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A new protocol for the Baylis–Hillman reaction: the reaction of iminium salts prepared in situ with methyl acrylate

Najmedin Azizi and Mohammad R. Saidi*

Department of Chemistry, Sharif University of Technology, PO Box 11365-9516 Tehran, Iran

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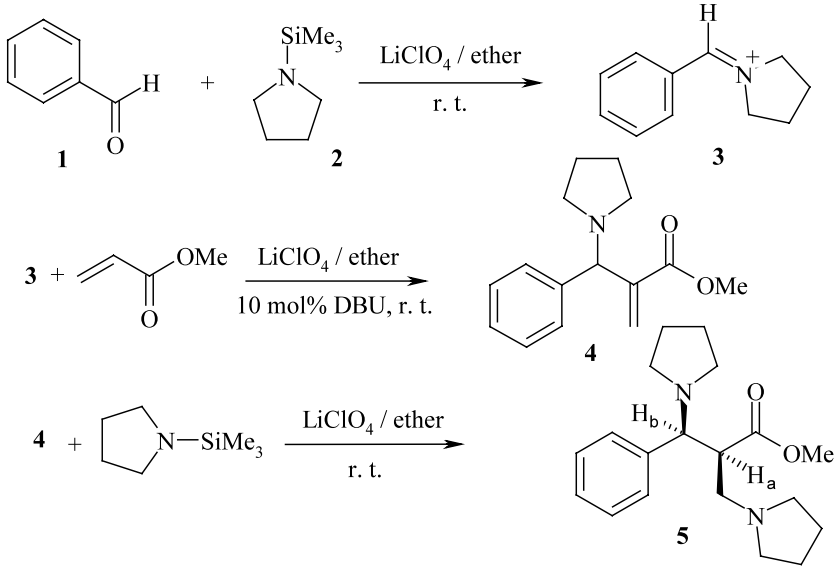
Abstract—In situ prepared iminium salts are very effective electrophiles in Baylis–Hillman reactions and react with methyl acrylate in the presence of a catalytic amount of a tertiary amine at ambient temperatures to afford the corresponding Baylis–Hillman adducts. The product undergoes conjugated addition with (trimethylsilyl)dialkylamines to give the diamine **5** in good yields.

The Baylis–Hillman reaction involves carbon–carbon bond formation between an activated alkene and an aldehyde in the presence of a tertiary amine. As well as aldehydes, α-ketoesters, fluorinated ketones and aldimine derivatives have been used as electrophiles in the Baylis–Hillman reaction.[1] The Baylis–Hillman reaction has drawn considerable attention over the past few years and a large number of modified conditions have been reported in the literature.[2] Although the Baylis–Hillman reaction is a three component reaction between an activated alkene, an electrophile and a tertiary amine, to date there are no reports of this reaction using an iminium salt as the electrophile.[3] Here we would like to report a one-pot Baylis–Hillman reaction of methyl acrylate with in situ prepared iminium salts as the electrophile.

During the course of our efforts towards the aminoalkylation of aldehydes mediated by lithium perchlorate in diethyl ether,[4] we found that in situ pre-



Scheme 1.

Keywords: Baylis–Hillman reaction; iminium salt; diamine; lithium perchlorate.
* Corresponding author. Fax: +98-21-601 2983; e-mail: saidi@sharif.edu

