Synthesis of Rearranged *N*-Tosyl *Aza*-Baylis-Hillman Adducts under Acidic Conditions Catalyzed by CH_3SO_3H or Montmorillonite K10

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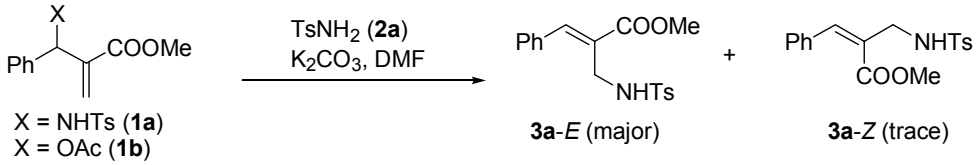
The Baylis-Hillman reaction and its *aza*-version have made great progress since the original Baylis-Hillman reaction was first reported in 1972.[1] We and other research groups have used extensively the *aza*-Baylis-Hillman adducts and their rearranged derivatives for the synthesis of many heterocyclic compounds.[1-3] Usually the rearranged *N*-tosyl *aza*-Baylis-Hillman adduct **3a** has been prepared from *N*-tosyl *aza*-Baylis-Hillman adduct **1a** or Baylis-Hillman acetate **1b** under the influence of K_2CO_3 in DMF as in Scheme 1.[2,3] The reported stereochemistry of the product **3a** is predominantly *E*.[2,3] The synthesis of the corresponding rearranged *N*-tosyl *aza*-Baylis-Hillman adduct having nitrile moiety has not been reported.

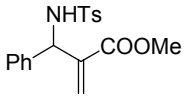
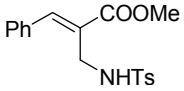
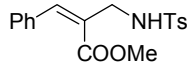
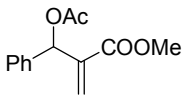
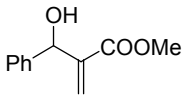
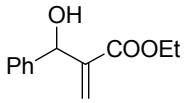
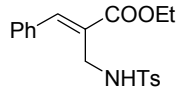
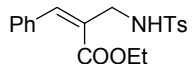
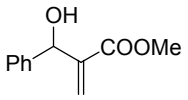
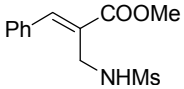
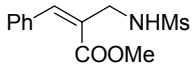
During our recent studies on the radical cyclization and Heck type cyclization with modified Baylis-Hillman adducts,[4,5] the *Z*-form of rearranged *N*-tosyl *aza*-Baylis-Hillman adduct was required. However, there was no precedent method for the synthesis of *Z*-form of rearranged *N*-tosyl *aza*-Baylis-Hillman adducts in appreciable amounts. Thus we decided to examine the preparation of these compounds under acidic conditions.

Actually, the reaction of **1a** and tosylamide (**2a**) under basic conditions (DMF, K_2CO_3) produced *E*-form (**3a**-*E*) selectively (73%) together with only 6% of *Z*-isomer as in Table 1 (entry 1), as mentioned above.[2,3] The reaction of Baylis-Hillman acetate **1b** and **2a** gave also similar results (entry 2).[2,3]



Scheme 1

Table 1. Conversion of Baylis-Hillman adducts into rearranged *N*-tosyl *aza*-Baylis-Hillman adducts

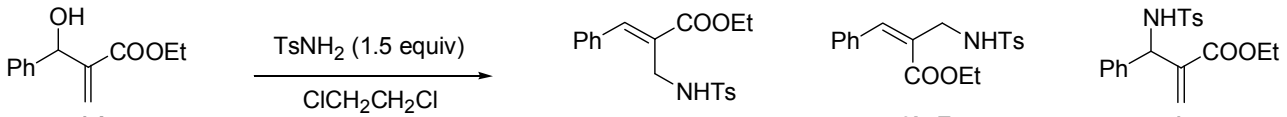
Entry	Substrate		Conditions	Products (%)	
1		**1a**	$TsNH_2$ (**2a**, 0.2 equiv) K_2CO_3 (2 equiv) DMF, 70-80 °C, 3 h	 **3a** - *E* (73)	 **3a** - *Z* (6)
2		**1b**	$TsNH_2$ (5 equiv) K_2CO_3 (5 equiv) DMF, 40-50 °C, 1 h	**3a** - *E* (74)	**3a** - *Z* (5)
3		**1c**	$TsNH_2$ (1.5 equiv) K10, $ClCH_2CH_2Cl$ 80 °C, 24 h	**3a** - *E* (62)	**3a** - *Z* (26)
4		**1d**	$TsNH_2$ (1.5 equiv) K10, $ClCH_2CH_2Cl$ 80 °C, 24 h	 **3b** - *E* (57)	 **3b** - *Z* (24)
5		**1c**	$CH_3SO_2NH_2$ (**2b**, 1.5 equiv) K10, $ClCH_2CH_2Cl$ 80 °C, 48 h	 **3c** - *E* (67)	 **3c** - *Z* (23)

