 76.59; H, 3.86; N, 5.95. Found C, 76.68; H, 3.77; N, 5.83.

References

1. (a) Gribble, G. W. *The Alkaloids* **1990**, *39*, 239. (b) Potier, P. *Chem. Soc. Rev.* **1992**, 113.
2. (a) Harmenberg, J.; Wahren, B.; Bergman, J.; Åkerfeldt, S.; Lundblad, L. *Antimicrob. Agents Chemother.* **1988**, *32*, 1720. (b) Harmenberg, J.; Åkesson-Johansson, A.; Gräslund, A.; Malmfors, T.; Bergman, J.; Wahren, B.; Åkerfeldt, S.; Lundblad, L.; Cox, S. *Antivir. Res.* **1991**, *15*, 193.
3. Bergman, J.; Engqvist, R.; Stålhandske, C.; Wallberg, H. *Tetrahedron* **2003**, *59*, 1033.
4. (a) Dave, V.; Warnhoff, E. W. *Tetrahedron* **1975**, *31*, 1255. (b) Winterfeldt, E.; Altmann, H. J. *Angew. Chem.* **1968**, *80*, 486. (c) Stadlbauer, W.; Karem, A.-S.; Kappe, T. *Monatsh. Chem.* **1984**, *115*, 467. (d) Stadlbauer, W.; Karem, A.-S.; Kappe, T. *Monatsh. Chem.* **1986**, *117*, 1305. (e) Stadlbauer, W.; Karem, A.-S.; Kappe, T. *Monatsh. Chem.* **1987**, *118*, 81. (f) De Diesbach, H. *Helv. Chim. Acta* **1951**, *34*, 1050.
5. Hamel, P. *J. Org. Chem.* **2002**, *67*, 2854.
6. Hamel, P.; Girard, M.; Tsou, N. N. *J. Heterocycl. Chem.* **1999**, *36*, 643.
7. (a) Eiden, F.; Dobinsky, H. 1970, German Patent 2,037,047. (b) Eiden, F.; Dobinsky, H. *Justus Liebigs Ann. Chem.* **1970**, 365.
8. Eiden, F.; Dobinsky, H. *Justus Liebigs Ann. Chem.* **1974**, 1981.
9. Gairns, R. S.; Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, *3*, 497.