The Preparation of Lidocaine

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This synthesis of 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, commonly known as Lidocaine or Xylocaine, has been used in our introductory organic chemistry laboratory for several years in support of lecture material on reactions of amines. It effectively illustrates the acylation and alkylation of amines and dramatically emphasizes the difference in rate between the two processes. Procedures are simple, yields are high, and the known pharmacological properties of this widely used local anesthetic successfully capture the attention of most students. The procedure given here is based on the original patent (*1*) with modification to permit isolation of the crude product by average students in a single three-hour laboratory period.

Materials

All reagents were used as supplied by Aldrich Chemical Co. Seriously discolored samples of 2,6-dimethylaniline may be used with only slight reduction in yield.

Procedure

CAUTION: *2,6-Dimethylaniline is toxic and readily absorbed through the skin. Chloroacetyl chloride is toxic and corrosive.* These reagents should be dispensed directly into the reaction vessel from an automatic-delivery pipet. If these reagents are poured from the bottle, the students must wear gloves and work in an efficient hood.

N-*(2,6-Dimethylphenyl)chloroacetamide*

2,6-Dimethylaniline (3.0 mL, 2.9 g, 24.4 mmol) is added to 15 mL of glacial acetic acid in a 125-mL Erlenmeyer flask followed by chloroacetyl chloride (2.0 mL, 2.85 g, 25.1 mmol) and 25 mL of half-saturated aqueous sodium acetate.

CAUTION: *Glacial acetic acid is corrosive and can cause serious burns.*

Precipitation of the amide is virtually instantaneous.The product is stirred thoroughly with 60 mL of cold water and isolated by vacuum filtration. It should be pressed as dry as possible in the Buchner funnel and used immediately in the next step.

2-(Diethylamino)-N-*(2,6-dimethylphenyl)acetamide*

The amide is placed in a 50-mL round-bottom flask containing diethylamine (7.5 mL, 5.29 g, 72.5 mmol) and 25 mL of toluene and refluxed for one hour. The reaction mixture is cooled to room temperature and transferred to a separatory funnel, where it is washed 4× with 50-mL portions of water to remove diethylamine hydrochloride and excess diethylamine. The organic layer is extracted with one 20-mL portion of 3 M hydrochloric acid and washed once with 20 mL of water. The combined aqueous extracts are placed in a 125-mL Erlenmeyer flask, cooled to 10 °C in an ice bath, and neutralized by addition of 3 M sodium hydroxide in portions with stirring while maintaining the temperature below 20 °C.

The product separates as a granular white solid and is isolated by vacuum filtration. It is washed with cold water, pressed dry, and air-dried as long as possible. The yield of dry product is 4.1 grams, mp 64–66 °C (lit. 67–69 °C), 71.1% based on 2,6-dimethylaniline. ^{1}H NMR (300 MHz, $CDCl_3$) triplet δ 1.13 6H, singlet δ 2.23 6H, quartet δ 2.68 4H, singlet δ 3.22 2H, singlet δ 7.08 3H, singlet δ 8.92 (broad) 1H.

Recrystallization

Lidocaine is highly soluble in all common organic solvents but it can be recrystallized from warm hexane using 1 mL of solvent per gram of crude product. The product crystallizes in large colorless spars, mp 65–67 °C (lit. 67–69 °C).

Acknowledgment

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Literature Cited

1. Lofgren, N. M.; Lundquist, B. J. *Alkyl Glycinanilides*. U.S. Patent 2 441 498, May 11,1948.