HETEROCYCLES, Vol. 85, No. 10, 2012, pp. 2523 - 2529. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 11th July, 2012, Accepted, 31st July, 2012, Published online, 3rd August, 2012
DOI: 10.3987/COM-12-12544

SYNTHESIS OF 3-SUBSTITUTED 4-ALKOXYISOQUINOLIN-1-AMINES BY THE REACTION OF 2-[ALKOXY(LITHIO)METHYL]-BENZONITRILES WITH NITRILES

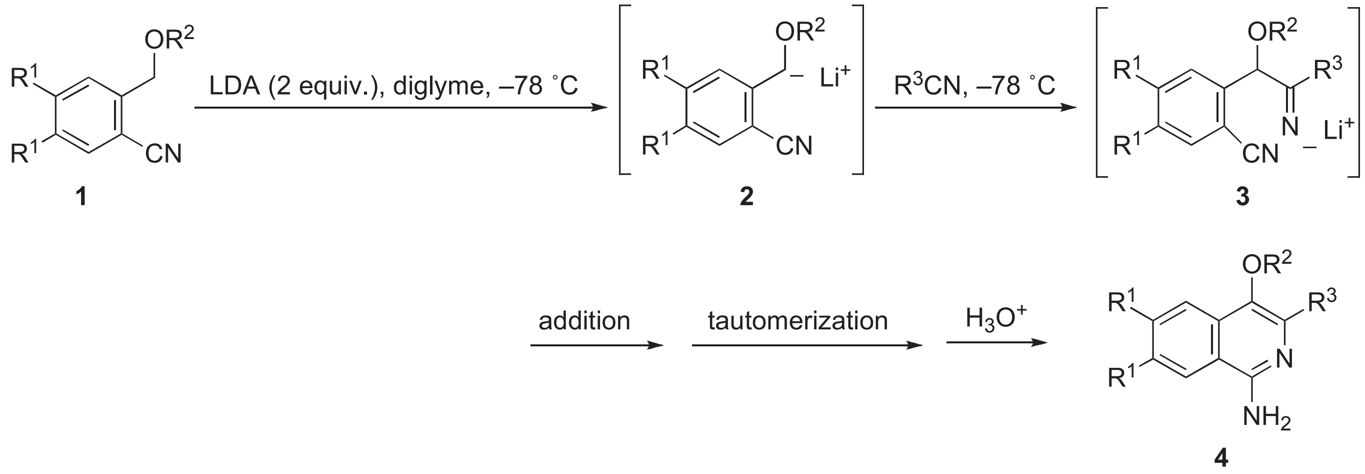
Kazuhiro Kobayashi,* Kota Matsumoto, and Kosuke Ezaki

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – It has been found that the reaction of 2-[alkoxy(lithio)methyl]benzonitriles, generated *in situ* from 2-(alkoxymethyl)benzonitriles and two equivalents of lithium diisopropylamide in diglyme at –78 ˚C, with aliphatic and aromatic nitriles provides an efficient method for the one-pot preparation of 3-substituted 4-alkoxyisoquinolin-1-amines.

Considerable attention is paid to isoquinolin-1-amines because of their biological activities.[1] This class of isoquinolines have been generally synthesized by the action of ammonia on isoquinoline-1(2*H*)-ones.[1] A method based on the reaction of 2-(lithiomethyl)benzonitrile, generated by treating 2-methylbenzonitlrile with lithium dimethylamide in THF–hexamethylphosphoric triamide (HMPA) at –78 ˚C, with aromatic nitriles for the preparation of 3-arylisoquinolin-1-amines has also been reported.[2] However, there have been few reports on the synthesis of 4-alkoxyisoquinolin-1-amines, though 4-ethoxyquinolin-1-amine has been prepared by the treatment of 1-bromo-4-ethoxyisoquinoline with potassium amide.[3] On the other hand, we have recently reported that 2-[alkoxy(lithio)methyl]benzonitriles, generated *in situ* from 2-(alkoxymethyl)benzonitriles and two equivalents of lithium diisopropylamide (LDA) in diglyme at –78 ˚C, react with ethyl benzoates to give 2-[alkoxy(aroyl)methyl]benzonitriles, which in turn are treated with hydrogen peroxide in aqueous sodium hydroxide to afford, after subsequent acidification of the resulting solutions of 2-[alkoxy(aroyl)methyl]benzamides, 4-alkoxy-3-arylisoquinoline-1(2*H*)-ones.[4] Therefore, we investigated the extensive use of these lithiated 2-(alkoxymethyl)benzonitriles for the direct and general preparation of 3-substituted 4-alkoxyisoquinolin-1-amines. We now report the results of their reactions with aliphatic and aromatic nitriles.

