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Remarkable rate acceleration of water-promoted nucleophilic substitution of Baylis–Hillman acetate: a facile and highly efficient synthesis of *N*-substituted imidazole

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Abstract—Without additional reagents, the Baylis–Hillman acetates **2** underwent nucleophilic substitution reaction with imidazole readily in aqueous THF solution to afford the corresponding *N*-substituted imidazole derivatives **3** in good to excellent yields. Moreover, the reaction between the in situ generated DABCO salt of Baylis–Hillman acetates **4** and imidazole occurs in aqueous THF providing the S_N2 type products **5**. The simpler operational procedure, better stereoselectivity and higher efficiency over conventional method make the present protocol practical for the preparation of imidazole derivatives.

The imidazole moiety is usually found in segments of numerous natural products and in many biologically active pharmaceuticals.[1] Moreover, a number of *N*-substituted imidazole derivatives, such as miconazole, ketoconazole, genaconazole, and bifonazole have become well-established drugs for the treatment of many mycotic infections.[2] Consequently, a variety of methods have been developed for the preparation of *N*-substituted imidazole derivatives. The most popular method previously used for constructing *N*-arylated imidazoles is traditional Ullmann-type reaction through the cross-coupling of imidazole with aryl halides.[3] More recently, compounds other than aryl halides including arylboronic acid and α-diazocarbonyl have also been exploited allowing such transformation catalyzed by copper reagents.[4] Although these methods may provide efficient access to a wide range of imidazole derivatives, only one functional group (usually aryl group) can be introduced into the corresponding imidazole molecule. Up to now, the preparation of multifunctional imidazole compounds with fewer steps is quite limited. As a result, the development of more efficient methods to construct *N*-substituted imidazole units remains desirable.

The Baylis–Hillman reaction is well-known as one of the powerful carbon–carbon bond formation methods in organic synthesis.[5] The adducts of the reactions, 3-hydroxy-2-methylene-alkanoates (derived from acrylate esters), have been utilized as important precursors for stereoselective synthesis of different multifunctional molecules.[6] Among these transformations, the syntheses of multisubstituted alkenes with stereo-defined double bonds from Baylis–Hillman adducts have been well-documented given the frequent occurrence of trisubstituted alkenes with defined stereochemistry in naturally occurring bioactive molecules.[7,8] Herein, we wish to report a facile synthesis of *N*-substituted imidazole from the acetates of Baylis–Hillman adducts based on our previous work.[9] Our attempt was to synthesize a series of *N*-substituted imidazoles with multifunctionalities (Scheme 1) and provide more options for pharmaceutical use.

According to common knowledge, the presence of base would facilitate or sometimes be indispensable for this substitution reaction, because base can help the formation of the nitrogen anion at the *N*-1 position thereby enhancing the nucleophilicity of imidazole molecule. However, our investigation showed that the reaction

Keywords: Water; *N*-Substituted imidazole; Nucleophilic substitution; Baylis–Hillman adducts, DABCO.
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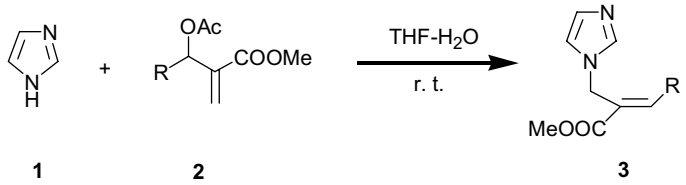
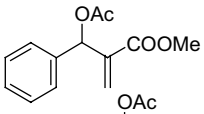
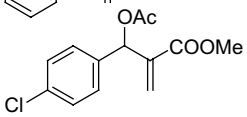
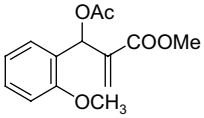
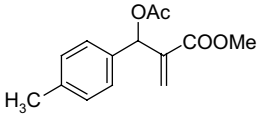
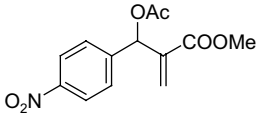
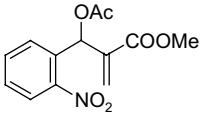
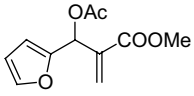
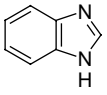
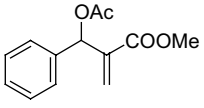
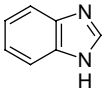
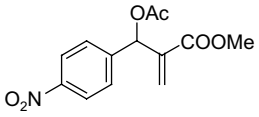
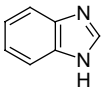
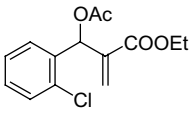
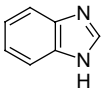
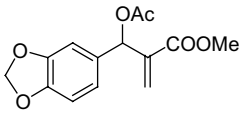


