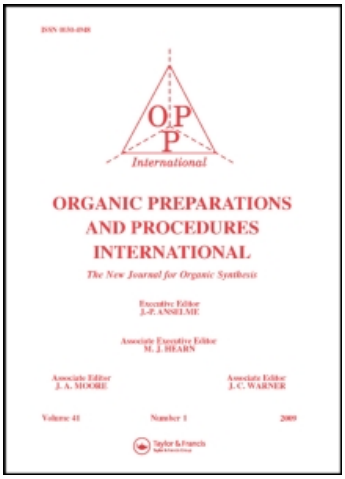

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AN IMPROVED SYNTHESIS OF 9-CHLORO-2-METHOXYACRIDINE

Lynn James Sanfilippo[a]
[a] Department of Chemistry, New Mexico State University, Las Cruces, NM, USA

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AN IMPROVED SYNTHESIS OF 9-CHLORO-2-METHOXYACRIDINE

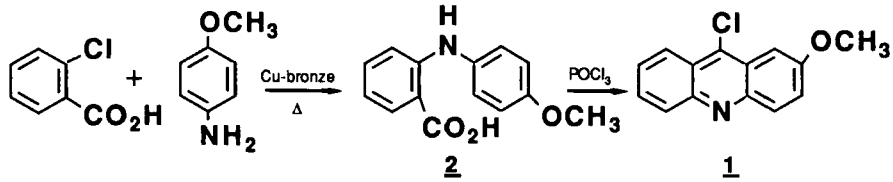
Submitted by (9/26/90) Lynn James SanFilippo

Department of Chemistry
New Mexico State University
Las Cruces, NM 88003, USA

Substituted chloroacridines are useful precursors for various important classes of biologically active molecules. The antiviral activity of acridine derivatives has been well documented.[1] Heterocyclic alkylating agents with unusual antitumor activity can be readily prepared from the chloroacridine skeleton.[2] Unique chromosomal staining derivatives have also been constructed from the chloroacridine precursor.[3] We report an improved synthesis of

9–chloro–2–methoxyacridine (**1**).

The previous approaches to **1** involved the addition of o-chlorobenzoic acid to p-anisidine in the presence of a catalytic amount of copper bronze to form



2 **1**

N–(4'–methoxyphenyl)anthranilic acid (**2**).[4] The second step involved the treatment of **2** with phosphorus oxychloride affording via cyclization and chlorination the 9-chloroacridine derivative **1**.[1,3,5]

Several problems were encountered in this two-step procedure. The original paper describing the preparation of the anthranilic acid derivative **2** used tetralin as a solvent and gave very little description of workup.[4] Yields varied from 0 to 10% using this procedure. Change of the solvent from tetralin to DMF and extraction of the product at a controlled pH of 4 allowed isolation of **2** in yields of up to 42%. There were difficulties in the conversion of **2** to **1** as well. Three different melting points of **1** have been reported in the literature: 107°[1], 124–126°[5], and 154°[6]. All three preparations used a large excess of phosphorus oxychloride. We found that the removal of residual phosphorus oxychloride was crucial in obtaining the desired product reproducibly. If phosphorus oxychloride was not completely destroyed prior to isolation of crude product, hydrogen chloride was generated upon workup leading to partial salt formation thus explaining the varying melting points. The procedure we found to be the most useful was to remove excess phosphorus oxychloride under reduced pressure and then pouring the resulting viscous liquid into an ammonium hydroxide/ice mixture to destroy any remaining phosphorus oxychloride. Workup afforded **1** as yellow needles, mp. 153°. The procedure outlined here should have general application and may be useful in the preparation of other 9–chloroacridine derivatives.

EXPERIMENTAL SECTION

General experimental conditions have been previously reported.[7]

N–(4'–Methoxyphenyl)anthranilic Acid (**2**).- In a 250 mL round bottom flask fitted with a reflux condenser was placed o-chlorobenzoic acid (0.02 mol, 3.12 g), p-anisidine (0.026 mol, 3.2 g), potassium carbonate (0.24 mol, 3.2 g) and dimethylformamide (60 mL). To this mixture was added copper-bronze (1 g). The mixture was refluxed under nitrogen for 4 hrs, cooled and filtered by suction. The filtrate was diluted with water, acidified to pH 4 and extracted twice with ethyl acetate. The combined ethyl acetate layers were washed with 0.1 N HCl and brine and dried over $MgSO_4$. Filtration and removal of solvent produced a green

solid which was recrystallized from absolute ethanol affording 2.1g (42%) of **2** as light green crystals, mp. 185-188°, lit.[4] 186°. IR ($CHCl_3$): 3320, 3010, 1660, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.84 (s, 3H), 6.74 (t, 2H), 7.0 (m, 3H), 7.30 (m, 3H), 8.08 (d, 1H), 9.24 (s, 1H).

9–Chloro–2–methoxyacridine (**1**).- A mixture of **2** (250 mg, 1 mmol) and phosphorus oxychloride (5 mL) was refluxed in an oil bath at 110° under nitrogen for 3 hrs. The mixture was cooled, the excess phosphorus oxychloride removed at aspirator pressure via a rotoevaporator affording a mustard yellow residue [Excess phosphorus oxychloride could also be removed using a vacuum pump with extreme care to trap any volatile material. We found that such vapors could easily damage pumps rendering them unusable]. The residue was treated with a mixture of ammonium hydroxide and ice. After stirring for several minutes, this mixture was extracted with chloroform twice and the combined organic layers washed with brine and dried over Na_2SO_4. Removal of solvent resulted in dark yellow crystals, which were recrystallized from methanol/0.5% ammonium hydroxide affording 168 mg (66%) of **1** as bright yellow needles, mp. 153°. IR (KBr): 2966, 1631, 1554 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 4.01 (s, 3H), 7.46-7.51 (m, 2H), 7.60 –7.80 (m, 2H), 8.10-8.23 (m, 2H), 8.39 (d, 1H).

Anal. Calcd. for $C_{14}H_{10}ClNO$: C, 69.15; H, 4.14; N, 5.75. Found: C, 69.21; H, 3.93; N, 5.41

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