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1-Benzopyran-4(4*H*)-ones as novel activated alkenes in the Baylis–Hillman reaction: a simple and facile synthesis of indolizine-fused-chromones

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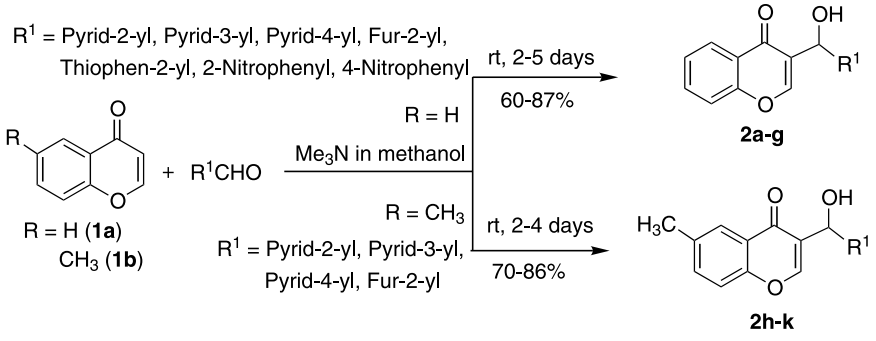
Abstract—1-Benzopyran-4(4*H*)-one derivatives have been successfully employed as novel activated alkenes in the Baylis–Hillman coupling with heteroaromatic-aldehydes, nitrobenzaldehydes and isatin-derivatives and the corresponding adducts, derived from pyridine-2-carboxaldehyde, have been transformed into a novel indolizine-fused-chromone framework.

The Baylis–Hillman reaction continues to attract the attention of organic chemists because this reaction produces an interesting class of highly useful densely functionalized molecules in a three-component atom-economic one-pot procedure.[1–3] Although a variety of activated alkenes,[4] electrophiles[5] and catalysts/catalytic systems[6] have been successfully employed in this reaction, application of chromone derivatives as activated alkenes has not been studied so far. We herein report chromone derivatives, for the first time, as activated alkenes in the Baylis–Hillman coupling with heteroaromatic-aldehydes, nitrobenzaldehydes and isatin-derivatives and also the facile conversion of the corresponding Baylis–Hillman adducts derived from pyridine-2-carboxaldehyde into a novel tetracyclic heterocyclic framework.

We have recently reported aqueous/methanolic trimethylamine as a catalyst/medium for performing the Baylis–Hillman reaction of various activated olefins with aldehydes.[7] With a view to expanding the scope of methanolic trimethylamine, the tertiary amine containing the minimum number of carbon atoms, and also with the objective of applying this medium to hitherto unexplored chromone derivatives[8] as activated alkenes, we selected 1-benzopyran-4(4*H*)-one **1a** for the Baylis–Hillman coupling with pyridine-2-carboxaldehyde under the influence of methanolic trimethylamine. In this direction, the best results were obtained when 1-benzopyran-4(4*H*)-one **1a** (1 mmol) was treated with pyridine-2-carboxaldehyde (1 mmol) in the presence of methanolic trimethylamine (25% w/w) (1 mmol) for 2 days, which provided the corresponding adduct, 3-



Scheme 1. Baylis–Hillman reactions of chromone derivatives with various heteroaromatic-aldehydes and nitrobenzaldehydes.

Keywords: chromone derivatives; activated alkenes; Baylis–Hillman reaction; isatin derivatives; indolizines.
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[hydroxy(pyrid-2-yl)methyl]-4*H*-chromen-4-one **2a**[9] in 84% isolated yield (after purification by silica gel chromatography, 20% EtOAc in hexanes) (Scheme 1 and Table 1). We then extended this strategy to representative heteroaromatic-aldehydes and nitrobenzaldehydes to furnish the resulting adducts **2b–g** in 60–87% isolated yields (Scheme 1 and Table 1). However, aromatic aldehydes such as benzaldehyde and 2,4-dichlorobenzaldehyde (less reactive than heteroaromatic-aldehydes and nitrobenzaldehydes) did not undergo the coupling reaction with the chromone derivative **1a** under similar conditions and we did not, in fact, notice any significant amounts of products even after longer reaction times (9 days).

With a view to understanding the generality of this reaction we next employed another chromone derivative, i.e. 6-methyl-1-benzopyran-4(4*H*)-one **1b** as an activated alkene for the Baylis–Hillman coupling with various heteroaromatic-aldehydes, which afforded the corresponding adducts **2h–k** in 70–86% isolated yields (Scheme 1 and Table 1).

In order to expand the scope of chromone derivatives as activated alkenes in the Baylis–Hillman reaction we next directed our attention towards application of the isatin-derivatives[10] as electrophiles for coupling with chromone derivatives. Accordingly, we first examined the reaction of 1-benzopyran-4(4*H*)-one **1a** (1 mmol) with *N*-methylisatin (1 mmol) under the influence of methanolic trimethylamine (25% w/w) (1 mmol) for 12 h, which provided the corresponding adduct, 3-hydroxy-1-methyl-3-(4-oxo-4*H*-chromen-3-yl)indolin-2-one **3a**[11] in 85% isolated yield (after purification by silica gel chromatography, 20% EtOAc in hexanes) (Fig. 1 and Table 2). Encouraged by this result, we then subjected various isatin-derivatives to coupling with chromone derivatives to provide the corresponding adducts **3b–g** in 78–83% isolated yields (Fig. 1 and Table 2).