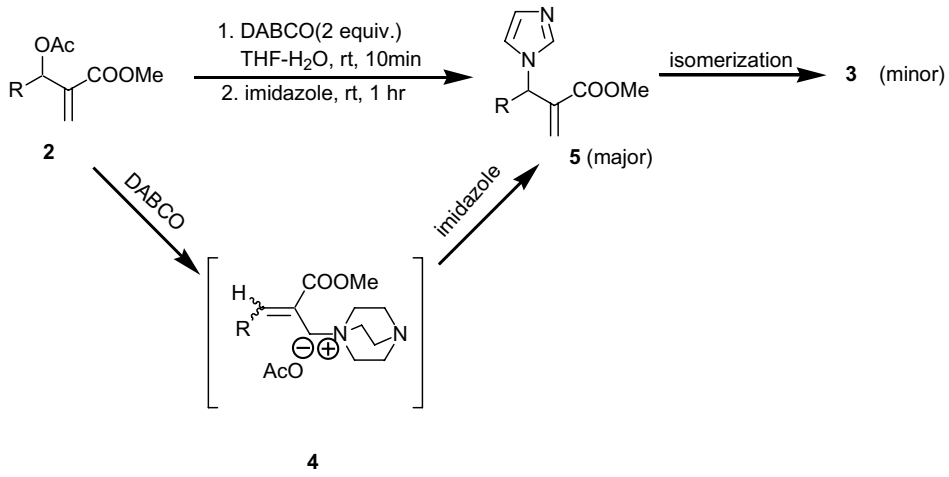
Scheme 1.

could proceed readily without any additional reagents in THF–H_2O solution (Scheme 1). It is worth noting that the presence of water shows remarkable acceleration effect on the above substitution reaction. While this pro-

Table 1. Stereoselective synthesis of *N*-substituted imidazole **3** from Baylis–Hillman acetates[a]

Entry	Imidazole **1**	Baylis–Hillman acetates **2**	Temp (°C)	Time (h)	Product[b]	Yield[c] (%)	*E*:*Z*
1			rt	2.5	**3a**	90	100:0
2			rt	3	**3b**	93	100:0
3			rt	2	**3c**	98	100:0
4			rt	3	**3d**	94	100:0
5			rt	2.5	**3e**	90	100:0
6			rt	2.5	**3f**	93	100:0
7			rt	3	**3g**	85	100:0
8			60	4	**3h**	88	96:4
9			60	5	**3i**	76	100:0
10			60	4	**3j**	79	100:0
11			60	5	**3k**	81	91:9

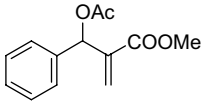
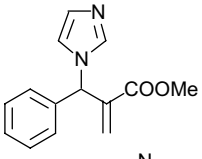
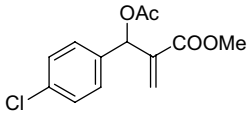
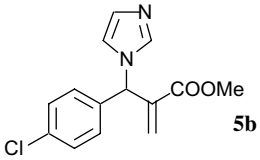
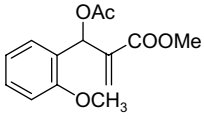
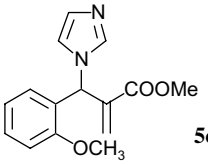
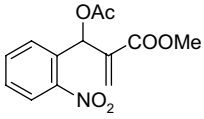
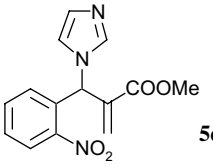
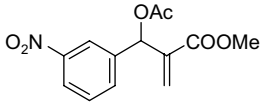
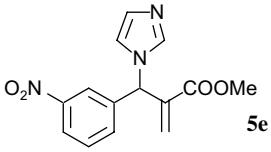
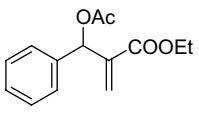
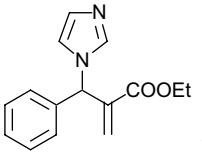
[a] All reactions were carried out in THF–H_2O (5:1, v/v) solution without additional reagents.
[b] All products were characterized by ^1H NMR, IR, and mass spectroscopy.
[c] Isolated yields based on Baylis–Hillman acetates **2**.



