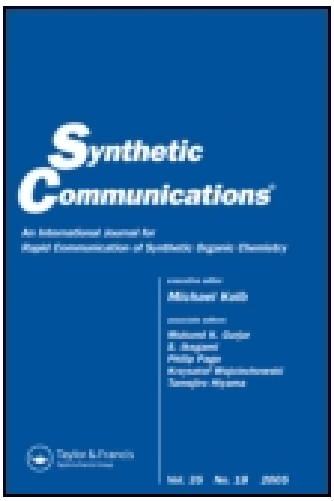


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Effective Method for the Preparation of 21-Chlorosteroids Using the Vilsmeier Reagent

P. G. M. Wuts [a], J. E. Cabaj [a] & K. D. Maisto [a]

[a] Chemical Process Research and Development , 1500-91-2, The Upjohn Co, Kalamazoo, MI, 49001

Published online: 23 Sep 2006.

To cite this article: P. G. M. Wuts , J. E. Cabaj & K. D. Maisto (1993) An Effective Method for the Preparation of 21-Chlorosteroids Using the Vilsmeier Reagent, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:15, 2199-2211, DOI: 10.1080/00397919308018615

To link to this article: http://dx.doi.org/10.1080/00397919308018615

SYNTHETIC COMMUNICATIONS, 23(15), 2199-2211 (1993)

AN EFFECTIVE METHOD FOR THE PREPARATION OF 21-CHLOROSTEROIDS USING THE VILSMEIER REAGENT

P. G. M. Wuts[1], J. E. Cabaj and K. D. Maisto

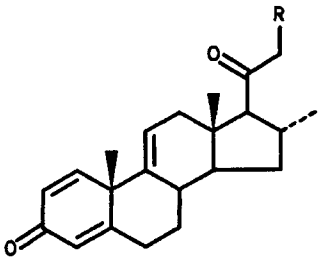
Chemical Process Research and Development, 1500-91-2, The Upjohn Co, Kalamazoo, MI 49001

Abstract: A simple procedure for the conversion of 21-steroidal alcohols to the corresponding 21-chlorides using the Vilsmeier reagent is described.

The development of a suitable procedure for coupling the amine **6** with the steroid **1** to form tirilazad **5**[1] neccessitated finding a procedure for converting the alcohol **1** to chloride **3** a known stable crystalline compound[2], prepared from the mesylate by chloride displacement. Although the mesylate **2** is effective in this conversion, it is thermaly unstable and noncrystalline and was thus not suited for the production of hundreds of kilograms of final product especially since the coupling reaction with amine **6** must be run hot. In light of this we looked to see what was available in the literature and found that there are few effective and direct methods for the conversion of 21-hydroxysteroids to 21-chlorosteroids.

---

[1] To whom correspondence should be addressed.

