

CONVENIENT PREPARATION OF 1,3-BIS(DIMETHYLAMINO)-TRIMETHINIUM PERCHLORATE, TETRAFLUOROBORATE AND HEXAFLUOROPHOSPHATE

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Formylation of ethyl vinyl ether with (chloromethylene)dimethylammonium chloride prepared from dimethylformamide and oxalyl chloride or phosgene followed by successive treatment with dimethylamine and 70% perchloric acid leads to 1,3-bis(dimethylamino)trimethinium perchlorate **1a** in high yield. Similarly, work-up of the reaction mixture after formylation with hexafluorophosphoric acid or dimethylamine tetrafluoroborate afforded 1,3-bis(dimethylamino)trimethinium hexafluorophosphate **1b** or tetrafluoroborate **1c**, respectively.

Key words: Formylation; Trimethinium salts.

1,3-Bis(dimethylamino)trimethinium perchlorate **1a**, the simplest member of the polymethinium salts, has found numerous applications in the organic synthesis. Among them, three-carbon annelation procedure¹ is the most important example. We have recently demonstrated the synthetic utility of 1,3-bis(dimethylamino)trimethinium perchlorate for the preparation of aromatic², heteroaromatic³, and unsaturated aliphatic⁴ methylenemalonaldehydes as well as diarylmethylenemalonaldehydes⁵.

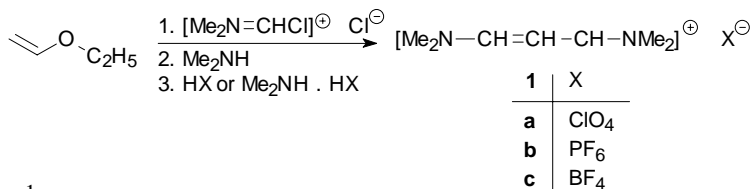
1,3-Bis(dimethylamino)trimethinium perchlorate is usually prepared by formylation of a suitable substrate like acetaldehyde diethyl acetal⁶ or butyl vinyl ether⁷ followed by a work-up in the presence of dimethylamine and perchlorate anion. Similarly, trimethinium salts of other anions like halides can be prepared. A different approach is based on the reaction of 3-(dimethylamino)acrolein with dimethylamine perchlorate⁸. This methodology was also used for the synthesis of trimethinium tetrafluoroborate⁹. In the course of our study of the reactivity of methylenemalonaldehydes we had to prepare large quantities of 1,3-bis(dimethylamino)trimethinium perchlorate. In this paper we

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report on formylation of ethyl vinyl ether with (chloromethylene)dimethylammonium chloride which appeared to be the most efficient method.

In the first step, ethyl vinyl ether was formylated with (chloromethylene)dimethylammonium chloride prepared from *N,N*-dimethylformamide and oxalyl chloride or phosgene in dry chloroform. Treatment of the resulting mixture successively with ethanolic dimethylamine and 70% perchloric acid gave the desired 1,3-bis(dimethylamino)trimethinium perchlorate **1a** in 80% yield (Scheme 1). The obtained product is sufficiently pure and can be used for synthetic purposes without any further purification.

The same procedure was used for the preparation of previously unknown 1,3-bis(dimethylamino)trimethinium hexafluorophosphate **1b**, the yield of the crude product being even higher (88%). However, its very broad melting point (120–147 °C) indicated the presence of impurities originating probably from the commercial 60% hexafluorophosphoric acid, reported to contain about 10% of hydrolyzed products. Whereas attempts to remove these impurities by simple crystallization failed, crystallization from ethanol in the presence of a small amount of triethylamine gave pure 1,3-bis(dimethylamino)trimethinium hexafluorophosphate **1b**. The role of triethylamine probably consists in replacement of the volatile dimethylamine in the salts of the hydrolytic products of hexafluorophosphoric acid. The soluble triethylammonium salts are then separated by crystallization.



SCHEME 1

For the preparation of 1,3-bis(dimethylamino)trimethinium tetrafluoroborate **1c** the use of ethanolic solution of dimethylamine tetrafluoroborate instead of commercial aqueous solution of tetrafluoroboric acid appeared to be advantageous (see Experimental). In this case the yield (60%) was somewhat lower.

For relatively small-scale preparations (up to about 1 mol), the method of choice was using oxalyl chloride in the preparation of the formylating agent and working with commercial 33% solution of dimethylamine in absolute ethanol. For large-scale preparations (up to 4 mol in our laboratory) it was more economic to use phosgene instead of oxalyl chloride for the preparation of the formylating reagent and to prepare ethanolic solution of dimethylamine in situ by reaction of NaOH with dimethylamine hydrochloride in ethanol. In this case it was also possible to reduce the amount of dimethylamine and to replace two equivalents of dimethylamine with NaOH without affecting the yield.

