Application of Baylis-Hillman Methodology in a New Synthesis of 3-Oxo-2,3-dihydro-1*H*-isoindoles

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The Baylis-Hillman reaction of 2-cyanobenzaldehyde with some activated alkenes leading to the formation of 3-oxo-2,3-dihydro-1*H*-isoindoles has been described.

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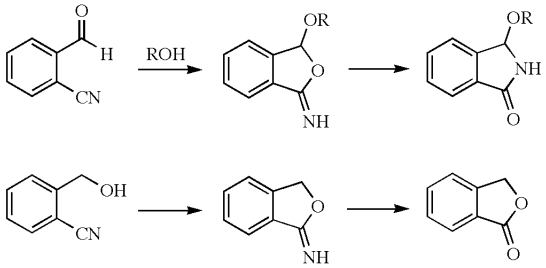
In recent years, the Baylis-Hillman reaction has become a powerful tool for construction of carbon-carbon bonds in organic chemistry because it is completely atom economical and provides densely functionalized structural units, which have been successfully employed in a veriety of interesting organic transformations [1]. Among them, the Baylis-Hillman adducts have been used to provide convenient access to benzannulated or other heterocyclic systems. These include indolizines [2], quinolines [3], chromenes [4], thiochromenes [5], indenes [6], pyridopyrimidones [7], 1,4-oxazepin-7-ones [8], coumarins [9] and isobenzofuranones [10].

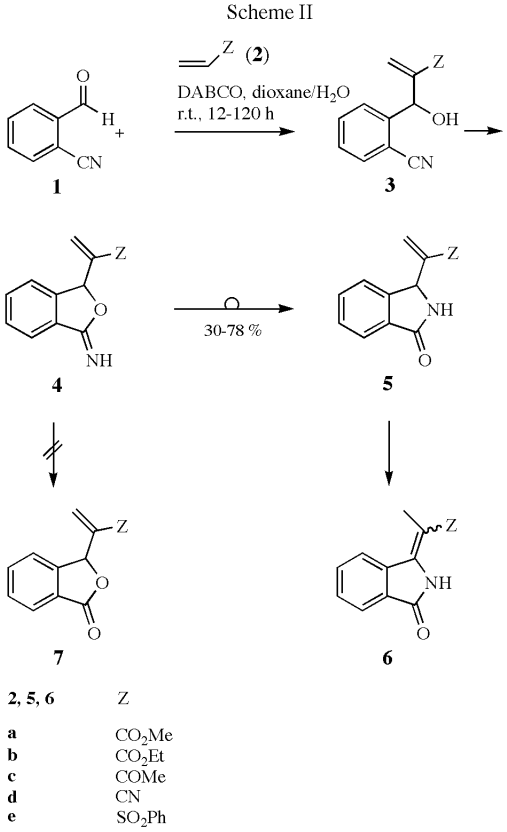
Meanwhile, 1-imino-1,3-dihydroisobenzofurans are a well known class of heterocycles, the syntheses of which commonly involve acid- or base-induced cyclization of 2-cyanobenzaldehyde with alcohols [11] or cyclization of 2-cyanobenzyl alcohols, and readily transformed into phthalimides or phthalides in moist organic solvent (Scheme I) [12]. We presumed that we could obtain the 3-substituted-1-imino-1,3-dihydroisobenzofuran derivatives **4** or their isomerized phthalimidines **5** from the

Scheme I



Baylis-Hillman reaction of 2-cyanobenzaldehyde with activated alkenes (Scheme II) [13]. In this direction we first carried out the reaction of 2-cyanobenzaldehyde with methyl acrylate (**2a**) and a catalytic amount (0.2 equivalents) of 1,4-diazabicyclo[2.2.2]octane (DABCO) under various conditions. The best results were obtained when the reaction was run in dioxane/water (15:1) at room temperature for 24 hours [14]. After the usual work-up and column chromatography followed by crystallization with ethyl acetate, the expected methyl 2-(3-imino-1,3-dihydroisobenzofuran-1-yl)acrylate (**4a**) or hydrolysis product,

