A New and More Efficient Synthesis of Methylene Acetals

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Abstract: A new and efficient synthesis of benzyl chlorides and methylene acetals by use of 2,4-dichloro-6-methoxy[1,3,5]triazine (MeOTCT) and dimethyl sulfoxide has been developed. Chlorides are the major products for benzyl alcohols, while methylene acetals are the major products for secondary alcohols. This procedure provides the highest yields so far for methylene acetals of steroids. A plausible mechanism is proposed on the basis of the experiments.

Key words: 2,4-dichloro-6-methoxy[1,3,5]triazine, dimethyl sulfoxide, alcohols, benzyl chlorides, methylene acetals

Methylene acetals of alcohols are useful compounds.[1] The formation of methylene acetals is also one of the most useful and versatile reactions in protective organic chemistry.[2] Various regents such as formaldehyde,[3] sodium hydride/dibromo- or dichloromethane,[4] or dimethyl sulfoxide/phosphoryl chloride,[5] dimethyl sulfoxide/*N*-bromosuccinimide, or dimethyl sulfoxide/bromine systems[6] have been reported previously to give methylene acetals from alcohols. Many of the methods, however, suffer from limitations such as longer reaction times or lower yields.

Recently, we have reported an improved method which employed dimethyl sulfoxide activated by 2,4-dichloro-6-methoxy[1,3,5]triazine (MeOTCT) as a source of methylene to convert amides into bisamides.[7] 2,4,6-Trichloro-1,3,5-triazine (TCT) and derivates have been reported as efficient reagents in a number of processes involving functional-group transformations.[8] These cost-effective reagents are amenable to large-scale processes. Therefore, we became interested in synthesis of methylene acetals by the reaction of alcohols with MeOTCT-activated dimethyl sulfoxide.

Table 1 summarizes reactions of alcohols with dimethyl sulfoxide activated by MeOTCT. The reactions were performed using MeOTCT and dimethyl sulfoxide in various solvents, such as toluene, acetonitrile, chloroform, and dimethyl sulfoxide. The best results were obtained with toluene. The optimized procedure consisted of the addition of alcohol (1 equiv) to the solution of MeOTCT (1.2 equiv) and dimethyl sulfoxide (5 equiv) in anhydrous toluene (8 mL) at 80 °C. Decreasing the amount of MeOTCT or lowering the reaction temperature caused longer reaction times and lower yields. An excess amount of dimethyl sulfoxide (5.0 equiv) was used partially because of its ability to dissolve the substrates.

When benzyl alcohols (Table 1, entries 1–4) were treated with MeOTCT/dimethyl sulfoxide, the corresponding benzyl chlorides were obtained in excellent yields. No methylene acetals were detectable. This compared favorably to our previous procedure where TCT/dimethyl sulfoxide was used to chlorinate benzyl alcohols, in term of reaction scale and operation, although this reaction had to be performed at a higher temperature, which is harsher than the previous method.[9]

When aliphatic alcohols (Table 1, entries 6–8) were subjected to the above reaction conditions, both chlorides and methylene acetals were obtained. We were delighted to find that secondary alcohols (Table 1, entries 9–17) were exclusively converted into methylene acetals. No chlorides were detectable. When cholesterol was subjected to the above procedure, the methylene acetal of cholesterol directly precipitated from the reaction mixture in 80% yield and pure enough by ^{1}H NMR analysis so that no chromatographic purification was needed. In the literature,[10] the yields of the acetals were all below 30%, far below ours. Diosgenin possesses an acid-labile ketal functional group, which was transformed into its methylene acetal in 82% yield in short reaction time (3 h). Estradiol possesses two hydroxy groups. The chemoselectivity is excellent and only the aliphatic hydroxy group formed acetal in 72% yield (Table 1, entry 11). d-17,17′-Methylenedioxybis[3-methoxyestra-1,3,5(10)-triene] shows mild estrogenic and antilipemic activity, and was synthesized in 29.4% yield (Scheme 1) starting from the methyl ether of estradiol in the literature.[11] Similarly, 2-formylestradiol (Table 1, entry 12) was converted into methylene acetal in high yield (76%). This procedure is also efficient in forming intramolecular acetals. Diols (Table 1, entries 13–16) were all transformed into their methylene acetals in fair to good yields within a few hours. Although the trityl group is acid-labile, the methylene acetal of the inositol derivate (Table 1, entry 16) was obtained in 63% yield. The methylene acetal ring of the product is highly strained, which was not accessible from the reaction of the inositol diol (Table 1, entry 16) with formaldehyde, diiodomethane, dibromomethane, or diazomethane.[12]