Although we have not experienced any problems, organic perchlorates should be treated as potential explosion hazards. The above method allows also preparation of the nonexplosive trimethinium tetrafluoroborate **1c** and hexafluorophosphate **1b**. We proved in our laboratory that in the synthesis of methylenemalonaldehydes these salts can be used instead of 1,3-bis(dimethylamino)trimethinium perchlorate^{2,3}. The yields of arylmethylenemalonaldehydes prepared with tetrafluoroborate **1c** were identical with those obtained with 1,3-bis(dimethylamino)trimethinium perchlorate **1a** while hexafluorophosphate **1b** gave 10–20% lower yields.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. DMF was dried over P₂O₅ and distilled in vacuo, chloroform was washed successively with concentrated H₂SO₄, water, aqueous sodium bicarbonate, dried over CaCl₂ and distilled. Oxalyl chloride, ethyl vinyl ether, dimethylamine hydrochloride and 33% solution of dimethylamine in absolute ethanol were obtained from Fluka and used without further purification. Analytical samples were dried over phosphorus pentoxide at 25 °C/27 Pa for 24 h. ¹H NMR spectra were taken on a Varian Gemini 300 (300 MHz) instrument in deuteriochloroform with tetramethylsilane as internal standard.

1,3-Bis(dimethylamino)trimethinium Perchlorate **1a**

To a stirred ice-cooled solution of DMF (16.52 g, 0.23 mol) in CHCl₃ (65 ml) 98% oxalyl chloride (19.7 ml, 0.22 mol) was added dropwise during 20 min. The mixture was stirred for 20 min without cooling, than cooled again in an ice bath and a mixture of ethyl vinyl ether (19.2 ml, 0.2 mol) and CHCl₃ (10 ml) was added during 20 min. The solution was stirred for 10 min in ice bath and for 4 h without cooling. The reaction mixture was than heated in an oil bath, allowing to reach the bath temperature 65 °C in 0.5 h and gently refluxed at this temperature for 1 h. After cooling (ice bath), 99% ethanol (30 ml) was added dropwise, then the reaction mixture was diluted with another portion of 99% ethanol (190 ml) and added dropwise into an ice-cooled mixture of 33% dimethylamine in absolute ethanol (197 ml, approximately 1.1 mol) and 99% ethanol (130 ml). The resulting mixture was left at room temperature overnight, cooled in an ice bath and 70% perchloric acid (22 ml, 0.26 mol) was added dropwise with stirring. After concentration in vacuo to about 1/3–1/4 volume (bath temperature 30 °C) and cooling, the product was filtered off under suction, washed with 99% ethanol and dried on air. 1,3-Bis(dimethylamino)trimethinium perchlorate was obtained as yellowish crystals, 36.38 g (80%), m.p. 118–120.5 °C (ref¹⁰. 124–125 °C). *Caution: Under certain conditions, organic perchlorates can explode.*

1,3-Bis(dimethylamino)trimethinium Hexafluorophosphate **1b**

The formylation step was performed as described for 1,3-bis(dimethylamino)trimethinium perchlorate, starting from DMF (8.30 g, 0.11 mol), oxalyl chloride (9.9 ml, 0.11 mol) in CHCl₃ (35 ml) and ethyl vinyl ether (9.6 ml, 0.10 mol) in CHCl₃ (5 ml). After quenching with 99% ethanol (15 ml), the reaction mixture was diluted with 99% ethanol (95 ml) and treated with a mixture of 33% ethanolic dimethylamine (95 ml, 0.53 mol) and 99% ethanol (65 ml) overnight. The mixture was cooled in an ice bath and 60% hexafluorophosphoric acid (14 ml, 0.1 mol) was added dropwise. After stirring and ice-cooling for another 0.5 h, the solid was filtered off, washed with 99% ethanol and dried yielding 23.60 g of crude yellow product with m.p. 120–147 °C. Crystallization from a mixture of 99% ethanol

(350 ml) and triethylamine (1 ml) gave 19.59 g (72%) of pure 1,3-bis(dimethylamino)trimethinium hexafluorophosphate as pale yellow crystals with m.p. 153–156 °C. An analytical sample was obtained by another crystallization from ethanol–triethylamine mixture, m.p. 155.5–157 °C. For $C_7H_{15}F_6N_2P$ (272.2) calculated: 30.89% C, 5.55% H, 10.29% N; found: 30.90% C, 5.69% H, 10.01% N. 1H NMR spectrum: 3.07 s, 6 H ($2 \times CH_3$); 3.25 s, 6 H ($2 \times CH_3$); 5.42 t, 1 H, $J = 11.6$ Hz (CH); 7.72 d, 1 H, $J = 11.6$ Hz ($2 \times CH$).