Whereas, the reaction of Baylis-Hillman adduct **1c** and **2a** in the presence of montmorillonite K10 (entry 3)[6] produced appreciable amounts of desired **3a**-*Z* (26%). Under such acidic conditions the reaction of ethyl ester **1d** (entry 4) and the reaction between **1c** and $CH_3SO_2NH_2$ (**2b**) also showed similar results (entry 5).

Encouraged by the results we examined the possibility for the synthesis of *Z*-isomer in an increased yield under various acidic conditions with ethyl ester **1d** as a model substrate, and the results are summarized in Table 2. As shown, the use of montmorillonite K10 showed the formation of **3b**-*Z* in appreciable amounts (19-26%, entries 1-3). When we stopped the reaction in short time (2 h), we obtained desired compound **3b**-*Z* in 26% yield and *aza*-Baylis-Hillman adduct **1e** was isolated in 21% (entry 1). The compound **1e** was converted completely to **3b**-*E* and **3b**-*Z* for 24 h refluxing, however, the ratio of **3b**-*Z*/**3b**-*E* was decreased slightly (entry 2). Increasing reaction time decreased the ratio of **3b**-*Z*/**3b**-*E* (entries 2-3).[7] Methanesulfonic acid showed somewhat higher catalytic activity than the use of K10 (entries 4-7), however, the selectivity for **3b**-*Z* was not improved. The use of sulfuric acid was not satisfactory (entry 8). From the results, the conditions of entry 2 turned out to be the best choice for the preparation of **3b**-*Z* although the yield is still low (24%).

As a next trial, we examined the synthesis of rearranged *N*-tosyl *aza*-Baylis-Hillman adduct of nitrile derivative **3d** (Table 3). We obtained the product **3d** in only 40% yield as an inseparable *E/Z* mixture from the reaction of **1f** under basic

Table 2. Optimization of reaction conditions

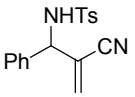
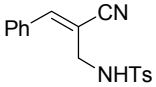
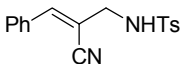
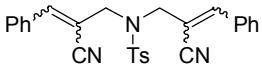
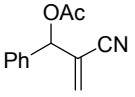
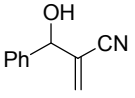
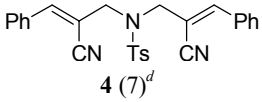
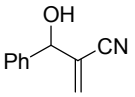
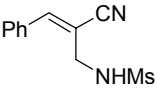
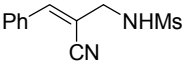
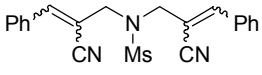
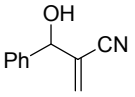


1d **3b**-*E* **3b**-*Z* **1e**

Entry	Conditions	**3b** – *E* (%)[a]	**3b** – *Z* (%)[a]	**1e** (%)[a]
1	K10, reflux, 2 h	43	26	21
2	K10, reflux, 24 h	57	24	-
3	K10, reflux, 120 h	68	19	-
4	$MeSO_3H$, rt, 24 h	58	28	8
5	$MeSO_3H$, 80 °C, 15 min	71	22	-
6	$MeSO_3H$, 80 °C, 1 h	81	13	-
7	$MeSO_3H$, 80 °C, 5 h	75	8	-
8	H_2SO_4, 80 °C, 30 min	44	23	14

[a]Isolated yield.

