The Reaction of Heterocyclic Nucleophiles and the DABCO Salts of the Baylis-Hillman Acetates

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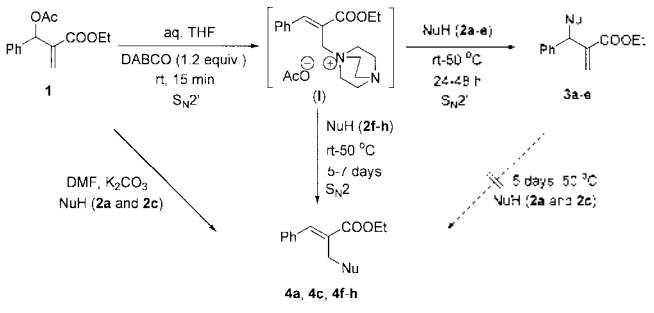
Recently, we and others have reported on the reaction of the DABCO (1,4-diazabicyclo[2.2.2]octane) salts of the Baylis-Hillman acetates with some nucleophiles.[1,2] In the reaction we could obtain the allylic substitution products (*nucleophile at the secondary position of product*) in good yields. Examined nucleophiles included sodium borohydride,[1a] potassium cyanide[1b] and *p*-toluenesulfonamide.[1c]

As a continuous work we examined the reaction of the DABCO salts of the Baylis-Hillman acetate and some heterocycles such as uracil or thymine. However, we could obtain the rearrangement product (*nucleophile at the primary position of product*)[2c] as the major. Drewes *et al.* have reported the reaction of Baylis-Hillman acetate and 2-formylimidazole.[2c] This is the only report that dealt with the heterocyclic nucleophile, where either allylic substitution product or rearrangement product can be selectively obtained by controlling the reaction conditions. Thus, we intended to study on the reaction of the DABCO salts of Baylis-Hillman acetates with various heterocyclic nucleophiles in order to obtain some insights on the reaction pathway depending on the nucleophiles and reaction conditions.

As shown in Scheme 1, the reaction proceeded *via* the DABCO salt of the Baylis-Hillman acetate. The products were either allylic substitution product **3** or the rearrangement one **4** depending on the nucleophiles. We used Baylis-Hillman acetate **1** as a model substrate and isatin (**2a**), benzotriazole (**2b**), phthalimide (**2c**), oxindole (**2d**), barbituric acid (**2e**), uracil (**2f**), thymine (**2g**), 1-hydroxybenzotriazole (**2h**) and 1,2,4-triazole (**2i**) as heterocyclic nucleophiles. The results are summarized in Table 1 and 2. We could obtain the allylic substitution products **3a-e** selectively in 50-91% yields for **2a-e** within relatively short time (Table 1). While, rearrangement products **4f-h** were isolated as the major (51-63%) in the cases of **2f-h** (Table 2). For the synthesis of **4f-h** somewhat long reaction time was needed.



Scheme 1

We could tentatively propose the regiochemistry as follows (Scheme 1). When the nucleophiles have good reactivity toward the DABCO salts (**I**) under the reaction conditions, S_N2' type reaction proceeded to give **3**.[1] Whereas when we used nucleophiles such as **2f-h**, rearranged products **4** might be formed *via* either the corresponding **3** by successive intermolecular S_N2' reaction by the same nucleophile or direct S_N2 type reaction from (**I**). Thus, we examined the

Table 1. Synthesis of allylic substitution products **3**

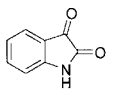
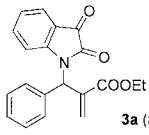
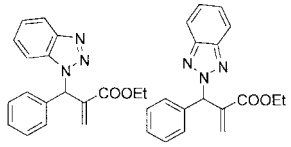
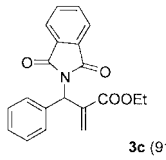
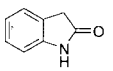
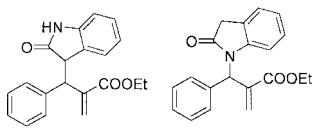
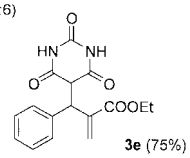
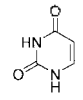
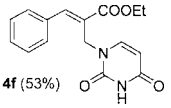
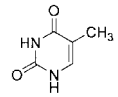
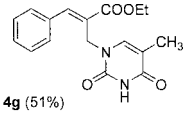
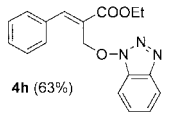
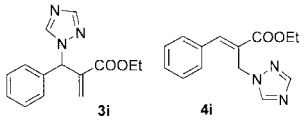
Entry	Nucleophile (**2**)	T (°C), time (h)	Products (%)
1	 **2a**	50 °C, 24 h	 **3a** (80%)
2	 **2b**	rt, 24 h	 **3b** (51%) **3b'** (35%)
3	 **2c**	rt, 48 h	 **3c** (91%)
4	 **2d**	50 °C, 24 h	 **3d** (39%) (*syn/anti* = 4:6) **3d'** (11%)
5	 **2e**	rt, 24 h	 **3e** (75%)

Table 2. Synthesis of rearrangement products **4**

Entry	Nucleophile (**2**)	T (°C), time (d)	Products (%)
1	 **2f**	rt, 5 days	 **4f** (53%)
2	 **2g**	rt, 7 days	 **4g** (51%)
3	 **2h**	50 °C, 7 days	 **4h** (63%)
4	 **2i**	rt, 5 days	 **3i** **4i** 5 : 1 (59%)[a]

[a]The ratio was determined from ^{1}H NMR spectrum and the position of nitrogen atom is arbitrary.

reaction of **3a** and **3c** in the presence of isatin (**2a**) or phthalimide (**2c**) under the same reaction conditions. However, the formation of **4a** and **4c** was not detected (5 days at 50 °C in aqueous THF in the presence of DABCO). From the results, we tentatively conclude that **4** might be formed from (**I**) by a S_N2 reaction directly. As shown in Scheme 1, rearrangement products **4a** (90%) and **4c** (84%) could be prepared simply by changing the reaction conditions (the use of K_2CO_3 in DMF).

