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DIRECT N-ALKYLATION OF ISATIN BY HALOMETHYL KETONES

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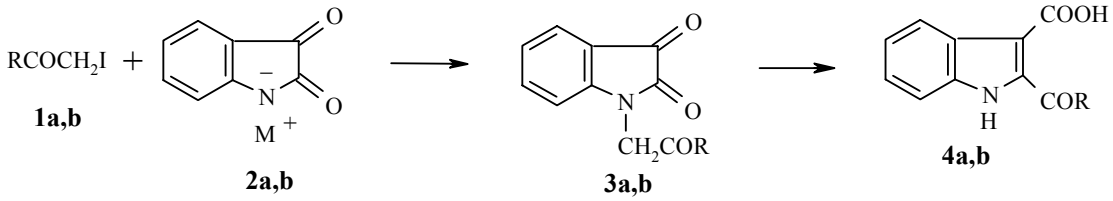
Solid-phase syntheses are reported for 1-(2-oxoalkyl)indoline-2,3-diones.

Keywords: halomethyl ketones, 1-(2-oxoalkyl)indoline-2,3-diones.

Isatins may react with halomethyl ketones at the β-CO or NH group. If the reaction begins with N-alkylation, the products formed smoothly isomerize to give 2-acylindole-3-carboxylic acids under mild conditions as a result of the facile opening of the five-membered isatin ring in aqueous alkali and alcoholic sodium alcoholates [1].



1, 3, 4, **a** R = Ph, **b** R = Me; **2 a** M = Na, **b** M = Li

Epoxy ketones are formed in the reaction at the β-CO group as a result of the Darzin condensation. The five-membered ring of these epoxy ketones is cleaved at high temperature in solutions with high alkali concentration and the products of their decarboxylation are mainly isolated instead of the acids [2]. Thus, as indicated in our previous review [1], the direct alkylation of isatins by halomethyl ketones appears to be a good approach for such syntheses. Radul et al. [3] have described the N-alkylation of isatin by α-bromo ketones in aprotic solvents such as benzene and toluene in the presence of weakly basic condensing reagents such as pyridine, triethylamine, and potassium carbonate. We should note that the solubility of isatin in these solvents is very limited.

In the present work, we demonstrate the feasibility of carrying out this reaction in DMF, which is a polar solvent, and in the solid phase. In the former case, phenacyl iodide (**1a**) was used as the N-alkylating reagent due to the reduced tendency of **1a** to generate the $RCOC^{-}HX$ carbanion (X = halogen) in comparison with its chloride and bromide analogs. The $RCOC^{-}HX$ carbanion rapidly reacts with the β-CO group. The addition of isatinsodium (**2a**) or isatinlithium (**2b**) (obtained from equimolar amounts of isatin and the hydride of the corresponding metal) in DMF to a solution of ketone **1a** in DMF at from -10 to -15°C led to N-phenacylisatin **3a** in 46% and 38% yield, respectively. In the latter case, mixing iodoacetone (**1b**) with salt **2a**

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(the **1b:2a** mole ratio was 1:1.5) at 20°C over 120 h gave N-acetonylisatin (**3b**) in 40% yield. Further studies may lead to higher yields for this reaction. The structures of products **3a** and **3b** were supported by the conversion of these compounds into 2-acylindole-3-carboxylic acids **4a** and **4b**, respectively.

EXPERIMENTAL

Phenacyl Iodide (1a). A sample of phenacyl bromide (25-30 mmol) or phenacyl chloride and then KI or anhydrous NaI (50 mmol) were added to absolute DMF (25-30 ml) at -10°C and the mixture was maintained for ~16 h at this temperature. The reaction mixture was used for the N-alkylation of isatin without isolation of iodide **1a**.

N-Phenacylisatin (3a). A sample of salt **2a** or **2b** obtained according to Tacconi et al. [4] from isatin (30 mmol) and NaH or LiH (30 mmol) in anhydrous DMF (75 ml) was added in portions to the solution of phenacyl iodide maintained at from -10 to -15°C such that each portion was reacted before addition of the next portion. The reaction was monitored by thin-layer chromatography on Silufol plates using 4:1 benzene–acetone as the eluent. After completing the addition of salt **2**, the reaction mixture was stirred for 1 h at the same temperature. Cooling was discontinued. The mixture was poured into a 10-fold volume of water at room temperature and brought to pH 1. The precipitate formed was separated. Chromatography on a silica gel column using 4:1 benzene–acetone as the eluent gave 3.66 g (46%) **3a** (in the case of salt **2a**) or 3.02 g (38%) **3a** (in the case of salt **2b**). The melting point of **3a** was 144-145°C (145-146°C [5]).

N-Acetonylisatin (3b). A sample of **2a** (3.38 g, 20 mmol) was thoroughly mixed with freshly distilled iodoacetone (5.52 g, 30 mmol). The mixture obtained was maintained for 120 h in a flask protected with a calcium chloride tube at room temperature and then extracted with dry benzene. The extract was evaporated. Chromatography of the residue on a silica gel column with benzene as the eluent gave 1.62 g (40%) **3b**; mp 154-156°C (156-157°C [6]).

2-Benzoylindole-3-carboxylic Acid (4a). A sample of **3a** (2.65 g, 10 mmol) was dissolved in 80% aq. ethanol containing NaOH (5 g) and maintained for 3 h at ~20°C. Hydrochloric acid was added to bring the mixture to pH 1. The precipitate of **4a** was filtered off, washed with water, and dried to give **4a** in 87% yield; mp 218-219°C (218-219°C [7]).

2-Acetylindole-3-carboxylic Acid (4b) was obtained according to our previous procedure [6] in 73% yield; mp 217-218°C (217-218°C [6]).

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