A literature survey revealed that the chromone[12] moiety and indolizine[13] framework have indeed a special place in the field of heterocycles, as these skeletons constitute an integral part of several natural products and biologically active molecules. It would therefore be interesting to synthesize tetracyclic molecules possessing both chromone and indolizine moieties. A careful look at the Baylis–Hillman adducts obtained from the chromone

Table 1. Baylis–Hillman reactions of chromone derivatives with various heteroaromatic-aldehydes and nitrobenzaldehydes[a,b,c,d]

Substrate	R	R^1	Product	Time (days)	Mp (°C)	Yield (%)
1a	H	Pyrid-2-yl	**2a**	2	82–84	84
1a	H	Pyrid-3-yl	**2b**	2	154–156	82
1a	H	Pyrid-4-yl	**2c**	2	166–168	87
1a	H	Fur-2-yl	**2d**	4	84	74
1a	H	Thiophen-2-yl	**2e**	5	96–98	60
1a	H	2-Nitrophenyl	**2f**	2	150–152	81[e]
1a	H	4-Nitrophenyl	**2g**	2	186–187	86[f]
1b	CH_3	Pyrid-2-yl	**2h**	2	90	81
1b	CH_3	Pyrid-3-yl	**2i**	2	150–152	78
1b	CH_3	Pyrid-4-yl	**2j**	2	156–158	86
1b	CH_3	Fur-2-yl	**2k**	4	124–126	70

[a] All reactions were carried out using 1 mmol of the chromone derivatives (the activated alkene) with aldehydes (1 mmol) under the influence of Me_3N in methanol (25% w/w) (1 mmol) at room temperature for 2–5 days.

[b] All the compounds **2a–k** were obtained as colorless solids and were characterized by IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) and elemental analyses. Further, the compounds **2a**,**e**,**j** and **2k** were also characterized by mass spectral analysis.

[c] Melting points are of the pure products.

[d] Isolated yields of the pure products obtained after silica gel column chromatography (20% EtOAc in hexanes in the case of **2a**,**h**, 50% EtOAc in hexanes in the case of **2b**,**c**,**i**,**j**, and 10% EtOAc in hexanes in the case of **2d**,**e**,**k**).

[e] Isolated yield of the pure product obtained after the crystallization of the crude solid from CH_2Cl_2.

[f] Isolated yield of the pure product obtained after the crystallization of the crude solid from CH_3OH/CH_3CN (1/1, v/v).

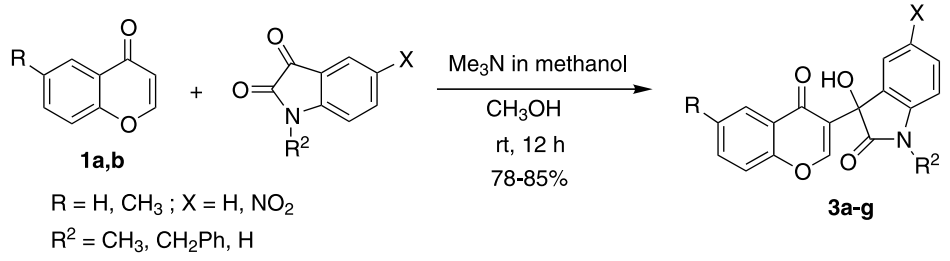


Figure 1. Baylis–Hillman reactions of chromone derivatives with various isatin-derivatives.

Table 2. Baylis–Hillman reactions of chromone derivatives with various isatin-derivatives[a,b,c,d]

Substrate	R	X	R^2	Product	Mp. (°C)	Yield (%)
1a	H	H	CH_3	**3a**	220–222	85
1a	H	H	CH_2Ph	**3b**	216–218	83
1a	H	H	H	**3c**	255 (dec.)	78[e]
1b	CH_3	H	CH_3	**3d**	170–172	83
1b	CH_3	H	CH_2Ph	**3e**	212–214	80
1b	CH_3	H	H	**3f**	260 (dec.)	81[e]
1a	H	NO_2	H	**3g**	262 (dec.)	78[e]

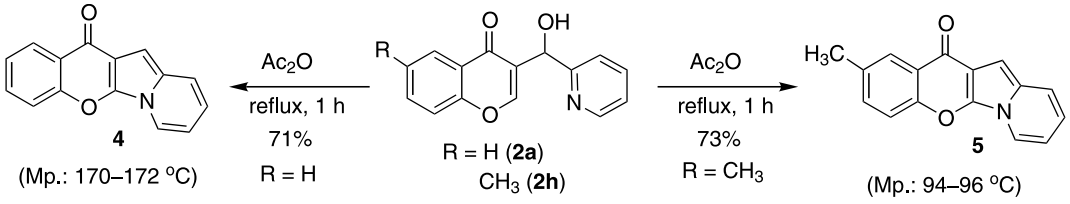
[a] All reactions were carried out using 1 mmol of the chromone derivatives (the activated alkene) with isatin-derivatives (1 mmol) in CH_3OH (2 mL) under the influence of Me_3N in methanol (25% w/w) (1 mmol) at room temperature for 12 h.

