Synthesis of Highly Functionalized Spirobenzofuranols and Spirobenzofuranones by Baylis–Hillman Reaction

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Abstract: Baylis–Hillman reaction of salicylaldehydes with *N*-aryl/alkyl maleimides under neat conditions for the synthesis of chromenes resulted in an unusual cyclization to form spirobenzofuranol derivatives in moderate to good yield. PDC oxidation of the resultant products yielded the corresponding spirobenzofuranone derivatives.

Key words: Baylis–Hillman reaction, salicylaldehyde, maleimide, DABCO, spirobenzofuranol, spirobenzofuranone

Heterocycles are of great value in the design and discovery of new biologically active compounds.[1] The development of efficient processes to construct heterocycles, using metal-free catalysts has been drawing much attention over the past decades.[2] Spirocyclic systems containing one carbon atom common to two rings are structurally interesting.[3] Especially among them, the spirocyclic benzofurans have attracted considerable attention due to their useful pharmaceutical activities. Griseofulvin (**I**; Figure 1), with a spirobenzofuranone moiety, is used to treat ringworm infections of the skin and nails in animals and humans.[4] The telomerase inhibitor griseorhodin A (**II**; Figure 1) with a spirobenzofuranol moiety, is probably the most heavily oxidized bacterial polyketide.[5]

Baylis–Hillman reaction is one of the most atom-economical and important carbon–carbon bond-forming reactions.[6,7] It has made great progress recently due to the considerable reduction of reaction time, wide range of the substrates employed and its asymmetric version as compared to the classical reaction.[8–10] Recently, the Baylis–Hillman reaction of salicylaldehydes or salicyl *N*-tosylimines with various α,β-unsaturated compounds has been well studied and formation of different kinds of heterocycles were reported.[11–13] However, Baylis–Hillman reaction of salicylaldehydes with maleimides as activated olefin is unprecedented. Intrigued by these facts, we planned to study the Baylis–Hillman reactions of salicylaldehyde with maleimide for the synthesis of chromene.

griseofulvin (I)

griseorhodin A (II)

Figure 1

Initial studies were carried out using 3-ethoxysalicylaldehyde (**1b**; 1.2 equiv) with *N*-methylmaleimide (**2a**: 1.0 equiv) as model substrates in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO, 30 mol%) as catalyst in methanol at room temperature (Scheme 1). The reaction yielded a mixture of two products, but only the major product was isolated in pure form and the minor product was isolated as a mixture along with the major product.

1b **2a** **3b**, **4b** **5b**

Scheme 1

The ^{1}H NMR spectrum of the major product did not match with the anticipated chromene structure **5b**. The two singlets that were expected for **5b** were absent, instead four doublets at δ = 2.88, 3.37, 5.19 and 6.17 ppm were observed. The two doublets at δ = 5.19 (*J* = 6.9 Hz) and 6.17 (*J* = 6.9 Hz), exhibited H–H COSY correlation with each other and on D_2O exchange, the former signal collapsed to a singlet and the latter signal vanished. Based on these facts, the signals at δ = 5.19 and 6.17 ppm were assigned to methyne (H-3) and hydroxy (OH) proton, respectively. The DEPT 135 experiment of the product showed the absence of a signal at δ = 89.6 ppm indicating the presence

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of a quaternary carbon (spiro carbon, C2). Furthermore, the two doublets at δ = 2.88 and 3.37 ppm were mutually coupling with each other and had a large coupling constant J = 18.3 Hz indicating a geminal relationship (H-4′ protons). From the above facts and from C–H COSY experiment we arrived at the spirocyclic structure **3b** for the major product. From the ^{1}H NMR spectrum of the mixture we could assign the minor product **4b** to be the diastereoisomer of **3b**.

Having obtained the spiro products, we next varied the reaction conditions in order to increase the yield of products from its initial low yield of 25% (Table 1, entry 1). Increase of temperature moderately increased the yield to 42% after 10 hours (Table 1, entry 2). Change of solvent from methanol to THF and DMSO again moderately increased the yield to 54% and 59%, respectively (Table 1, entries 3–5). The reaction under neat conditions at room temperature for unsubstituted salicylaldehyde gave nearly 70% yield. However the yields with substituted salicylaldehydes were not impressive. But when the reaction temperature was increased to 70 °C under neat conditions, we were delighted to find that the yield increased to 74% with the diastereoisomeric ratio of **3b/4b** as 89:11 (Table 1, entry 7).

