Improved one-pot synthesis of 6-methylpurines under microwave irradiation

Hai-Ming Guo,[a]* Zhi-Jie Mao,[a] Hong-Ying Niu,[b] Dong-Chao Wang,[a] Gui-Sheng Zhang,[a] and Gui-Rong Qu[a]*

[a]*College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang 453007, Henan, China*

[b]*School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China*

E-mail: guohm518@hotmail.com, guguir@sina.com

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.928

Abstract

A facile and efficient method for direct synthesis of 6-methylpurines was developed through S_NAr-based addition reactions between various 6-halopurine derivatives and ethyl acetoacetate with assistance of microwave irradiation, which underwent direct coupling reaction, in situ deacetylation and decarboxylation to yield 6-methylated purines in high to excellent yields within 10 min.

Keywords: Microwave, one-pot reaction, 6-methylpurine

Introduction

6-Methylpurine is highly cytotoxic[1] and its liberation by purine nucleoside phosphorylases from its non-toxic deoxyribonucleoside was proposed as a novel principle in the gene therapy of cancer.[2] And 6-methylpurine-β-D-riboside (6, β-D-MPR), an antibiotic isolated from culture broths of the basidiomycetes fungi *Collybia dryophilia* and *Collybia maculata*, was found to have good antifungal, antiviral and antitumor activities.[1,3] A lot of efforts have been made on the modification of 6-methylpurine and its ribonucleoside since their biological effects were found. Recently, Hocek et al. reported a series of analogs of 6-methylpurine and its ribonucleoside, such as 6-(hydroxymethyl)-,[4a,4b] 6-(fluoromethyl)-,[4c] 6-(difluoromethyl)-,[4d] 6-(trifluoromethyl)-,[4e] 6-(2-hydroxyethyl)-,[4f] 6-(oxiran-2-yl)-[4g] bases and nucleosides, and many of them display significant cytostatic activities.

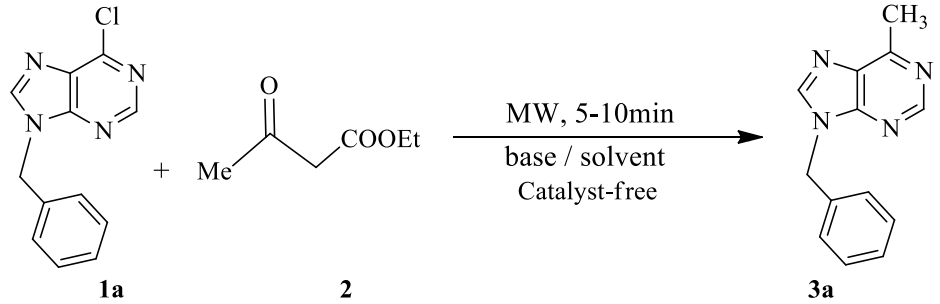
6-Methylpurine bases were prepared previously by the conventional method of heterocyclization[5] from 6-methyluracil which was tedious and usually gave low yields. Another method involved the displacement of a suitable leaving group on the heterocycle by Wittig reagent[6] which usually required rigorous reaction conditions (anhydrous, nitrogen atm at -30 to -35 ºC). Transition metal-catalyzed cross-coupling reaction which is more prevalent does provide a general and efficient methodology for the synthesis of 6- methylpurines in the presence of methylzinc bromide[7] or trimethylaluminum.[8] Recently, regioselective methylation reactions[9] of 2, 6-dichloropurines with methylzinc bromide or trimethylaluminum under catalytic effects of Cu(I) or Pd(I) species were also investigated by Hocek et al. However, the expensive catalyst and rigorous reaction conditions often make this method less desirable. In addition to the above-mentioned methods, 6-methylpurines could also be prepared[10] in two steps in moderate yields by deacetylation and decarboxylation of the coupling products of 6-tosyloxypurines with ethyl acetoacetate.

Microwave heating has been widely recognized as an efficient synthetic tool and its benefits have been well-documented.[11] Many reactions have been demonstrated to result in higher yield and/or selectivity under microwave heating compared with conventional heating.[11b,12] Based on our preliminary study on various nucleoside analogues, [13] herein, we report a novel and efficient method for the synthesis of 6-methylpurines from various 6-halopurine derivatives and ethyl acetoacetate with assistance of microwave irradiation.

