A Versatile Synthesis of 7-Azaindoles

Hartmut Schirok*

Bayer HealthCare AG, Pharma Research, 42096 Wuppertal, Germany
Fax +49(202)364624; E-mail: hartmut.schirok@bayerhealthcare.com

Received 11 March 2005

Dedicated to Professor Lutz F. Tietze

Abstract: 1,3-Disubstituted 7-azaindoles were synthesized from 2,6-dichloropyridine using DoM and intramolecular aromatic substitution after epoxide opening by an amine. Even the sterically demanding adamantylamine may be incorporated leading to derivatives which are not accessible by alkylation of the parent compound.

Key words: azaindoles, pyridines, metalations, nucleophilic aromatic substitutions, ring closure

In nature 7-azaindoles (1*H*-pyrrolo[2,3-*b*]pyridines) appear only as a substructure in a small number of alkaloids. However, much interest in this heterocyclic moiety has arisen in recent pharmacological programs, wherein it serves as bioisoster of indole or purine.[1] Numerous publications on its synthesis and derivatization reflect the increasing attention paid to this heterocyclic system.[2,3]

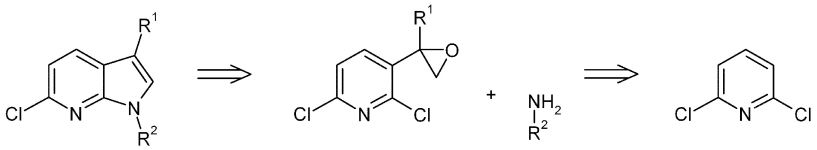
In connection with a medicinal chemistry program, we required a practical synthesis of 1,3-substituted azaindoles of the general formula **1** (Scheme 1). Inspired by two reports on the synthesis of indoles from 2-(2-chlorophenyl)oxiranes[4] and 2-(2-bromophenyl)oxiranes,[5] we decided to develop a new azaindole synthesis based on the retrosynthetic analysis depicted in Scheme 1. An amine should open the epoxide **2** to an amino alcohol, which expels the adjacent halogen by intramolecular nucleophilic aromatic substitution. Subsequent dehydration should yield the desired heterocycle **1**. We planned to start with 2,6-dichloropyridine (**4**) for the synthesis of oxiranes **2**. The directed *ortho* metalation (DoM) of **4** should allow its functionalization in the 3-position.[6]

The lithiation[7] of fluoro- and chloropyridines[8] has been thoroughly studied by Quéguiner[9] and Schlosser.[10] In our hands, after deprotonation of 2,6-dichloropyridine (**4**) with LDA, the addition to ketones like acetone, acetophenone, or trifluoroacetone occurred smoothly (Scheme 2), and the desired tertiary alcohols **5** could be easily separated from unconsumed starting material by column filtration due to their higher polarity. In agreement with repeated reports in the literature, we detected small amounts of the regioisomeric adducts resulting from lithiation at the 4-position. In the course of our investigations it turned out to be unnecessary to separate the regioisomers, since the minor component leads to a polar, unproductive intermediate in the last step of the sequence. The dehydration of **5** yielding α-substituted styrene derivatives **6** was performed in a mixture of acetic and sulfuric acid (3:1) at 130 °C for 30 minutes. The elimination products were isolated after basic work-up and did not need further purification. Unfortunately, **5c** failed to dehydrate due to the strong electron-withdrawing effect of the trifluoromethyl group. Even after heating in concentrated sulfuric acid to 120 °C for 14 hours we recovered the alcohol **5c** almost quantitatively. With other reagents like thionyl chloride, thionyl chloride/pyridine[11] or Burgess' reagent we were also unsuccessful, demonstrating that this approach is not applicable for the synthesis of 3-trifluoromethyl 7-azaindole.

The epoxides **2** were generated from the alkenes by oxidation with MCPBA in dichloromethane, and were essentially pure after basic extraction.

In the final step of the sequence the epoxides were reacted with primary amines leading to the 7-azaindoles. The transformation was performed in 1-butanol at 100–120 °C (Scheme 3). Mechanistically, a domino[12] epoxide-opening-cyclization, and dehydration take place:

The amine **3** attacks the oxirane **2** at the sterically less hindered position, and an 1,2-aminoalcohol **7** is generated.