Scheme II



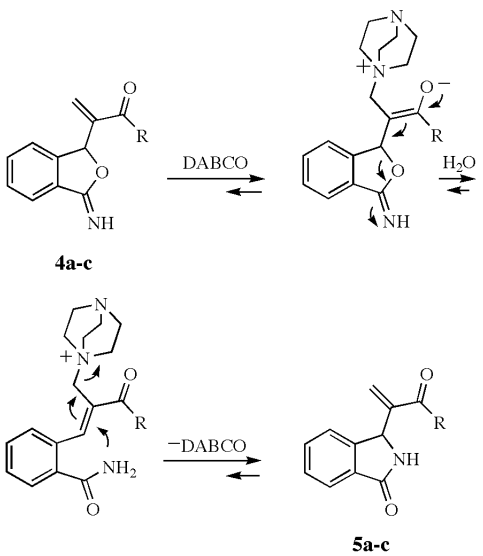
phthalide **7a** was not obtained. Instead the rearrangement product, methyl 2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)acrylate (**5a**) was produced in 45% yield as the sole product. This protocol was successfully extended to other activated alkenes such as ethyl acrylate (**2b**) and methyl vinyl ketone (**2c**), the corresponding products **5b** (46%) and **5c** (33%) being isolated. However, in the cases of acrylonitrile (**2d**) and phenyl vinyl sulfone (**2e**) the highly substituted olefin products, 2-(3-oxo-2,3-dihydroisoindol-1-ylidene)propionitrile (**6d**) and 3-(1-benzenesulfonylethylidene)-2,3-dihydro-1*H*-isoindol-1-one (**6e**) were produced in 78% and 30% yields, respectively. An effort for the transformation of **5a-c** into the **6a-c** was unsuccessful in refluxing chloroform for 24 hours with or without *p*-toluenesulfonic acid catalyst.

The structure **5** was established on the basis of spectroscopic data. Compound **5a,** for instance, had the molecular

formula $C_{12}H_{11}NO_3$, as indicated by mass spectra (M^+, 217) as 5% relative intensity. In the ^1H nmr spectrum, the signals from the three methine protons appeared as three singlets at 5.62, 5.84 and 6.33 ppm. The signal corresponding to the NH proton appeared as a singlet at 7.61 ppm and exchangeable in deuterium oxide. The ^{13}C nmr showed two carbonyl carbon signals at 166.4 (ester) and 171.1 ppm (amide). Also in the HMBC spectrum and the DEPT ^{13}C nmr spectrum of **5a** NH proton was correlated with quaternary carbon atoms at δ = 131.8 and 146.0 ppm. The infrared spectrum showed absorption bands in 3196 and 1708 cm^{-1} assignable for the lactam NH bond and the lactam carbonyl bond, respectively [15]. The stereochemistry of the obtained alkylidene phthalimidine **6d** as *E* and **6e** as *Z* was determined by two-dimensional NOESY experiments. In **6d**, correlation between methyl peak (s, δ = 2.13 ppm) and NH proton (s, δ = 11.23 ppm) was observed, and no correlation between methyl peak and any aromatic protons was shown, whereas correlation between methyl peak (s, δ = 2.36 ppm) and aromatic proton (m, δ = 7.69-7.82 ppm) was observed for **6e**. The reason for the selective formation of alkylidene phthalimidines in the cases of acrylonitrile and phenyl vinyl sulfone cannot be explained at this moment.

The conversion of **1** into **5** and **6** would appear to proceed in such a way that an intramolecular nucleophilic addition reaction of the hydroxyl group at the nitrile bond of the Baylis-Hillman adduct **3** gives 1-imino-1,3-dihydroisobenzofurans **4**, which immediately rearranges to afford **5a-c** or **6d**,**e** after proton transfer by the well known process [11]. Another possible explanation of conversion of **4** to **5** which is illustrated in Scheme III involves DABCO assisted fission of the C-O bond and recombination of the C-N bond by the addition-elimination pathway. The thermodynamic stability of the lactam **5a-c** from attack of the $-NH_2$ would select out over the regeneration of the less stable imino form **4a-c** derived from re-addition of the carbonyl oxygen which is probably kinetically favored.

Scheme III



4a-c

5a-c

3-Oxo-2,3-dihydro-1*H*-isoindoles have attracted much attention from the scientific community in recent years, because they represent the core unit of a wide range of naturally occurring substances [16] or bio-active compounds [17].

In conclusion, the Baylis-Hillman reaction of 2-cyanobenzaldehyde with some activated alkenes constitutes a new convenient route to 3-oxo-2,3-dihydro-1*H*-isoindoles-products with obvious potential for elaboration to 1-substituted derivatives.

EXPERIMENTAL

Melting points were obtained using an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. ^1H nmr (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Varian Gemini 300 spectrometer. The HMBC, DEPT and NOSEY spectra were obtained on a 300 MHz Bruker spectrometer. Mass spectra were recorded on a ThermoQuest Polaris Q mass spectrometer operating at 70 eV. Elemental analyses were obtained on a Carlo Erba EA 1180 element analyzer.

Methyl 2-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)acrylate (**5a**); Typical Procedure.