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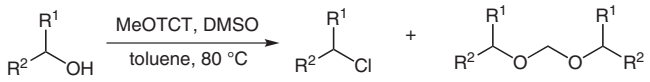
Table 1 Preparation of Benzyl Chlorides and Methylene Acetals



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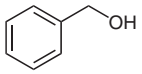
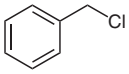
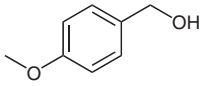
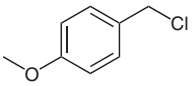
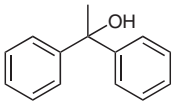
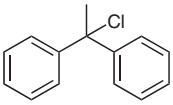
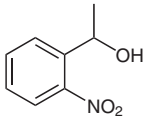
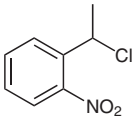
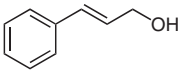
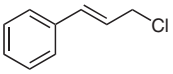
1				3	90	
2				3	86	
3				2.5	91	
4				3	94	
5				4	88	
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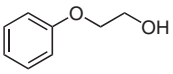
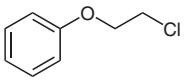
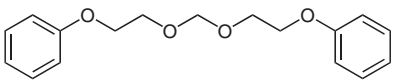
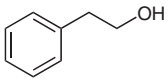
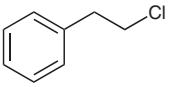
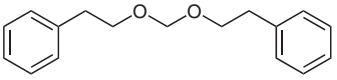
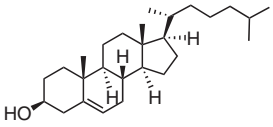
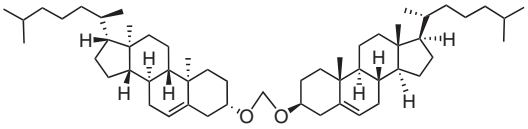
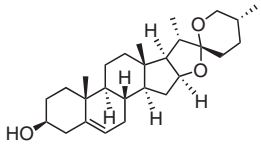
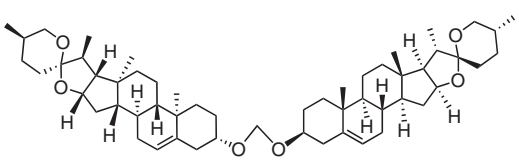
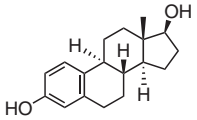
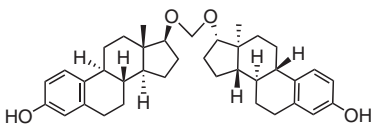
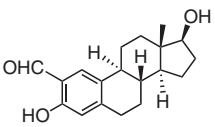
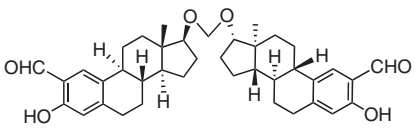
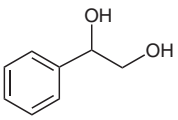
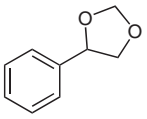
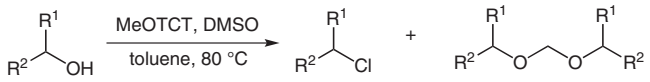
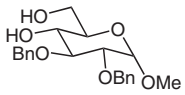
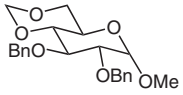
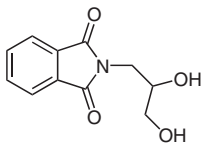
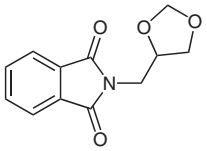
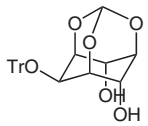
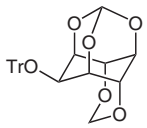
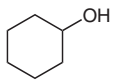
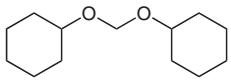
7				4	35	52
8				4	32	50
9[b]				2.5		80
10				3		82
11				6		72
12				5		76
13				4.5		48