The synthesis of 3-substituted 4-alkoxyisoquinolin-1-amines (**4**) was accomplished according to the sequence illustrated in Scheme 1 in one pot from 2-(alkoxymethyl)benzonitriles (**1**). On treatment with two equivalents of LDA at –78 ˚C, the benzyl carbon of **1** was lithiated to generate 2-[alkoxy(lithio)methyl]benzonitriles (**2**) as reported previously.[4] These benzyl anions (**2**) were then allowed to react with a range of nitriles. Addition of the anions to the nitrile carbon gave the imino anion intermediates (**3**), of which subsequent intramolecular cyclization by the attack of on the *o*-cyano carbon followed by tautomerization afforded, after workup with aqueous ammonium chloride solution and purification by column chromatography on silica gel, the desired products (**4**) in moderate to fair yields as summarized in Table 1.



Scheme 1

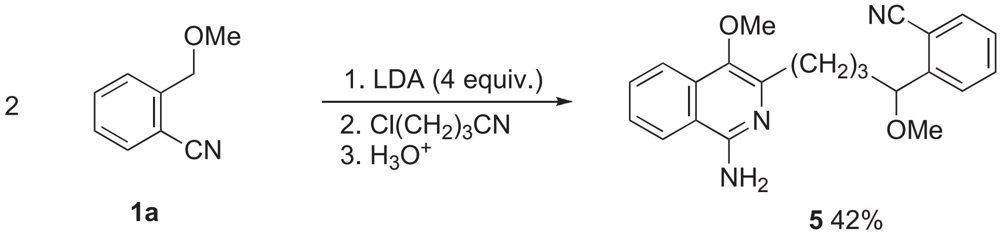
Table 1. Preparation of 3-substituted 4-alkoxyisoquinolin-1-amines (**4**)

Entry	**1**	R^3	**4**	Yield/%[a]
1	**1a** (R^1 = H, R^2 = Me)	Ph	**4a**	56
2	**1a**	3-MeC_6H_4	**4b**	54
3	**1a**	4-MeC_6H_4	**4c**	56
4	**1a**	3-MeOC_6H_4	**4d**	48
5	**1a**	4-MeOC_6H_4	**4e**	48
6	**1a**	Et	**4f**	52
7	**1a**	*i*-Pr	**4g**	48
8	**1b** (R^1 = OMe, R^2 = Et)	Ph	**4h**	43
9	**1b**	3-MeC_6H_4	**4i**	41

[a] Isolated yields.

As can be seen from Entries 6 and 7, even using aliphatic nitriles carrying α-hydrogen(s) the desired products (**4f**) and (**4g**) were formed cleanly and in the yields comparable to those using aromatic nitriles. Unfortunately, however, the reactions 2-(methoxymethyl)benzonitrile (**1a**) with 3-chlorobenzonitrile or 4-chlorobenzonitrile resulted in the formation of a considerably intractable mixture of products in each case, though the reason for this is not clear. When 2-ethoxymethyl-4,5-dimethoxybenzonitrile (**1b**) was used (Entries 8 and 9), the yields of the corresponding products (**4h**) and (**4i**) were somewhat lower than those using **1a**. These results may be ascribed to lower acidity of the benzyl protons of **1b** than those of **1a** due to two electron-donating methoxy groups.

Subsequently, we examined the reaction of 2-[lithio(methoxy)methyl]benzonitrile (**2a**) with 4-chlorobutanenitrile. First, the benzyl anion was allowed to react with an equivalent of the chloro nitrile in expectation of the procurement of 3-(3-chloropropyl)-4-methoxyisoquinolin-1-amine, which may be of use synthetically. Unfortunately, however, it could not be obtained and 2-[4-(1-amino-4-methoxyisoquinolin-3-yl)-1-methoxybutyl]benzonitrile (**5**) was produced in 22% yield. When the reaction was conducted at the molar ratio of 2:1, compound (**5**) was obtained in moderate yield, as shown in Scheme 2.



