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Sulpholane—A new solvent for the Baylis–Hillman reaction ☆

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Abstract—Sulpholane, a commercially available solvent, is used for the first time as a new solvent for the Baylis–Hillman reaction under ambient conditions; a wide variety of olefins as well as aldehydes participate very efficiently resulting in good to excellent yields of products. Acrylamide also underwent the Baylis–Hillman reaction with 4-nitrobenzaldehyde under these reaction conditions.
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The Baylis–Hillman reaction,[1–5] a well-known carbon–carbon bond forming reaction, is notoriously sluggish thus limiting its use for the generation of combinatorial libraries of the multi-functional adducts that emerge as products thereof. Notable among the disadvantages of this important atom economic reaction are (1) slow reaction rates, (2) low to moderate yields (especially when acrylic esters or acrylonitriles are used as Michael acceptors because of hydrolysis in aqueous media) and (3) unavailability of a 'Universal' solvent system or base compatible with all electrophiles and activated olefins. Consequently, there have been attempts to overcome these limitations and accelerate the reaction to reasonable levels for wider use. Towards this endeavour, noteworthy are the use of aqueous media,[6] salt effects[7] on the kinetics the use of basic catalysts such as DBU[8a] and quinuclidine,[8b] microwave irradiation,[9] ionic liquids,[10] excess catalyst,[1,3] hydrogen bonding effects (having a hydroxyl group in the catalyst or in the substrate),[11] high pressure[12] and sonication.[3] The plethora of publications bears testimony to the significant improvements made to Baylis–Hillman reactions by these modifications. However, there still remains scope for identifying new solvents for Baylis–Hillman reactions.

In continuation of our work on the Baylis–Hillman reaction,[13] we describe the use of commercially available sulpholane as a new solvent for the Baylis–Hillman reaction. Sulpholane, an aprotic polar solvent was chosen for study since polar solvents are known to increase the equilibrium constant of the zwitterionic intermediate formed during Baylis–Hillman reactions.[3] This study also discloses its influence on the improvement of the rate of reaction and yields of the resulting adducts.

Initially, the Baylis–Hillman reaction between 4-nitrobenzaldehyde **1** and ethyl acrylate **9** in sulpholane was carried out to give **1a**[13a] in the presence of different bases such as NMM (*N*-methylmorpholine), imidazole, Hunig's base, DBU, DMAP, urotropine and DABCO (Table 1) in order to find the best basic catalyst compatible with the new solvent. Consequently, DABCO was found to be an appropriate base and hence was used as the standard in all further reactions. Enhancement of the pK_a value of the bases[8b] (DABCO in the present study) in aprotic solvents is an added advantage.

In a further study to ascertain the utility of sulpholane as a solvent for Baylis–Hillman reactions, in addition to

Table 1. Baylis–Hillman reactions of **1** and **9** with different bases in sulpholane

Entry	Base	Time (h)	Product yield (%)
1	NMM	12	No reaction
2	Imidazole	24	No reaction
3	Hunig's base	24	No reaction
4	DBU	0.5	**1a**, 30
5	DMAP	6	**1a**, 55
6	Urotropine	6	**1a**, 80
7	DABCO	2	**1a**, 96

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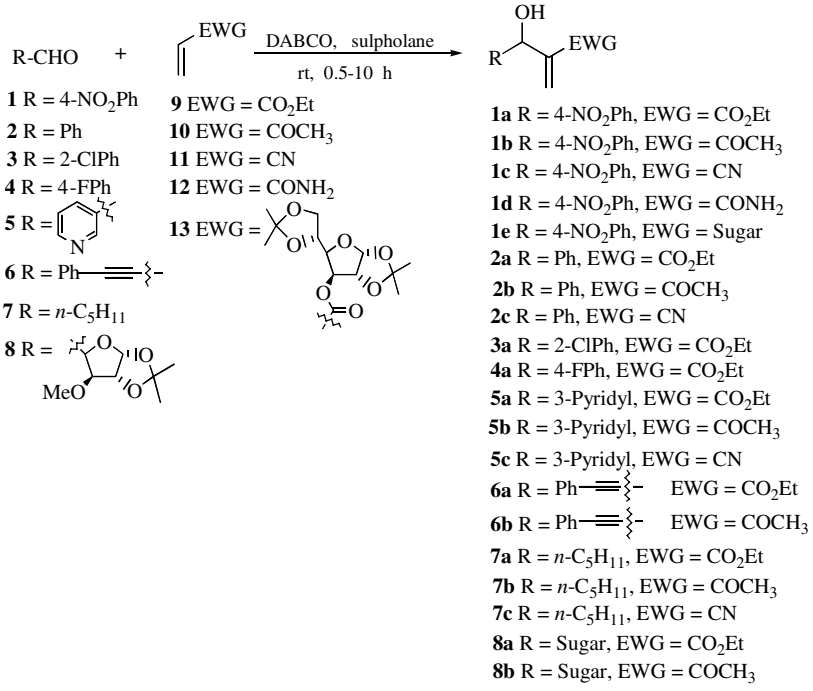