Table 1 Preparation of Benzyl Chlorides and Methylene Acetals (continued)



Entry	Substrate	Chloride	Methylene acetal	Time (h)	Yield of chloride[a] (%)	Yield of acetal[a] (%)
14				6		52
15				4.5		65
16				5		63
17				8		65

[a] Isolated yields.
[b] DMSO as solvent instead of toluene.

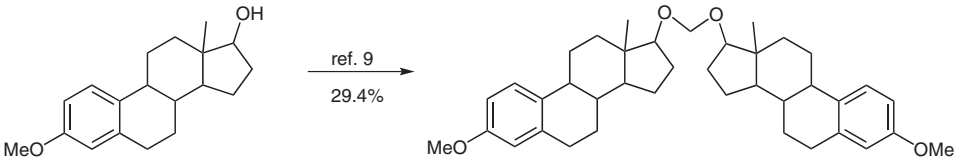
On the basis of the above experiments and our previous research,[7,9] a plausible mechanism is proposed (Scheme 2). The adduct of MeOTCT and dimethyl sulfoxide reacts with the alcohol to form a dimethyl alkoxysulfonium salt (**I**), which reacts in two pathways. A dimethyl(arylmethyl)sulfonium salt is active enough to yield the corresponding chloride (**VI**), and the major pathway of the reaction is S_N2 for less hindered benzylic alcohols (Table 1, entries 1 and 2). In contrast, a primary aliphatic sulfonium salt is not active enough for complete chloride substitution, and decomposes to regenerate the alcohol and the sulfonium ion (**II**). The sulfonium salt (**I**) formed by the secondary alcohols (Table 1, entries 9–17) and dimethyl sulfoxide gives no corresponding chloride due to its lower activity and steric effects. Similar to the Pummerer rearrangement, thioether **III** is formed by the addition of the alcohol to intermediate **II**. Thioether **III** is a good nucleophile and capable of substituting the chloride of 4-chloro-6-methoxy-1,3,5-triazin-2-ol (CMTO) to generate sulfonium salt **IV**. The alcohol substitutes sulfonium **IV** to form methylene acetal **V**.

In conclusion, we have developed a new and more efficient method to synthesize benzyl chlorides from benzyl alcohols and methylene acetals from secondary alcohols using dimethyl sulfoxide activated by MeOTCT. This represents the synthesis of steroidal methylene acetals in the highest yields so far. The procedure reported herein is operationally simple, and requires inexpensive and commercially available reagents. A plausible mechanism of the reaction is proposed and supported by the experiments.