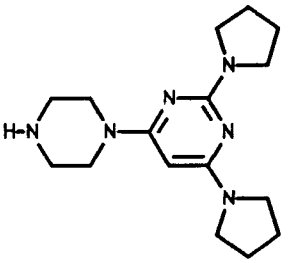


1 R = OH

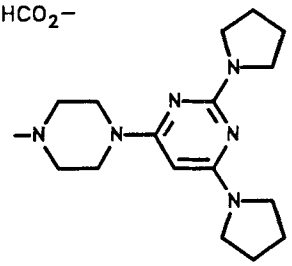
2 R = OMs

3 R = Cl

4 R = HCO_2–



6

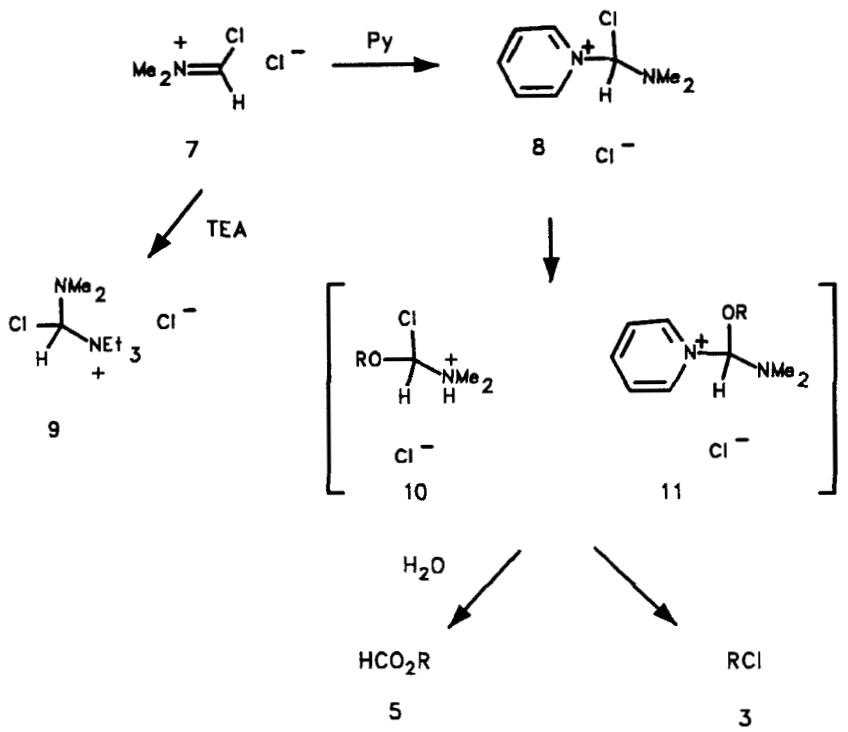
5 R = 

Most methods also result in the formation of the 17-acyloxy derivative.[3] With the few methods that do exist most involve the use of expensive and toxic reagents and often require multiple steps.[4] An initial exploration of the common low cost reagents such as thionyl chloride and $POCl_3$ gave completely unsatisfactory results affording low yields and poor quality product. As a result of the readily available and low cost Vilsmeier reagent[5] and a report by Hanessian on its use for converting carbohydrate alcohols to chlorides[6, 7], we examined it in the chlorination of alcohol **1**. Initial experiments were quite promising except that we consistently observed some A-ring degradation of the product during the course of the reaction. We felt that this was caused by an

acid induced dienone phenol rearrangement since HCl is liberated during the reaction. When pyridine was added to scavenge the HCl an excellent yield of the desired chloride **3** with minimal A-ring degradation was achieved. If pyridine is replaced with triethylamine the reaction no longer works, but if diisopropylethylamine is used chlorination again proceeds along with A-ring degradation. Also, the addition of water to the reaction before completion results in the formation of formate **4** implicating **10** or **11** as an intermediate[8]. A control experiment shows that A-ring degradation is caused by the Vilsmeier reagent and not by the liberated HCl from the reaction.

Scheme 1 delineates the various alternatives as they are currently understood. The difference between diisopropylethylamine and triethylamine is a result of steric factors. TEA can add to the Vilsmeier reagent forming adduct **9** which is inactive as a chlorinating agent, and DIEA cannot form an adduct because of its greater bulk. Presumably the adduct **9** is sufficiently stable that displacement with ROH does not occur and thus chlorination is not observed. On the other hand when pyridine is used the complex **8** is formed and because of its greater reactivity can react with the alcohol to form an adduct which decomposes to the halide. Proof of the existence of **8** was secured by isolation and NMR spectroscopy which shows a substantial down field shift of the pyridine protons. When the same experiment was repeated with TEA the only signals in the NMR where those of TEA·HCl with only traces of other carbon atoms in the C-13. A possible explanation for our ability to isolate only

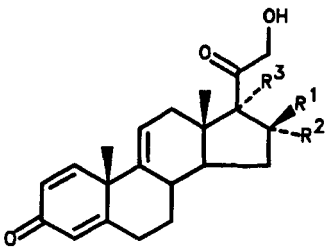
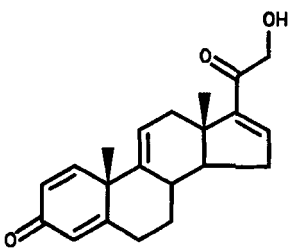
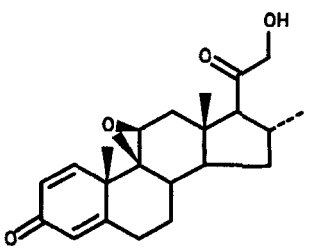
Scheme 1



TEA·HCl is that the TEA removes a proton from the Vilsmeier reagent to form a volatile aziridine which is lost upon solvent removal.

