Facile Synthesis of *Aza*-Baylis-Hillman Adducts of Cycloalkenones: $FeCl_3$-Mediated Direct Amination of Baylis-Hillman Alcohols

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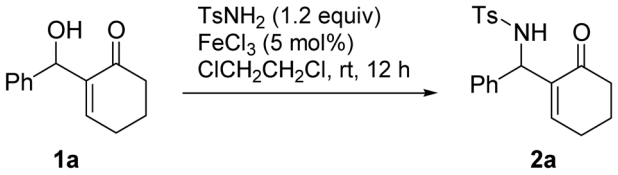
The Baylis-Hillman adducts of cycloalkenones have been used widely in organic synthesis.[1] The synthesis of Baylis-Hillman adducts from the reaction of cycloalkenones and aldehydes has been carried out with a variety of catalyst system[2] including the use of TMPDA[2a] or DMAP.[2b] However, the synthesis of *aza*-Baylis-Hillman adducts of cycloalkenones was not reported much.[3] Direct synthesis of *aza*-Baylis-Hillman adducts from the reaction of cycloalkenenones and *N*-tosylimines was examined by using DMAP[3a,b] or *N*-heterocyclic carbene catalyst very recently.[3d] However, the methods suffer from low yields of products[3a,b] and the use of special catalyst.[3d] In addition, these direct methods require the preparation of *N*-tosylimines, which could be hydrolyzed to some extent into the corresponding aldehydes and tosylamide during the separation of *N*-tosylimine and during the next Baylis-Hillman reaction, and this makes the separation of product tedious and lowers the yield.

Recently, direct amination of allylic, benzylic and/or propargylic alcohols has received much attention,[4,5] which could be achieved directly using sulfonamide derivatives with the aid of $AuCl_3$,[4a] $MoCl_5$,[4b] $[Ir(COD)Cl]_2$,[4c] $Bi(OTf)_3$/KPF_6,[4d] or $FeCl_3$.[5] In these contexts, we decided to develop a practically efficient synthetic method of *N*-tosyl *aza*-Baylis-Hillman adducts of cycloalkenones by adopting benzylic amination protocol (*vide infra*, Scheme 1).

Starting material **1a** was prepared by the known method,[2] and examined for amination reaction with tosylamide under various conditions. When $AuCl_3$ was used (5 mol%, rt, 24 h) the reaction was sluggish and observed the formation of product **2a** in low yield (30%). The use of *p*-TsOH (5 mol%, rt, 24 h) showed similar results (*ca* 10% of **2a** and *ca* 30% of remaining **1a**). Fortunately, the use of $FeCl_3$ (5 mol%) produced the desired product **2a** in 88% isolated yield (rt, 12 h, Scheme 1).[6] Although $FeCl_3$-catalyzed amidation reaction of allylic/benzylic alcohol system was published very recently,[5] the successful synthesis of *N*-tosyl *aza*-Baylis-Hillman adduct **2a** in high yield from the easily available Baylis-Hillman alcohol could be highly influential in Baylis-Hillman chemistry.

Encouraged by the results various representative Baylis-Hillman adducts were prepared and examined for $FeCl_3$-catalyzed amination reaction with $TsNH_2$ and methanesulfonamide (Table 1). As shown in Table 1, the reactions of Baylis-Hillman adducts derived from 2-cyclohexen-1-one,

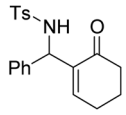
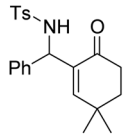
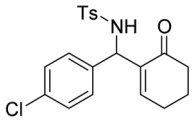
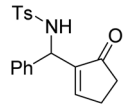
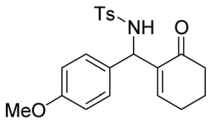
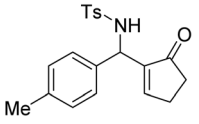
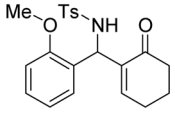
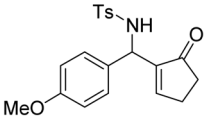
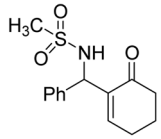
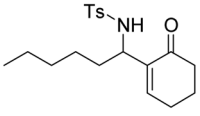


1a **2a**

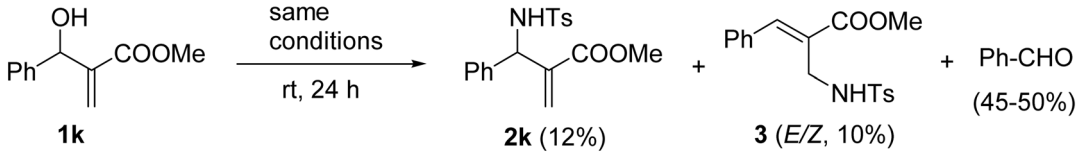
Scheme 1

4,4-dimethyl-2-cyclohexen-1-one, and 2-cyclopenten-1-one provided the corresponding *aza*-Baylis-Hillman adducts **2a-i** in good yields (80-93%). The substituent of the aryl moiety did not affect much on the reaction. Methanesulfonamide showed similar reactivity (entry 5). However, when we used

