Communication

Synthesis of 2-Arylbenzoxazoles from Flash Vacuum Pyrolysis of 2-Methoxy-*N*-(arenylidene)anilines

Chin-Hsing Chou,* Yu-Tan Hsueh and Bo-Chi Wang
Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 80424, Taiwan, R.O.C.

Received January 22, 2011; Accepted April 7, 2011; Published Online April 14, 2011

Flash vacuum pyrolysis of 2-methoxy-*N*-(arenylidene)anilines **2a-g** at 700 °C and 1×10^{-2} Torr gave the corresponding 2-arylbenzoxazoles **1a-g**.

Keywords: Flash vacuum pyrolysis; 2-Arylbenzoxazole; 2-Methoxy-*N*-(arenylidene)aniline.

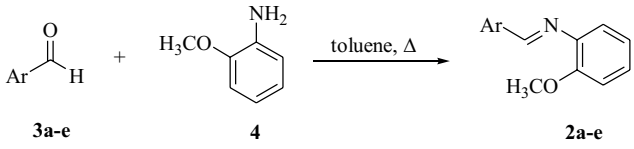
INTRODUCTION

2-Arylbenzoxazoles **1** play an important role in pharmaceutical scenes and exhibit a variety of biological activities, including antitumor, antimicrobial, and antiviral properties.[1] Consequently, there are numerous methods for synthesizing these compounds have been reported. That includes the coupling of 2-aminophenols with carboxylic acid derivatives they are catalyzed by strong acids and at high temperatures[2] or reacts under microwave-assisted conditions,[3] oxidative cyclization of imine intermediates by using various oxidants,[4-11] and intramolecular metal-catalyzed reactions of 2-haloaniline precursors.[12] Recently, we have prepared **1** from flash vacuum pyrolysis (FVP) of the corresponding 2-methoxy-*N*-(arenylidene)anilines **2**. We wish to report our results herein.

RESULTS AND DISCUSSION

2-Methoxy-*N*-(arenylidene)anilines **2a-e** were prepared from the condensation of 2-substituted aromatic aldehydes **3a-e** with *o*-anisidine (**4**) (Scheme I).[13] FVP of **2a-e** were performed using the pyrolysis set-up that has been previously described.[14] The furnace was maintained at temperatures in the range 600 °C-900 °C. A sample of **2** (100-200 mg) for pyrolysis was placed into the sample chamber and the system was evacuated to ca. 1×10^{-2} Torr. The pyrolysis process was completed in 1 h. Pyrolysis at 700 °C and 1×10^{-2} Torr appeared to be the optimum reaction conditions for our study. FVP of **2a-e** at temperatures lower than 700 °C would leave unreacted starting materials, whereas FVP of **2a-e** at temperatures higher than 750 °C would give lower yields of the desired products **1a-e**. FVP of **2a-e** gave 2-arylbenzoxazoles **1a-e** as the major products, along with cyanoarenes **5a-e** and 2-hydroxybenzonitrile (**6**). The yields for the pyrolysis products from FVP of **2a-e** at 700 °C are listed in Table 1.

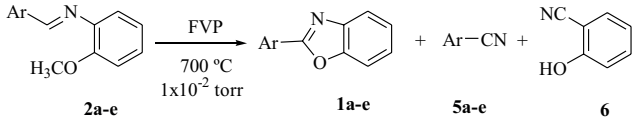
Scheme I



3a-e **4** **2a-e**

a, Ar = phenyl; **b**, Ar = 2-furyl; **c**, Ar = 2-thienyl; **d**, Ar = 2-benzo[*b*]furyl; **e**, Ar = 2-benzo[*b*]thienyl

Table 1. Pyrolysis products from FVP of 2-methoxy-*N*-(arenylidene)anilines **2a-e**



2a-e **1a-e** **5a-e** **6**

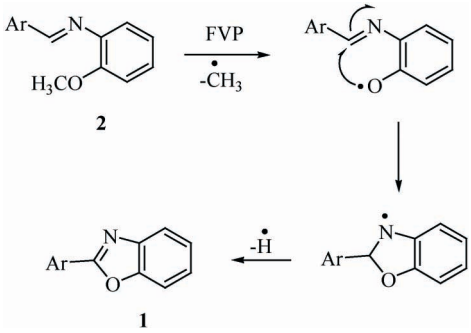
Substrate	Ar	Products yield (%)[a]		
2a	phenyl	**1a** (68)	**5a** (12)	**6** (10)
2b	2-furyl	**1b** (45)	**5b** (18)	**6** (6)
2c	2-thienyl	**1c** (65)	**5c** (8)	**6** (10)
2d	2-benzo[*b*]furyl	**1d** (70)	**5d** (20)	**6** (5)
2e	2-benzo[*b*]thienyl	**1e** (66)	**5e** (15)	**6** (12)

[a] The yields of products were measured by quantitative analysis of NMR with weighed dibromomethane as an internal standard.