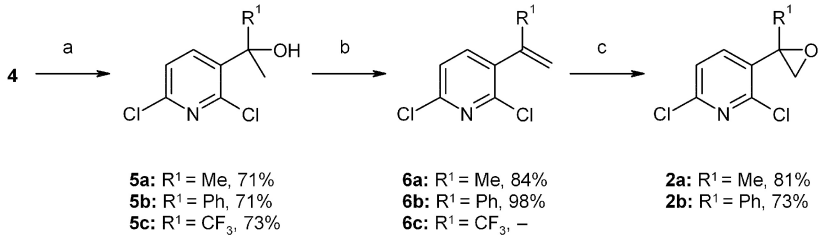


1 2 3 4

Scheme 1 Retrosynthesis.

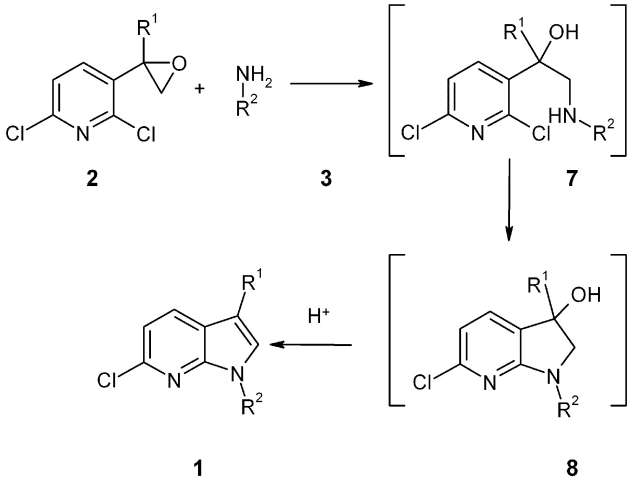
SYNLETT 2005, No. 8, pp 1255–1258
Advanced online publication: 21.04.2005
DOI: 10.1055/s-2005-865243; Art ID: G08305ST
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: The University of Hong Kong. Copyrighted material.



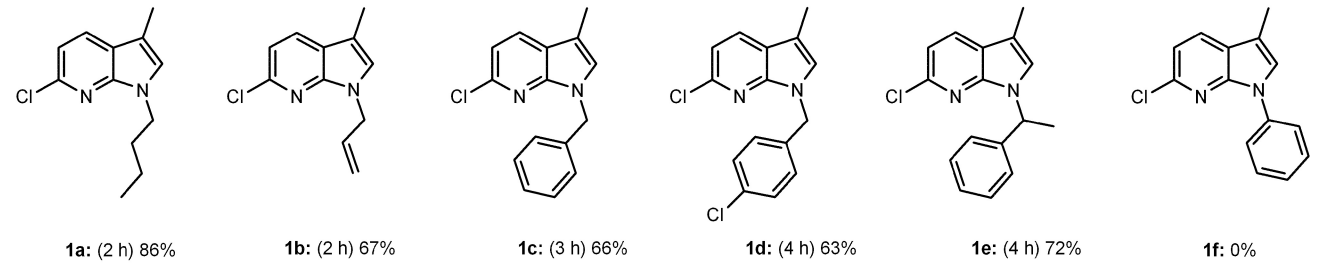
Scheme 2 Synthesis of epoxides **2**. *Reagents and conditions:* a) LDA, THF, –78 °C, then R^1COMe, –78 °C → r.t.; b) H_2SO_4–AcOH (1:3), 130 °C; c) MCPBA, CH_2Cl_2, r.t.

The subsequent intramolecular nucleophilic aromatic substitution leads to the annellated system **8**. The speed of the reaction is determined by the steric hindrance of the amine **3**. With linear amines like butyl- or allylamine it was complete within three to five hours, whilst α-branched amines like cyclopentylamine required heating overnight. Consequently, using α-trisubstituted amines like *tert*-amylamine or adamantylamine the reaction required heating for several days to obtain the azaindoles in high yields. The intermediate tertiary alcohol **8** can be isolated. However, it is very prone to aromatization yielding **1**, and therefore we normally ran the sequence to completion. In most of the examples, only a small portion of **8** spontaneously collapsed to **1** and the addition of hydrochloric acid was needed to catalyze the dehydration. The target compounds were isolated in medium to high yields (Figure 1), demonstrating the high versatility of our approach.