Under the above optimized conditions the reactions of various substituted salicylaldehydes **1a–f** with maleimides **2a–c** were examined and the corresponding spirobenzofuranol derivatives **3a–j** and **4a–j** were obtained in moderate to good yields (Scheme 2). The results are summarized in Table 2 (entries 1–10). Even for the sterically hindered substrate 2-hydroxy-1-naphthaldehyde (**1g**), the reaction proceeded smoothly to give the corresponding spirobenzofuranols **3k,l** and **4k,l** in moderate to good yields (Table 2, entries 11 and 12).[14]

A tentative mechanism for the formation of the spiro compound is proposed. (Scheme 3) The reaction is believed to involve the Baylis–Hillman reaction of **1** and **2** to form the intermediate **6** which by the abstraction of proton from the α-position of the carbonyl group forms the intermediate **7**. Subsequent elimination of the catalyst gives the Baylis–Hillman product **8**. Finally, intramolecular Michael addition follows path A to form the spirobenzofuranols **3** and **4**. The structure and the relative stereochemistry of the product **3** were established by single crystal X-ray diffraction study of compound **3a**[15] (Figure 2).

Considering the importance of the spirobenzofuranone derivatives,[4] we intended to oxidize the spirobenzofuranols **3b** and **4b** with various oxidants such as $PhI(OAc)_2$, PCC and PDC. Among these, PDC effectively oxidized spirobenzofuranols in dichloromethane under

Table 1 Baylis–Hillman Reaction of 3-Ethoxysalicylaldehyde (**1b**) with *N*-Methylmaleimide (**2a**) in the Presence of Various Solvents and Catalysts

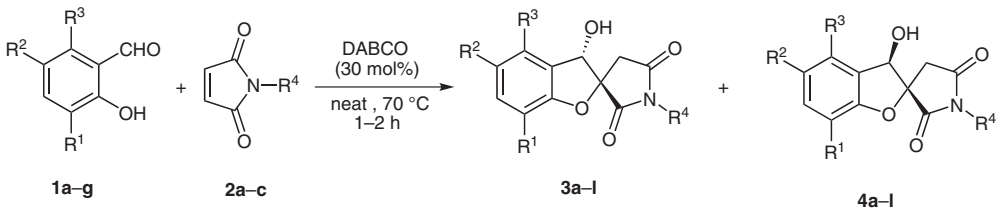
Entry	Solvent	Catalyst	Time (h)	Yield (%)[a] **3b** & **4b**	dr ratio[b] **3b**:**4b**
1	MeOH, r.t.	DABCO	24	25	91:09
2	MeOH, reflux	DABCO	10	42	90:10
3	THF, r.t.	DABCO	24	54	85:15
4	THF, reflux	DABCO	8	62	85:15
5	DMSO, r.t.	DABCO	24	59	88:12
6	CH_2Cl_2, r.t.	DABCO	36	trace	–
7	neat, 70 °C	DABCO	1.5	74	89:11
8	neat, 70 °C	DBU	12	trace	–

[a] Isolated yield of two diastereoisomers.
[b] Determined by ^{1}H NMR spectrum of the crude product.

