



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

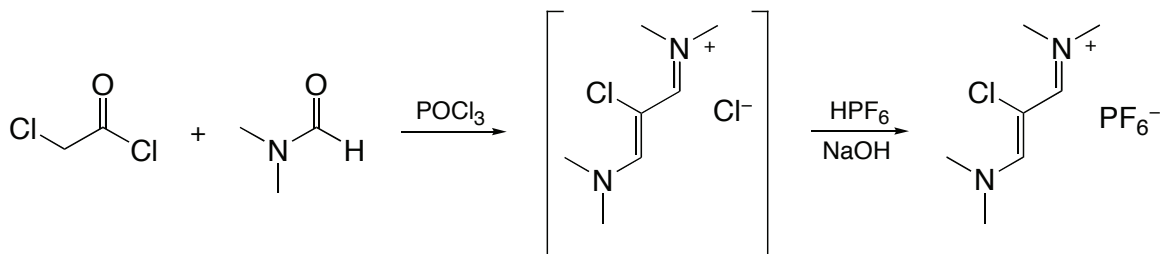
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

**PREPARATION OF 2-CHLORO-1,3 BIS(DIMETHYLAMINO)
TRIMETHINIUM HEXAFLUOROPHOSPHATE**
[[Methanaminium, *N*-[2-chloro-3-(dimethylamino)-2-propenylidene]-*N*-
methyl-, hexafluorophosphate(1-)]]



Submitted by Ian W. Davies, Jean-Francois Marcoux, and Jeremy Taylor.¹
Checked by Yu Fan and Scott E. Denmark.

1. Procedure

A 250-mL, three-necked, round-bottomed flask, equipped with a stir bar, nitrogen bubbler (Note 1), thermocouple, and pressure-equalizing addition funnel, is charged with dimethylformamide (DMF) (60 mL) (Note 2). Chloroacetyl chloride (14.13 g, 0.125 mol) (Notes 3-5) is added over 5 min at 50 °C. The mixture is then heated to 65-70 °C to give a clear, yellow solution. Phosphorus oxychloride (19.20 g, 0.125 mol) (Notes 6, 7) is added at ≈ 5 mL/h maintaining the temperature of the mixture at 70 °C. After completion of the addition, the mixture is heated for 3 h to give a deep red solution. The reaction mixture is cooled to 20-30 °C and transferred to a pressure-equalizing addition funnel. The reaction flask is rinsed with DMF (10 mL), which is added to the addition funnel. A solution of sodium hexafluorophosphate is prepared by the addition of 5N aqueous sodium hydroxide (NaOH) solution (37 mL) to a solution of hexafluorophosphoric acid (*Caution: Hexafluorophosphoric acid is toxic and corrosive*) (33.15 g of 60 wt%, 0.135 mol) in water (150 mL) in a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer (Note 8). The vinamidinium chloride solution (≈ 80 mL) and 5N aqueous NaOH solution (70 mL) are added concurrently over 1 h to the solution of sodium hexafluorophosphate in water (150 mL) with stirring at a temperature of <10 °C to give a yellow

slurry (Note 9). The mixture is aged for 1 h, then the solids are collected under vacuum. The crude solids are washed with water (75 mL) (Note 10), then transferred to a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer and thermocouple. Water (225 mL) and 2-propanol (60 mL) are added to the flask. The mixture is heated to 70 °C to dissolve the solids (Note 11). The mixture is then cooled to 0-5 °C over 1 h. The light-yellow solids are collected by filtration, washed with cold water/2-propanol (50 mL, 20/1), and dried under reduced pressure at <40 °C (Note 12) to give 2-chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate as a light-yellow solid (29.1 g, 77%) (Notes 13, 14). *Caution: The salt is a skin and eye irritant and was positive in the Ames mutagenesis assay. It should be handled in a hood with adequate personal protective equipment.* The product is >99.9% pure by HPLC analysis (Note 15).