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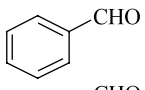
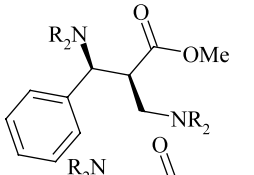
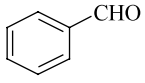
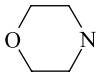
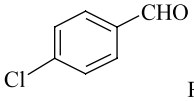
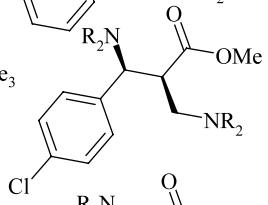
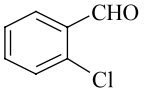
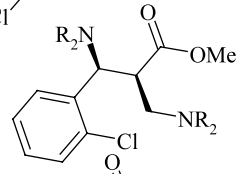
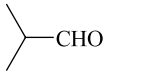
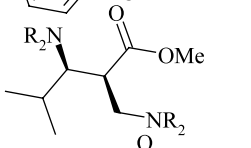
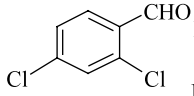
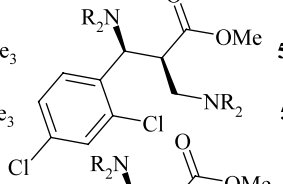
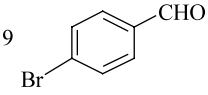
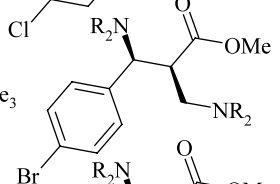
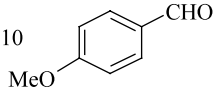
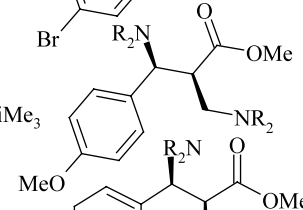
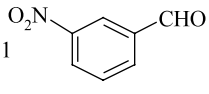
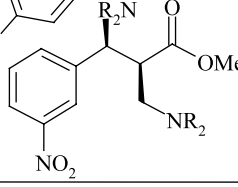
pared iminium salts are very effective electrophiles in Baylis–Hillman reactions and the reaction products differ considerably from those reported so far. In the present work, we attempted to develop a novel, one-pot, and tandem Baylis–Hillman reaction by employing the aldehyde **1** and an excess of the (trimethylsilyl)dialkylamine **2** (2.5 equiv.), which forms the iminium salt **3** in a concentrated ethereal solution of lithium perchlorate.[5] By the addition of methyl acrylate in the same pot, without any further purification, and in the presence of a catalytic amount of a tertiary amine such as 1,5-diazabicyclo[5.4.0]-5-undecene, DBU, the Baylis–Hillman adduct **4** was formed as shown in Scheme 1. Conjugate addition of the (trimethylsilyl)dialkylamine to the Baylis–Hillman adduct **4** in situ, then afforded diamine **5** in good yield. The ^{1}H NMR of the crude product showed only one signal for the OMe group in the diamine **5**. Therefore, we assumed the formation of only one diastereomer. The relative configuration was confirmed as *syn* by comparison of the coupling constants for H_a and H_b (Scheme 1 and entry 5, Table 2) with those reported for similar compounds in the literature.[5] As the differences between coupling constants in the ^{1}H NMR spectra can be ascribed to the molecular geometry of the two diastereomers, we have calculated the ground state

Table 1. Products obtained from the Baylis–Hillman reactions of in situ preformed iminium salts with methyl acrylate

Entry	Aldehyde	Amine	Product	%Yield[a]
1		R_2NSiMe_3	 **5a**, R_2N = NEt_2	90
2		R_2NSiMe_3	**5b**, R_2N = 	95
3		R_2NSiMe_3	 **5c**, R_2N = NEt_2	92
4		R_2NSiMe_3	**5d**, R_2N = 	95
5		R_2NSiMe_3	 **5e**, R_2N = NEt_2	88
6		R_2NSiMe_3	 **5f**, R_2N = 	65
7		R_2NSiMe_3	 **5g**, R_2N = NEt_2	90
8		R_2NSiMe_3	**5h**, R_2N = NMe_2	86
9		R_2NSiMe_3	 **5i**, R_2N = NMe_2	84
10		R_2NSiMe_3	 **5j**, R_2N = 	78
11		R_2NSiMe_3	 **5k**, R_2N = NEt_2	84