With a good understanding of the reaction's requirements we briefly examined the chlorination of several other steroidal 21-alcohols. As can be seen from the table the reaction is quite general even the traditionally difficult 17-hydroxyl derivative gave a reasonable yield. Other α-hydroxy ketones should give similar results.

Table I: Chlorination of 21-hydroxysteroids

Steroid	% Chloride
	
1 $R^1 = H, R^2 = CH_3, R^3 = H$	3 (92.0%)
12 $R^1 = CH_3, R^2 = H, R^3 = H$	15 (94.9%)
13 $R^1 = H, R^2 = CH_3, R^3 = OH$	16 (51.0%)
	
14	17 (80.0%)
	
15	18 (80.5%)

Experimental

General Methods. All melting points are uncorrected and were taken on a Buchi 510 capillary melting point machine. All proton and ^{13}C NMR spectra were obtained on a Bruker AM 300 spectrophotometer in $CDCl_3$ with Me_4Si as internal standard. Infrared spectra were recorded on a Digilab FTS-40 spectrometer from a mineral oil mull unless otherwise noted. Elemental analyses were obtained on a Heraeus CHN Rapid and chloride analyses on a Dionex 2000I using the Heraeus processor. Flash column chromatographies were performed on Merck silica gel (Kieselgel 60). All reactions and weighing of the Vilsmeier reagent were performed under a nitrogen atmosphere.

21-Chloropregna-16α-methyl-1,4,9(11)-triene-3,20 dione 3.

To a nitrogen purged 250 mL 3 neck flask equipped with a mechanical stirrer, temperature probe, and nitrogen inlet is added 10.0 g (29.4 mmol) of **1** followed by 50 mL of toluene. The slurry is stirred at room temperature until the slurry thins out. The thin slurry is then cooled to -3.0°C at which point 4.93 g (38.5 mmol) of Vilsmeier reagent is quickly added with a nitrogen purge through the flask. The Vilsmeier reagent is then rinsed in with 15 mL of toluene. The internal temperature rises to 2.0°C. After 5 minutes the slurry becomes thicker. After 3 h the reaction is complete as evidenced by TLC (1/1, EtOAc/cyclohexane, short wave uv and phosphomolybdic acid

development). At 1.0°C 25 mL of water is slowly added via add funnel. The reaction mixture exotherms to 5.0°C during the add. The layers are then separated and the organic is washed with 15 mL of 10% HCl followed by 15 mL of saturated $NaHCO_3$. The aqueous phase is back extracted with 15 mL of toluene. Magnesol (1.5 g) is added to the combined organics and the thin slurry is stirred at room temperature for 1 h. The magnesol is then filtered and washed twice with 5 mL of toluene to give a light yellow solution of the steroid. The solution is concentrated to approximately 5 mL at which point solids come out of solution. Toluene (10 mL) is added and the slurry is heated to dissolve the solids. The solution is transferred to a 250 mL three neck flask equipped with a mechanical stirrer, temperature probe, and nitrogen inlet. The steroid is rinsed in with 5 mL of hot toluene. At 73°C 40 mL of heptane is slowly added. After 5 mL are added the steroid begins to crystallize out of solution. When the add is complete the oil bath is removed and the slurry is stirred overnight at room temperature. The slurry is stirred at 0-3°C for 1.5 h, filtered, washed twice with 10 mL of 0°C heptane, and dried via high vacuum to give 9.71 g, 92% of the chloride 3. Mp. 148-151°C. $[\alpha]_D = +81°$ ($CHCl_3$). IR (Nicolet MX-1/KBr): 1725, 1664, 1622, 1602, 1451, 1440, 1392, 1371 cm^{-1}. ^{1}NMR: 7.18 (d, 1H, J = 10.2 Hz), 6.28 (dd, 1H, J = 10.1 & 1.8 Hz), 6.07 (t, 1H, J = 1.7 Hz), 5.52 (d, 1H, J = 5.8 Hz), 4.08 (s, 2H), 2.78 (m, 1H), 2.66 (dd, 1H, J = 20 & 5 Hz), 2.42 (dm, 2H, J = 9.2 Hz), 2.18 (m, 4H), 1.73 (m, 1H,), 1.52 (m, 2H), 1.41 (s, 3H), 1.21 (ddd, 1H, J = 20, 10, & 2 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.69 (s,

3H) ppm. ^{13}C NMR: 201.62, 186.18, 166.45, 154.35, 143.54, 127.33, 123.83, 119.51, 58.77, 51.88, 49.63, 45.85, 44.75, 40.41, 36.31, 34.60, 34.36, 32.28, 32.02, 26.51, 21.78, 13.84 ppm. Anal. Calcd for $C_{22}H_{27}O_2Cl$: C, 73.62; H, 7.58; Cl, 9.88. Found: C, 73.55; H, 7.60; Cl, 9.88.