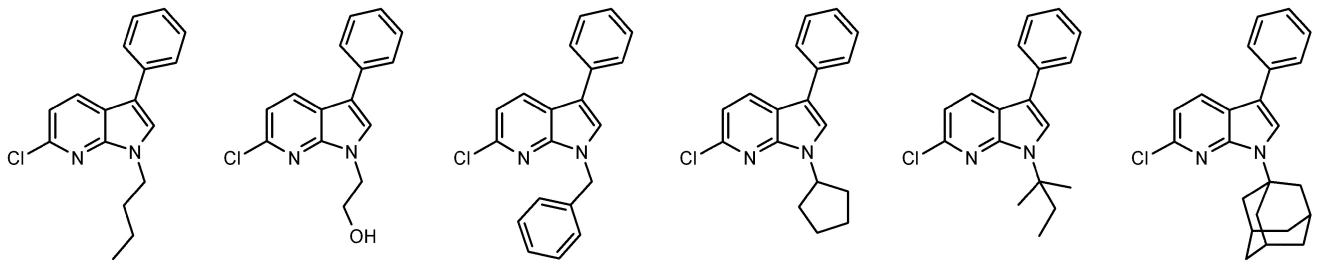


Scheme 3 Mechanism for the 7-azaindole formation.

The synthesis of the epoxides **2** via the styrenes **6** proved to be facile since only one purification step was needed in the 3-step sequence. However, we were interested in a shorter approach. As depicted in Scheme 4, the reaction of



1a: (2 h) 86% **1b:** (2 h) 67% **1c:** (3 h) 66% **1d:** (4 h) 63% **1e:** (4 h) 72% **1f:** 0%

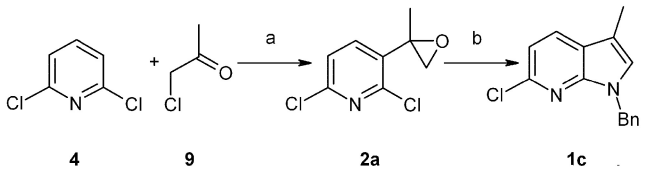


1g: (8 h) 95% **1h:** (12 h) 74% **1i:** (3 h) 66% **1j:** (16 h) 86% **1k:** (36 h) 78% **1l:** (72 h) 84%

Figure 1 Synthesized 1,3-disubstituted 7-azaindoles; reaction time in parentheses.

Downloaded by: The University of Hong Kong. Copyrighted material.

the deprotonated pyridine **4** with chloroacetone **9** should yield the oxirane **2a** in a single step. In our hands, we isolated the desired compound in 60% purity. Since the accompanying compound was unreacted starting material, which should not interfere in the subsequent step, we used the crude product without purification. The reaction with benzylamine gave 1-benzyl-3-methyl-7-azaindole (**1c**) in 50% overall yield.



Scheme 4 Two-step synthesis of 7-azaindoles from 2,6-dichloropyridine. *Reagents and conditions:* a) LDA, THF, –78 °C, then **9**; b) $BnNH_2$, 1-butanol, 120 °C, then HCl (aq), 50% overall yield.

We were also interested in the regioselectivity of the cyclization step for 2,4-dichloropyridine derivatives **11** (Scheme 5). The styrene **10** was prepared from **5a** in three steps comprising N-oxidation (54%), elimination (96%), and chlorination (38%). An alternative route towards **10** started with the oxidation of 2,6-dichloropyridine (**4**; 69%)[13] and reaction with acetone after deprotonation (57%) to yield the same product as isolated from the oxidation of **5a**. The epoxidation of **10** was significantly slower than for the dichloro derivative **6**, and **11** was isolated in 71% yield. Its cyclization with benzylamine resulted in the formation of the two regioisomers **12** and **13** (Scheme 5) in a 1:1.1 ratio. The lack of regioselectivity demonstrates that the same strategy can be applied to the synthesis of the regioisomeric 5-azaindoles (1*H*-pyrrolo[3,2-*c*]pyridines) starting with 4-chloro- or 4-fluoropyridine. Further work in this area is currently underway.