2. Notes

1. The reaction is run under dry nitrogen.
2. A fresh bottle of anhydrous DMF from Aldrich Chemical Co., Inc. was used. The water content of the DMF was 0.024 g/L by Karl Fischer titration.
3. The checkers purchased chloroacetyl chloride from Aldrich Chemical Co., Inc.
4. Chloroacetic acid may be used in place of chloroacetyl chloride by adjusting the charge of phosphorus oxychloride to 0.25 mol. The submitters purchased chloroacetic acid from Säurefabrik Schweizerhall (CH). The material is also available from Aldrich Chemical Co., Inc.
5. The addition is mildly exothermic.
6. A syringe pump was used for this addition by the checkers.
7. When chloroacetic acid is used in place of chloroacetyl chloride, the charge of phosphorus oxychloride is increased to 0.25 mol.
8. The checkers purchased hexafluorophosphoric acid from Aldrich Chemical Co., Inc.
9. The addition is mildly exothermic. Sodium hexafluorophosphate is commercially available although significantly more expensive. The sodium

salt may be used in place of the hexafluorophosphoric acid by omitting the initial sodium hydroxide charge.

10. The crude solids may be dried and were ≈ 98 area% pure by HPLC analysis according to the submitters. The crude material may be used in a number of applications without recrystallization.

11. The submitters have observed that aging at elevated temperature for long periods (>8 h) will lead to a 3-5% decrease in yield. Over-heating the solids on the walls of the flask may discolor the product.

12. According to the submitters there is a minor exotherm initiating at 60 °C by differential scanning (Reactive System Screening Tool) (dT/dt °C/min 2.0, dP/dt °C/min <1). The exotherm is non-hazardous but will lead to deterioration of product quality presumably due to hydrolysis.

13. The submitters have run this procedure at various scales up to 300 kg with yields ranging from 73-79%.

14. The product is fully characterized: mp 125-126 °C; ^1H NMR (400 MHz, DMF- d_7) δ : 3.44 (s, 6 H), 3.60 (s, 6 H), 7.97 (s, 2 H); ^{13}C NMR (125 MHz, DMF- d_7) δ : 39.9, 49.7, 92.6, 161.1; ^{19}F NMR (470 MHz DMF- d_7) δ : -72.3 (d, $J = 708$); ^{31}P NMR (202 MHz, DMF- d_7) 143.2 (septet, $J = 709$); Anal. Calcd. for $\text{C}_7\text{H}_{14}\text{ClN}_2\text{PF}_6$: C, 27.42; H, 4.60; N, 9.14; Cl, 11.56; F, 37.18; P, 10.10. Found: C, 27.09; H, 4.86; N, 8.85; Cl, 11.47; F, 37.14; P, 10.09%. IR (KBr) cm^{-1} : 1610(s), 1492(w), 1424(s), 1404(s), 1291(s), 1200(s), 1117(s), 1045(m), 963(w), 840(s), 740(w); MS (FAB 70 eV): 161(100), 162(3), 163(32), 164(3). X-ray crystallographic analysis reveals a "W"-conformation.

15. A reverse phase ion-pairing HPLC method was developed by the submitters for analysis. Chromatographic conditions: A 10- μL sample (0.1 mg/mL in acetonitrile) is injected onto a suitable liquid chromatograph equipped with a Waters Symmetry Shield RP18 column, 250 \times 4.6 mm, 5 μm particle size at 40 °C with a mobile phase of 0.404 g/L heptanesulfonic acid, sodium salt + 0.1% phosphoric acid (Component A, pH 2.2) and acetonitrile (Component B) at a flow rate of 1.0 mL/min, programmed with a linear gradient from 95:5 A:B (v/v) to 30:70 A:B (v/v) over 20 min. Detection is achieved by UV at 300 nm. The retention time is approximately 10 min.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press, Washington, DC, 1995.

