Baylis-Hillman Reaction of Isatin Derivatives: Isatins as a New Entry for the Baylis-Hillman Reaction

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The Baylis-Hillman reaction is well known as a coupling reaction of activated vinyl compounds and aldehydes or N-sulfonylimines.1 Besides aldehydes and N-sulfonylimines, substituted ketones with electron withdrawing substituents can be used specially in the Baylis-Hillman reaction.1b,2 Simple ketones such as acetone showed sluggish reactivity in the normal Baylis-Hillman reaction conditions.1b High pressure or special techniques must be needed. However, activated ketones such as halogenated ketones, α-keto esters and α-keto lactones can generate the corresponding Baylis-Hillman adducts under normal reaction conditions.2 Activated ketones with another carbonyl group such as ninhydrin (1,2,3-indanetrione) or isatin have never been studied systematically.3 Only one report dealing with the Baylis-Hillman reaction of ninhydrin and methyl acrylate was studied.3a During the course of our studies on the Baylis-Hillman reaction4 we intended to study on the Baylis-Hillman reaction of activated ketones such as ninhydrin, isatin, alloxan and parabanic acid.3b We thought that the reaction would proceed without difficulty. The adducts derived from these compounds have interesting backbone for further transformation in order to prepare biologically important compounds.4,5 Initially, the reaction of ninhydrin (1) with acrylates was carried out without additional solvent by using DABCO as a catalyst. Ethyl- or methyl acrylate was used as a solvent and we could obtain the adducts 2a and 2b in reasonable yields (Scheme 1, Table 1). For alkyl vinyl ketones, methylene chloride must be used for reasonable yields of products. Otherwise, severe contamination with dimer or polymers of the used alkyl vinyl ketones was observed. When we used acrylonitrile as the activated alkene, complex mixtures were observed in various reaction conditions. Among the conditions, the best result was observed when we used DMF as solvent (entry 5).

We examined the Baylis-Hillman reaction of isatin and its derivatives also. Various solvents were examined for the solubility problem of starting materials. Reasonable results were observed for isatin (3a), N-alkyl isatins (3b and 3c) or N-phenylisatin (3d) in THF. When the substrates have good solubility in methyl acrylate such as 3b-d, additional solvent was not necessary (see, Table 2).

However, for N-acetylisatin (3e) we could not obtain good results without solvent. As an example, we could obtain the desired product 4j in 11% isolated yield after 42 days when the reaction was performed without solvent. Unfortunately, however, the use of THF, methylene chloride or ethanol gave complex mixtures of products. After scrutinizing the obtained side products in the reaction and literature survey, we concluded that N-acetylisatin is unstable toward nucleophilic solvent. Especially, nucleophilic solvents such as methanol, ethanol or water cannot be used for N-acetylisatin. The

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenes*</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>COOMe</td>
<td>DABCO (0.1 equiv.) 50-60 °C, 60 min</td>
<td>2a</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>COOEt</td>
<td>DABCO (0.1 equiv.) 50-60 °C, 60 min</td>
<td>2b</td>
<td>82</td>
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<tr>
<td>3</td>
<td>COMe</td>
<td>DABCO (0.16 equiv.) CH₂Cl₂, rt, 90 min</td>
<td>2c</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>COEt</td>
<td>DABCO (0.15 equiv.) CH₂Cl₂, rt, 30 min</td>
<td>2d</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>CN</td>
<td>DABCO (0.08 equiv.) DMF, rt, 5 days</td>
<td>2e</td>
<td>25</td>
</tr>
</tbody>
</table>

*Methyl- or ethyl acrylate was used as solvent. In other cases 1.5 equiv. of alkenes were used.
property of \(N\)-acetyl- or \(N\)-tosylisatin toward nucleophiles such as ammonia, amines, alcohols and hydroxylamine has been reported.\(^6\) Ring opening reaction by the nucleophile at the \(N_1-C_2\) bond of these compounds can occur easily.\(^6\) After many trials we eventually found the best conditions for the Baylis-Hillman reaction of \(N\)-acylisatin derivatives: (1) The use of \(N,N\)-dimethylformamide as a solvent, (2) the use of somewhat larger amounts of DABCO catalyst (0.2-0.5 equiv.), and (3) short reaction time. The results are shown in Table 3. Quite recently, Garden and Skakle have reported on the Baylis-Hillman reaction of isatin derivatives.\(^3c\) They used ethanol or ethanol/THF system as solvents and examined on the reaction of isatin, \(N\)-methylisatin and \(N\)-benzylisatin. They did not examine the reaction with \(N\)-acetylisatin or related derivatives. Unfortunately, alloxan and parabanic acid did not undergo the reaction under the examined conditions.