Scheme 2.

cess could be finished within 3 h in aqueous THF, the same reaction is rather tedious when conducted in dry THF (about 7 h). In fact, a similar substitution reaction had also been reported with even poorer performance,[11]

Table 2. Highly efficient synthesis of *N*-substituted imidazole **5** with Baylis–Hillman acetate[a]

Entry	Baylis–Hillman acetates **2**	Reaction time (h)	Product	Yield[b] (%)
1		1.5	 **5a**	82
2		1	 **5b**	50
3		1.5	 **5c**	72
4		1	 **5d**	61
5		1	 **5e**	53
6		1.5	 **5f**	89

[a] All reactions were carried out with imidazole in THF–H_2O (5/1, v/v) with 2 equiv DABCO at room temperature.
[b] All cases were referred to the yields of substituted imidazole **5** otherwise noted.

which indicated that the presence of a protic solvent had promoted the reaction. Water, a good protic solvent was therefore used to act as a co-solvent here. Conditional optimization experiments found that when the ratio of H_2O and THF reaches 1:5 (v/v), satisfactory results were achieved. And H_2O–THF (1:5, v/v) was selected as our standard reaction medium.

As shown by Scheme 1 and Table 1, a variety of Baylis–Hillman acetates **2** (with either electron-donating or electron-withdrawing groups attached to the aromatic rings) underwent nucleophilic substitution smoothly with imidazole **1** in aqueous THF at room temperature affording the *N*-substituted imidazole **3** in good to excellent yields. Moreover, the reaction exhibits excellent stereoselectivity and no *Z*-isomers were observed.[10]

To examine the effectiveness of this protocol for the generation of *N*-substituted imidazole **3**, similarly, benzimidazole was also used to undergo *N*-functionalization with substrates **2** in aqueous THF. In contrast, more vigorous conditions were needed and products **3** were obtained as a mixture of *E*- and *Z*-isomers in some cases,[12] which might result from the increasing steric hindrance of benzimidazole molecule. Under elevated temperature, the corresponding *N*-functionalized benzimidazole derivatives were afforded in good yields within a few hours and the results are listed in Table 1.

Although the exact mechanism of the above transformation has not yet been clarified, we deduced that the weak nucleophilicity of imidazole molecule might be improved in water, which makes the attack of the electrophilic Baylis–Hillman acetates **2** easier. Further exploration into the mechanism is currently underway in our laboratory.

It is reported that the nucleophilic substitution at the vinyl position of the Baylis–Hillman acetates can be altered in the presence of DABCO.[13] In this regard, we expect to prepare the corresponding S_N2 substitution type imidazole derivatives **5**, some of which are structurally unique. Several Baylis–Hillman acetates were treated with imidazole in the presence of DABCO in aqueous THF and the desired products **5** were obtained in good yields (Scheme 2). In the presence of water as a co-solvent, as we can see from Table 2, all runs were finished in 1.5 h with moderate to good yields. The method presented here is quite attractive compared with the sluggish process (5 days) of the conventional method.[11]

Mechanistically, the above protocol could be considered as a tandem S_N2'–S_N2' pathway. Firstly, mixing of Baylis–Hillman acetates **2** and DABCO in aqueous THF led to formation of the corresponding DABCO salt **4** (TLC detection), which then underwent similar substitution reaction with imidazole to give **5**. It is noteworthy that product **5** is thermodynamically unstable, thus the isomerization from **5** to **3** would be favored on standing or under reflux. During our research, some amount of product **3** was isolated as by-products in all cases.