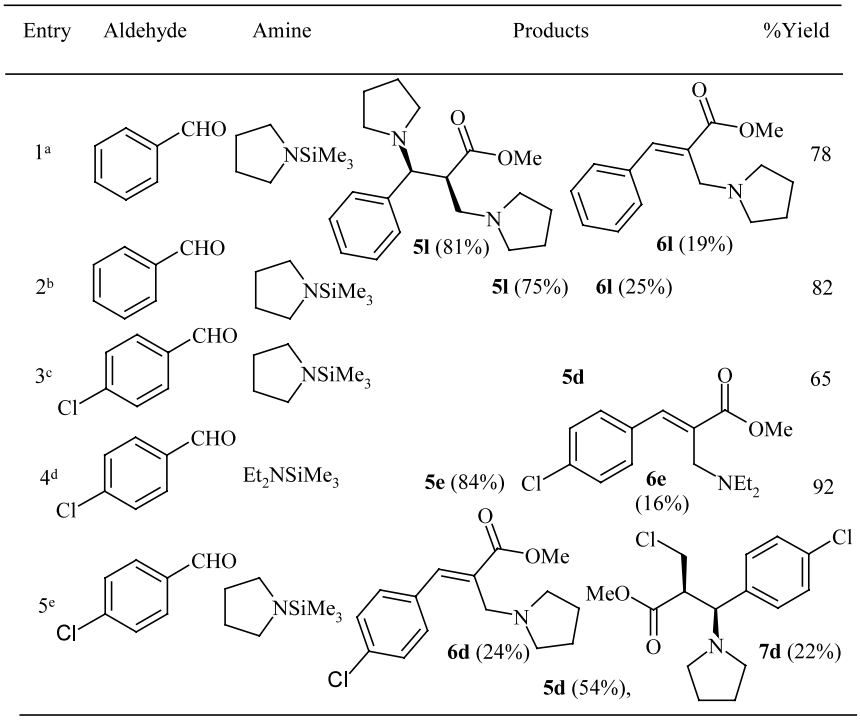
[a]isolated yields

geometry for each diastereomer using a semi-empirical MNDO method. These calculations also show that the *syn* diastereomer is the more stable.

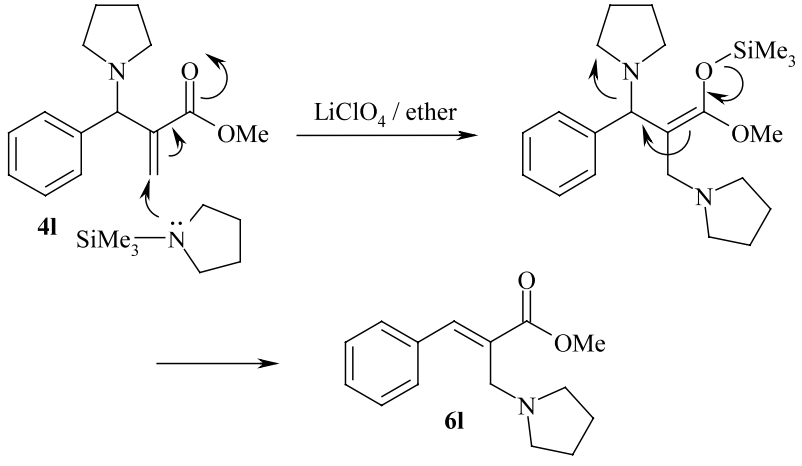
The reaction can be applied to both enolizable and non-enolizable aldehydes and a range of substituted secondary amines. All transformations were carried out at room temperature in a 5 M ethereal solution of lithium perchlorate in one-pot with a short reaction time (Scheme 1, Table 1).

The reactions are clean and the products are obtained in high yield except for the reaction with 2-methylpropanal. As shown before, the yield of the iminium salt is lower for enolizable aldehydes perhaps due to the formation of enamines as side products in the reaction of the aldehyde with a (trimethylsilyl)-dialkylamine in 5 M $LiClO_4$ in diethyl ether.[6] In addition, the reaction conditions are mild so that no side products or decomposition of the products are observed.

Table 2. Formation of the rearranged Baylis–Hillman adducts by changing the reaction conditions



[a] 1.1 equvalents of (trimethylsilyl)dialkylamine was used.
[b] When 4 mL of 2.5 M or 4 mL of 1.0 M solution of lithium perchlorate solution in diethyl ether was used.
c Triethylamine was used as the tertiary amine.
[d] 10 mol% of $CeCl_3$ was used as the Lewis acid.
[e] 1.0 equivalent of $CeCl_3$ was used as the Lewis acid.



Scheme 2.