In conclusion, we described optimized reaction conditions for the preparation of the Baylis-Hillman adducts of ninhydrin and isatin derivatives. For \(N\)-acylisatins the use of DMF as a solvent in the presence of somewhat larger amounts of DABCO is crucial for high yields of products. Thus, ninhydrin and isatin derivatives can be added as new entries for the Baylis-Hillman reaction.

### Experimental Section

Solvents and other chemicals were used as purchased. Starting materials were purchased (ninhydrin, isatin, \(N\)-phenylisatin, 5-bromoisatin) or prepared from isatin in good yields: \(N\)-allylisatin (allyl bromide, \(K_2CO_3\), DMF, rt, 5 h, 43\%), \(N\)-benzylisatin (benzyl bromide, \(K_2CO_3\), DMF, rt, 4 h, 63\%), \(N\)-acetylisatin (Ac\(_2\)O, 80-90 °C, 6 h, 79\%), 5-bromo-
N-acetylisiatin (Ac2O, 80-90 °C, 3 h, 84%), N-propionylisatin (propionyl chloride, pyridine, CH2Cl2, rt, 2 h, 94%), N-benzyloisatin (benzoic anhydride, Et3N, CH2Cl2, rt, 3 h, 80%).

**Typical procedure for the synthesis of the Baylis-Hillman adduct 2a:** To a stirred solution of ninhydrin (178 mg, 1.0 mmol) and methyl acrylate (2.0 mL) was added DABCO (11 mg, 0.1 mmol) and stirred 50-60 °C for 60 min. After removal of methyl acrylate and flash column chromatography (hexane/ethyl acetate, 1:1), we could obtain the desired compound 2a in 86% isolated yield as a white solid, 212 mg: mp 137-138 °C; IR (KBr) 3422, 1755, 1715, 1693 cm⁻¹; ¹H NMR (CDCl3) δ 3.27 (br s, 1H), 3.60 (s, 3H), 6.52 (s, 1H), 6.72 (s, 1H), 7.88-8.07 (m, 4H); ¹³C NMR (CDCl3) δ 52.31, 76.35, 124.35, 130.33, 136.21, 136.74, 140.98, 165.52, 197.00; Mass (70 eV) m/z (rel. intensity) 76 (23), 104 (35), 130 (19), 186 (34), 214 (100), 246 (M⁺, 2). The following compounds were synthesized analogously.

133.61, 138.68, 139.91, 164.84, 170.83, 176.27. 4m: 50%; oil; 1H NMR (CDCl3) δ 2.68 (s, 3H), 3.78 (br s, 1H), 6.28 (s, 1H), 6.33 (s, 1H), 7.52-7.62 (m, 2H), 8.17 (d, J = 8.7 Hz, 1H); 13C NMR (CDCl3) δ 26.41, 76.17, 114.79, 118.85, 119.36, 122.19, 127.69, 132.65, 134.67, 139.09, 170.05, 174.26 (one carbon is overlapped). 4n: 55%; pale pink solid; mp 159-160 °C; 1H NMR (CDCl3) δ 1.23 (t, J = 7.2 Hz, 3H), 3.02 (q, J = 7.2 Hz, 2H), 5.28 (br s, 1H), 6.22 (s, 1H), 6.32 (s, 1H), 7.26-8.25 (m, 1H); 13C NMR (CDCl3) δ 26.41, 76.17, 114.79, 118.85, 119.36, 122.19, 127.69, 132.65, 134.67, 139.09, 170.05, 174.26 (one carbon is overlapped).

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References and Notes