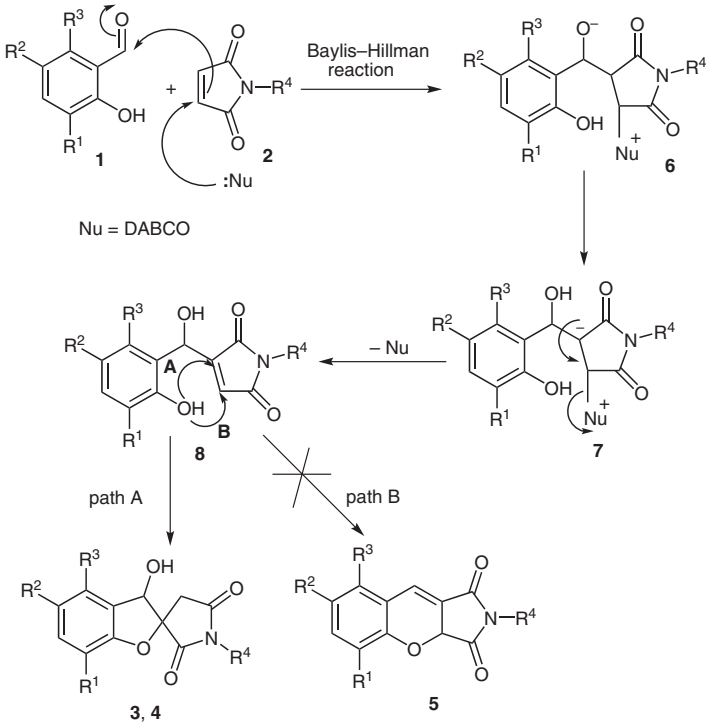
Table 2 Synthesis of Spirobenzofuranols

Entry	R^1	R^2	R^3		R^4	Products[a] **3** and **4**	Yield (%)[b]	Ratio[c] **3/4**
1	H	H	H	**1a**	Me	**3a**, **4a**	78	90:10
2	OEt	H	H	**1b**	Me	**3b**, **4b**	74	89:11
3	H	Br	H	**1c**	Me	**3c**, **4c**	68	85:15
4	H	Cl	H	**1d**	Me	**3d**, **4d**	67	85:15
5	Br	Br	H	**1e**	Me	**3e**, **4e**	64	83:17
6	I	I	H	**1f**	Me	**3f**, **4f**	62	84:16
7	H	H	H	**1a**	Bn	**3g**, **4g**	75	92:08
8	OEt	H	H	**1b**	Bn	**3h**, **4h**	71	88:12
9	OEt	H	H	**1b**	Ph	**3i**, **4i**	55	82:18[d]
10	H	Br	H	**1c**	Ph	**3j**, **4j**	51	80:20[d]
11	H	CH=CHCH=CH		**1g**	Me	**3k**, **4k**	68	88:12
12	H	CH=CHCH=CH		**1g**	Bn	**3l**, **4l**	65	90:10

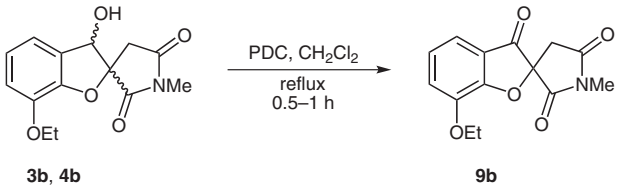
[a] All reactions were complete within 2 h.
[b] Isolated yield of two diastereoisomers.
[c] Determined by ^{1}H NMR spectrum of the crude product.
[d] Isolated as a mixture of two diastereoisomers.



Scheme 2 Synthesis of spirobenzofuranols



Scheme 3 Plausible mechanism for the formation of spirobenzofuranols



Scheme 4 Synthesis of spirobenzofuranone

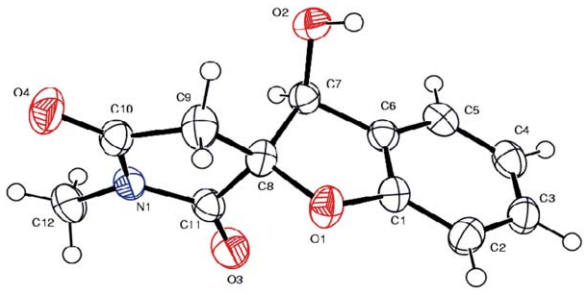


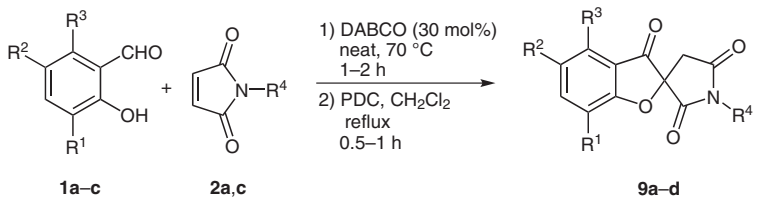
Figure 2 ORTEP diagram of compound **3a**

reflux conditions[16] to give the spirobenzofuranone **9b** in excellent yield (Scheme 4).

Having obtained the spirobenzofuranone derivative, we attempted the sequential one-pot synthesis of the same. Accordingly, we stirred the mixture of **1b**, **2a** and DABCO (30 mol%) under neat conditions at 70 °C for 1.5 hours. After the formation of spirobenzofuranols, dichloromethane and PDC were added. The mixture was refluxed to provide the corresponding spirobenzofuranone derivatives **9b**.[17]

The generality of this sequential one-pot synthesis of spirobenzofuranones was established by treating various substituted salicylaldehydes with N-substituted maleimides to furnish the corresponding spirobenzofuranone derivatives (Scheme 5). The results are presented in Table 3.

