

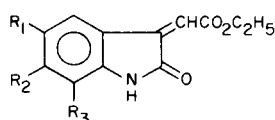
Preparation of Ethyl 3-Isatylideneacetates *Via* the Wittig Reaction in Acetic Acid

H. A. Brandman

Givaudan Corporation, Clifton, New Jersey 07014

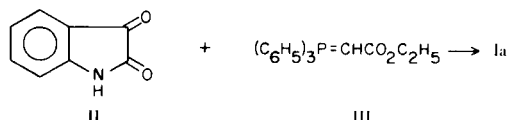
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In the course of other work substantial quantities of the ethyl 3-isatylideneacetates (Ia-c) were needed. The only reported preparation of compounds of this type is a



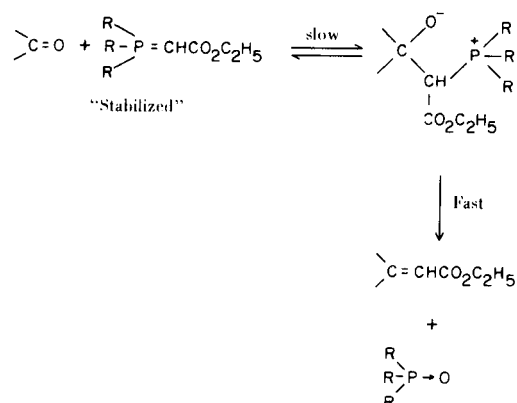
- Ia: R₁ = R₂ = R₃ = H
 Ib: R₁ = R₃ = Cl; R₂ = H
 Ic: R₁ = R₃ = H; R₂ = Br

three step synthesis from oxindole (I). We investigated the Wittig reaction of isatin (II) and ethoxycarbonylmethylenetriphenylphosphorane (III) in the hopes of obtaining the desired compound in one step from readily available starting materials.



Our initial attempts at running the reaction in the usual solvents (benzene, dioxane, ethanol, tetrahydrofuran) (2) provided the compound in poor yield. Addition of catalytic amounts of benzoic acid (3) to these solvents brought no improvement in yield. However, when acetic acid was used as solvent, a 69% yield of Ia was easily obtained. Similar results were obtained for Ib (64%) and Ic (62%).

We believe this is the first time that acetic acid has been used as a solvent for the Wittig reaction. Since addition of catalytic amounts of benzoic acid did not affect the yield, it would seem unlikely that the role of the acetic acid is to protonate the carbonyl group (3). Speziale and Bissing (4) have shown that a) the rate determining step of the Wittig reaction with stabilized ylids is formation of the betaine and b) the rate of reaction is dependent on the polarity of the solvent.



Therefore, the role of the highly polar acetic acid is simply stabilization of the dipolar intermediate. Its use as a solvent for other sluggish, stabilized ylids is being investigated.

EXPERIMENTAL

All melting points are uncorrected, nmr spectra were taken on a Varian A-60A spectrometer. Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York. General Procedure for Ethyl 3-Isatylideneacetates (Ia-c).

A mixture of 0.05 mole each of the isatin and ethoxycarbonylmethylenetriphenylphosphorane and 50-100 ml. glacial acetic acid was heated 4 hours at 70-95°. The acetic acid was removed under vacuum and the residue was washed onto a filter funnel with a small quantity of methanol. Recrystallization from ethanol gave pure material.

Ethyl 3-Isatylideneacetate (Ia).

This compound was obtained in 69% yield, m.p. 168-170° [lit. (1) m.p. 169-170°]; nmr (acetone-d₆) δ: 1.42 (t, 3, CH₃, J = 7 Hz); 4.42 (q, 2, CH₂, J = 7 Hz); 6.84 (s, 1, =CH-); 6.95-7.70 (m, 4, aromatic); 8.60 (s, 1, NH).

Anal. Calcd. for C₁₂H₁₁NO₃: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.48; H, 5.17; N, 6.44.

Ethyl 5,7-Dichloro-3-isatylideneacetate (Ib).

This compound was obtained in 64% yield, m.p. 192-194°; nmr (DMSO-d₆) δ: 1.37 (t, 3, CH₃, J = 7 Hz); 4.35 (q, 2, CH₂, J = 7 Hz); 6.61 (s, 1, =CH-); 7.43 (d, 1, H₄, J = 2 Hz); 8.28 (d, 1,

H₆, J = 2 Hz); 11.30 (s, 1, NH).

Anal. Calcd. for C₁₂H₉Cl₂NO₃: C, 50.38; H, 3.17; N, 4.90.
Found: C, 50.47; H, 3.25; N, 5.00.

Ethyl 5-Bromo-3-isatylideneacetate (Ic).

This compound was obtained in 62% yield, m.p. 234-235°; nmr (DMSO-d₆) δ: 1.30 (t, 3, CH₃, J = 7 Hz); 4.28 (q, 2, CH₂, J = 7 Hz); 6.62 (s, 1, =CH-); 6.78 (d, 1, H₇, J = 8 Hz); 7.50 (d, 1, H₆, J_{H₄-H₆} = 1 Hz, J_{H₄-H₇} = 8 Hz); 8.47 (d, 1, H₄, J = 1 Hz); 10.80 (s, 1, NH).

Anal. Calcd. for C₁₂H₁₀BrNO₃: C, 48.67; H, 3.40; N, 4.73.
Found: C, 48.39; H, 3.23; N, 4.55.

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