Table 1. Synthesis of *N*-tosyl *aza*-Baylis-Hillman adducts of cycloalkenones[a]

Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		**2a** (88)	6		**2f** (90)
2		**2b** (83)	7		**2g** (93)
3		**2c** (80)	8		**2h** (90)
4		**2d** (87)	9		**2i** (88)
5		**2e** (88)	10		**2j** (0)

[a]Conditions: Baylis-Hillman alcohol (1.0 equiv), $TsNH_2$ or $CH_3SO_2NH_2$ (entry 5, 1.2 equiv), $ClCH_2CH_2Cl$, $FeCl_3$ (5 mol%), room temperature, 12 h.



Scheme 2

aliphatic chain-attached substrate (entry 10) we did not observe the formation of the product **2j** and the failure can be explained by the difficulty for the generation of the corresponding carbocation.[7] Unfortunately, the expected *N*-tosyl *aza*-Baylis-Hillman adduct (**2k**) was not obtained by applying the present methodology using the substrate **1k** (Scheme 2).[8]

In summary, we disclosed an efficient synthetic approach for *N*-tosyl *aza*-Baylis-Hillman adducts of cycloalkenones *via* the $FeCl_3$-mediated benzylic amination protocol from the easily available Baylis-Hillman adducts.

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4. For direct amination of allylic, benzylic or propargylic alcohols, see: (a) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964-968. (b) Reddy, C. R.; Madhavi, P. P.; Reddy, A. S. *Tetrahedron Lett*. **2007**, *48*, 7169-7172. (c) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2007**, *129*, 7508-7509. (d) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 409-413, and further references cited therein. (e) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett*. **2006**, *8*, 4617-4620. (f) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063-2067.
5. During the preparation of this manuscript, an efficient $FeCl_3$-catalyzed amidation reaction of various allylic and benzylic alcohols in nitromethane was reported, see: Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858-862.
6. *Typical experimental procedure for the synthesis of* ***2a***: A mixture of **1a** (202 mg, 1.0 mmol), $TsNH_2$ (205 mg, 1.2 mmol), $FeCl_3$ (8 mg, 5 mol%) in $ClCH_2CH_2Cl$ (3 mL) was stirred at room temperature for 12 h. After removal of solvent the residue was purified by column chromatography (hexanes/ether, 4:1) to give **2a** (313 mg, 88%) as a white solid. Other compounds were synthesized similarly and identified by comparison of their mp, ^1H and ^{13}C NMR data with the reported.[3] Spectroscopic data of new compounds, **2e** and **2f**, are as follows.
Compound **2e**: 88%; white solid, mp 103-104 °C; IR (KBr) 3282, 1668, 1319, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.93-2.01 (m, 2H), 2.39-2.45 (m, 4H), 2.81 (s, 3H), 5.36 (d, J = 9.0 Hz, 1H), 6.00 (d, J = 9.0 Hz, 1H), 7.01 (t, J = 4.2 Hz, 1H), 7.20-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.21, 25.75, 38.42, 41.36, 58.12, 126.50, 127.45, 128.45, 138.53, 139.82, 148.84, 198.65; ESIMS *m/z* 280 (M^++H). Anal Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.34; H, 6.37; N, 4.96.
Compound **2f**: 90%; white solid, mp 158-159 °C; IR (KBr) 3284, 1668, 1333, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 3H), 1.09 (s, 3H), 1.43-1.55 (m, 1H), 1.63-1.72 (m, 1H), 2.11-2.22 (m, 1H), 2.24-2.35 (m, 1H), 2.39 (s, 3H), 5.06 (d, J = 9.6 Hz, 1H), 6.10 (d, J = 9.6 Hz, 1H), 6.46 (s, 1H), 7.15-7.26 (m, 7H), 7.64 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.40, 27.37, 27.46, 32.90, 34.78, 35.23, 59.03, 126.15, 127.12, 127.31, 128.34, 129.50, 133.82, 138.08, 139.47, 143.10, 157.88, 198.84; ESIMS *m/z* 384 (M^++H). Anal Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.57; N, 3.65. Found: C, 68.81; H, 6.77; N, 3.47.
7. We think the reaction mechanism tentatively comprised of the first generation of stable benzylic carbocation by the assistance of $FeCl_3$ and the following reaction with tosylamide. We also examined other amine nucleophile such as aniline, but we observed no reaction presumably due to preferential interaction of $FeCl_3$ with the basic aniline.
8. When we applied the reaction conditions to the Baylis-Hillman adduct **1k**, we observed the formation of desired product **2k** in low yield (12%). Instead we observed the formation of benzaldehyde (presumably *via* retro-Baylis-Hillman reaction), rearranged derivative **3** (10%), and appreciable amounts of remaining starting material **1k** (*ca* 20%).