Scheme 2

In conclusion, we have demonstrated that the reaction of 2-[alkoxy(lithio)methyl]benzonitriles with nitriles offers a direct route to the general preparation of 3-substituted 4-alkoxyisoquinolin-1-amines. The present method may find some value in organic synthesis because of the readily availability of the starting materials and the easiness of operations.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 600 MHz or a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 150 MHz or a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 2-(Methoxymethyl)benzonitrile (**1a**)[4,5] and 2-bromomethyl-4,5-dimethoxybenzonitrile[6] were prepared according to the appropriate reported methods. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

2-Ethoxymethyl-4,5-dimethoxybenzonitrile (1b). This compound was prepared from 2-bromomethyl-4,5-dimethoxybenzonitrile[6] and EtOH in 65% yield under conditions reported for the preparation of **1a**;[4,5] a white solid; mp 108–110 °C (hexane–Et_2O); IR (neat) 2216, 1603 cm^{-1}; ^1H NMR (500 MHz,) δ 1.28 (t, *J* = 6.9 Hz, 3H), 3.62 (q, *J* = 6.9 Hz, 2H), 3.90 (s, 3H), 3.95 (s, 3H), 4.63 (s, 2H), 7.04 (s, 1H), 7.05 (s, 1H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.05; H, 6.91; N, 6.26.

Typical Procedure for the Preparation of 3-Substituted 4-Alkoxyisoquinolin-1-amines (4) and (5).

4-Methoxy-3-phenylisoquinolin-1-amine (4a). To a stirred solution of LDA (2.2 mmol), generated by the standard procedure from *n*-BuLi and *i*-Pr_2NH, in diglyme (3 mL) at –78 °C was added a solution of **1a** (0.16 g, 1.1 mmol) in diglyme (1 mL) dropwise; the solution immediately turned deep purple. After the solution was stirred for 15 min at the same temperature, PhCN (0.22 g, 2.2 mmol) was added dropwise and stirring was continued for an additional 1 h. Water (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:4) to give **4a** (0.15 g, 56%); a pale-yellow needles; mp 119–120 °C (hexane); IR (KBr) 3482, 3381, 1616 cm^{-1}; ^1H NMR (600 MHz) δ 3.60 (s, 3H), 5.04 (br s, 2H), 7.36 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.46 (dd, *J* = 8.0, 7.5 Hz, 2H), 7.53 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.3 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (150 MHz) δ 61.07, 118.31, 122.23, 123.03, 126.28, 127.88, 128.23, 129.09, 130.31, 133.51, 137.83, 140.01, 142.50, 151.96; MS *m/z* 250 (M^+, 100). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.77; H, 5.74; N, 11.14.

4-Methoxy-3-(3-methylphenyl)isoquinolin-1-amine (4b): a pale-yellow needles; mp 113–115 °C (hexane); IR (KBr) 3484, 3376, 1616 cm^{-1}; ^1H NMR (600 MHz) δ 2.44 (s, 3H), 3.60 (s, 3H), 5.06 (br s, 2H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.35 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.53 (td, *J* = 7.4, 1.1 Hz, 1H), 7.70 (td, *J* = 7.4, 1.1 Hz, 1H), 7.80–7.84 (m, 3H), 8.11 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz) δ 21.57, 61.07, 118.25, 122.18, 122.94, 126.13, 126.22, 128.07, 128.57, 129.67, 130.11, 133.46, 137.69, 138.05, 140.58, 142.49, 151.85; MS *m/z* 264 (M^+, 100). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.20; H, 6.37; N, 10.67.