Results and Discussion

Initially, to examine the effect of temperature, solvent, reaction time and the type of bases in more detail, we conducted a brief screen of microwave-enhanced synthesis of 9-Bn-6-methylpurine from 9-Bn-6-chloropurine[14] and ethyl acetoacetate (Table 1). Excellent yield was obtained when the reaction was performed in the condition of 200 W, 80 ºC, 10 min and K_2CO_3 as the base in DMSO (entry 1). When the reation time was shorten, a slight decrease in yield was observed (entries 2-3). Temperature and microwave power did play an important role in deacetylation and decarboxylation. A sharp decline of yield took place at lower temperature or higher microwave power (entries 4-5). In all the investigated solvents (DMSO, DMAc, DMF), DMSO turned out to be the best choice (entries 1, 6-7). Compared with other bases, both $K_3PO_4.3H_2O$ and K_2CO_3 gave good results (entries 1, and 9), while Cs_2CO_3 and Na_2CO_3 gave moderate yields (entries 8, and 10). When NaH was used, the reaction gave many complex unidentified products (entry 11).

Table 1. Optimization of the microwave-enhanced synthesis of 9-Bn-6-methylpurine[a]



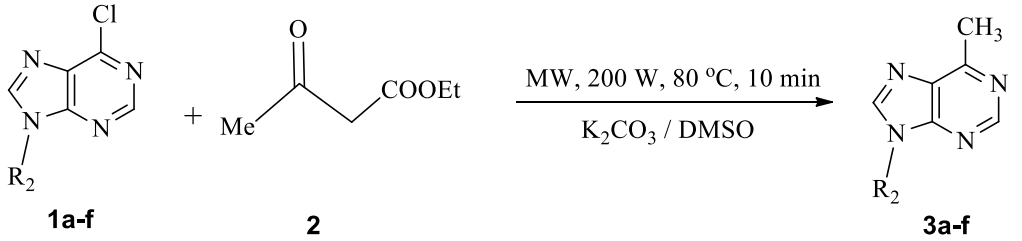
1a **2** **3a**

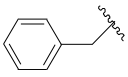
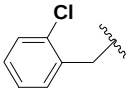
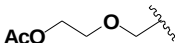
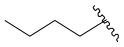
Entry	Solvent	Base (equiv)	Temp. (°C)	Time (min)	Yield (%)[b]
1	DMSO	K_2CO_3 (7.5)	80	10	91
2	DMSO	K_2CO_3 (7.5)	80	8	89
3	DMSO	K_2CO_3 (7.5)	80	5	75
4	DMSO	K_2CO_3 (7.5)	70	5	38
5[c]	DMSO	K_2CO_3 (7.5)	70	5	20
6	DMF	K_2CO_3 (7.5)	80	10	17
7	DMAc	K_2CO_3 (7.5)	80	10	21
8	DMSO	Cs_2CO_3 (7.5)	80	10	62
9	DMSO	$K_3PO_4.3H_2O$ (7.5)	80	10	90
10	DMSO	Na_2CO_3(7.5)	80	10	70
11	DMSO	NaH (7.5)	80	10	trace

[a]Reagents and conditions: **1a** (0.5 mmol), base (3.75 mmol, 7.5 eq), ethyl acetoacetate **2** (2.5 mmol, 5 eq), solvent (2 mL), MW: 200 W. [b]Isolated yield based on **1a**. [c]The reaction was carried out at 400 W.

The applicability of the optimized reaction conditions to other 6-chloropurine derivatives was then studied (Table 2). Various 6-chloropurine derivatives could react with ethyl acetoacetate smoothly with high to excellent yields under the optimized reaction conditions (entries 1-5). When n-butyl was present at the 9 position, the methylated product **3e** was obtained in slightly lower yield (entry 5). 6-Chloro-9*H*-purine did not give the methylated products (entry 6), which was in agreement with previous literature.[4f, 15]

Table 2. Reactions of ethyl acetoacetate with various 6-chloropurine derivatives to yield 6-methylpurines with assistance of microwave irradiation[a]