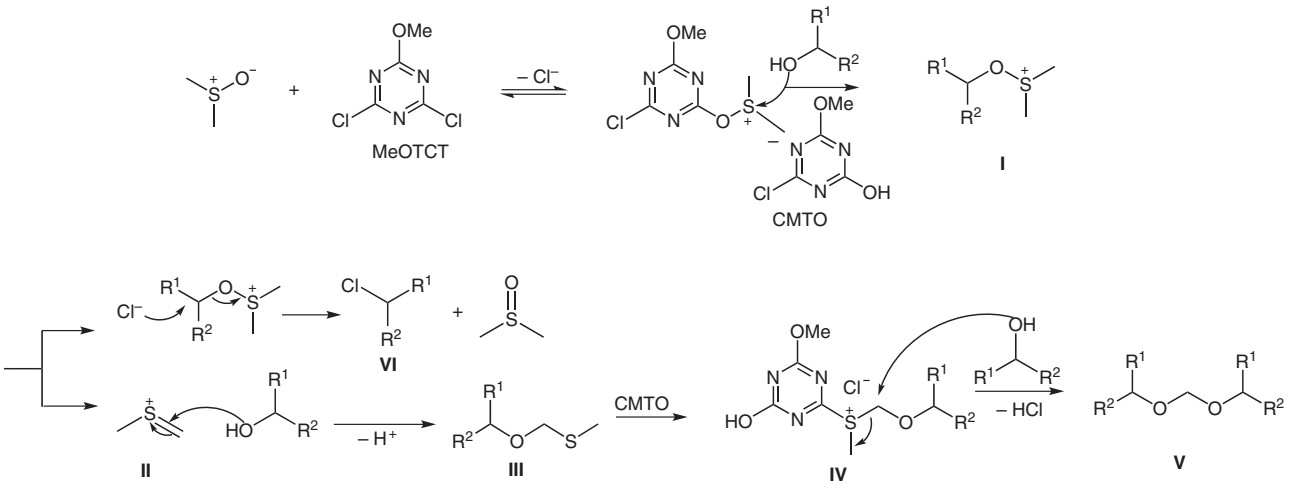
All the chemicals were obtained from commercial sources or prepared according to standard methods. All the chemicals and solvents used in reactions were dried by standard procedures prior to use. IR spectra were recorded on a Bio-Rad Excalibur FTS3000 spectrometer. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Varian Oxford 500 spectrometer. Chemical shifts are reported relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). Mass spectra (ESI) were obtained on a Finnigan LCQ Advantage MAX spectrometer. Elemental analyses for C, H, and N were performed on a Yanaco CHNCORNER MF-3 elemental analyzer, and the analytical results were within ±0.4% of the theoretical values.

Benzyl Chloride (Table 1, Entry 1); Typical Procedure for the Chlorination of Benzyl Alcohols

The procedure for the chlorination of benzyl alcohol (Table 1, entry 1) is representative for all benzyl alcohols in Table 1. Benzyl alcohol (500 mg, 4.63 mmol) was added to the soln of MeOTCT (994



Scheme 1



Scheme 2

mg, 5.56 mmol) and anhyd DMSO (1.86 g, 23.2 mmol) in anhyd toluene (8 mL). The mixture was stirred at 80 °C and monitored by TLC until completion (6 h). Then it was neutralized with sat. aq $NaHCO_3$ (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The extract was washed with H_2O (5 × 5 mL), and dried over anhyd Na_2SO_4. The solvent was concentrated in vacuo to give crude product, which was then filtered through a silica gel pad with PE to afford benzyl chloride; yield: 525 mg (90%).

Bis(octyloxy)methane (Table 1, Entry 6); Typical Procedure for the Preparation of Methylene Acetals from Aliphatic Alcohols

The procedure for the reaction of MeOTCT-activated DMSO and octan-1-ol (Table 1, entry 6) is representative for all aliphatic alcohols in Table 1. Octan-1-ol (500 mg, 3.85 mmol) was added to the soln of MeOTCT (826 mg, 4.62 mmol) and anhyd DMSO (1.50 g, 19.2 mmol) in anhyd toluene (8 mL). The mixture was stirred at 80 °C and monitored by TLC until completion (4 h). Then it was neutralized with sat. aq $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The extract was washed with H_2O (5 × 5 mL), and dried over anhyd Na_2SO_4. The solvent was concentrated in vacuo to give crude product, which was further purified by column chromatography (silica gel, (PE–Et_2O, 6:1) to afford 1-chlorooctane; yield: 141 mg (25%) and bis(octyloxy)methane; yield: 242 mg (46%). [The reactions of diols (Table 1, entries 13–16) with activated DMSO need a double dosage of DMSO and MeOTCT.]

3,3′-Methylenedioxybischolesterol (Table 1, Entry 9)

Cholesterol (500 mg, 1.34 mmol) was added to the soln of MeOTCT (288 mg, 1.61 mmol) in anhyd DMSO (8 mL). The mixture was stirred at 80 °C, and solid appeared 2.5 h later. Then the mixture was added to aq $NaHCO_3$ (20 mL). After filtration, washing with H_2O, and drying with anhyd Na_2SO_4, pure product was obtained; yield: 428 mg (80%).

