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Lithium Perchlorate-Accelerated Baylis-Hillman Reactions

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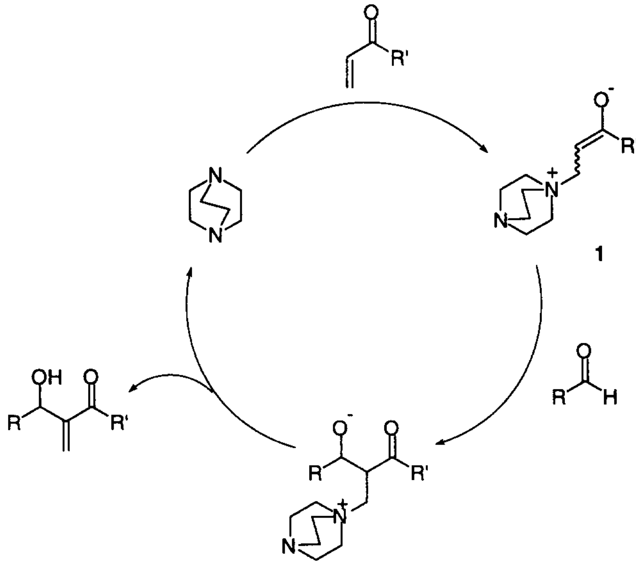
Abstract: *The coupling of α,β-unsaturated carbonyl compounds with aldehydes (the Baylis-Hillman reaction) was accelerated in the presence of a catalytic amount of 1,4-diazabicyclo[2,2,2]octane (DABCO) and lithium perchlorate in ether. A preliminary kinetic study revealed that the relative rate of the reaction using* $LiClO_4$ *in ether was* 8.0×10^2 *times faster than that of the reaction without* $LiClO_4$*.*

The Baylis-Hillman reaction, the coupling of α,β-unsaturated carbonyl compounds with aldehydes, is one of the most important carbon-carbon bond-forming processes in organic synthesis.[1,2] While the original protocol used a tertiary amine, prolonged reaction time was needed even when a stoichiometric amount of a rather strong basic amine such as 1,4-diazabicyclo[2,2,2]octane (DABCO) was used. In this paper, we report remarkable acceleration of the Baylis-Hillman reaction using lithium perchlorate ($LiClO_4$) as a co-catalyst.



Scheme 1. A Proposed Mechanism of the Baylis-Hillman Reaction

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Our idea to accelerate the Baylis-Hillman reaction was to stabilize intermediate **1** using metal salts (Scheme 1).[3] Since a tertiary amine plays an important role in this process, the metal salt and the tertiary amine have to work independently. We searched for metal salts that work efficiently even in the presence of a tertiary amine. After testing several metal salts, it was found that the Baylis-Hillman reaction was accelerated dramatically by using $LiClO_4$ as a co-catalyst.[4,5] Namely, while only a trace amount of the desired adduct between benzaldehyde and methyl acrylate was detected in dichloromethane without $LiClO_4$ (DABCO 5 mol%, 20 h), the adduct was obtained in 12% yield by adding 5 mol% of $LiClO_4$. Several solvents were then tested (Table 1) and it was found that the best yield was obtained when ether was used.[6] The amount of $LiClO_4$ also influenced the yield dramatically (Table 1). The best yield was obtained when 70 mol% of $LiClO_4$ was used in the presence of 5 mol% of DABCO,[7] while the yield decreased severely when using more than 70 mol% of $LiClO_4$. A preliminary kinetic study in the reaction of benzaldehyde with ethyl acrylate revealed that the relative rate of the reaction using 5 mol% of DABCO and 70 mol% of $LiClO_4$ in ether was 8.0×10^2 times faster than that of the reaction using 5 mol% of DABCO (without $LiClO_4$). Moreover, it is noted that only a small amount of $LiClO_4$ (5-10 mol%) is enough to accelerate the reactions of propionaldehye (a representative aliphatic aldehyde).