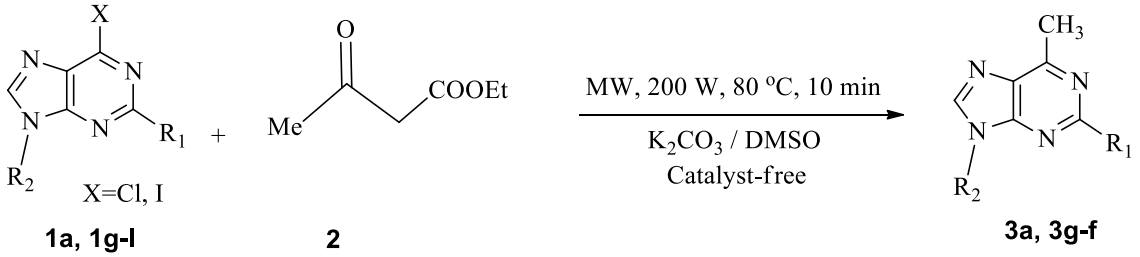


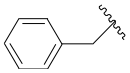
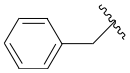
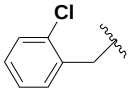
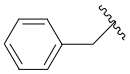
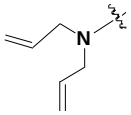
Entry	R_2	Product	Yield (%)[b]
1		**3a**	91
2		**3b**	90
3		**3c**	94
4		**3d**	95
5		**3e**	75
6	**H**	**3f**	0

[a]Reagents and conditions: **1a** (0.5 mmol), base (3.75 mmol, 7.5 eq), ethyl acetoacetate **2** (2.5 mmol, 5 eq), DMSO (2 mL), MW: 200 W, 80 °C, 10 min. [b]Isolated yield based on **1a**.

The effects of different substituents at C6 and C2 were also discussed (Table 3). 6-Iodopurine derivatives[16] **1g-1i** gave similar results compared with 6-chloropurine derivatives (entries 2-4), indicating that the leaving group at 6 position did not make a great difference in this reaction. The effect of substituent groups at C2 was also studied. Replacement of H by Cl gave the monomethylation product **3g** regioselectively (entry 5). When H at C2 was replaced by a nitrogen-containing substituent, we could not obtain the methylated product **3h** at all, possibly due to the electron-donating effect (entry 6). While 6-iodo-9*H*-purine did not give the methylated products likewise (entry 7).

Table 3. Reactions of ethyl acetoacetate with various 6-halopurine derivatives to yield 6-methylpurines with assistance of microwave irradiation[a]



Entry	X	R_1	R_2	Product	Yield (%)[b]
1	Cl	H		**3a**	91
2	I	H		**3a**	90
3	I	H		**3b**	92
4	I	H		**3c**	93
5	Cl	Cl		**3g**	91
6	Cl			**3h**	0
7	I	H	H	**3f**	0

[a]Reagents and conditions: **1a** (0.5 mmol), base (3.75 mmol, 7.5 eq), ethyl acetoacetate **2** (2.5 mmol, 5 eq), DMSO (2 mL), MW: 200 W, 80 °C, 10 min. [b]Isolated yield based on **1a**.

Conclusions

In conclusion, we have developed a straightforward and cost-effective method for the synthesis of 6-methylpurines with assistance of microwave irradiation from ethyl acetoacetate and 6-halopurine derivatives based on S_NAr addition reactions. In this method, no metal catalyst and metal reagents was used. The use of microwave irradiation allowed a decrease in reaction time from 5 or 8 hours to ten minutes with yields as good as or even better than the yields obtained in classical heating. The simplicity of this short and clean procedure and generally satisfactory yields render this method particularly attractive. Further studies of this methodology to other active methylene compounds are in progress.

Experimental Section

General. Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 NMR spectrometer for ^{1}H-NMR, 100 MHz for ^{13}C-NMR. Proton chemical shifts δ are given in ppm relative to tetramethylsilane (0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent DMSO-d_6 (2.50 ppm) for ^{1}H and ^{13}C NMR. High resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-TofMS/MS system. For column chromatography silica gel (200-300 mesh) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All regents and solvents were purchased from commercial sources and purified commonly before used.

All microwave irradiation experiments were carried out in the cavity of a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity infrared sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, P. R. of China) with continuous irradiation power from 0 to 1000 W. The reactions were carried out in open glass vials. The temperature was measured with an IR sensor on the outer surface of the reaction vials.

All the products were identified by comparison of their spectra, melting points, and analytical data with those in the literature.[13a]

Typical procedure for the synthesis of 9-Bn-6-methylpurine (3a)

The Bn-protected 6-chloropurine **1a** (0.5 mmol), anhydrous potassium carbonate (3.75 mmol, 7.5 eq) and ethyl acetoacetate **2** (2.5 mmol, 5 eq) were sequentially added to 2 mL of DMSO (A.R. grade without any previous workup). With use of a microwave power of 200 W, the reaction mixture was ramped from room temperature to 80 ^{o}C over 30-40 s, and then held at this temperature for 10 min. After cooling to room temperature, the resulting mixture was diluted with an ample amount of water (ca. 10 mL). The mixture was then extracted with methylene chloride (3×5 mL). The collected organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography (petroleum ether / ethyl acetate) to give the methylated product **3a** in 91% yield.