21-Chloropregna-1,4,9(11),16-tetraene-3,20 dione (17). To a nitrogen purged flask is added 5.0 g (15.4 mmol) alcohol **14**, 2.65 mL (34.5 mmol) DMF and 70 mL toluene. In another purged flask 3.03 g (23.7 mmol) of theVilsmeier reagent and 2.72 mL (33.9 mmol) pyridine are combined, the tan slurry is cooled to -15°C to -20°C, and the above alcohol solution is added with a 5 mL toluene rinse while maintaining cooling. After 1 1/2 h, the orange colored slurry is warmed to 2°C and stirred (overnight) untill TLC/HPLC shows the reaction to be complete. Excess Vilsmeier reagent is quenched with 10 mL cold water. The phases are separated and the organic phase is washed with 10 mL 5% HCl followed by 10 mL water. Solvent was removed under reduced pressure and the 21-chloride **17** precipitated from 1 mL toluene and 15 mL MTBE (methyl *t*-butyl ether). After cooling to 0°C to 5°C, the product is filtered, washed with two 10 mL portions of -20°C MTBE and dried at 50°C under vacuum. A total of 4.20 g (80.0%) solids are recovered that are purified by flash chromatography (50% CyHex/EtOAc). An analytical sample was prepared by recrystallization from toluene/MTBE in 68.4% yield, mp 139-141.5°C. $[\alpha]_D$ = +117° ($CHCl_3$). IR: 1680, 1664, 1605, 1588, 1463, 1458, 1376, 1353 cm^{-1}. ^{1}NMR: 7.23 (d, 1H, J = 10.2

Hz), 6.82 (dd, 1H, J = 3.1 & 2.2 Hz), 6.28 (dd, 1H, J = 10.2 & 1.9 Hz), 6.07 (t, 1H, J = 1.6 Hz), 5.58 (d, 1H, J = 6.0 Hz), 4.39 (ABq $\Delta\upsilon$ = 36.8, 14.5 Hz, 2H), 2.58 (m, 5H), 2.16 (m, 3H), 1.55 (m, 1H), 1.44 (s, 3H), 1.23 (m, 1H), 0.93 (s, 3H) ppm. ^{13}C NMR: 188.80, 186.19, 166.35, 154.47, 150.46, 144.86, 143.42, 127.24, 123.81, 121.04, 52.39, 45.98, 45.81, 45.14, 37.35, 34.27, 34.27, 33.40, 31.89, 26.66, 15.28 ppm. Anal. Calcd for $C_{21}H_{23}O_2Cl$: C, 73.56; H, 7.14; Cl, 10.34. Found: C, 73.43; H, 6.75; Cl, 10.41.

21-Chloro-9(11)epoxy-16α-methylpregna-1,4-diene-3,20 dione (18). To a nitrogen purged flask is added 6.0 g (16.8 mmol) of alcohol **15**, 2.91 mL (37.6 mmol) DMF and 35 mL toluene. In another purged flask 3.02 g (23.6 mmol) Vilsmeier reagent and 2.99 mL (37.1 mmol) pyridine are combined, the tan slurry cooled to 0°C to 5°C, and the above alcohol solution added with a 5 mL toluene rinse while maintaining cooling. The orange colored slurry is stirred until complete by TLC/HPLC. Excess Vilsmeier reagent is quenched with 15 mL cold water. The phases are separated and the organic phase is washed with 30 mL 10% HCl followed by 2X25 mL water washes. Solvent is removed under reduced pressure and the 21-chloride **18** is precipitated from 3.5 mL EtOAc and 10 mL MTBE. After cooling to -20°C to -25°C, the product is filtered, washed with two 4 mL portions of -20°C MTBE and dried at 50°C under vacuum. A total of 5.08 g (80.5%) of solids are recovered which are purified by flash chromatography (50% CyHex/EtOAc). After

