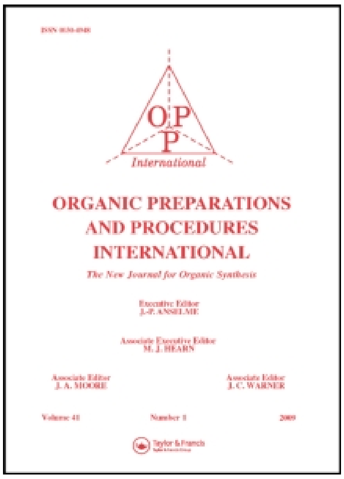

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

METHYLAMINOACETONE ETHYLENE KETAL HYDROCHLORIDE

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To cite this Article Benington, F. and Morin, R. D.(1973) 'METHYLAMINOACETONE ETHYLENE KETAL HYDROCHLORIDE', Organic Preparations and Procedures International, 5: 6, 281 — 284
To link to this Article: DOI: 10.1080/00304947309356857
URL: http://dx.doi.org/10.1080/00304947309356857

ORGANIC PREPARATIONS AND PROCEDURES INT. 5(6), 279-282 (1973)

METHYLAMINOACETONE ETHYLENE KETAL HYDROCHLORIDE

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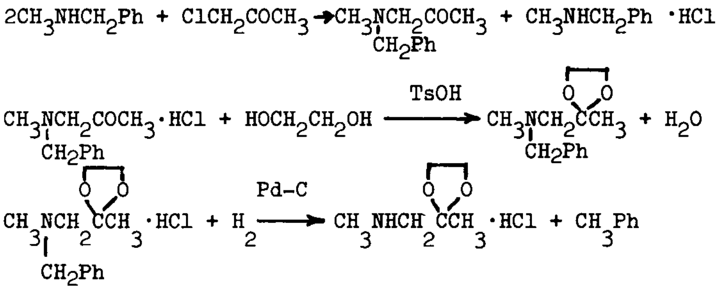
In connection with our studies concerning synthetic analogs of lysergic acid amides, we prepared repeatedly methylaminoacetone ethylene ketal hydrochloride as an intermediate. Kornfeld _et al._[1] have reported the large scale preparation of methylaminoacetone ethylene ketal from the reaction of either chloro- or bromoacetone ethylene ketal with liquid methylamine in a high-pressured bomb. In the instance where the chloroacetone ketal was used, the product required separation from unchanged reactants. The present procedure, which can be carried out in ordinary laboratory glassware and a low-pressure hydrogenator, gives in addition, two useful aminoketone intermediates in good yield. A preparation of N-methylbenzylaminoacetone in 45% yield has been reported by Magee and Henze[2] using benzylamine and bromoacetone in ether.



$$2CH_3NHCH_2Ph + ClCH_2COCH_3 \rightarrow CH_3N(CH_2Ph)CH_2COCH_3 + CH_3NHCH_2Ph\cdot HCl$$

Although the scope of the reactions reported here has not been explored adequately, they would appear to be applicable to numerous reactive haloketones whose penultimate functionality would withstand hydrogenolysis.

EXPERIMENTAL

N-Methylbenzylaminoacetone hydrochloride.— To a stirred solution of 121 g (1 mole) of N-methylbenzylamine in 350 ml of benzene in a 1-l three-necked flask equipped with a stirrer and thermometer was added 92.5 g (81 ml, 1 mole) of redistilled chloro-2-propanone in one portion. Within a few minutes, a precipitate of N-methylbenzylamine hydrochloride began to form and the temperature started to rise, reaching a maximum of 58-62° within 20-30 min; stirring was continued for an additional 2 hr. The reaction mixture was then filtered by suction and the cake of N-methylbenzylamine hydrochloride was washed thoroughly with benzene to give 75-77 g (95-98%), mp. 174-175°. The filtrate in a 1-l beaker was cooled in an ice bath and treated with a solution of 18.3 g (0.5 mole) of anhydrous HCl in 200 ml of anhydrous ether, while stirring with a glass rod. The crude product precipitates as a brown gum which hardens to a solid on standing overnite. The supernatant liquid was removed by decantation and the dark solid residue dissolved in 40 ml of boiling ethanol. To the dark alcoholic solution was added about 400 ml of ethyl acetate and 100 ml of ether. Upon cooling to room temperature the crude product crystallized; it was collected by suction filtration, washed with ethyl acetate and ether and sucked as dry as possible; the yield is 85-90 g (80-84%); mp. 123-128°. One recrystallization from a mixture of 40 ml of hot ethanol, 400 ml of ethyl acetate and 100 ml ether gave 75-80 g (70-75%)