In conclusion, a highly efficient synthesis of 7-azaindoles was developed. Starting from readily available 2,6-dichloropyridine **4**, the epoxides **2** can be synthesized in three steps via styrenes **6** or in a single transformation with α-chloroketones after directed *ortho* metalation (DoM). Thorough purification of the intermediates is not necessary due to the robustness of the final reaction in the sequence. Its simplicity and broad substrate tolerance allows a combinatorial access to the target compounds.

2-(2,6-Dichloropyridin-3-yl)propan-2-ol (5a); Typical Procedure

To a freshly prepared solution of LDA (89.2 mmol) in THF at –78 °C, 2,6-dichloropyridine (12.0 g, 81.1 mmol) in THF (20 mL) was added. After stirring for 2 h at this temperature acetone (8.94 mL, 122 mmol) was added. The mixture was stirred for an additional 2 h and then slowly warmed to r.t. The mixture was poured into ice water and extracted twice with *tert*-butylmethyl ether. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2, then CH_2Cl_2–MeOH, 50:1) to yield 11.8 g (71%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.59 (s, 6 H), 5.58 (s, 1 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 8.23 (d, *J* = 8.3 Hz, 1 H).

2,6-Dichloro-3-isopropenylpyridine (6a)

Tertiary alcohol **5a** (1.20 g, 5.82 mmol) was dissolved in AcOH (6.0 mL) and concd H_2SO_4 (2.0 mL) was added. The mixture was heated to reflux for 30 min. It was poured into ice water, basified with concd NaOH solution and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated to yield 868 mg (79%) of the title compound as a yellow oil.

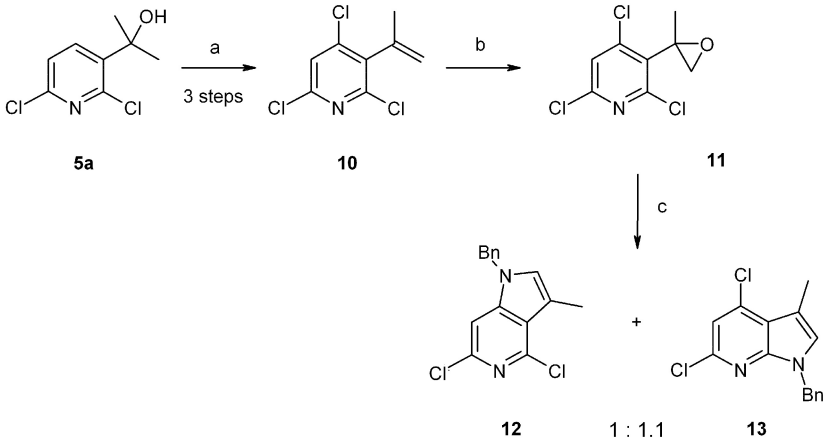
^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.06 (dd, *J* = 1.3, 0.9 Hz, 3 H), 5.08 (m, 1 H), 5.38 (dq, 1.5, 1.3 Hz, 1 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 7.82 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.6, 118.7, 123.8, 137.5, 140.6, 142.1, 146.7, 147.5.

HRMS: *m*/*z* calcd for $C_8H_7Cl_2N$: 186.9956; found: 186.9956.

2,6-Dichloro-3-(2-methyloxiran-2-yl)pyridine (2a)

Styrene **6a** (4.10 g, 21.8 mmol) was dissolved in CH_2Cl_2 (120 mL) and MCPBA (70%, 10.8 g, 43.6 mmol) was added in portions. The reaction was stirred at r.t. for 20 h, then diluted with CH_2Cl_2 and extracted three times with a cold 1 N NaOH solution. The organic layer was dried over sodium sulfate and the solvent was evaporated to yield the epoxide (3.6 g, 81%) as a light yellow oil.



Scheme 5 Regioselectivity of the cyclization. *Reagents and conditions:* a) 1. H_2O_2, CF_3CO_2H, reflux, 2. H_2SO_4–AcOH (1:3), 130 °C, 3. $POCl_3$, $CHCl_3$, reflux; b) MCPBA, CH_2Cl_2, reflux; c) $BnNH_2$, 1-butanol, 120 °C.