Table 3. Conversion of Baylis-Hillman adducts into rearranged *N*-tosyl *aza*-Baylis-Hillman adducts

Entry	Substrate	Conditions	Products (%)		
1	 **1f**	$TsNH_2$ (0.2 equiv) K_2CO_3 (2 equiv) DMF, 50-60 °C, 14 h	 **3d** – *E*	 **3d** – *Z* 40% (*E*/*Z* = 2:3)[a]	 **4** (10)[b]
2	 **1g**	$TsNH_2$ (5 equiv) K_2CO_3 (2 equiv) aq THF, rt, 45 h	**3d** – *E*	**3d** – *Z* 5% (*E*/*Z* = 2:3)[a]	**4** (83)[b]
3	 **1h**	$TsNH_2$ (1.5 equiv) $MeSO_3H$, $ClCH_2CH_2Cl$ 80 °C, 2 h	**3d** – *E* (nd)[c]	**3d** – *Z* (69)	 **4** (7)[d]
4	 **1h**	$CH_3SO_2NH_2$ (1.5 equiv) $MeSO_3H$, $ClCH_2CH_2Cl$ 80 °C, 4 h	 **3e** – *E* (nd)[c]	 **3e** – *Z* (71)	 **5** (nd)[c]
5	 **1h**	$TsNH_2$ (1.5 equiv) K10, $ClCH_2CH_2Cl$ 80 °C, 72 h	**3d** – *E* (nd)[c]	**3d** – *Z* (41%)[e]	**4** (trace)

[a]*E*/*Z* was not separated and the ratio was determined based on ^{1}H NMR spectrum. [b]Three stereoisomers (*E,E*/*E,Z*/*Z,Z*) were mixed together. [c]Not detected. [d]Pure isomer (*Z*/*Z*) was isolated in 7% yield. [e]The compound **3d**-*Z* was contaminated with unreacted **1h**.

conditions (entry 1). The separation of *E* and *Z* isomers was impossible and we confirmed the ratio by ^{1}H NMR as *E*:*Z* = 2:3. A bis-adduct **4** was also obtained in 10% yield.[8] The synthesis of **3d** from the reaction of Baylis-Hillman acetate **1g** and tosylamide was not successful due to the formation of **4** as the major product even in the presence of excess amounts (5.0 equiv) of tosylamide in order to reduce the formation of **4**.

However, to our delight, we obtained **3d**-*Z* in 69% isolated yield when we carried out the reaction under acidic conditions with Baylis-Hillman adduct **1h** under the influence of $MeSO_3H$ (entry 3). It is interesting to note that the corresponding *E*-isomer was not formed even in trace amounts. In the reaction mixture we observed the formation of bis-adduct **4** (7%) and the stereochemistry of this compound was also found to be as *Z*/*Z*. Similarly, **3e**-*Z* was synthesized in good yield (71%) under same acidic conditions from **1h** and $CH_3SO_2NH_2$ (entry 4). The use of K10 in this case was found to be less effective than the use of K10 (entry 5).

In summary, we examined the synthesis of *N*-tosyl *aza*-Baylis-Hillman adducts from the reaction of various Baylis-Hillman adducts and tosylamide. We obtained *Z*-isomers up to 26% for the Baylis-Hillman adducts having ester moiety and 71% for the Baylis-Hillman adducts having nitrile moiety.

Experimental Section

Typical procedure for the synthesis of 3a. A solution of **1c** (192 mg, 1 mmol), $TsNH_2$ (257 mg, 1.5 mmol), and montmorillonite K10 (Aldrich, 550 mg) in 1,2-dichloroethane (5 mL) was heated to reflux for 24 h. After filtration of the reaction mixture, removal of solvent, and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 6:1:3) we obtained **3a**-*E* (214 mg, 62%) and **3a**-*Z* (90 mg, 26%). The other compounds were synthesized analogously and the spectroscopic data of **3a**-*E*,[3g] **3a**-*Z*, **3b**-*E*,[2a,2c] **3b**-*Z*, **3c**-*E*, and **3c**-*Z* are as follows.

Compound **3a**-*E*:[3g] 62%; white solid, mp 109-111 °C; IR (film) 3263, 1705, 1326, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.76 (s, 3H), 3.96 (d, *J* = 7.0 Hz, 2H), 5.18 (t, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.38-7.40 (m, 5H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.49, 40.53, 52.27, 126.42, 127.24, 128.74, 129.47, 129.50, 129.62, 133.86, 136.46, 143.45, 143.48, 167.67.