9-Bn-6-methylpurine (3a). Yellow crystals, M.p. 68–70 ^{o}C (lit. 75–77 ^{o}C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.88 (s, 1H), 8.02 (s, 1H), 7.24-7.34 (m, 5H), 5.43 (s, 2H), 2.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.4, 47.2, 127.8, 128.5, 129.1, 132.8, 135.1, 143.5, 150.5, 152.4, 159.3. HRMS calcd for $C_{13}H_{13}N_4$ [M + H^+] 225.1140, found 225.1141.

9-(2-Chlorobenzyl)-6-methyl-9*H*-purine (3b). Yellow crystals, M.p. 135–136 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.89 (s, 1H), 8.10 (s, 1H), 7.45 (d, *J*= 8.0 Hz, 1H), 7.25-7.31 (m, 3H), 5.57 (s, 2H), 2.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.3, 152.4, 150.6, 143.7, 133.4, 132.7, 132.6, 130.3, 130.0, 129.9, 127.4, 44.8, 19.4. HRMS: calcd for $C_{13}H_{12}ClN_4$ [M + H^+] 259.0750, found 259.0748.

9-Allyl-6-methyl-9*H*-purine (3c). Yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.81 (s, 1H), 8.01 (s, 1H), 6.01 (m, 1H), 5.29 (d, *J*= 10.0 Hz, 1H), 5.18 (d, *J*= 16.8 Hz, 1H), 4.85 (d, *J*= 6.0 Hz, 2H), 2.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.2, 152.2, 150.3, 143.5, 132.8, 131.3, 119.2, 45.6, 19.3. HRMS: calcd for $C_9H_{11}N_4$ [M + H^+] 175.0984, found 175.0981.

9-[(2-Acetyl-ethoxy) methyl]-6-methyl-9*H*-purine (3d). White powder. M.p. 52 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.84 (s, 1H), 8.17 (s, 1H), 5.68 (s, 2H), 4.15 (t, *J*= 4.8 Hz, 2H), 3.74 (t, *J*= 4.8 Hz, 2H), 2.84 (s, 3H), 1.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 170.7, 159.6, 152.7, 150.8, 143.6, 132.7, 72.6, 67.8, 62.7, 20.7, 19.4. HRMS: calcd for $C_{11}H_{14}N_4NaO_3$ [M + Na^+] 273.0964, found 273.0965.

9-Butyl-6-methyl-9*H*-purine (3e). Yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.77 (s, 1H), 7.96 (s, 1H), 4.18 (t, *J*= 7.2 Hz, 2H), 2.78 (s, 3H), 1.79-2.03 (m, 2H), 1.20-1.33 (m, 2H), 0.88 (t, *J*= 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 158.7, 151.7, 150.1, 143.4, 132.5, 43.3, 31.5, 19.5, 19.0, 13.1. HRMS: calcd for $C_{10}H_{15}N_4$ [M + H^+] 191.1297, found 191.1297.

9-Benzyl-2-chloro-6-methyl-9*H*-purine (3g). Yellow crystals, M.p. 109-112 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.94 (s, 1H), 7.26-7.38 (m, 5H), 5.38 (s, 2H), 2.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 161.4, 153.6, 151.9, 143.9, 134.3, 131.6, 128.9, 128.4, 127.7, 47.1, 19.2. HRMS: calcd for $C_{13}H_{12}ClN_4$ [M + H^+] 259.0750, found 259.0750.

Acknowledgements

We are grateful for financial support from the National Nature Science Foundation of China (grants 20772024 and 20802016), the Program for New Century Excellent Talents in University of Ministry of Education (NCET-09-0122), the Program for Innovative Research Team in University of Henan Province (2008IRTSTHN002), and the Henan National Nature Science Foundation (092300410225).