3. Discussion

Vinamidinium salts are important intermediates in the synthesis of heterocycles.² The 2-chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate salt has been used in the preparation of the highly selective Cox-2 inhibitor etoricoxib (Scheme 1).³ This method describes a straightforward preparation of the hexafluorophosphate salt which is a crystalline, thermally and shock-stable, non-hygroscopic solid. The submitters have extensively studied the preparation of vinamidinium salts and demonstrated that the method is applicable to substituted acetic acids that contain an electron-withdrawing group (Table 1).⁴ The annulation reaction is also general and useful for the preparation of pyridines, pyridones and pyridine *N*-oxides.⁵

Scheme 1

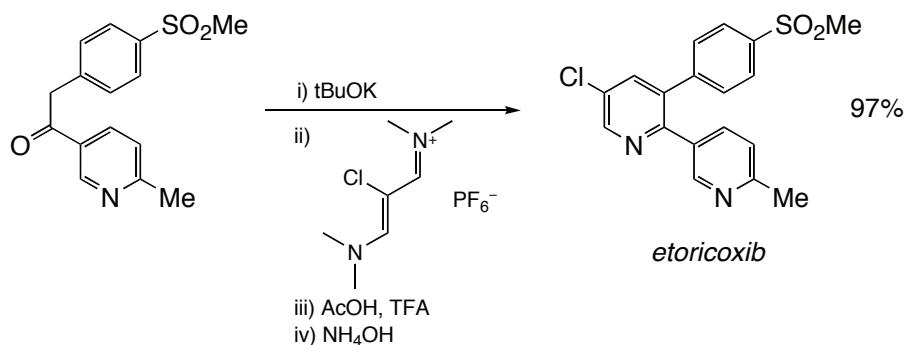
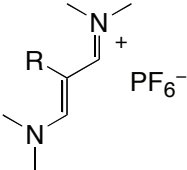
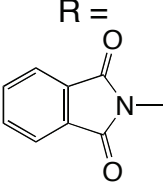


Table 1

Entry		Yield
1	R = Cl	78 %
2	R = Br	78 %
3	R = I	60 %
4	R = CF ₃	68 %
5	R = Ph	90 %
6	R = 4-NO ₂ -C ₆ H ₄ -	80 %
7	R = 4-MeO-C ₆ H ₄ -	75 %
8	R = 	68 %

1. Department of Process Research, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065-0900.
2. (a) For examples see: Gupton, J. T.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Vargas, M.; Hosein, K. N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689. (b) Kase, K.; Katayama, M.; Ishihara, T.; Yamanaka, H.; Gupton, J. T. *J. Fluor. Chem.* **1998**, *90*, 29.
3. Davies, I. W.; Marcoux, J. -F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 8415.
4. (a) Davies, I. W.; Marcoux, J.-F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M. A.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. *J. Org. Chem.* **2000**, *65*, 4571. (b) The method is general, but the reaction times/temperatures may require some slight modification to give optimal yields of the desired vinamidinium. In the case of the trifluoromethylvinamidinium 60 °C is optimal: Davies, I. W.; Tellers, D. M.; Shultz, C. S.; Fleitz, F. J.; Cai, D. -W.; Sun, Y. *Org. Lett.* **2002**, *4*, 2969.
5. (a) Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339. (b) Marcoux, J.-F.; Marcotte, F.-A.; Wu, J.; Dormer, P. G.; Davies, I. W.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 4194. (c) Davies, I. W.; Marcoux, J.-F.; Reider, P. J. *Org. Lett.* **2001**, *3*, 209.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

2-Chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate:
Methanaminium, N-[2-chloro-3-(dimethylamino)-2-propenylidene]-N-methyl-, hexafluorophosphate(1-) (9); (249561-98-6)

Chloroacetyl chloride: Acetyl chloride, chloro- (8, 9); (79-04-9)

Dimethylformamide: Formamide, N,N-dimethyl- (8, 9); (68-12-2)

Phosphorus oxychloride: Phosphoric trichloride (9); (10025-87-3)

Hexafluorophosphoric acid: Phosphate (1-), hexafluoro-, hydrogen (8, 9); (16940-81-1)