Scheme 1.

ethyl acrylate, a variety of Michael acceptors such as methyl vinyl ketone **10**, acrylonitrile **11**, and acrylamide **12** were subjected to reaction with **1** in the presence of DABCO (50 mol%) at room temperature to furnish the corresponding adducts **1b**, **1c** and **1d** in good yields (Scheme 1 and Table 2). The less reactive **12**, which was earlier reported[14] to react either at high pressure (5 kbar) or in aqueous dioxane[6b] as solvent at room temperature, on reaction with **1** in sulpholane afforded **1d**[15] in 84% yield. Acrylate **13** also reacted with **1** to furnish the corresponding adduct **1e**[13a] (76%) under the present reaction conditions.

The versatility of sulpholane as a solvent for Baylis–Hillman reactions was further strengthened when a variety of aldehydes such as benzaldehyde **2**, 2-chlorobenzaldehyde **3**, 4-fluorobenzaldehyde **4**, heteroaryl aldehyde **5**, acetylenic aldehyde **6**, hexanal **7**, and the sugar-derived aldehyde **8** were allowed to react with various Michael acceptors **9**, **10**, **11**, **12** and **13** at room temperature to give the adducts **2a–c**, **3a**, **4a**, **5a–c**, **6a–b**,[13c] **7a–c** and **8a–b**, respectively, in good to excellent yields (see Table 2). It is noteworthy to mention that the sugar derived aldehyde **8** in sulpholane reacted with **9** and **10** to give the adducts **8a**[13b] and **8b**, respectively (entries 19 and 20, Table 2) in short reaction times with moderate diastereoselectivity, unlike in our earlier[13b] report. Furthermore, aldehydes such as **2**, **3** and **4** reacted with the less reactive alkene **9** under the present reaction conditions (entries 6, 9 and 10, Table 2). Indeed, the rate of reaction of aldehydes **3** and **4** with **9** and the yields of the products were found to be much higher in sulpholane than in an aqueous medium.[6a] Moreover, hydrolysis of the acrylate was avoided by the use of sulpholane and hence good to high yields of the corresponding products **2a–8a** were obtained.

Table 2. Baylis–Hillman reactions of aldehydes with activated alkenes in sulpholane[a,b]

Entry	Aldehyde	Activated alkene	Time (h)	Product yield (%)[c]
1	**1**	**9**	2	**1a**, 96
2	**1**	**10**	3	**1b**, 71
3	**1**	**11**	0.5	**1c**, 91
4	**1**	**12**	10	**1d**, 84
5	**1**	**13**	0.75	**1e**, 76 (40% *de*)
6	**2**	**9**	6	**2a**, 86
7	**2**	**10**	1.5	**2b**, 70
8	**2**	**11**	4	**2c**, 81
9	**3**	**9**	4.5	**3a**, 93
10	**4**	**9**	10	**4a**, 85
11	**5**	**9**	6	**5a**, 73
12	**5**	**10**	0.75	**5b**, 75
13	**5**	**11**	7	**5c**, 73
14	**6**	**9**	1	**6a**, 69
15	**6**	**10**	1	**6b**, 74
16	**7**	**9**	4	**7a**, 86
17	**7**	**10**	1	**7b**, 66
18	**7**	**11**	8	**7c**, 72
19	**8**	**9**	3	**8a**, 92 (60% *de*)
20	**8**	**10**	2	**8b**, 85 (60% *de*)

[a] All the reactions were carried out with aldehyde (1 mmol), activated alkene (3 mmol), and DABCO (0.5 mmol) at ambient temperature for 0.5–10 h.[16]

[b] All the products were characterised by ^{1}H NMR and other spectral data.[17]

[c] Yields of isolated products.

In conclusion, the use of sulpholane as a new solvent for the Baylis–Hillman reactions is demonstrated for the first time. A variety of olefins and aldehydes reacted in sulpholane catalyzed by DABCO in shorter reaction times with good to high yields of the products (Table 2) without the need of any co-catalyst.