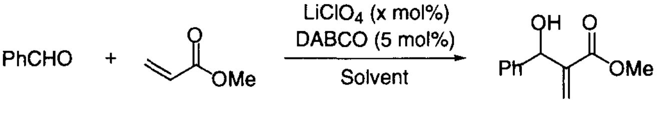


Table 1. Effect of Solvents and $LiClO_4$

Solvent	$LiClO_4$ (x mol%)	Substrate Ratio[a]	Yield (%)
CH_2Cl_2	5	5.0	23
THF	5	5.0	45
THF-H_2O (9:1)	5	5.0	42
Et_2O	5	5.0	68
DME	5	5.0	52
CH_3CN	5	5.0	33
Et_2O	0	0.83	trace
Et_2O	5	0.83	12
Et_2O	10	0.83	40
Et_2O	50	0.83	63
Et_2O	70	0.83	72 (81)[b]
Et_2O	100	0.83	25
Et_2O	200	0.83	12
Et_2O	500	0.83	trace

[a] Molar ratio of benzaldehyde/methyl acrylate.
[b] Fifteen mol% of DABCO was used.

Other combinations of α,β-unsaturated carbonyl compounds and aldehydes were tested and the results are summarized in Table 2. In all cases, the reactions proceeded smoothly in the presence of 10-15 mol% of DABCO and 10 mol% (aliphatic aldehydes) or 70 mol% (aromatic aldehydes) of $LiClO_4$ in ether to afford the corresponding adducts in good to high yields at -20 °C to room temperature. α,β-Unsaturated esters as well as α,β-unsaturated ketones, aldehydes, and nitriles reacted smoothly under these conditions. It is noted that *t*-butyl acrylate reacted with benzaldehyde to produce the desired adduct in 50% yield (48 h) and that the cross-coupling of α,β-unsaturated aldehydes was successfully carried out under these conditions.

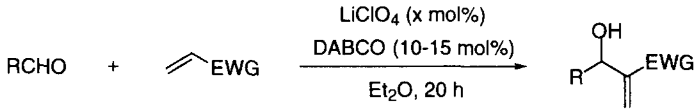
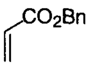
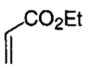
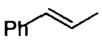
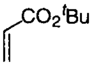
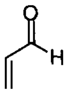
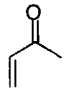
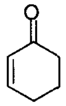
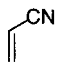


Table 2. Baylis-Hillman Reactions Between Aldehydes and α,β-Unsutulated Carbonyl Compounds

R		$LiClO_4$ (x mol%)	Temp (℃)	Yield (%)
C_2H_5		10	-25	79
C_8H_{17}		10	-25	82
Ph		70	0	81
		70	0	56
Ph		70	0 - rt	35 (50)[a]
Ph		70	-20 - 0	69
C_2H_5		10	-20 - 0	72
Ph		70	-20 - 0	75
C_2H_5		10	-20 - 0	82
Ph		70	0	56
Ph		70	rt	85

[a] Reaction Time, 48 h.

A typical experimental procedure is described for the reaction of benzaldehyde with ethyl acrylate. To a mixture of benzaldehyde (1.0 mmol), ethyl acylate (1.0 mmol), and $LiClO_4$ (0.70 mmol, 70 mol%) in ether (0.5 ml) was added DABCO (0.15 mmol, 15 mol%) in ether (0.3 ml) at 0 °C. The mixture was stirred for 20 h at the same temperature, and 1N HCl was then added to quench the reaction. The aqueous layer was extracted with dichloromethane. After a usual work up, the crude product was chromatographed on silica gel to give the desired adduct (81%).

In summary, $LiClO_4$ was found to accelerate the Baylis-Hillman reaction. In the presence of small amounts of DABCO and $LiClO_4$, α,β-unsaturated carbonyl compounds reacted with aldehydes in ether to afford the corresponding adducts in high yields. Further investigations to develop more efficient processes including asymmetric catalysis are now in progress.

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References and Notes

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6 Grieco *et al.* reported several useful synthetic reactions which proceed smoothly in highly concentrated ether solution of $LiClO_4$. (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. (b) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488.

7 The yield was further improved when 15 mol% of DABCO was used. See Table 1.