Synthesis of 2,4,5-Trisubstituted Pyrimidines from Baylis-Hillman Adducts and Amidines

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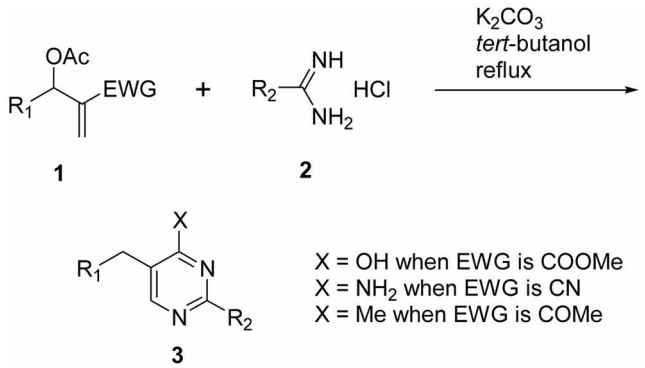
The pyrimidine moiety is one of the most widespread heterocycles in biologically occurring compounds, such as nucleic acids and vitamin B_1, and is an important constituent of numerous drug molecules in many therapeutic areas.[1-4] Although various procedures for the synthesis of pyrimidine derivatives have been developed,[2-4] it is convenient to synthesize substituted pyrimidines by the reaction of amidine or guanidine derivatives with a variety of 1,3-dielectrophilic three-carbon units such as α,β-unsaturated carbonyl compounds.[3,4]

During the continuous studies on the chemical transformation of Baylis-Hillman adducts our recent interest was focused on the synthesis of oxygen and nitrogen-containing heterocyclic compounds.[4-6] In addition, we were interested in the reaction of Baylis-Hillman adducts and 1,3-dinucleophile like as 1,3-dinitroalkanes[6] and dimethyl 1,3-acetonedicarboxylate.[6] In these respects we presumed that we could synthesize trisubstituted pyrimidine derivatives **3** by using some amidine derivatives **2** as shown in Scheme 1. In the reaction, Baylis-Hillman acetates **1** act as 1,3-dielectrophilic component and amidine derivatives **2** served the role of 1,3-dinucleophile.

The reaction of the Baylis-Hillman acetate **1a** and benzamidine hydrochloride (**2a**) in *tert*-butanol in the presence of K_2CO_3 produced desired compound **3a** in 91% isolated yield (entry 1 in Table 1). Similarly we prepared 2,4,5-trisubstituted pyrimidines **3b-h** in 27-92% yields from the reaction of Baylis-Hillman acetates **1a-f** and amidine derivatives **2a** and **2b**, and the results are summarized in Table 1. As shown in Table 1, the reaction of acetamidine hydrochloride (**2b**) gave relatively lower yields than the cases of **2a** (see entries 1&2, entries 6&7) presumably due to low solubility of **2b** in *tert*-butanol. The Baylis-Hillman acetates containing ester moiety (entries 1-5) or acetyl group (entries 6 and 7) showed moderate to good reactivity, however, nitrile-containing substrate **1f** showed very low reactivity (entry 8). The reaction of **1a** and 1,3-diphenyl guanidine (**2c**) gave the corresponding 2-aminopyrimidine derivative **3i** in moderate yield (entry 9).[4b] Initially we examined the reaction of Baylis-Hillman adduct itself and benzamidine hydrochloride (**2a**), however, we could not obtain the desired product **3a** directly.[7]



Scheme 1

In summary, we synthesized some 2,4,5-trisubstituted pyrimidines from the reaction of Baylis-Hillman acetates and amidine derivatives in a one-pot reaction in moderate yields.