Downloaded by: The University of Hong Kong. Copyrighted material.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.59 (s, 3 H), 2.85 (d, *J* = 4.9 Hz, 1 H), 3.07 (d, *J* = 4.9 Hz, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.4, 53.8, 56.1, 123.7, 135.2, 141.0, 147.2, 148.0.

HRMS: *m*/*z* calcd for $C_8H_7Cl_2NO$: 202.9905; found: 202.9895.

1-Benzyl-6-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1c)

Epoxide **2a** (120 mg, 0.59 mmol) and benzylamine (126 mg, 1.18 mmol) were heated to 110 °C in 1-butanol (0.5 mL) for 3 h. Subsequently, 4 N HCl (1 mL) was added, and the mixture was stirred at r.t. for 4 h). The mixture was basified with 1 N NaOH and extracted three times with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. The crude product was purified by preparative HPLC to yield 100 mg (66%) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3 H), 5.37 (s, 2 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 7.20 (d, *J* = 7.1 Hz, 2 H), 7.24–7.33 (m, 3 H), 7.38 (s, 1 H), 8.01 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.37, 46.9, 108.9, 114.7, 119.2, 126.8, 127.1, 127.3, 128.5, 130.2, 138.0, 143.1, 146.0.

HRMS: *m*/*z* calcd for $C_{15}H_{13}ClN_2$: 256.0767; found: 256.0770.

6-Chloro-1-cyclopentyl-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (1j)

The compound was prepared analogously to **1c** from **2b**.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67–1.80 (m, 2 H), 1.86–2.00 (m, 4 H), 2.11–2.22 (m, 2 H), 5.16 (quint, *J* = 7.4 Hz, 1 H), 7.22 (d, *J* = 8.3 Hz, 1 H), 7.28 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 7.3 Hz, 2 H), 7.73 (d, *J* = 7.3 Hz, 2 H), 8.08 (s, 1 H), 8.33 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.6, 32.1, 54.7, 114.3, 115.9, 116.5, 124.3, 126.0, 126.3, 128.8, 131.0, 134.0, 143.1, 146.5.

HRMS: *m*/*z* calcd for $C_{18}H_{17}ClN_2$: 296.1080; found: 296.1069.

References

(1) For recent publications see: (a) Ujjainwalla, F.; Walsh, T. F. *Tetrahedron Lett.* **2001**, *42*, 6441. (b) Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621. (c) Sanderson, P. E. J.; Stanton, M. G.; Dorsey, B. D.; Lyle, T. A.; McDonough, C.; Sanders, W. M.; Savage, K. L.; Naylor-Olsen, A. M.; Krueger, J. A.; Lewis, S. D.; Lucas, B. J.; Lynch, J. J.; Yan, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 795. (d) Kuo, G.-H.; Prouty, C.; DeAngelis, A.; Shen, L.; O'Neill, D. J.; Shah, C.; Connolly, P. J.; Murray, W. V.; Conway, B. R.; Cheung, P.; Westover, L.; Xu, J. Z.; Look, R. A.; Demarest, K. T.; Emanuel, S.; Middleton, S. A.; Jolliffe, L.; Beavers, M. P.; Chen, X. *J. Med. Chem.* **2003**, *46*, 4021. (e) Wang, T.; Zhang, Z.; Wallace, O. B.; Deshpande, M.; Fang, H.; Yang, Z.; Zadjura, L. M.; Tweedie, D. L.; Huang, S.; Zhao, F.; Ranadive, S.; Robinson, B. S.; Gong, Y.-F.; Riccardi, K.; Spicer, T. P.; Deminie, C.; Rose, R.; Wang, H.-G. H.; Blair, W. S.; Shi, P.-Y.; Lin, P.-f.; Colonno, R. J.; Meanwell, N. A. *J. Med. Chem.* **2003**, *46*, 4236. (f) Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607. (g) Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J. A.; Delagrange, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med. Chem.* **2004**, 515. (h) Zhang, H.-C.; Ye, H.; Conway, B. R.; Derian, C. K.; Addo, M. F.; Kuo, G.-H.; Hecker, L. R.; Croll, D. R.; Li, J.; Westover, L.; Xu, J. Z.; Look, R.; Demarest, K. T.; Andrade-Gordon, P.; Damiano, B. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3245. (i) Oh, S.-J.; Choe, Y.-S.; Chi, D.-Y.; Ryu, E. K.; Saji, H.; Choe, Y. S.; Chi, D. Y.; Kim, S. E.; Lee, J.; Kim, B.-T. *Bioorg. Med. Chem.* **2004**, *12*, 5505. (j) Wang, S.; Wan, N. C.; Harrison, J.; Miller, W.; Chuckowree, I.; Sohal, S.; Hancox, T. C.; Baker, S.; Folkes, A.; Wilson, F.; Thompson, D.; Cocks, S.; Farmer, H.; Boyce, A.; Freathy, C.; Broadbridge, J.; Scott, J.; Depledge, P.; Faint, R.; Mistry, P.; Charlton, P. *J. Med. Chem.* **2004**, *47*, 1339. (k) Hilmy, K. M. H. *Arch. Pharm.* **2004**, *337*, 15.