To a stirred solution of 2-cyanobenzaldehyde (**1**, 0.20 g, 1.52 mmoles) in aqueous dioxane (H_2O: 0.4 ml, dioxane: 5 ml) was added methyl acrylate (**2a**, 0.47 g, 5.48 mmoles) and DABCO (0.03 g, 0.31 mmoles) at room temperature. After 24 hours, the mixture was diluted with water (10 ml) and neutralized with 5% hydrochloric acid (0.23 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to afford 0.15 g (45%) of **5a** as a colorless crystalline solid, mp 172-174 °C; ir (potassium bromide): 3196, 1708, 1634 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.87 (s, 3 H), 5.62 (s, 1 H), 5.84 (s, 1 H), 6.33 (s, 1 H), 7.47-7.59 (m, 3 H), 7.61 (s, 1 H, exchangeable in deuterium oxide), 7.86 (d, 1 H, J = 6.7 Hz); ^{13}C nmr (deuteriochloroform): δ 52.3, 56.5, 123.5, 124.0, 126.3, 128.5, 131.3, 132.0, 137.8, 145.6, 166.4, 171.1; ms: m/z (%) 217 (M^+, 5), 186 (16), 185 (100), 158 (65), 157 (42), 132 (56), 130 (59), 129 (30).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.14; H, 4.89; N, 6.20.

Ethyl 2-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)acrylate (**5b**).

The procedure was the same as described above. Yield: 46%; colorless solid; mp 114-115 °C; ir (potassium bromide): 3203, 1708, 1634 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (t, 3 H, J = 7.0 Hz), 4.31 (q, 2 H, J = 7.0 Hz), 5.61 (s, 1 H), 5.82 (s, 1 H), 6.33 (s, 1 H), 7.29 (s, 1 H, exchangeable in deuterium oxide), 7.47-7.57 (m, 3 H), 7.87 (d, 1 H, J = 7.6 Hz); ^{13}C nmr (deuteriochloroform): δ 14.1, 56.6, 61.4, 123.4, 123.9, 126.0, 128.4,

131.4, 132.0, 138.1, 145.7, 165.9, 171.1; ms: m/z (%) 231 (M^+, 7), 202 (18), 186 (16), 185 (100), 158 (75), 157 (56), 132 (55), 130 (50), 129 (32).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.38; H, 5.43; N, 5.83.

3-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)-3-buten-2-one (**5c**).

The procedure was the same as described above except that the reaction mixture was stirred for 12 hours. Yield: 33%; colorless solid; mp 168 °C; ir (potassium bromide): 3196, 1716, 1662 cm^{-1}. ^1H nmr (deuteriochloroform): δ 2.46 (s, 3 H), 5.71 (s, 1 H), 5.99 (s, 1 H), 6.17 (s, 1 H), 6.69 (s, 1 H, exchangeable in deuterium oxide), 7.38 (d, 1 H, J = 7.3 Hz), 7.46-7.58 (m, 2 H), 7.86 (d, 1 H, J = 7.3 Hz); ^{13}C nmr (deuteriochloroform): δ 26.1, 55.3, 123.6, 123.9, 126.2, 128.4, 131.1, 132.1, 146.0, 146.1, 171.3, 199.2; ms: m/z (%) 201 (M^+, 8), 159 (24), 158 (100), 132 (13), 130 (24).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.70; N, 6.64.

2-(3-Oxo-2,3-dihydroisoindol-1-ylidene)propionitrile (**6d**).

The procedure was the same as described in **5a**. Yield: 78%; colorless solid; mp 282 °C; ir (potassium bromide): 3180, 2205, 1716, 1650 cm^{-1}. ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.13 (s, 3 H), 7.71 (d, 1 H, J = 6.7 Hz), 7.82 (br s, 2 H), 8.31 (d, 1 H, J = 7.0 Hz), 11.23 (s, 1 H, exchangeable in deuterium oxide); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 15.9, 83.6, 120.4, 122.7, 123.7, 130.0, 131.4, 133.7, 134.3, 145.5, 167.5; ms: m/z (%) 184 (M^+, 100), 183 (32), 156 (27), 155 (35), 130 (22), 129 (26), 103 (17).

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.49; H, 4.55; N, 15.48.

3-(1-Benzenesulfonylethylidene)-2,3-dihydro-1*H*-isoindol-1-one (**6e**).

The procedure was the same as described in **5a** except that 1 equivalent of DABCO was used and stirred for 120 hours. Yield: 30%; colorless solid; mp 199-200 °C; ir (potassium bromide): 3370, 1720, 1634, 1285, 1141 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (s, 3 H), 7.54-7.69 (m, 5 H), 7.69-7.82 (m, 1 H), 7.92-7.98 (m, 3 H), 10.03 (s, 1 H, exchangeable in deuterium oxide); ^{13}C nmr (deuteriochloroform): δ 14.1, 111.9, 124.5 125.2, 127.5, 129.4, 130.3, 131.4, 132.9, 133.8, 136.0, 139.8, 139.9, 167.0; ms: m/z (%) 299 (M^+, 61), 235 (15), 206 (22), 174 (100), 158 (25), 157 (78), 130 (33), 129 (66), 103 (25).

Anal. Calcd. for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.02; H, 4.09; N, 4.42.

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* Author to whom correspondence should be addressed.

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