A possible mechanism to account for the formation of 2-arylbenzoxazoles **1a-e** is proposed as shown in Scheme II. Under the pyrolysis conditions, phenoxy radical was generated by elimination of a methyl radical from **2**. Cy-

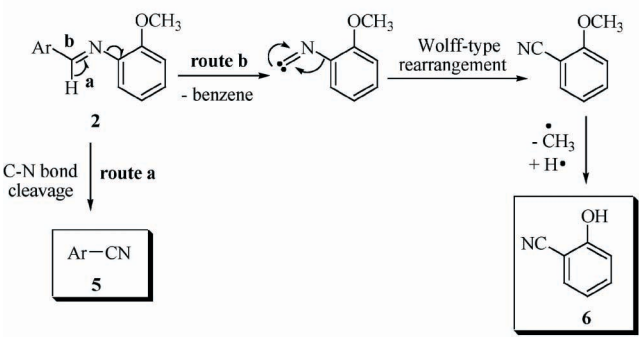
clization of the resulting phenoxy radical then lead to the final product **1**.

Scheme II



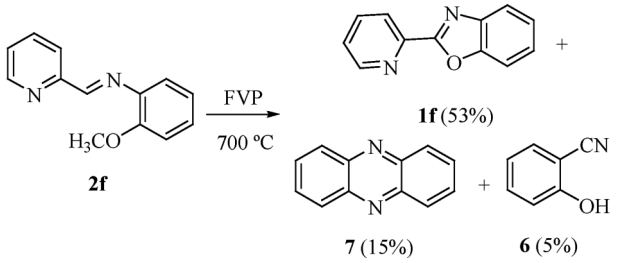
The mechanism for the formation of **5** and **6** from FVP of **1** is proposed as shown in Scheme III. Cleavage of C-N bond from **1** (route a) would lead to **5**. On the other hand, elimination of a benzene molecule followed by a Wolff-type rearrangement of the resulting carbene[15] and a conversion of the methoxyl group into a hydroxyl group then give **6** (route b).

Scheme III

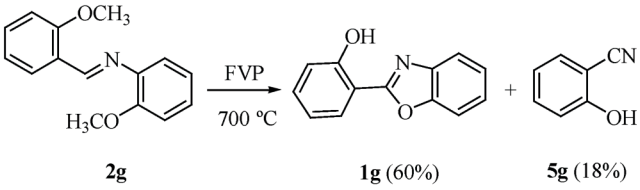


Consequently, application of the pyrolysis method was then employed for the synthesis of 2-(2-pyridyl)benzoxazole (**1f**) and 2-(2′-hydroxyphenyl)benzoxazole (**1g**). **1f** showed herbicidal activity against knag and annual sedge[16] and **1g** was an antimicrobial agent.[17] Compounds **2f** and **2g** were prepared from the condensation of the corresponding 2-substituted aromatic aldehydes with *o*-anisidine (**4**). Under the same pyrolysis conditions, FVP of 2-methoxy-*N*-(2-pyridylidene)aniline (**2f**) gave **1f** and phenazine (**7**) as the major products (Scheme IV), whereas FVP of 2-methoxy-*N*-(2′-methoxybenzylidene)aniline (**2g**) gave **1g** and **6** in 60% and 18% yields, respectively (Scheme V).

