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Imidazole-catalysed Baylis–Hillman reactions: a new route to allylic alcohols from aldehydes and cyclic enones

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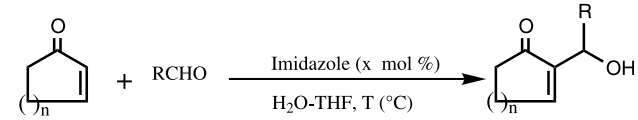
Abstract—An efficient one-pot synthesis of cyclic Baylis–Hillman adducts is described. An imidazole-catalysed coupling reaction between cyclic enones and both aliphatic and aromatic aldehydes leads to allylic alcohols in moderate to good yields.

The coupling reaction between activated non-cyclic alkenes and aldehydes, through the Baylis–Hillman reaction, is commonly catalysed by 1,4-diazabicyclo[2.2.2]octane (DABCO).[1] However, this tertiary amine was found to be inefficient in α-hydroxyalkylation[2] of cyclic enones. In addition, DBU[3] and aqueous trimethylamine[4] lead to self dimerisation of the cyclic enones. Recently the first examples of coupling reactions between cyclohexenones and aqueous formaldehyde using 4-dimethylaminopyridine (DMAP)[2] as catalyst have been reported and various catalysts, such as chalcogenides-$TiCl_4$[5] or $TiCl_4$[6] without a Lewis base, have been proposed to effect α-hydroxyalkylation of cyclic enones.

In continuation of our study on α-functionalisation of cyclic enones using new catalysts, we wish to report herein our results on the imidazole mediated Baylis–Hillman reaction between cyclic enones and both aliphatic and aromatic aldehydes in aqueous media.

We first explored the hydroxymethylation of 2-cyclohexenone **1** catalysed by imidazole in aqueous THF. The best results were obtained when the reaction between this enone and 30% aqueous formaldehyde (2 equiv.) was carried out in the presence of 20 mol% imidazole, at room temperature. The desired adduct **2a** was obtained after 17 days in 93% isolated yield (Scheme 1, Table 1: entry 1). It is worth noting that the yield decreased severely when using more than 20 mol% of imidazole.

Encouraged by the mild reaction conditions and the high yield (93%) of the allylic alcohol **1**, we successfully carried this coupling reaction between 2-cyclopentenone **3** and formaldehyde in the presence of 5 mol% imidazole in aqueous THF at room temperature. Thus, the useful intermediate in organic synthesis **4a**,[6] leading to applications in biology,[7–10] was obtained after 17 days in 86% yield[11] (Scheme 1, Table 1: entry 2).



Scheme 1.

Table 1. Baylis–Hillman reaction of enones **1** and **3** with formaldehyde

Entry	*n*	Product	R	Catalyst (mol%)	Temp.	Time (days)	Yield (%)
1	2	**2a**	H	Imidazole (20)	rt	17	93
2	1	**4a**	H	Imidazole (5)	rt	17	86

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Table 2. Baylis–Hillman reaction of enones **1** and **3** with aliphatic and aromatic aldehydes (10 mol% of imidazole as catalyst)

Entry	*n*	Product	R	Temp. (°C)	Time (days)	Yield (%)
1	2	**2b**	Ph	rt	65	69
2	2	**2b**	Ph	50	20	61
3	2	**2c**	*p*-NO_2Ph	rt	10	65
4	2	**2d**	Me[a]	50	15	70
5	2	**2e**	*s*-Bu	50	16	60
6	1	**4b**	Ph	50	2	35
7	1	**4c**	*p*-NO_2Ph	rt	6	62
8	1	**4d**	Me[a]	50	3	51
9	1	**4e**	*s*-Bu	50	16	60

[a] Excess of acetaldehyde (10 equiv.) was used.

In order to investigate the scope and limitations of this synthetic methodology, we examined, in the second part of this study, the coupling reaction of enones **1** and **3** with a variety of aldehydes. Our preliminary attempts were carried out using 2-cyclohexenone **1** and benzaldehyde, at room temperature, in the presence of 10 mol% imidazole in aqueous THF. This coupling reaction took a very long time (65 days) but led to the desired compound **2b** in 69% yield (Scheme 1, Table 2: entry 1). Interestingly, by heating the reaction mixture, at 50 °C, compound **2b** was isolated after 20 days with only a slight decrease in yield (61% yield) (Scheme 1, Table 2: entry 2).

Finally, the reaction of enones **1** and **3** with activated aromatic and aliphatic aldehydes was examined in the presence of catalytic amounts of imidazole (10 mol%). Therefore, the allylic alcohols **2c–e** (Table 2: entries 3–5) and **4b–e** (Table 2: entries 6–9) were prepared under the experimental conditions described in Table 2.

In conclusion, we have developed a short and simple procedure for the preparation of cyclic Baylis–Hillman derivatives in moderate to good yields. Moreover, this large-scale method, using imidazole as a catalyst, allows both hydroxymethylation and hydroxyalkylation of cyclic enones.

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11. Preparation of 2-(hydroxymethyl)-2-cyclopentenone **4a**: A 100 mL round-bottomed flask was charged with 2-cyclopentenone **3** (4.9 g, 60 mmol), 30% aqueous formaldehyde (12 mL, 120 mmol), 12 mL of THF and imidazole (0.4 g, 3 mmol). The resulting mixture was stirred for 17 days at room temperature. When the reaction, followed by TLC was finished, the mixture was acidified with aqueous HCl (1.5 M) and extracted with methylene chloride. After the usual work up, chromatography of the crude product on silica gel, using ether as eluent, gave pure 2-(hydroxymethyl)-2-cyclopentenone **4a**[8] in 86% yield; IR (cm^{-1}, $CHCl_3$): 3450, 1690; ^1H NMR (300 MHz, $CDCl_3$): 7.58 (m, 1H), 4.34 (s, 2H), 3.15 (br s, O*H*), 2.64 (m, 2H), 2.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 209.7, 159.3, 145.0, 56.7, 34.8, 26.6; MS (EI) *m*/*z*: 70 (54), 83 (42), 84 (31), 97 (16), 112 (M+, 100); HRMS calcd for $C_6H_8O_2$: 112.0524. Found: 112.0527.