References

1. Montgomery, J. A.; Hewson, K.; *J. Med. Chem.* **1968**, *11*, 48.
2. Parker, W. B.; King, S. A.; Allan, P. W.; Bennett, L. L. Jr.; Secrist III, J. A.; Montgomery, J. A.; Gilbert, K. S.; Waud, W. R.; Wells, A. H.; Gillespie, G. Y.; Sorscher, E. J. Hum. *Gene Ther.* **1997**, *8*, 1637.
3. Leonhardt, K; Anke, T. Z. *Naturforsch* **1987**, *42c*, 420.
4. (a) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Org. Lett.* **2004**, *6*, 3225. (b) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1669. (c) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2005**, *3*, 3001. (d) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Synthesis.* **2006**, 1848. (e) Hocková, D.; Hocek, M.; Dvořáková, H.; Votruba, I.

Tetrahedron **1999**, *55*, 11109. (f) Hasník, Z.; Šilhár, P.; Hocek, M. *Tetrahedron Lett.* **2007**, *48*, 5589. (g) Kuchař, M.; Pohl, R.; Klepetářová, B.; Hocek, M. *Tetrahedron* **2008**, *64*, 10355.

5. (a) Gabriel, S.; Colman, J. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 1234. (b) Prasad, R. N.; Noell, C. W.; Robins, R. K. *J. Am. Chem. Soc.* **1959**, *81*, 193. (c) Woenckhaus, C. W. *Chem. Ber.* **1964**, *97*, 2439.
6. Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 8095.
7. (a) Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; Øveras, H.; Rise, F. *Tetrahedron.* **1994**, *50*, 9743. (b) Hassan, A. E. A.; Abou-Elkair, R. A. I.; Montgomery, J. A.; Secrist III, J. A. *Nucleosides, Nucleotides, Nucleic Acids.* **2000**, *19*, 1123.
8. Česnek, M.; Hocek, M.; Holý, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357.
9. (a) Čerňa I.; Pohl, R.; Klepetov, B. and Hocek, M. *Org. Lett.* **2006**, *8*, 5389. (b) Hocek, M.; Dvořáková, H. *J. Org. Chem.* **2003**, *68*, 5773. (c) Hocek, M.; Pohl, R. and Císařová, I. *Eur. J. Org. Chem.* **2005**, 3026.
10. Sakata, S.; Yonei, S.; Yoshino, H. *Chem. Pharm. Bull.* **1982**, *30*, 2583.
11. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Lidström, P.; Tierney, J.; Wathey, J.; Westman J. *Tetrahedron* **2001**, *57*, 9225. (c) Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596. (d) Westman, J. *Org. Lett.* **2001**, *3*, 3745. (e) Brain,C. T.; Brunton, S. A. *Synlett* **2001**, 382.
12. (a) Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* **2005**, *70*, 2361. (b) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515. (c) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2006**, *47*, 5171. (d) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563. (e) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (f) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653. (g) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128.
13. (a) Qu, G. R.; Mao, Z. J.; Niu, H. Y.; Wang, D. C.; Xia, C.; Guo, H. M. *Org. Lett.* **2009,** *11*, 1745. (b) Qu, G. R.; Xia, R.; Yang, X. N.; Li, J. G.; Wang, D. C.; Guo, H. M. *J. Org. Chem.* **2008**, *73*, 2416. (c) Qu, G. R.; Zhao, L.; Wang, D. C.; Wu, J.; Guo, H. M. *Green Chem.* **2008**, *10*, 287. (d) Qu, G. R.; Zhang, Z.-G.; Geng, M. W.; Xia, R.; Zhao, L.; Guo, H. M. *Synlett* **2007**, *5*, 721.
14. (a) Gundersen, L. L; Bakkestuen A. K. Aaaen, A. J.; Øverás, H. and Rise, H. *Tetrahedron* **1994**, *50*, 9743. (b) Kasibhatla, S. R.; Hong, K.; Biamonte, M. A.; Busch, D. J.; Karjian, P. L.; Sensintaffar, J. L.; Kamal, A.; Lough, R. E.; Brekken, J.; Lundgren, K.; Grecko, R.; Timony, G. A.; Ran, Y.; Mansfield, R.; Fritz, L. C.; Ulm, E.; Burrows, F. J.; and Boehm, M. F. *J. Med. Chem.* **2007**, *50*, 2767.
15. Huang, L. K.; Cherng, Y. C.; Cheng, Y. R.; Jang, J. P.; Chao, Y. L. and Cherng ,Y. J. *Tetrahedron* **2007**, *63*, 5323.
16. McKenzie, T. C. and Epstein, J. W. *J. Org. Chem.* **1982**, *47*, 4881.