In order to examine the effect of the amine on the formation of the Baylis–Hillman adducts **4**, 1.1 equiv. of (trimethylsilyl)dialkylamine were used (entry 1, Table 2, ca. 2.0 mmol of aldehyde and 2.2 mmol amine **2** were used). In this case, diamine **5l** and the rearranged Baylis–Hillman adduct, **6l**, were formed in 81 and 19% yields, respectively.[7] A plausible mechanism for the formation of **6l** is shown in Scheme 2.[1b]

When the reaction was carried out at room temperature in a 2.5 or 1.0 M ethereal solution of lithium perchlorate, mixtures of **5l** and **6l** were formed in 75 and 25% yields, respectively. In this case, the rearranged Baylis–Hillman adduct **6l** was also the minor product (entry 2, Table 2), which maybe due to the decreasing solvent polarity. By using triethylamine as the tertiary amine, the yield of diamine **5d** decreased (entry 3, Table 2). The addition of a catalytic amount of cerium trichloride (ca. 10 mol%) improved the yield of the diamine **5e** up to 92% (entry 4, Table 2). The addition of 1 equiv. of cerium trichloride produced a mixture of the diamine **5d** (54%), the rearranged Baylis–Hillman adduct **6d**, (24%) and 2-chloromethyl-substituted **7d** (22%). The chlorine adduct was also produced when $TiCl_4$ is used as the Lewis acid (entry 5, Table 2).[8]

In summary, we report that in situ prepared iminium salts in a concentrated ethereal solution of lithium perchlorate can react with methyl acrylate in the presence of a catalytic amount of a tertiary amine such as DBU to produce Baylis–Hillman adducts. The products react with the (trimethylsilyl)dialkylamine and produce the diamine in good yield. The procedure for the reaction is mild and operationally simple.

Experimental

The general procedure for the Baylis–Hillman reaction: Reaction of in situ prepared iminium salts with methyl acrylate.

The aldehyde (2 mmol) and 4 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 mL flask under argon and stirred for 5 min. The (trimethylsilyl)dialkylamine (5 mmol) was added via a syringe. After 30 min, methyl acrylate (2.5 mmol) and DBU (0.2 mmol) were added and the mixture was stirred at room temperature for about 5 h, then water (20 mL) and dichloromethane (20 mL) were added. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The crude product was further purified by column chromatography on basic alumina eluting with petroleum ether/ethyl acetate. All new compounds were characterized on the basis of spectroscopic data (IR, NMR, MS).[9]

Caution: Although we did not have any accident while using $LiClO_4$, it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

Acknowledgements

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9. Selected spectral data. **5c**: Oil, IR (neat): 1742 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 500 MHz): δ_H 1.10–1.22 (m, 12H), 2.25–2.85 (m, 9H), 3.56 (m, 2H), 3.67 (s, 3H), 4.10 (d, $J=2$ Hz, 1H), 7.21–7.60 (m, 4H); m/z (%) 354 (M^+), 281 (10), 222 (51), 196 (100), 168 (14), 86 (84). **5d**: Oil, IR (neat): 1738 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 500 MHz): δ_H 1.42–1.60 (m, 8H), 2.25–2.68 (m, 9H), 3.40 (d, $J=4$ Hz, 2H), 3.72 (s, 3H), 3.92 (d, $J=2$ Hz, 1H), 7.12–7.35 (m, 4H); m/z (%) 350 (M^+), 279 (16), 266 (22), 220 (66), 194 (100), 156 (22), 84 (88). **5h**: Oil, IR (neat): 1738 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 500 MHz): δ_H 2.25 (s, 12H), 2.70 (m, 1H), 3.42 (m, 2H), 3.85 (s, 3H), 4.52 (d, $J=3$ Hz, 1H), 7.22–7.60 (m, 3H); m/z (%) 333 (M^+), 287 (26), 228 (80), 202 (100), 188 (28), 130 (32), 58 (88). **6l**: Oil, IR (neat): 1722 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 500 MHz): δ_H 1.52 (m, 4H), 2.56 (m, 4H), 3.52 (s, 2H), 3.92 (s, 3H), 7.20–7.45 (m, 5H), 7.82 (s, 1H).