of product sufficiently pure (light tan), mp. 128-129°, for use in the next step. One more crystallization raised the mp. to 129-130° and this material is colorless and analytically pure.

Anal. Calc'd. for $C_{11}H_{16}ClNO$: C, 61.8; H, 7.5; Cl, 16.6; N, 6.51. Found: C, 62.1; H, 7.7; Cl, 16.2; N, 6.0.

N-Methylbenzylaminoacetone ethylene ketal hydrochloride. - In a 1-l flask equipped with a 25 ml Dean-Stark trap and a reflux condenser are placed 85.5 g (0.4 mole) of N-methylbenzylaminoacetone hydrochloride, 49.5 g (45 ml, 0.8 mole) of ethylene glycol, 2 g of p-toluenesulfonic acid monohydrate and 350 ml of benzene. After 60 hrs of reflux 10-10.5 ml of water had collected. The mixture was allowed to cool and transferred to a 1-l separatory funnel, using about 100-150 ml water to transfer all of the mixture from the reaction flask. After thorough shaking the brown aqueous layer was returned to the separatory funnel and made alkaline by the addition of 45% aqueous potassium hydroxide. The liberated base was then extracted with 125 ml of ether and the separated aqueous layer extracted with an additional 100 ml portion of ether. The combined extracts were washed once with 125 ml of water, dried ($MgSO_4$), filtered, the ether removed under reduced pressure and the residue distilled in vacuuo. A low-boiling forecut (bp. 45-95°/0.5 mm) amounting to 10-15 g was discarded and the fraction boiling at 96-103°/0.5 mm collected to yield 58 g of colorless oil. Addition of a solution of 10 g of anhydrous HCl in 100 ml of ether to an ice-cooled solution of this oil in 400 ml of anhydrous ether gave the amine hydrochloride as a gum which solidified on standing overnight. To a solution of the air-dried product in 50 ml of boiling ethanol was added 300 ml of ethyl acetate and 100 ml ether; pure N-methylbenzylaminoacetone ethylene ketal hydrochloride crystallized at once: yield 46-48 g (45.0-46.5%), mp. 174-175°.

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: C, 60.6; H, 7.8; Cl, 13.8; N, 5.4. Found: C, 60.6; H, 7.9; Cl, 13.5; N, 5.3.

Methylaminoacetone ethylene ketal hydrochloride. - Hydrogenation of a solution of 51.5 g (0.2 mole) of N-methylbenzylaminoacetone ethylene ketal hydrochloride in 200 ml of ethanol over 1 g of 10% palladium on charcoal catalyst at 50 psi proceeded rapidly (1 hr). After addition of 2 g of Norite A, the mixture was filtered and the filtrate immediately concentrated to about 1/4 of its volume by evaporation under reduced pressure. The resulting precipitate was redissolved by heating to boiling; the resulting hot solution was transferred to a 1-l beaker and 300 ml of ethyl acetate and 100 ml ether added to crystalline the methylaminoacetone ethylene ketal hydrochloride as a colorless solid: yield, 27 g (82%), mp. 165-167°; lit.[1] mp. 165-167°. In order to obtain a colorless product, it is necessary to carry out all of these steps without delay. The product so obtained is colorless and can be stored at room temperature in stoppered containers for several months without darkening.

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(Received September 10, 1973; in revised form October 12, 1973)