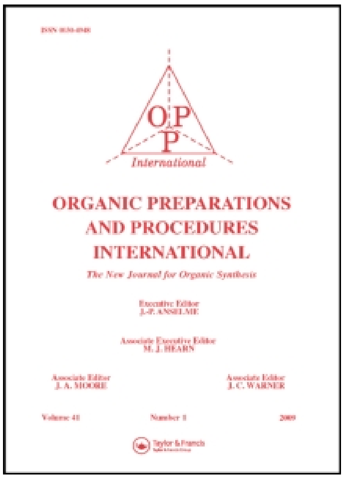

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A. H. Lewin[a]; S. R. Parker[a]; N. B. Fleming[a]; F. I. Carroll[a]
[a] Chemistry and Life Sciences Group, Research Triangle Institute, Research Triangle Park, North Carolina

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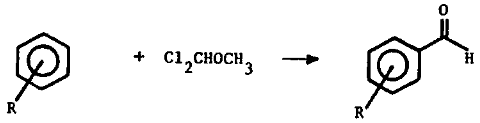
FORMYLATION OF ARENES BY α,α-DICHLOROMETHYL METHYL ETHER. AN IMPROVED EXPERIMENTAL PROCEDURE

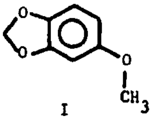
A. H. Lewin,* S. R. Parker, N. B. Fleming and F. I. Carroll

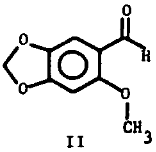
Chemistry and Life Sciences Group
Research Triangle Institute
Research Triangle Park, North Carolina 27709

A relatively common method of formylation of arenes involves treatment with α,α-dichloromethyl methyl ether in the presence of a Lewis acid such as titanic chloride[1] or stannic chloride.[2] Although excellent yields have been reported in some cases $(\geq 90\%)$,[1,3,4] poor $(\leq 25\%)$[3,5] and moderate $(\sim 50\%)$[2,5] yields have been found in other cases. Purification of the final product sometimes requires the rather tedious isolation of the aldehyde *via* its bisulfite addition product.[2,3] In the course of the preparation of several substituted benzaldehydes by this method, we obtained only moderate yields and discovered two by-products. These have suggested modifications in the reaction conditions which led to cleaner reactions and improved yields.



The formylation of 3,4-methylenedioxyanisole (I) using stannic chloride gave, in addition to the expected product, 2-methoxy-4,5-methylenedioxybenzaldehyde (II), a compound identified as tris(2-methoxy-4,5-methylenedioxyphenyl)methane (III).


I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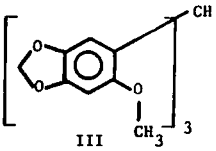
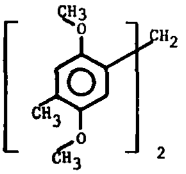
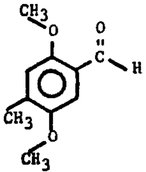

III

In an analogous experiment with 2,5-dimethoxytoluene (IV), a by-product identified as bis(2,5-dimethoxy-4-methylphenyl)methane (V) was obtained along with the desired 2,5-dimethoxy-4-methyl benzaldehyde (VI).