(2) (a) Desarbre, E.; Coudret, S.; Meheust, C.; Mérour, J.-Y. *Tetrahedron* **1997**, *53*, 3637. (b) Park, S. S.; Choi, J.-K.; Yum, E. K. *Tetrahedron Lett.* **1998**, *39*, 627. (c) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355. (d) Alvarez, M.; Fernández, D.; Joule, J. A. *Synthesis* **1999**, 615. (e) Chi, S. M.; Choi, J.-K.; Yum, E. K.; Chi, D. Y. *Tetrahedron Lett.* **2000**, *41*, 919. (f) Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, 609. (g) Konradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571. (h) Thibault, C.; L'Heureux, A.; Bhide, R. V.; Ruel, R. *Org. Lett.* **2003**, *5*, 5023. (i) Hong, C. S.; Seo, J. Y.; Yum, E. K.; Sung, N.-D. *Heterocycles* **2004**, *63*, 631. (j) L'Heureux, A.; Thibault, C.; Ruel, R. *Tetrahedron Lett.* **2004**, *45*, 2317. (k) Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935. (l) Debenham, S. D.; Chan, A.; Liu, K.; Price, K.; Wood, H. B. *Tetrahedron Lett.* **2005**, *46*, 2283.

(3) For a review see: Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471.

(4) Tambute, A. *C. R. Seances Acad. Sci., Ser. C* **1974**, *278*, 1239.

(5) (a) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 827. (b) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 829.

(6) (a) Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793. For reviews of the DoM technique see: (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, **2002**.

(7) For a recent report on the deprotonation with lithium magnesates see: Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron Lett.* **2004**, *45*, 7873.

(8) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059.

(9) (a) Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139. (b) Mallet, M.; Branger, G.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319. (c) See also: Mallet, M. *J. Organomet. Chem.* **1991**, *406*, 49.

(10) (a) Mongin, F.; Tognini, A.; Cottet, F.; Schlosser, M. *Tetrahedron Lett.* **1998**, *39*, 1749. (b) Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018.

(11) Rodrigues, I.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2001**, *66*, 2098.

(12) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; *Angew. Chem.* **1993**, *105*, 137. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Vögtle, F.; Stoddart, J. F.; Shibasaki, M., Eds.; Wiley-VCH: Weinheim, **2000**, 39.

(13) D'Andrea, S. V.; Bonner, D.; Bronson, J. J.; Clark, J.; Denbleyker, K.; Fung-Tomc, J.; Hoeft, S. E.; Hudyma, T. W.; Matiskella, J. D.; Miller, R. F.; Misco, P. F.; Pucci, M.; Sterzycki, R.; Tsai, Y.; Ueda, Y.; Wichtowski, J. A.; Singh, J.; Kissick, T. P.; North, J. T.; Pullockaran, A.; Humora, M.; Boyhan, B.; Vu, T.; Fritz, A.; Heikes, J.; Fox, R.; Godfrey, J. D.; Perrone, R.; Kaplan, M.; Kronenthal, D.; Mueller, R. H. *Tetrahedron* **2000**, *56*, 5687.

Downloaded by: The University of Hong Kong. Copyrighted material.