4-Methoxy-3-(4-methylphenyl)isoquinolin-1-amine (4c): a pale-yellow solid; mp 144–146 °C (hexane–Et_2O); IR (KBr) 3491, 3454, 1629, 1617 cm^{-1}; ^1H NMR (500 MHz) δ 2.41 (s, 3H), 3.61 (s, 3H), 5.01 (br s, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.51 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.0, 6.9, 1.1

Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 21.32, 60.93, 118.20, 122.14, 122.93, 125.97, 128.92, 128.95, 130.04, 133.48, 135.31, 137.56, 140.42, 142.37, 151.82; MS *m/z* 264 (M^+, 100). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.20; H, 6.18; N, 10.57.

4-Methoxy-3-(3-methoxyphenyl)isoquinolin-1-amine (4d): a pale-yellow solid; mp 135–137 ˚C (hexane–CH_2Cl_2); IR (KBr) 3460, 3364, 1620 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.62 (s, 3H), 3.89 (s, 3H), 5.12 (br s, 2H), 6.93 (ddd, *J* = 8.0, 1.6, 0.9 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.53 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.60 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.63 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H), 7.71 (ddd, *J* = 8.3, 7.0 1.3 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (150 MHz) δ 55.34, 61.11, 114.04, 114.23, 116.40, 121.71, 122.26, 122.97, 126.24, 129.18, 130.17, 133.50, 139.51, 140.08, 142.62, 151.86, 159.57; MS *m/z* 280 (M^+, 100). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.54; H, 5.53; N, 10.02.

4-Methoxy-3-(4-methoxyphenyl)isoquinolin-1-amine (4e): colorless needles; mp 147–148 ˚C (hexane–Et_2O); IR (KBr) 3480, 3372, 1607 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.61 (s, 3H), 3.87 (s, 3H), 5.01 (br s, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.50 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.6, 6.9, 1.1 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz) δ 55.26, 60.77, 113.60, 118.04, 122.02, 122.94, 125.82, 130.03, 130.35, 130.70, 133.50, 140.00, 142.00, 151.83, 159.32; MS *m/z* 280 (M^+, 100). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.72; H, 5.85; N, 9.70.

3-Ethyl-4-methoxyisoquinolin-1-amine (4f): a white solid; mp 125–126 ˚C (hexane–Et_2O); IR (KBr) 3480, 3387, 3326, 1656, 1623 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.31 (t, *J* = 7.4 Hz, 3H), 2.82 (q, *J* = 7.4 Hz, 2H), 3.85 (s, 3H), 4.94 (br s, 2H), 7.45 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.65 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 13.87, 24.75, 62.09, 117.59, 121.52, 123.01, 125.25, 129.88, 132.67, 141.35, 145.93, 152.05; MS *m/z* 202 (M^+, 100). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.04; H, 7.04; N, 13.74.

4-Methoxy-3-(1-methylethyl)isoquinolin-1-amine (4g): a pale-yellow solid; mp 86–88 ˚C (hexane–Et_2O); IR (KBr) 3535, 3436, 3342, 1639, 1623 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.28 (d, *J* = 6.9 Hz, 6H), 3.52 (sept, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 4.95 (br s, 2H), 7.43 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.62 (ddd, *J* = 8.6, 6.9, 1.1 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz) δ 22.07, 27.85, 62.31, 117.52, 121.66, 122.97, 125.17, 129.71, 132.57, 140.37, 149.42, 152.16; MS *m/z* 216 (M^+, 100). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.23; H, 7.64; N, 12.87.

4-Ethoxy-6,7-dimethoxy-3-phenylisoquinolin-1-amine (4h): a colorless viscous oil; R_f 0.26 (AcOEt–hexane 2:3); IR (neat) 3468, 3370, 1624 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.26 (s, *J* = 7.4 Hz, 3H), 3.71 (q, *J* = 7.4 Hz, 2H), 4.02 (s, 3H), 4.06 (s, 3H), 4.81 (br s, 2H), 7.02 (s, 1H), 7.34 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.42 (s, 1H), 7.44 (dd, *J* = 8.0, 7.4 Hz, 2H), 8.01 (dd, *J* = 8.0, 1.1 Hz, 2H); ^{13}C NMR (125 MHz) δ 15.81, 55.95, 55.97, 69.30, 101.27, 102.23, 113.30, 127.54, 128.11, 128.99, 130.14, 138.49, 139.42, 141.36, 149.45, 150.47, 152.67; MS *m/z* 324 (M^+, 100). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.21; H, 6.50; N, 8.59.