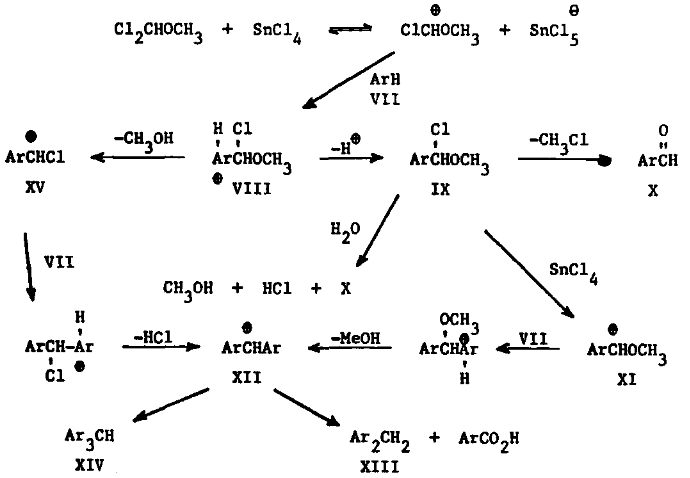


V



VI

Our working hypothesis regarding the mode of formation of these by-products,[6] shown in the chart below, suggested that the formation of the by-products could be minimized by carrying out a reverse addition. Thus, addition of the arene VII to the preformed complex between α,α-dichloromethyl methyl ether and stannic chloride should eliminate the reaction between XI and/or XV with arene VII because there would not be any excess arene. An experiment in which 2,5-dimethoxytoluene was added to equimolar α,α-dichloromethyl methyl ether and twofold excess stannic chloride at -5°C gave a slightly improved yield of aldehyde VI (55% *vs*. 50%) but failed to entirely eliminate the bis by-product V. Use of 25% excess ether (in order to enhance its reaction with VII *vs*. the reaction of XI and/or XV



Chart

with VII) under the same conditions gave 75% aldehyde and neither the bis nor the tris by-product. The advantages of the modified procedure are improved yields, shortened reaction times (no exothermic steps), ease of purification (no organic by-products) and ease of scaling-up.

EXPERIMENTAL

General Procedure.-A three-necked, round bottomed flask equipped with magnetic stirrer, thermometer, addition funnel and condenser with drying tube, containing 62.5 ml dry CH_2Cl_2, was cooled in a salt-slush bath to *ca*. -7°. To this was added 24.1 ml (0.20 mol) stannic chloride followed by the rapid dropwise addition of 14.4 g (0.13 mol) α,α-dichloromethyl methyl ether. The arene (0.10 mol) was then added dropwise over 1 hr, keeping the temperature below 5°. The resulting dark red solution was allowed to come to room temperature and then refluxed for 1 1/2 hr. After cooling, the solution was poured over 200 ml of ice-water, whereupon the organic layer turned dark green. The layers were separated, and the aqueous layer was extracted repeatedly until colorless. The combined organic phases were washed with 3N HCl (∿200 ml) and water (∿200 ml), dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from EtOH (sometimes after decolorization with neutral Norit). For large-scale preparations (1-2 mol), a short SiO_2 cleanup column (CH_2Cl_2) followed by decolorizing with Norit was found to remove essentially all the color and facilitate crystallization. Typical yields were 65-75%.

Separation and Identification of Bis(2,5-dimethoxy-4-methylphenyl)-methane.-Crude product from the preparation of 2,5-dimethoxy-4-methylbenzaldehyde VI was dissolved in hot absolute EtOH, and after cooling to room temperature, the solution was refrigerated overnight. The precipitate which formed was collected and was found not to be the desired aldehyde. The new compound had m.p. 138-140°; I.R., no carbonyl or hydroxy bands; ^{1}H-N.M.R. ($CDCl_3$) δ = 2.18 (s, 6H, CH_3), 3.67 (s, 6H, OCH_3), 3.76 (s, 6H, OCH_3), 3.90 (s, 2H, CH), 6.60 (s, 2H, aromatic), and 6.66 ppm (s, 2H, aromatic); ^{13}C-N.M.R. ($CDCl_3$) δ = 16.01 (q, $\underline{C}H_3$), 29.56 (t, $\underline{C}H_2$), 55.89 and 56.04 (q, $O\underline{C}H_3$), 113.14, and 113.73 (d, unsubstituted aromatic), and 124.50, 127.04, 151.08, and 151.37 ppm (substituted aromatic); M.S., m/e = 316 (M^+).

Separation and Identification of Tris(2-methoxy-4,5-methylenedioxyphenyl)-methane.-Concentration of the mother liquors from the crystallization of 2-methoxy-4,5-methylenedioxybenzaldehyde II gave a small quantity of translucent crystals, m.p. ca. 200°C; I.R., no carbonyl band; ^{1}H-N.M.R. ($CDCl_3$) δ = 3.60 (s, 9H, OCH_3), 5.77 (s, 6H, OCH_2O), 6.07 (s, lh, CH), and 6.40 ppm (s, 3H, aromatic); ^{13}C-N.M.R. ($CDCl_3$) δ = 36.68 (d, $\underline{C}H$), 57.06 (q, $O\underline{C}H_3$), 100.75 (t, $O\underline{C}H_2O$), 95.54 and 109.34 (d, unsubstituted aromatic), and 125.48, 140.69, 145.96, and 152.00 ppm (substituted aromatic); M.S., m/e = 466 (M^+).

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