In summary, we have demonstrated a convenient and highly efficient protocol for the stereoselective synthesis of *N*-substituted imidazole **3** in good to excellent yields. Moreover, our strategy also provides ready access to the corresponding S_N2 type product **5** from the acetates of Baylis–Hillman adducts.[14] The simpler operational procedure, better stereoselectivity, and higher efficiency over the conventional method makes the present protocol practical for the preparation of multifunctional imidazole derivatives.[15] As a result, it is expected that the present method will find its application in future organic synthesis and pharmaceutical use.

Acknowledgements

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10. The *E* stereochemistry of the products was assigned on the basis of the chemical shift values of the vinyl and allylic protons in the ^{1}H NMR spectra of the products and also by the analysis of NOESY spectra of **3b**.
11. According to Drews' work, several days were required to give the analogous imidazole derivatives from 2-formyl imidazole in dry methanol in poor yield (7–60%): Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun.* **2000**, *30*, 1045–1055.
12. The ratio of the isomers was determined from the integration ratios of the isomeric vinyl and allylic methylene protons in the ^{1}H NMR spectra of the products.
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14. All Baylis–Hillman acetates are prepared according to the literature: (a) Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795–796; (b) David, H. O.; Kenneth, M. N. *J. Org. Chem.* **2003**, *68*, 6427–6430.
15. A typical procedure for preparation of **3** is as follows: to a solution of 1.2 mmol imidazole **1** in THF–H_2O (5:1, v/v, 10 mL), 1 mmol Baylis–Hillman acetate **2** was added and the resulting mixture was stirred at room temperature until complete consumption of substrate **2** (Table 1). Then the reaction mixture was extracted with diethyl ether (3×20 mL). The organic phase was successively washed with saturated brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure to give the crude product, which was purified by preparative TLC using ethyl acetate and cyclohexane (5:1) as eluent. Selected spectral data of products **3** are listed as follows: compound **3a**: IR (film): 2952, 1713, 1634, 1504, 907 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (s, 1H), 7.44 (s, 1H), 7.40–7.27 (m, 5H), 6.99 (1H, s), 6.83 (1H, s), 4.94 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) 168.9, 144.8, 137.0, 133.9, 129.6, 129.2, 129.0, 128.8, 127.0, 118.7, 52.4, 42.9. *m/z* (%): 242 (M^+, 13), 175 (14), 115 (100), 91 (37). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82. Found: C, 69.31; H, 5.74. Compound **3b**: IR (film): 3113, 2952, 1714, 1635, 1591, 1490, 907, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.99 (s, 1H), 7.48 (s, 1H), 7.41 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.03 (1H, s), 6.87 (1H, s), 4.96 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) 166.6, 143.4, 136.8, 135.7, 132.2, 130.1, 129.3, 129.2, 127.4, 118.6, 52.5, 42.8. *m/z* (%): 276 (M^+, 11), 209 (19), 149 (55), 115 (66); 59 (100). Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74. Found: C, 60.93; H, 4.68. Compound **3d**: IR (film): 3111, 2951, 1714, 1634, 1608, 1507, 1436, 1106, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (s, 1H), 7.45 (s, 1H), 7.20 (s, 4H), 6.98 (1H, s), 6.85 (1H, s), 4.96 (s, 2H), 3.76 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) 167.1, 145.0, 140.1, 136.9, 130.9, 129.7, 129.1, 129.0, 125.8, 118.7, 52.4, 43.0, 21.3. *m/z* (%): 256 (M^+, 14), 189 (26), 129 (100), 59 (38). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29. Found: C, 70.38; H, 6.12.

A typical procedure for preparation of **5** is as follows: to a stirred solution of 1 mmol Baylis–Hillman acetates **2** in aqueous THF (THF–H_2O, 5:1, v/v) was added 2 mmol DABCO and stirred at room temperature for 10 min. To the mixture 1 mmol imidazole **1** was added and the whole mixture was stirred until completion of the reaction. Then the reaction was quenched with dilute hydrochloric acid (0.1 M, 5 mL) and extracted with diethyl ether (3×20 mL). The organic phase was successively washed with saturated brine (10 mL) and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure to give the crude product, which was purified by preparative TLC using ethyl acetate and cyclohexane (3:1) as eluent.