A New Reagent for the Synthesis of Diethyl Arylaminomethylenemalonates

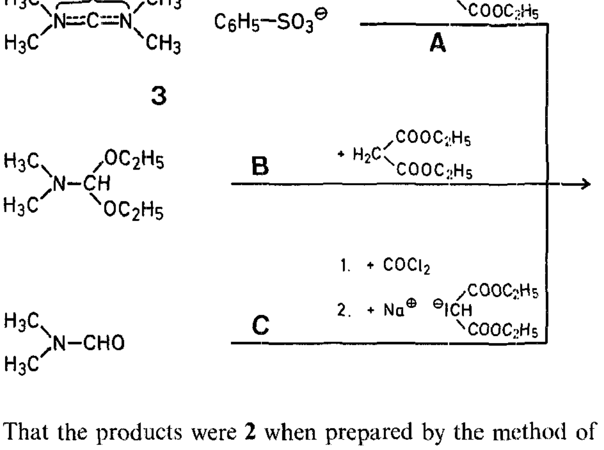
Nicholas D. Harris

The Norwich Pharmacal Company, Norwich, N.Y. 13815, U.S.A.

Our interest in quinolines led us to investigate reagents for the preparation of diethyl arylaminomethylenemalonates (**1**) which lead to ethyl 4-hydroxyquinoline-3-carboxylates[1]. In these studies it was determined that the dimethylamino group of diethyl dimethylaminomethylenemalonate[2] (**2**) was readily displaced by arylamines to give **1**. Since **2** is a new reagent for the preparation of **1**, alternate syntheses for **2** were explored.

Meerwein has shown that the acetals of dimethylformamide are useful for introduction of the dimethylaminomethylene group into active hydrogen compounds[3]. The reaction of the diethyl acetal of dimethylformamide with diethyl malonate by this method is was found to give **2**.

Recently, the preparation of tetramethylformamidinium benzenesulfonate (**3**) was reported[4]. Since formamidinium salts are known to react with active hydrogen compounds[5], the reaction of **3** with diethyl malonate anion was investigated and found to give **2**.



That the products were **2** when prepared by the method of Meerwein or from **3** was shown by their I.R. spectra, which were identical to the I.R. spectrum of **2** prepared according to Bredereck[2], and by their reactions with aromatic amines, which produced the corresponding **1**.

Melting points are corrected and were taken on a Fischer-Johns melting point apparatus. I.R. spectra were obtained on a Perkin-Elmer 137 spectrophotometer. Microanalyses were performed by the Physical and Analytical Section of The Norwich Pharmacal Company.

Diethyl Dimethylaminomethylenemalonate (2):

Method A: To the sodium salt of diethyl malonate [prepared in ethanol from sodium (5.5 g, 0.24 g-atom) and diethyl malonate (38.3 g, 0.24 mol)] was added a solution of tetramethylformamidinium benzenesulfonate[4] (54 g, 0.24 mol) in ethanol (140 ml). The reaction mixture was allowed to stand at ambient temperature for 20 hr and then was filtered. The alcohol was distilled from the filtrate and the residue was treated with a mixture of saturated aqueous potassium carbonate solution (190 ml) and benzene/ethanol (190 ml, 3+1). The mixture was filtered, the layers were separated, and the aqueous layer was re-extracted with benzene/ethanol. The solvents were distilled from the combined organic extracts. The oily residue (35 g) was distilled under vacuum; yield: 26 g (50%); b.p. 109°/0.075 mm (reported[2]: b.p. 123°/0.07 mm). This material was identical to the material prepared according to Bredereck[2] (Method C) in its reactions with aromatic amines and in its I.R. spectrum.

Method B: The diethyl acetal of dimethylformamide[2] (7.75 g, 0.057 mol) and diethyl malonate (8.5 g, 0.053 mol) were heated at 130–150° (oil bath temperature) for 90 min., collecting the ethanol as it was formed. The oily residue (9.4 g, 77%) was identical to the **2** prepared by Method A as shown by its I.R. spectrum and its reactions with aromatic amines.

Diethyl Arylaminomethylenemalonates (1):

A solution of the aromatic amine (0.023 mol) and distilled **2** (5 g, 0.023 mol) in acetic acid (25 ml) was allowed to stand over night. The residue was dissolved in ether and was washed with saturated aqueous sodium bicarbonate solution, 5% aqueous hydrochloric acid, and water. The ether was then evaporated from the extract, the residue was dissolved in ethanol, and the solid product was precipitated by the addition of ice to the ethanolic solution. The solid product was collected on a Buchner funnel and was washed with water.

Aniline→diethyl anilinomethylenemalonate; yield: 3.5 g (57%); m.p. 45–46° (reported[6] m.p. 50°).

3,4-Dimethoxyaniline→diethyl 3,4-dimethoxyanilinomethylenemalonate[7]: yield: 5 g (67%); m.p. (crude) 55–57°; after recrystallization from ethanol/water (1+1) and ether/petroleum ether (1+1), m.p. 59–60°.

$C_{16}H_{21}NO_6$	calc.	C 59.43	H 6.55	N 4.33
	found	59.40	6.40	4.31.

3,4-Diethoxy-aniline→diethyl 3,4-diethoxyanilinomethylenemalonate[1]; yield: 6 g (74%); m.p. (crude) 63–65°; after recrystallization from ethanol/water, m.p. 67–67.5°.

$C_{18}H_{25}NO_6$	calc.	C 61.52	H 7.17	N 3.99
	found	61.60	7.03	3.88.

Received: January 18, 1971

---

[1] C. F. Spencer et al., J. Med. Chem. **9**, 934 (1966).

[2] H. Bredereck, K. Bredereck, Chem. Ber. **94**, 2278 (1961).

[3] H. Meerwein, W. Florian, N. Schön, G. Stopp, Liebigs Ann. Chem. **641**, 1 (1961).

[4] H. E. Ulery, J. Org. Chem. **30**, 2464 (1965).

[5] Z. Arnold, J. Žemlička, Collect. Czech. Chem. Commun. **25**, 1302 (1960); C.A. **54**, 17253 (1960).
E.C. Taylor, W.A. Ehrhart, J. Amer. Chem. Soc. **82**, 3138 (1960).

[6] L. Claisen, E. Hasse, Liebigs Ann. Chem. **297**, 77 (1897).

[7] B. Riegel et al., J. Amer. Chem. Soc. **68**, 1264 (1946).