Scheme IV

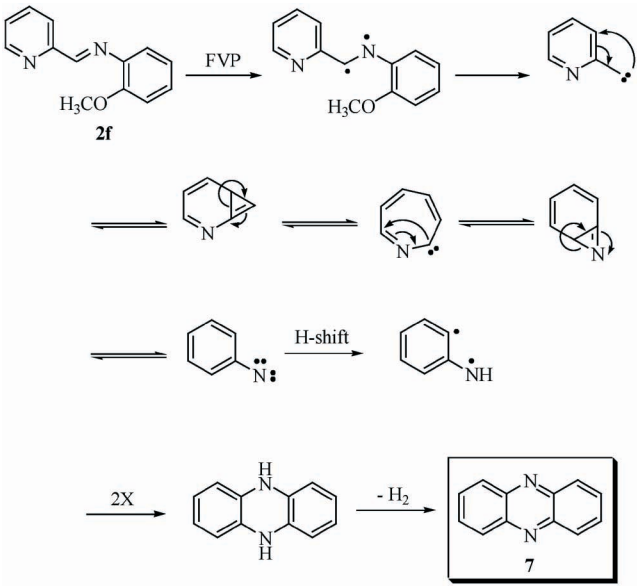


Scheme V



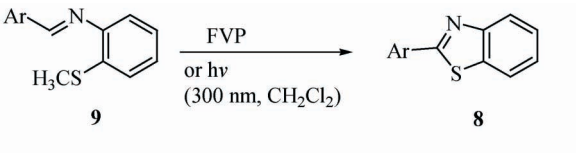
A possible mechanism to account for the formation of phenazine (**7**) is proposed as shown in Scheme VI, which involves a conversion of a carbene intermediate into the more stable nitrene intermediate.[18,19]

Scheme VI



It is noteworthy that although 2-arylbenzothiazoles (**8**) can be prepared both from FVP and photolysis of 2-methylthio-*N*-(arenylidene)anilines (**9**) (Scheme VII), as we have reported recently,[20] photolysis of **2** under similar conditions only resulted in decomposition of **2**.

Scheme VII



Ar = phenyl, 2-furyl, 2-thienyl, 2-benzo[*b*]furyl, 2-benzo[*b*]thienyl

SUMMARY

In summary, we have developed a new method to synthesize 2-arylbenzoxazoles **1a-g** from FVP of 2-methoxy-*N*-(arenylidene)anilines **2a-g**. It is noteworthy that under the pyrolysis conditions, as in the case of synthesizing **2g**, we are able to carry out cyclization reaction and conversion of alkoxyl group into hydroxyl group, simultaneously. Applications of such an advantage to the synthesis of other heterocyclic compounds are currently underway.

EXPERIMENTAL SECTION

General methods

Infrared spectra were measured with a FTS-155 IR spectrophotometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded using $CDCl_3$ as solvent on a Varian UXR-500 NMR spectrometer. Chemical shifts are expressed in δ parts per million (ppm) values with tetramethylsilane (TMS) as the internal reference, and coupling constants are expressed in hertz (Hz). Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on VG QUATTRO 5022 and VG70-250S instruments.

General pyrolysis procedure[14]

The furnace was maintained at temperatures in the range 600 °C-950 °C. A sample for pyrolysis was placed into the sample chamber and the system was evacuated to ca. 1×10^{-2} torr. During the pyrolysis, $CDCl_3$ was deposited into the trap through a side arm. After pyrolysis was completed, nitrogen was introduced into the system and the trap cooled with liquid nitrogen was warmed to room temperature, the pyrolysis products were collected and separated by column chromatography on silica gel and examined by IR, ^{1}H, ^{13}C NMR and MS spectroscopies.

Preparation of 2-methoxy-*N*-(arenylidene)anilines (2a-g)

To a solution of corresponding 2-substituted aromatic aldehydes (**3a-g**) (20 mmol) in toluene (20 mL) was added *o*-anisidine (**4**) (22 mmol), and then the mixture was placed in the Dean-Stark apparatus at 110 °C for 3 days. Removal of solvent under reduced pressure left a crude product which was purified by the Kugehlor apparatus to give **2a-g** (90%), respectively.

Spectral data of precursors

Compounds **2b**,[21] **2f**[22] are identical to that of authentic compounds.

2-Methoxy-*N*-(benzylidene)aniline (2a)

IR (CH_2Cl_2, cm^{-1}) 3063, 1628, 1493, 1246, 1180, 1115, 1026. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.89 (s, 3H), 6.96-7.03 (m, 3H), 7.18-7.22 (m, 1H), 7.46-7.49 (m, 3H), 7.92-7.94 (m, 2H), 8.48 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.88, 111.50, 120.22, 121.02, 126.63, 128.65, 128.90, 131.30, 136.30, 141.88, 152.24, 161.35. MS (EI) *m*/*z* (%) 211 (M^+, 83), 196 (11), 134 (18), 80 (100), 77 (70).

2-Methoxy-*N*-(thenylidene)aniline (2c)

IR (CH_2Cl_2, cm^{-1}) 3054, 1620, 1489, 1427, 1180, 1119, 1026. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.88 (s, 3H), 6.94-6.98 (m, 2H), 7.03-7.05 (m, 1H), 7.11-7.13 (m, 1H), 7.18 (td, 1H, *J* = 7.5, 2.0 Hz), 7.49 (dd, 2H, *J* = 15.0, 5.0 Hz), 8.60 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.78, 111.51, 120.66, 120.89, 126.62, 127.55, 130.22, 131.94, 141.01, 142.98, 152.24, 154.06. MS (EI) *m*/*z* (%) 217 (M^+, 86), 186 (51), 173 (66), 120 (70), 110 (100). HRMS (ESI) (M+H) calculated for $C_{12}H_{12}NOS$: 218.0640, found: 218.0640.