In the case of benzotriazole (entry 2 in Table 1), competition between N_1-attack and N_2-attack was observed. The structures of **3b** and **3b'** could be easily discernable by the ^{13}C NMR spectra. Due to the symmetry of benzotriazole moiety in **3b'** only 13 peaks of carbon were observed.[3] When we used oxindole (entry 4 in Table 1), competition between *C*-attack and *N*-attack was observed. The structures of **3d** and **3d'** were also deduced from their ^{1}H NMR spectra easily. The compound **3d** exists as a *syn/anti* mixture (4 : 6 ratio).[3] In the case of 1,2,4-triazole (entry 4 in Table 2) **3i** and **4i** was generated as a 5 : 1 ratio. We could not separate them in pure state. The precise structure (the position of nitrogen atom) of **3i** and **4i** was not proved until now.

As a conclusion, we examined the reaction of the DABCO salt of the Baylis-Hillman acetate and various heterocyclic nucleophiles. Depending on the nature of nucleophiles and reaction conditions, regiochemistry of the nucleophilic substitution reaction could be controlled. Further studies on the relationships between the regiochemistry of products and nucleophiles are currently underway.

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References and Notes

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2. (a) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett.* **2001**, *42*, 477. (b) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85. (c) Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun.* **2000**, *30*, 1045.
3. Some selected spectroscopic data of products are as follows.
3a: clear oil; IR (KBr) 1737, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3H), 4.10 (m, 2H), 5.57 (d, J = 1.8 Hz, 1H), 6.37 (s, 1H), 6.52 (d, J = 1.8 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 7.24-7.38 (m, 6H), 7.54 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.96, 55.59, 60.34, 111.52, 116.90, 122.67, 124.35, 126.93, 127.44, 127.96, 128.53, 134.59, 136.70, 137.16, 149.94, 157.06, 164.37, 181.82.
3b: clear oil; IR (KBr) 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.1 Hz, 3H), 4.04 (m, 2H), 5.41 (s, 1H), 6.55 (s, 1H), 6.98 (s, 1H), 7.18-7.31 (m, 8H), 7.97 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.81, 61.25, 62.23, 109.84, 119.94, 123.91, 127.37, 127.91, 128.63, 128.85, 129.75, 132.91, 135.91, 138.61, 145.99, 165.14.
3b': clear oil; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 3H), 4.04 (m, 2H), 5.43 (s, 1H), 6.56 (s, 1H), 7.11 (s, 1H), 7.20-7.29 (m, 7H), 7.77-7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.89, 60.22, 68.72, 117.28, 125.43, 126.98, 127.72, 127.81, 128.92, 135.03, 137.78, 143.23, 164.09.
3d: clear oil; IR (KBr) 1749, 1696 cm^{-1}; 4:6 *syn/anti* mixture; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 1.2 H), 1.26 (t, J = 7.2 Hz, 1.8H), 4.01-4.29 (m, 3H), 4.57 (d, J = 6.6 Hz, 0.6H), 4.83 (d, J = 3.9 Hz, 0.4H), 5.59 (s, 0.6H), 5.64 (s, 0.4H), 6.41 (s, 0.4H), 6.44 (s, 0.6H), 6.77-7.26 (m, 9H), 8.80 (s, 0.6H), 8.90 (s, 0.4H); ^{13}C NMR ($CDCl_3$) δ 13.91, 14.08, 46.76, 48.19, 48.31, 49.95, 60.85, 60.97, 109.72, 109.79, 121.78, 122.01, 124.86, 125.26, 126.96, 127.11, 127.15, 127.81, 128.01, 128.04, 128.23, 128.28, 128.53, 129.02, 138.54, 138.86, 140.03, 141.48, 141.72, 166.57, 166.74, 178.46.
3d': clear oil; IR (KBr) 1776, 1721, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3H), 3.59 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 5.59 (d, J = 1.2 Hz, 1H), 6.53 (d, J = 1.2 Hz, 1H), 6.63 (t, J = 1.2 Hz, 1H), 6.70-7.33 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 13.93, 35.51, 55.61, 61.09, 110.98, 122.11, 124.35, 124.40, 127.49, 127.88, 128.10, 128.47, 128.63, 136.71, 138.59, 144.03, 165.71, 174.90.
4a: clear oil; IR (KBr) 1747, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3H), 4.12 (q, J = 7.2 Hz, 2H), 4.75 (s, 2H), 6.48 (d, J = 7.8 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 7.20-7.39 (m, 7H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.14, 37.28, 61.48, 117.07, 117.46, 123.51, 125.06, 125.93, 128.72, 128.85, 129.26, 134.04, 138.15, 144.13, 150.56, 157.84, 166.28, 183.05.
4f: white solid, mp 114-116 °C; IR (KBr) 3153, 3074, 2873, 1721, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 4.21 (q, J = 7.1 Hz, 2H), 4.74 (s, 2H), 5.55 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.31-7.38 (m, 5H), 7.98 (s, 1H), 9.11 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 12.39, 42.89, 59.82, 99.83, 123.95, 127.06, 127.31, 127.82, 132.10, 142.39, 143.93, 148.97, 161.87, 164.71.