[b] All the compounds **3a**–**g** were obtained as colorless solids and were characterized by IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) and elemental analyses. Further the compounds **3a**,**e** and **3g** were also characterized by mass spectral analysis.

[c] Melting points are of the pure products.

[d] Isolated yields of the pure products obtained after silica gel column chromatography (20% EtOAc in hexanes in the case of **3a**,**b**,**d**,**e**).

[e] Isolated yields of pure products obtained after crystallization of the crude solid from CH_3OH.



Scheme 2. Synthesis of indolizine-fused-chromone systems.

derivatives and pyridine-2-carboxaldehyde suggested that these molecules possessed the required orientation for cyclization to provide a tetracyclic heterocyclic framework containing both the chromone and indolizine[14] moieties. Accordingly, we first examined the reaction of 3-[hydroxy(pyrid-2-yl)methyl]-4*H*-chromen-4-one (1 mmol) **2a** with acetic anhydride (1 mL) at reflux temperature for 1 h, which provided the desired tetracyclic system, i.e. 17-aza-2-oxa-9-oxo-tetracyclo(8.7.0.0^{3,8}.0^{12,17})heptadeca-1(10),3,5,7,11,13,15-heptaene **4**[15] in 71% isolated yield (after usual work-up followed by silica gel column chromatography, 10% EtOAc in hexanes) (Scheme 2). We then extended this strategy to 3-[hydroxy(pyrid-2-yl)methyl]-6-methyl-4*H*-chromen-4-one **2h** to provide the corresponding adduct, 17-aza-6-methyl-2-oxa-9-oxotetracyclo(8.7.0.0^{3,8}.0^{12,17})-heptadeca-1(10),3,5,7,11,13,15-heptaene **5** in 73% isolated yield under similar conditions (Scheme 2).

In conclusion, we have successfully employed methanolic trimethylamine as a medium for the Baylis–Hillman reaction of chromone derivatives with various heteroaromatic-aldehydes, nitrobenzaldehydes and isatin-derivatives, thus for the first time demonstrating the application of 1-benzopyran-4(4*H*)-one derivatives as activated olefins in the Baylis–Hillman reaction. We have also transformed the Baylis–Hillman adducts obtained from chromone derivatives and pyridine-2-carboxaldehyde into an interesting tetracyclic heterocyclic framework, i.e. indolizine fused chromone systems.

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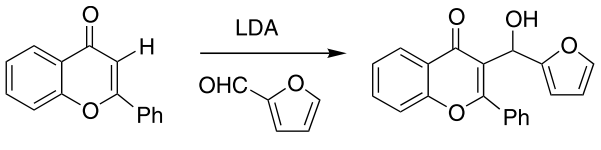

9. Spectral data for **2a**: IR (KBr): ν 3396, 1641, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.30 (bs, 1H), 6.00 (s, 1H), 7.15–7.28 (m, 1H), 7.35–7.50 (m, 2H), 7.61–7.77 (m, 3H), 8.07 (s, 1H), 8.18–8.28 (m, 1H), 8.52 (d, 1H, $J=4.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 68.7, 118.1, 121.4, 122.6, 123.9, 125.1, 125.6, 125.7, 133.6, 136.9, 148.0, 154.1, 156.2, 159.8, 177.3; EIMS (m/z): 253 (M^+); Anal. calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.90; H, 4.42; N, 5.56.
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11. Spectral data for **3a**: IR (KBr): ν 3321, 1699, 1641, 1610 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.17 (s, 3H), 6.77 (s, 1H), 6.85–7.18 (m, 3H), 7.24–7.36 (m, 1H), 7.38–7.52 (m, 1H), 7.64–7.93 (m, 3H), 8.62 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 26.4, 73.3, 108.5, 118.6, 122.3, 123.0, 123.4, 124.7, 125.0, 125.8, 129.7, 130.6, 134.6, 145.0, 155.1, 156.0, 174.7, 175.5; EIMS (m/z): 307 (M^+), 308 (M^++H). Anal. calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.45; H, 4.21; N, 4.54.
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15. Spectral data for **4**: IR (KBr): ν 1658, 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.57–6.80 (m, 2H), 6.84 (s, 1H), 7.36–7.53 (m, 2H), 7.58–7.80 (m, 2H), 8.06 (d, 1H, $J=6.8$ Hz), 8.46 (dd, 1H, $J=1.8$ and 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 91.0, 109.1, 111.5, 117.3, 118.7, 119.9, 120.4, 123.1, 124.1, 126.8, 127.8, 132.8, 140.7, 153.9, 174.7; EIMS (m/z): 235 (M^+). Anal. calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found: C, 76.75; H, 3.90; N, 5.92.