2-Methoxy-*N*-(benzo[*b*]furfurylidene)aniline (2d)

IR (CH_2Cl_2, cm^{-1}) 3060, 1630, 1490, 1120. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.91 (s, 3H), 6.67-7.00 (m, 2H), 7.12 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.21-7.29 (m, 3H), 7.40 (td, 1H, *J* = 7.8, 1.5 Hz), 7.61 (d, 1H, *J* = 8.5 Hz), 7.65 (d, 1H, *J* = 7.5 Hz), 8.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.75, 111.45, 112.20, 112.77, 120.49, 120.86, 122.10, 123.39, 126.87, 127.44, 127.79, 140.48, 149.12, 152.62, 153.21, 155.83. MS (EI) *m*/*z* (%) 251 (M^+, 31), 144 (100), 131 (50), 102 (48), 77 (39). HRMS (ESI) (M+H) calculated for $C_{16}H_{14}NO_2$: 252.1024, found: 252.1026.

2-Methoxy-*N*-(benzo[*b*]thienylidene)aniline (2e)

IR (CH_2Cl_2, cm^{-1}) 3368, 1606, 1578, 1489, 1431, 1244, 1113, 1020, 741. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.90 (s, 3H), 6.96-7.01 (m, 2H), 7.10 (d, 1H, *J* = 7.5 Hz), 7.21 (t, 1H, *J* = 8.0 Hz), 7.43-7.36 (m, 2H), 7.71 (s, 1H), 7.83 (d, 1H, *J* = 7.5 Hz), 7.88 (d, 1H, *J* = 7.5 Hz), 8.75 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.92, 111.78, 120.99, 121.08,

122.84, 124.60, 124.70, 126.35, 127.11, 129.28, 139.33, 140.66, 141.22, 143.34, 152.39, 154.76. MS (ESI) *m/z* 268 (M+H). HRMS (ESI) (M+H) calculated for $C_{16}H_{14}NOS$: 268.0796, found: 268.0794.

2-Methoxy-*N*-(2′-methoxybenzylidene)aniline (2g)

IR (CH_2Cl_2, cm^{-1}) 3356, 2917, 2836, 2014, 1687, 1599, 1493, 1463, 1364, 1242, 1159, 1116, 1021, 881, 745. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 6H), 6.83-6.95 (m, 6H), 7.07 (t, 1H, J = 8.0 Hz), 7.33 (t, 1H, J = 8.0 Hz), 8.10 (dd, 1H, J = 8.0, 1.5 Hz), 8.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.51, 55.86, 110.97, 111.38, 120.23, 120.78, 120.95, 124.88, 126.33, 127.82, 132.57, 142.71, 152.41, 159.44. MS (EI) *m/z* (%) 241 (M^+, 3), 211 (1), 136 (19). HRMS (EI) calculated for $C_{15}H_{15}NO_2$: 241.1102, found: 241.2905.

Spectral data of products

Spectral data for **1a**,[23] **1b**,[24] **1c**,[23] **1f**,[25] **6**,[26] **7**[27] are identical to that of authentic compounds.

2-(2-Benzo[*b*]furyl)benzoxazole (1d)

IR (CH_2Cl_2, cm^{-1}) 3050, 1640, 1450, 1060. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, 1H, J = 7.5 Hz), 7.40-7.45 (m, 3H), 7.59-7.71 (m, 4H), 7.80-7.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.21, 110.70, 112.02, 120.41, 122.21, 123.86, 125.02, 125.77, 126.90, 127.50, 141.56, 143.60, 150.38, 155.31, 155.79. MS (EI) *m/z* (%) 235 (M^+, 40), 143 (100), 115 (60), 114 (56), 92 (44), 89 (56), 75 (33). HRMS (EI) calculated for $C_{15}H_9NO_2$: 235.0633, found: 235.0633.

2-(2-Benzo[*b*]thienyl)benzoxazole (1e)

IR (CH_2Cl_2, cm^{-1}) 3416, 1586, 1553, 1428, 1228, 725. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.47 (m, 4H), 7.58-7.60 (m, 1H), 7.78-7.80 (m, 1H), 7.90-7.92 (m, 2H), 8.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.53, 120.11, 122.61, 124.86, 124.93, 125.07, 125.51, 126.42, 126.78, 129.28, 139.35, 141.22, 141.97, 150.68, 158.98. MS (EI) *m/z* (%) 252 (49), 251 (M^+, 100). HRMS (ESI) (M+H) calculated for $C_{15}H_{10}NOS$: 252.0483, found: 252.0484.