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16. General experimental procedure: To a stirred solution of aldehyde (1 mmol) in sulpholane (1 mL) were added DABCO (0.5 mmol) and the alkene (3 mmol) and the reaction mixture stirred for 0.5 to 10 h at room temperature. Then the reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residues thus obtained were purified by column chromatography to afford adducts **1a**–**1e**, **2a**–**2c**, **3a**, **4a**, **5a**–**c**, **6a**–**b**, **7a**–**c**, **8a** and **8b** in 66–96% yield. Compounds **2a**–**c**, **4a**, **5b**–**c** and **7b**–**c** are already reported in literature as cited in Ref. 5.
17. Spectral data for selected compounds: **1b**: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 8.20 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.54 (d, 2H, $J = 8.3$ Hz, Ar–H), 6.66 (s, 1H, olefinic), 6.23 (s, 1H, olefinic), 5.98 (s, 1H, benzylic), 3.12 (d, 1H, $J = 5.66$ Hz, –OH), 2.32 (s, 3H, $-CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.32, 29.65, 72.14, 123.55, 123.75, 127.23, 127.74, 147.29, 148.95, 200.07; IR (neat): ν 3418, 1713, 1619 1519 cm^{-1}; EIMS: m/z: 204 (M- 17)$^+$; Anal. calcd for $C_{11}H_{11}NO_4$; C, 59.73; H, 5.01; found: C, 59.57; H, 5.06. **1c**: Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 8.24 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.63 (d, 2H, $J = 8.4$ Hz, Ar–H), 6.39 (s, 1H, olefinic), 6.20 (s, 1H, olefinic), 6.02 (s, 1H, allylic), 5.38 (br s, 1H, –OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.07, 123.22, 126.07, 127.20, 130.59, 147.09, 147.88; IR (neat): ν 3440, 2228, 1607 cm^{-1}. **3a**: Colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.55 (d, 1H, $J = 7.0$ Hz, Ar–H), 7.39–7.21 (m, 3H, Ar–H), 6.28 (s, 1H, olefinic), 5.92 (d, 1H, $J = 3.7$ Hz, benzylic), 5.52 (s, 1H, olefinic), 4.22 (q, 2H, $J = 7.4$ Hz, $-CH_2$), 3.25 (d, 1H, $J = 3.7$ Hz, –OH), 1.28 (t, 3H, $J = 7.4$ Hz, $-CH_3$); IR (neat): ν 3396, 1720, 1614 cm^{-1}; EIMS: m/z: 241 (M$^+$+1); Anal. calcd for $C_{12}H_{13}ClO_3$; C, 59.88; H, 5.44; found: C, 59.71; H, 5.40. **5a**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 8.43–8.39 (m, 2H, ArH), 7.71 (d, 1H, $J = 7.8$ Hz, ArH), 7.24–7.20 (m, 1H, ArH), 6.34 (s, 1H, olefinic), 5.92 (s, 1H, olefinic), 5.55 (s, 1H, benzylic), 4.18 (q, 2H, $J = 6.9$ Hz, $-CH_2$), 1.23 (t, 3H, $J = 6.9$ Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.11, 51.62, 74.52, 117.68, 126.63, 126.68, 129.00, 130.58, 140.06; IR (neat): ν 3387, 1722, 1638 cm^{-1}; EIMS m/z 207 (M$^+$); Anal. calcd for $C_{11}H_{13}NO_3$; C, 63.76; H, 6.32; found: C, 63.65; H, 6.29. **7a**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 6.22 (s, 1H, olefinic), 5.79 (s, 1H, olefinic), 4.40 (t, 1H, $J = 6.4$ Hz, allylic), 4.24 (q, 2H, $J = 7.2$ Hz, $-CH_2$), 2.73 (br s, 1H, –OH), 1.70–1.62 (m, 2H, $-CH_2$), 1.39–1.25 (m, 9H), 0.93–0.84 (m, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 12.06, 19.84, 23.33, 29.56, 33.44, 58.72, 69.21, 122.87, 141.14, 164.07; IR (neat): ν 3385, 1717, 1628 cm^{-1}. EIMS m/z 201 (M$^+$+1); Anal. calcd for $C_{11}H_{20}O_3$; C, 65.97; H, 10.07; found: C, 65.83; H, 10.02. **8b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 0.2H, olefinic), 6.26 (s, 0.8H, olefinic), 6.18 (s, 0.2H, olefinic), 6.11 (s, 0.8H, olefinic), 5.86 (s, 1H, $J = 3.8$ Hz, H-1), 4.60–4.48 (m, 2H, H-5, H-2), 4.25–4.17 (m, 1H, H-4), 3.82 (d, 1H, $J = 3.7$ Hz, H-3), 3.51 (s, 3H, –OMe), 2.41 (s, 3H, $-CH_3$), 1.46 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): 26.75, 57.95, 69.54, 80.18, 81.49, 84.23, 86.47, 105.01, 111.70, 128.01, 147.11, 200.90; IR (neat): ν 3428, 1715, 1626 cm^{-1}; FABMS: m/z: 273 (M$^+$+1); Anal. calcd for $C_{13}H_{20}O_6$; C, 57.34; H, 7.40; found: C, 57.27; H, 7.36.