recrystallization from toluene/MTBE, white needles were obtained in 69.0% recovery, mp 144-146°C. $[\alpha]_D$ = +116° ($CHCl_3$). IR (mineral oil mull): 2927, 1712, 1662, 1625, 1605, 1456, 1376, 885, 693 cm^{-1}. ^{1}NMR: 6.60 (d, 1H, J = 10.2 Hz), 6.21 (dd, 1H, J = 10.1 & 0.9 Hz), 6.15 (s, 1H), 4.04 (s, 2H), 3.23 (s, 1H), 2.68 (m, 2H), 2.32 (m, 5H), 1.88 (d, 1H, J = 13.6 Hz), 1.62 (m, 1H), 1.44 (s, 3H), 1.40 (m, 3H), 0.94 (d, 3H, J = 6.8 Hz), 0.87 (s, 3H) ppm. ^{13}C NMR: 200.99, 185.72, 164.45, 151.69, 127.99, 124.79, 69.61, 66.14, 61.86, 53.20, 49.30, 44.09, 43.82, 38.94, 34.29, 33.92, 31.23, 30.91, 29.39, 23.43, 21.57, 16.63 ppm. Anal. Calcd for $C_{22}H_{27}O_3Cl$: C, 70.48; H, 7.26; Cl, 9.46. Found: C, 70.28; H, 7.28; Cl, 9.32.

21-Chloro-17α-hydroxy-16α-methylpregna-1,4,9(11)-triene-3,20 dione (16). To a nitrogen purged flask is added 3.0 g (8.42 mmol) diol **13**, 1.45 mL (18.8 mmol) DMF and 15 mL toluene. In another purged flask 1.51 g (11.78 mmol) of the Vilsmeier reagent and 1.49 mL (18.52 mmol) pyridine are combined, the tan slurry cooled to 0°C to 5°C in an ice bath, and the above diol slurry added with a 5 mL toluene rinse while maintaining cooling. The thick slurry is diluted with 20 mL of methylene chloride after 30 minutes to increase the solubility of the diol in the reaction mixture. After 2 1/2 hours the brown colored slurry reaction is complete by TLC, 6.0 mL water added to quench excess Vilsmeier reagent and the phases are separated (pH 6.5 - paper). The organic phase is washed with 15 mL 1N HCl and two 15 mL water washes. Much of the color exits to the aqueous phase during the water

washes. Solvents are removed under reduced pressure and the 21-chloride **16** precipitates from residual toluene and 15 mL additional MTBE. After cooling to 0°C to 5°C, the product is filtered, washed with two 5 mL portions of -20°C MTBE and dried under high vacuum. A total of 1.61 g (51%) of solids are recovered. An analytical sample was prepared by flash chromatography (50% CyHex/EtOAc) and recrystallization from toluene. Mp 200-207°C. $[\alpha]_D$ = +39° ($CHCl_3$). IR: 1729, 1662, 1622, 1615, 1604, 1406, 1388, 698, 619 cm^{-1}. ^{1}NMR: 7.19 (d, 1H, J = 10.2 Hz), 6.27 (dd, 1H, J = 10.2 & 1.8 Hz), 6.04 (s, 1H), 5.52 (d, 1H, J = 6.8 Hz), 4.46 (ABq, 2H, $\Delta\upsilon$ = 101.0 & 16.7 Hz), 3.15 (m, 1H), 2.86 (s, 1H), 2.66 (dt, 2H, J = 12.8 & 6.8), 2.41 (m, 1H), 2.28 (m, 1H), 2.15 (m, 1H), 1.76 (m, 3H), 1.45 (m, 1H), 1.40 (s, 3H), 1.18 (ddd, 1H, J = 25.4, 12.7, & 5.1), 0.94 (d, 3H, J = 7.2 Hz), 0.74 (s, 3H) ppm. ^{13}C NMR: 203.09, 186.36, 167.02, 154.73, 142.70, 127.15, 123.65, 120.32, 91.50, 48.22, 47.93, 47.48, 45.90, 36.87, 36.66, 34.75, 32.97, 32.71, 32.08, 26.63, 14.98, 14.41 ppm. Anal. Calcd for $C_{22}H_{27}O_3Cl$: C, 70.48; H, 7.26; Cl, 9.46. Found: C, 70.45; H, 7.29; Cl, 9.38.