2-(2′-Hydroxyphenyl)benzoxazole (1g)

IR (CH_2Cl_2, cm^{-1}) 3448, 1627, 1584, 1483, 1235, 1049, 739. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.02 (t, 1H, J = 8.0 Hz), 7.14 (d, 1H, J = 8.5 Hz), 7.38-7.47 (m, 3H), 7.61-7.63 (m, 1H), 7.74-7.75 (m, 1H), 8.04 (dd, 1H, J = 8.0, 1.5 Hz), 11.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.57, 110.66, 117.42, 119.25, 119.56, 124.99, 125.37, 127.11, 133.56, 140.02, 149.14, 158.72, 162.90. MS (EI) *m/z* (%) 211 (M^+, 100), 184 (8), 183 (57), 154 (18). HRMS (EI) calculated for $C_{13}H_9O_2N$: 211.2206, found: 211.0634.

ACKNOWLEDGEMENTS

We thank the National Science Council of Taiwan, Republic of China for financial support.

REFERENCES

1. (a) Deluca, M. R.; Kerwin, S. M. *Tetrahedron Lett.* **1997**, *38*, 199-202. (b) Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, L.; Konno, F. *J. Med. Chem.* **1998**, *41*, 3015-3021. (c) Temiz, O.; Oren, I.; Sener, E.; Yalcin, I.; Ucarturk, N. *Farmaco* **1998**, *53*, 337-341. (d) Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayashi, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102-104.
2. (a) Terashima, M.; Ishii, M.; Kanaoka, Y. *Synthesis* **1982**, 484-485. (b) Cho, C. S.; Kim, D. T.; Zhang, J. Q.; Ho, S. L.; Kim, T. J.; Shim, S. C. *J. Heterocycl. Chem.* **2002**, *39*, 421-423.
3. (a) Bourgrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055-8064. (b) Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. *Tetrahedron Lett.* **2003**, *44*, 175-178.
4. Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971-2972.
5. Nakagawa, K.; Onoue, H.; Sugita, J. *Chem. Pharm. Bull.* **1964**, *12*, 1135-1138.
6. Srivastava, R. G.; Venkataramani, P. S. *Synth. Commun.* **1988**, *18*, 1537-1544.
7. Park, K. H.; Jun, K.; Shin, S. R.; Oh, S. W. *Tetrahedron Lett.* **1996**, *37*, 8869-8870.
8. Varma, R. S.; Saini, R. K.; Prakash, O. *Tetrahedron Lett.* **1997**, *38*, 2621-2622.
9. Varma, R. S.; Kumar, D. *J. Heterocycl. Chem.* **1998**, *35*, 1539-1540.
10. Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951-954.
11. Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713-3715.
12. Virre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3425-3459.
13. Caronna, T.; Gabbiadini, S.; Mele, A.; Recupero, F. *Helv. Chin. Acta* **2002**, *85*, 1-8.
14. Chou, C. H.; Trahanovsky, W. S. *J. Am. Chem. Soc*. **1986**, *108*, 4138-4144.
15. Wentrup, C. *Adv. Heterocycl. Chem.* **1981**, *28*, 231-361.
16. Hisano, T.; Ichikawa, M.; Tsumoto, K.; Tasaki, M. *Chem. Pharm. Bull.* **1982**, *30*, 2996-3004.

17. Samota, M. K.; Seth, G. *Heteroat. Chem.* **2010**, *21*, 44-50.
18. Crow, W. D.; Wentrup, C. *Tetrahedron Lett.* **1968**, *9*, 6149-6152.
19. Wentrup, C. *Chem. Commun.* **1969**, 1386-1387.
20. Chou, C. H.; Yu, P. C.; Wang, B. C. *Tetrahedron Lett.* **2008**, *49*, 4145-4146.
21. Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891-1894.
22. Chattopadhyay, T. K.; Kumar, A. K.; Roy, A.; Batsanov, A. S.; Shamuratov, E. B.; Struchkov, Y. T. *J. Organomet. Chem.* **1991**, *419*, 277-282.
23. Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802-1808.
24. Kidwai, M.; Bansal, V.; Saxena, A.; Aerry, S.; Mozumdar, S. *Tetrahedron Lett.* **2006**, *47*, 8049-8053.
25. Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190-5196.
26. Black, M.; Cadogan, J. I. G.; Leardini, R.; McNab, H.; McDougald, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, *11*, 1825-1832.
27. Faust, R.; Weber, C.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1997**, *53*, 14655-14670.