3,3′-Methylenedioxybisdiosgenin (Table 1, Entry 10)

Yield: 82%.

IR (KBr): 2980, 2933, 2816, 1455, 1376, 1152, 1096, 1038, 1006, 981, 899 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.35 (d, *J* = 4.4 Hz, 2 H), 4.79 (s, 2 H), 4.41 (q, *J* = 7.5 Hz, 2 H), 3.46 (dd, *J* = 5.7, 9.4 Hz, 4 H), 3.38 (m, 2 H), 2.35 (dd, *J* = 3.1, 13.1 Hz, 2 H), 2.23 (t, *J* = 12.2 Hz, 2 H), 1.99 (m, 4 H), 1.90–0.98 (m, 64 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.0, 121.7, 109.5, 91.3, 181.0, 67.1, 62.3, 56.7, 50.3, 41.8, 40.5, 40.0, 39.7, 37.4, 37.1, 32.3, 32.1, 31.7, 31.6, 30.5, 29.9, 29.1, 29.0, 21.1, 19.6, 17.4, 16.5, 14.8.

ESI-MS: *m/z* (%) = 842.4 (100) $[M + H]^+$.

Anal. Calcd for $C_{55}H_{84}O_6$: C, 78.52; H, 10.06. Found: C, 78.48; H, 10.12.

17,17′-Methylenedioxybis[estra-1,3,5(10)-triene] (Table 1, Entry 11)

Yield: 72%.

IR (KBr): 3373, 2926, 2867, 1610, 1499, 1248, 1160, 1054, 1019 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.4, 2 H), 6.64–6.57 (m, 4 H), 4.76 (s, 2 H), 3.71 (t, *J* = 8.4 Hz, 2 H), 2.84–2.88 (m, 6 H), 3.71 (t, *J* = 8.4, 2 H), 2.89 (m, 4 H), 2.30–1.22 (m, 28 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 138.0, 131.5, 126.4, 115.6, 113.1, 93.9, 86.0, 50.1, 44.1, 43.2, 38.9, 37.7, 32.7, 29.8, 28.2, 27.0, 23.3, 12.0.

ESI-MS: *m/z* (%) = 556.5 (45) $[M]^+$, 579.2 (100) $[M + Na]^+$.

Anal. Calcd for $C_{37}H_{48}O_4$: C, 79.82; H, 8.69. Found: C, 79.88; H, 8.72.

2,2′-Diformyl-17,17′-methylenedioxybis[estra-1,3,5(10)-triene] (Table 1, Entry 12)

Yield: 76%.

IR (KBr): 3320, 2932, 2852, 1653, 1527, 1486, 1466, 1056, 1043 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.78 (s, 2 H), 9.81 (s, 2 H), 7.43 (s, 2 H), 6.70 (s, 2 H), 4.76 (s, 2 H), 3.71 (t, *J* = 8.4 Hz, 2 H), 2.89 (m, 4 H), 2.35–1.14 (m, 32 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 159.5, 148.3, 133.0, 130.8, 119.2, 117.2, 94.2, 86.0, 50.2, 43.7, 43.2, 38.5, 37.5, 32.2, 29.9, 28.3, 26.9, 23.3, 12.1.

ESI-MS: *m/z* (%) = 636.5 (38) $[M + Na]^+$, 1249.2 (100) $[2 M + Na]^+$.

Anal. Calcd for $C_{39}H_{48}O_6$: C, 76.44; H, 7.90. Found: C, 76.48; H, 7.95.

2-[(1,3-Dioxolan-4-yl)methyl]isoindoline-1,3-dione (Table 1, entry 15)

Yield: 65%.

IR (KBr): 3315, 2932, 2852, 1653, 1527, 1486, 1466, 1056, 1043, 715 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.74 (dd, *J* = 3.0, 5.4 Hz, 2 H), 5.09 (s, 1 H), 4.88 (s, 1 H), 4.42 (m, 1 H), 3.95 (m, 2 H), 3.77 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 134.3, 132.2, 123.7, 95.4, 73.4, 68.0, 40.0.