21-*Chloro*-16β-methylpregna-1,4,9(11)-triene-3,20 dione (15). To a nitrogen purged flask is added 2.0 g (5.87 mmol) of alcohol **12**, 1.02 mL (13.15 mmol) DMF and 10 mL toluene. In another purged flask 1.05 g (8.22 mmol) Vilsmeier reagent and 1.04 mL (12.91 mmol) pyridine are combined, the tan slurry cooled to 0°C to 5°C in an ice bath, and the above alcohol solution is added dropwise over a 10 minute period followed by a 1 mL toluene rinse

while maintaining cooling. After 2 1/2 hours the reaction is incomplete by TLC/HPLC and an additional 0.55 g (4.3 mmol) Vilsmeier reagent and 0.26 mL (3.23 mmol) pyridine are added. One hour after the second Vilsmeier reagent addition, 10.0 mL water was added to quench excess Vilsmeier reagent and the phases were separated. The organic phase is washed twice with 5 mL 1N HCl and two 10 mL water washes followed. All washes are back extracted with 5 mL of toluene and the organic phases are combined. Solvent was removed under reduced pressure to afford 2.00 g (94.9%) of solids. An analytical sample was prepared by flash chromatography (75% EtOAc/heptane) and recrystallization from EtOAc/heptane. Mp. 155-157°C. $[\alpha]_D$ = +43° ($CHCl_3$). IR: 1726, 1659, 1621, 1601, 1456, 1437, 1389, 1384 cm^{-1}. ^{1}NMR: 7.19 (d, 1H, J = 10.2 Hz), 6.27 (dd, 1H, J = 10.2 & 1.8 Hz), 6.06 (s, 1H), 5.49 (d, 1H, J = 5.8 Hz), 4.03 (dd, 2H, J = 19.6 & 16.1 Hz), 2.82 (d, 1H, J = 10.2 Hz), 2.65 (m, 2H), 2.43 (dm, 1H, J = 15.3 Hz), 2.22 (m, 4H), 1.92 (d, 1H, J = 17.9 Hz), 1.42 (s, 3H), 1.19 (m, 3H), 1.05 (d, 3H, J = 7.2 Hz), 1.00 (s, 3H) ppm. ^{13}C NMR: 202.19, 186.25, 166.60, 154.59, 143.12, 127.30, 123.84, 119.99, 61.26, 52.09, 50.02, 45.98, 43.46, 40.54, 36.99, 35.79, 34.79, 34.08, 32.14, 26.54, 20.16, 14.32 ppm. Anal. Calcd for $C_{22}H_{27}O_2Cl$: C, 73.62; H, 7.58; Cl, 9.88. Found: C, 73.53; H, 7.79; Cl, 9.62.

References

1. Tirilazad belongs to a group of 21-amino steroids that inhibit iron-dependent lipid peroxidation thus protecting against central nervous system trauma. E. J. Jacobsen, J. M. McCall, D. E. Ayer, F. J. VanDoornik, J. R. Palmer, K. L. Belonga, J. M. Braughler, E. D. Hall, D. J. Houser, M. A. Krook and T. A. Runge, *J. Med. Chem.* **1990** *33* 1145.

2. Unpublished results of Thomas A Runge, Chemical Research Preparations unit, The Upjohn Company.

3. Sugai, S.; Okazaki, T.; Akaboshi, S. *Synthesis* **1982** 1023, US patent 4,113,680 issued to Taisho Pharmaceutical Co.,Ltd, Sept. 12, 1978, Sugai, S.; Akaboshi, S.; Ikegami, S. *Chem Pharm Bull, Tokyo* **1983** *31* 12.

4. US patent 3,644,340, 1972 issued to Syntex.

5. Available from Aldrich Chemical Co.

6. Hanessian, S.; Plessas, N. R., *J. Chem. Soc. Chem. Commun.* **1967** 1152.

7. Dods, R. F.; Roth, J. S., *Tetrahedron Lett.* **1969** 165.

8. Hepburn, D. R.; Hudson, H. R., *J. Chem. Soc., Perkin Trans 1* **1976** 754.

(Received in USA 9 March 1993)