4-Ethoxy-6,7-dimethoxy-3-(3-methylphenyl)isoquinolin-1-amine (4i): a pale-yellow viscous oil; R_f 0.26 (AcOEt–hexane 1:1); IR (neat) 3452, 3376, 1626 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.27 (t, *J* = 7.4 Hz, 3H), 2.43 (s, 3H), 3.71 (q, *J* = 7.4 Hz, 2H), 4.03 (s, 3H), 4.05 (s, 3H), 4.82 (br s, 2H), 7.02 (s, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.33 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.42 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (125 MHz) δ 15.82, 21.53, 55.94, 56.05, 69.25, 101.22, 102.20, 113.24, 126.08, 127.96, 128.28, 129.59, 130.13, 137.55, 138.43, 139.64, 141.30, 149.38, 150.42, 152.61; MS *m/z* 338 (M^+, 100). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.81; H, 6.74; N, 8.27.

2-[4-(1-Amino-4-methoxyisoquinolin-3-yl)-1-methoxybutyl]benzonitrile (5): a pale-yellow viscous oil; R_f 0.29 (THF–C_6H_6 1:6); IR (neat) 3459, 3381, 2181, 1624 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.60–1.67 (m, 1H), 1.72–1.82 (m, 2H), 1.97–2.05 (m, 1H), 2.14–2.27 (m, 2H), 3.14 (s, 3H), 3.52 (s, 3H), 4.26 (dd, *J* = 8.0, 3.4 Hz, 1H), 5.08 (br s, 2H), 7.38 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.44–7.46 (m, 2H), 7.55–7.59 (m, 2H), 7.74 (dd, *J* = 8.6, 6.9 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 16.88, 22.35, 36.78, 56.53, 61.30, 79.13, 118.22, 120.13, 122.11, 123.08, 125.66, 126.45, 127.24, 128.47, 129.94, 130.33, 132.83, 137.53, 140.47, 141.22, 141.93, 151.79; MS *m/z* 361 (M^+, 100). Anal. Calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.04; H, 6.41; N, 11.54.

ACKNOWLEDGEMENTS

We are grateful to Mrs. Miyuki Tanmatsu of our university for recording mass spectra and performing combustion analyses.

REFERENCES

1. For recent reports: (a) S. H. Yang, H. T. M. Van, T. N. Le, D. B. Khadka, S. H. Cho, K.-T. Lee, H.-J. Chung, S. K. Lee, C.-H. Ahn, Y. B. Lee, and W.-J. Cho, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5277; (b) P. Ray, J. Wright, J. Adam, J. Bennett, S. Boucharens, D, Black, A. Cook, A. R. Brown, O. Epemolu, D. Flecher, A. Haunso, M. Huggett, P. Jones, S. Laats, A. Lyons, J. Meatres, J. de Man, R. Morphy, Z. Rankovic, B. Sherborne, L. Sherry, N. van Straten, P. Westwood, and G. Z. R. Zaman, *Bioorg. Med. Chem. Lett.*, 2011, **20**, 97; (c) P. Ray, J. Wright, J. Adam, S. Boucharens, D, Black, A. R. Brown, O. Epemolu, D. Flecher, M. Huggett, P. Jones, S. Laats, A. Lyons, J. de Man, R. Morphy, B. Sherborne, L. Sherry, N. van Straten, P. Westwood, and M. York, *Bioorg. Med. Chem. Lett.*, 2011, **20**, 1084. See also pertinent references cited in these papers.

2. E. M. Keiser, J. D. Petty, L. E. Solter, and W. R. Thomas, *Synthesis,* 1974, 805.
3. G. M. Sanders, M. Van Dijk, and H. J. Den Hertog, *Rec. Trav. Chim. Pays-Bas,* 1976, **95**, 31.
4. K. Kobayashi, K. Matsumoto, and A. Kobayashi, *Heterocycles,* 2011, **83**, 2635.
5. T.-L. Teo, M. Vetrichelvan, and Y.-H. Lai, *Org. Lett.*, 2003, **5**, 4207.
6. E. Reimann, R. Hertel, and J. Krauss, *Monatsh. Chem.*, 2008, **139**, 673.