Compound **3a**-*Z*: 26%; colorless oil; IR (film) 3275, 1714, 1327, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.56 (s, 3H), 3.93 (d, *J* = 6.0 Hz, 2H), 5.21 (t, *J* = 6.0 Hz, 1H), 6.84 (s, 1H), 7.09-7.10 (m, 2H), 7.25-7.29 (m, 5H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.40, 47.47, 51.68, 127.14, 127.44, 127.93, 128.50, 128.56, 129.67, 134.75, 137.39, 139.52, 143.44, 167.73.

Compound **3b**-*E*:[2a,2c] 57%; white solid, mp 112-114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, *J* = 7.5 Hz, 3H), 2.42 (s, 3H), 3.95 (d, *J* = 6.5 Hz, 2H), 4.21 (q, *J* = 7.5 Hz, 2H), 5.41 (t, *J* = 6.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.37-7.41 (m, 5H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 1H).

Compound **3b**-*Z*: 24%; colorless oil; IR (film) 3277, 1705, 1328, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, *J* = 7.0 Hz, 3H), 2.35 (s, 3H), 3.92 (d, *J* = 6.5 Hz, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 5.41 (br s, 1H), 6.84 (s, 1H), 7.08-7.10 (m, 2H), 7.23-7.26 (m, 5H), 7.75 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.48, 21.33, 47.30, 60.83, 127.06, 127.73, 127.99, 128.28, 128.42, 129.58, 134.92, 137.38, 139.00, 143.28, 167.27.

Compound **3c**-*E*: 67%; white solid, mp 77-78 °C; IR (film) 3283, 1709, 1322, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94 (s, 3H), 3.87 (s, 3H), 4.18 (d, *J* = 6.3 Hz, 2H), 4.95 (t, *J* = 6.3 Hz, 1H), 7.37-7.48 (m, 5H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.08, 40.38, 52.46, 126.87, 128.92, 129.36, 129.71, 133.78, 143.68, 167.73.

Compound **3c**-*Z*: 23%; colorless oil; IR (film) 3293, 1716, 1327, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.97 (s, 3H), 3.69 (s, 3H), 4.09 (d, *J* = 6.3 Hz, 2H), 5.09 (br s, 1H), 7.03 (s, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.49, 47.42, 51.87, 128.18, 128.53, 128.60, 128.78, 134.61, 138.91, 168.03.

Typical procedure for the synthesis of 3d. A solution of **1h** (159 mg, 1 mmol), $TsNH_2$ (257 mg, 1.5 mmol), and CH_3SO_3H (1.2 mL) in 1,2-dichloroethane (5 mL) was heated to reflux for 2 h. After usual aqueous workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 3:1:3) we obtained **3d**-*Z* (216 mg, 69%) as a white solid. The other compounds were synthesized analogously and the spectroscopic data of **3d**-*Z*, **3e**-*Z*, and **4** (*Z*/*Z*) are as follows.

Compound **3d**-*Z*: 69%; white solid, mp 147-149 °C; IR (film) 3268, 2213, 1328, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 3.95 (d, *J* = 6.6 Hz, 2H), 5.16 (t, *J* = 6.6 Hz, 1H), 7.02 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.36-7.41 (m, 3H), 7.56-7.60 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.43, 47.03, 106.38, 117.24, 127.25, 128.82, 128.88, 129.84, 130.84, 132.50, 137.01, 143.98, 145.63.

Compound **3e**-*Z*: 71%; white solid, mp 103-104 °C (decomp.); IR (film) 3343, 2213, 1312, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 4.13 (d, *J* = 6.3 Hz, 2H), 4.75 (br s, 1H), 7.20 (s, 1H), 7.45-7.47 (m, 3H), 7.76-7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.36, 47.28, 107.02, 117.52, 129.06 (2C), 131.20, 132.39, 146.09.

Compound **4**: 7%; white solid, mp 160-162 °C; IR (film) 2215, 1349, 1161, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 4.29 (s, 4H), 7.23 (s, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.38-7.43 (m, 6H), 7.67-7.70 (m, 4H), 7.76 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.50, 51.72, 105.33, 117.61, 127.58, 128.90, 129.13, 129.96, 131.07, 132.46, 136.33, 144.36, 147.42.

References and Notes

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