In summary, we have reported the synthesis of a range of novel spirobenzofuranols by Baylis–Hillman reaction. The use of maleimide as activated olefin in Baylis–Hillman reaction is unprecedented. The spirobenzofuranols were oxidized to the corresponding spirobenzofuranones, which is the core unit of natural products like griseofulvin.



Scheme 5 Synthesis of spirobenzofuranones in a sequential one-pot manner

Table 3 Synthesis of Spirobenzofuranones

Entry	R^1	R^2	R^3	R^4	Product	Yield (%)[a]
1	H	H	H	Me	**9a**	68
2	OEt	H	H	Me	**9b**	67
3	H	Br	H	Me	**9c**	62
4	OEt	H	H	Ph	**9d**	50

[a] Isolated yield after column chromatography.

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(14) **Experimental Procedure for the Synthesis of Spirobenzofuranol 3 and 4**:
A mixture of salicylaldehyde **1** (1.62 mmol, 1.2 equiv), N-substituted maleimide **2** (1.35 mmol, 1.0 equiv) and DABCO (30 mol%) was stirred at 70 °C under neat conditions for 1–2 h. The residue was dissolved in EtOAc (20 mL) and given a dilute HCl wash (1 × 20 mL) and H_2O wash (2 × 20 mL). The EtOAc layer was dried over anhyd Na_2SO_4 and removal of solvent under reduced pressure gave a crude product, which was purified by flash column chromatography with EtOAc–PE (20:80) as eluent to obtain spirobenzofuranols **3** and **4**.
Spectral Data of Compound 3b: colorless solid; mp 162–164 °C; R_f 0.33 (50% EtOAc–PE). IR: 3450, 2918, 1785, 1698, 1623, 1441, 1195 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.26 (t, 3 H, *J* = 6.9 Hz), 2.85 (s, 3 H), 2.88 (d, 1 H, *J* = 18.3 Hz), 3.37 (d, 1 H, *J* = 18.3 Hz), 3.98–4.03 (m, 2 H), 5.19 (d, 1 H, *J* = 6.9 Hz), 6.17 (d, 1 H, *J* = 6.9 Hz), 6.87–6.95

(m, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.1, 25.1, 35.0, 64.3, 73.8, 89.6, 114.5, 117.9, 122.6, 129.9, 143.7, 147.4, 174.3, 176.2. HRMS: *m*/*z* calcd for $C_{14}H_{15}NO_5$: 277.0952; found: 277.0957.

(15) Crystallographic data of the compound **3a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication no. CCDC-724171. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].

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(17) **Experimental Procedure for the Synthesis of Spirobenzofuranone 9**:
A mixture of salicylaldehyde **1** (1.62 mmol, 1.2 equiv), N-substituted maleimide **2** (1.35 mmol, 1.0 equiv) and DABCO (30 mol%) was stirred under neat conditions at 70 °C for 1–2 h. After the formation of spirobenzofuranols **3** and **4**, CH_2Cl_2 and PDC (1.2 equiv) were added to the reaction mixture and the mixture was refluxed. After 1 h the reaction mixture was filtered on a celite pad. The filtrate was concentrated, poured into H_2O, and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhyd Na_2SO_4 and removal of solvent under reduced pressure gave a crude product, which was purified by column chromatography with EtOAc–PE (10:90) as eluent to obtain the spirobenzofuranone **9**.
Spectral Data of Compound 9b: colorless solid; mp 136–138 °C; R_f 0.46 (40% EtOAc–PE). IR: 2930, 1715, 1602, 1383, 1159 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (t, 3 H, *J* = 6.9 Hz), 3.06 (s, 3 H), 3.13 (d, 1 H, *J* = 18.4 Hz), 3.20 (d, 1 H, *J* = 17.6 Hz), 4.16 (q, 2 H, *J* = 6.9 Hz), 7.08 (t, 1 H, *J* = 7.6 Hz), 7.17 (d, 1 H, *J* = 8.4 Hz), 7.24 (t, 1 H, *J* = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8, 25.9, 37.4, 65.0, 86.9, 115.9, 120.4, 120.8, 124.2, 145.9, 163.1, 170.3, 172.5, 196.2. MS: *m*/*z* = 276 [M$^+$ + 1]. Anal. Calcd for $C_{14}H_{13}NO_5$ (275.06): C, 61.09; H, 4.76; N, 5.09. Found: C, 61.17; H, 4.78; N, 5.01.