1,3-Bis(dimethylamino)trimethinium Tetrafluoroborate **1c**

The title compound was prepared by exactly the same procedure as described for 1,3-bis(dimethylamino)trimethinium perchlorate, starting from DMF (16.51 g, 0.23 mol), oxalyl chloride (19.7 ml, 0.22 mol), ethyl vinyl ether (19.2 ml, 0.20 mol) and 33% ethanolic dimethylamine (197 ml, 0.53 mol). After standing overnight with ethanolic dimethylamine, a solution of dimethylamine tetrafluoroborate in 99% ethanol (50 ml) (prepared by neutralization of 33% ethanolic dimethylamine (60 ml) with 35% tetrafluoroboric acid (52 ml) and evaporation) was added. Concentration of the resulting mixture in vacuo to about one third, filtration and washing with ethanol afforded 25.32 g of crude product. Another portion (1.73 g) of the product was obtained by concentration of mother liquors, filtration and careful washing with ethanol. Both portions of the product were combined and crystallized from 99% ethanol (55 ml); yield 26.04 g (61%) of yellow solid, m.p. 118–118.5 °C (ref.⁹ 112–114 °C).

Large Scale Preparation of 1,3-Bis(dimethylamino)trimethinium Perchlorate **1a**

Preparation of the formylating agent. A 2 l four-neck flask equipped with mechanical stirrer, thermometer, gas inlet tube leading to the bottom of the flask and low-temperature condenser with outlet connected to 250 ml washing bottle filled with conc. sulfuric acid was charged with DMF (219 g, 3 mol) and dry $CHCl_3$ (900 ml). The condenser was filled with dry ice, stirring was started and a stream of phosgene was introduced through another glass washing bottle filled with concentrated sulfuric acid. After a short period evolution of carbon dioxide started at the same rate as phosgene was introduced (1 mol $COCl_2$ forms 1 mol of CO_2); this was indicated by equal bubbling in both the gas washing bottles. Phosgene was introduced by such a rate that only a very small amount of liquid condensed in the condenser. The reaction was slightly exothermic and the internal temperature of the reaction mixture was kept between 16 and 20 °C by external cooling with cold water. At a lower temperature the reaction slowed down considerably and the unreacted phosgene accumulated in the reaction mixture. At higher temperatures a dark-colored solution of (chloromethylene)dimethylammonium chloride was formed. The end of the reaction was indicated by slowing down the CO_2 evolution. At this point the introduction of phosgene was slowed down too and when the evolution of CO_2 almost ceased (about 3 h) the introduction of $COCl_2$ was interrupted and the gas inlet tube was replaced with a stopper. The thus-prepared solution of (chloromethylene)dimethylammonium chloride contained free $COCl_2$ which was destroyed in the following way. The stirring was stopped, DMF (2 ml) was added and the stirring was started again. The evolution of CO_2 continued for a while and when it stopped, the whole procedure was repeated. After several additions of DMF (about 20 ml) no significant evolution of CO_2 was observed indicating that all $COCl_2$ was consumed. The amount of (chloromethylene)dimethylammonium chloride was calculated from the whole amount of DMF used (238 g, 3.25 mol in this case).

Preparation of 1,3-bis(dimethylamino)trimethinium perchlorate 1a. The solution was cooled to 5 °C with an ice–salt mixture and a solution of ethyl vinyl ether (277 ml, 2.90 mol) in $CHCl_3$ (165 ml) was added dropwise at such a rate, that the temperature did not exceeded 10 °C. The mixture was then stirred for 4 h without cooling and left overnight at room temperature. The low-tem-

perature condenser was replaced by a conventional reflux condenser and the mixture was gently refluxed for 1 h (bath temperature 65 °C). After cooling to 0 °C with an ethanol–dry ice mixture, 99% ethanol (350 ml) was added dropwise into the stirred mixture keeping the temperature below 10 °C. In the meantime, an ethanolic solution of dimethylamine was prepared: Sodium hydroxide (654 g, 16.35 mol) was added in several portions into stirred 99% ethanol (4 900 ml). After dissolving, which took several hours, the resulting solution was cooled to 5 °C with an ice–salt mixture and solid dimethylamine hydrochloride (818 g, 10 mol) was added in portions, while the temperature was maintained below 10 °C. The formylated reaction mixture was diluted with another portion of 99% ethanol (2 800 ml) and added dropwise under stirring into the dimethylamine solution while the temperature was kept below 10 °C by external cooling with an ice–salt mixture. The resulting mixture was left at room temperature overnight. The separated NaCl was filtered off and washed with 99% ethanol. The filtrate was cooled with ice and 70% perchloric acid (325 ml, 3.78 mol) was added dropwise under stirring. The mixture was then left at room temperature overnight. The first part of the product was filtered off and the filtrate was evaporated in vacuo (temperature below 30 °C) to about one fourth of the starting volume. After cooling, the product was filtered off, washed with ethanol and air-dried. Both portions were combined, giving 485.3 g of 1,3-bis(dimethylamino)trimethinium perchlorate, m.p. 120–121 °C (ref.¹⁰ 124–125 °C). Another 28.9 g of the product melting at 119–121 °C was obtained after concentration of the filtrate. The overall yield was 514.2 g (78%).

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