ESI-MS: *m*/*z* (%) = 489.6 (100) $[2 M + Na]^+$.

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.74; H, 4.78; N, 5.97.

4-Trityl-2,6-methylenedioxy-myo-inositol 1,3,5-Orthoformate (Table 1, Entry 16)
Yield: 63%.

IR (KBr): 3060, 2942, 2882, 1489, 1448, 1179, 1167, 1137, 1109, 1086, 1041, 1006, 965, 926, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.5 Hz, 6 H), 7.33 (t, *J* = 7.4 Hz, 6 H), 7.27 (t, *J* = 7.2 Hz, 3 H), 5.55 (s, 1 H), 5.02 (d, *J* = 5.8 Hz, 1 H), 4.71 (t, *J* = 4.6 Hz, 1 H), 4.57 (t, *J* = 4.8 Hz, 2 H), 4.43 (d, *J* = 5.9 Hz, 2 H), 3.61 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.5, 129.3, 129.2, 128.2, 128.1, 127.6, 102.4, 88.0, 84.6, 71.5, 66.4, 63.3, 61.9.

ESI-MS: *m*/*z* (%) = 912.6 (100) $[2M + Na]^+$.

Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.88; H, 5.48.

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References

(1) (a) Williams, A. A.; Lewis, M. J.; Tucknott, O. G. *Food Chem.* **1980**, *6*, 139. (b) Bennett, E. O. *Int. Biodeter. Bull.* **1973**, *9*, 95. (c) Dubois, J. L. Patent Application EP 1938684, **2008**; *Chem. Abstr.* **2008**, *149*, 98879.
(2) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: Indianapolis, **1999**, 201.
(3) Goodwin, J. C.; Hodge, J. E. *Carbohydr. Res.* **1973**, *28*, 213.
(4) Brimacombe, J. S.; Foster, A. B.; Jones, B. D.; Willard, J. J. *J. Chem. Soc. C* **1967**, 2404.
(5) Guiso, M.; Procaccio, C.; Fizzano, M. R.; Piccioni, F. *Tetrahedron Lett.* **1997**, *38*, 4291.
(6) (a) Hanessian, S.; Yang-Chung, G.; Lavallee, P.; Pernet, A. G. *J. Am. Chem. Soc.* **1972**, *94*, 8929. (b) Munavu, R. M. *J. Org. Chem.* **1980**, *45*, 3341.
(7) Wang, Q.; Sun, L.; Jiang, Y.; Li, C. *Beilstein J. Org. Chem.* **2008**, *4*, 51; DOI: 10.3762/bjoc.4.51.
(8) (a) Blotny, G. *Tetrahedron* **2006**, *62*, 9507. (b) Das, B.; Venateswarlu, K.; Krishnaiah, M. *Helv. Chim. Acta* **2007**, *90*, 149. (c) Kunishima, M.; Yamamoto, K.; Hioki, K.; Kondo, T.; Hasegaua, M.; Tani, S. *Tetrahedron* **2007**, *63*, 2604. (d) Bigdeli, M. A.; Heravi, M. M.; Mahdavinia, G. H. *Catal. Commun.* **2007**, *8*, 1595.
(9) Sun, L.; Pei, G.; Niu, H.; Wang, Q.; Li, C. *Synthesis* **2008**, 3919.
(10) (a) Suzuki, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1979**, 1277. (b) Herz, J. E.; Lucero, J.; Santoyo, Y.; Waight, E. S. *Can. J. Chem.* **1971**, *49*, 2418. (c) Kaya, I. A.; Jaret, R. S. *J. Chem. Eng. Data* **1971**, *16*, 485. (d) Kupchan, S. M.; Casy, A. F.; Swintosky, J. W. *J. Pharm. Sci.* **1965**, *54*, 514.
(11) Wendt, G. R.; Ledig, K. W. US Patent 3267120, **1964**; *Chem. Abstr.* **1966**, *65*, 13794f.
(12) Shao, M.; Chu, G.; Li, C. *unpublished results*.