Experimental Section

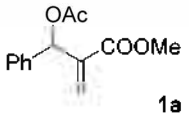
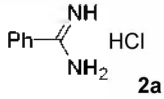
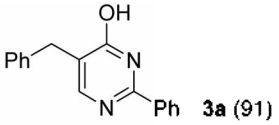
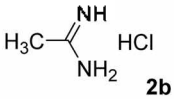
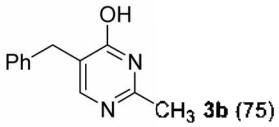
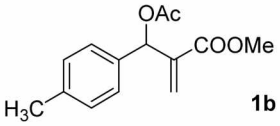
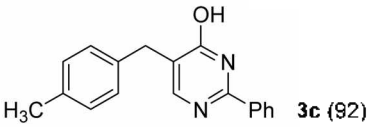
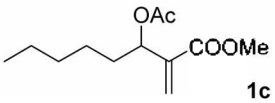
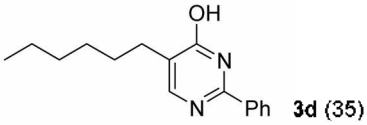
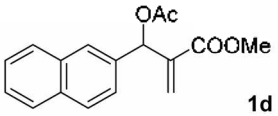
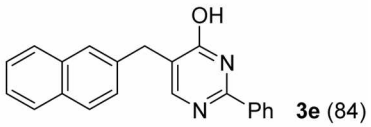
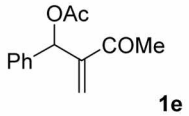
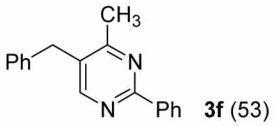
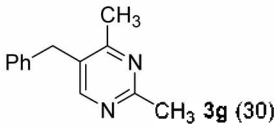
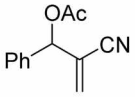
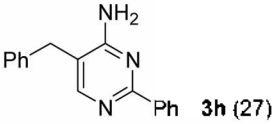
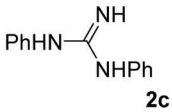
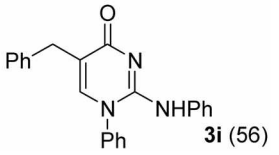
Typical procedure for the synthesis of 3a. A stirred solution of **1a** (234 mg, 1.0 mmol), **2a** (235 mg, 1.5 mmol), and K_2CO_3 (276 mg, 2.0 mmol) in *tert*-butanol (3 mL) was heated to reflux for 3 h. After usual aqueous extractive workup and column chromatographic purification process (CH_2Cl_2/EtOAc, 5:2) we obtained **3a** (239 mg, 91%) as a white solid. The spectroscopic data of **3a-i** are as follows.

Compound **3a**: 91%; white solid, mp 235-237 °C (dec.); IR (film) 3068, 2950, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 2H), 7.18-7.35 (m, 5H), 7.46-7.55 (m, 3H), 7.99 (s, 1H), 8.19-8.22 (m, 2H), 13.18 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.47, 126.02, 126.46, 127.43, 128.50, 128.92 (2C), 131.79, 132.01, 138.71, 152.98, 155.67, 164.40.

Compound **3b**: 75%; white solid, mp 175-177 °C; IR (film) 3345, 2927, 1714, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 3.76 (s, 2H), 7.17-7.34 (m, 5H), 7.76 (s, 1H), 13.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.24, 33.13, 124.99, 126.37, 128.39, 128.89, 138.67, 152.95, 157.49, 164.91.

Compound **3c**: 92%; white solid, mp 236-238 °C (dec.); IR (film) 2920, 2850, 1651, 1574 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 3.81 (s, 2H), 7.08 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 7.47-7.58 (m, 3H), 7.98 (s, 1H), 8.19-8.22 (m, 2H), 13.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.01, 33.07, 126.18, 127.53, 128.80, 128.86,

Table 1. Synthesis of 2,4,5-trisubstituted pyrimidines

Entry	B-H acetate **1**	Amidine **2**	Conditions[a]	Products (%)[b]
1	 **1a**	 **2a**	3 h	 **3a** (91)
2	**1a**	 **2b**	4 h	 **3b** (75)
3	 **1b**	**2a**	3 h	 **3c** (92)
4	 **1c**	**2a**	6 h	 **3d** (35)
5	 **1d**	**2a**	3 h	 **3e** (84)
6	 **1e**	**2a**	3 h[c]	 **3f** (53)
7	**1e**	**2b**	6 h[c]	 **3g** (30)
8	 **1f**	**2a**	4 h[d]	 **3h** (27)
9	**1a**	 **2c**	6 h	 **3i** (56)

[a]Conditions: B-H acetate (1.0 equiv), amidine (1.5 equiv), K_2CO_3 (2.0 equiv), *tert*-butanol, reflux. [b]Isolated yield. [c]Conditions: B-H acetate (1.5 equiv), amidine (1.0 equiv), K_2CO_3 (2.0 equiv), *tert*-butanol, reflux. [d]Conditions: B-H acetate (1.0 equiv), amidine (3.5 equiv), K_2CO_3 (4.0 equiv), *tert*-butanol, reflux.

129.16, 131.71, 132.07, 135.66, 135.97, 152.90, 155.67, 164.60.

Compound **3d**: 35%; white solid, mp 122-124 °C; IR (film) 3406, 3070, 2927, 2852, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 6.9 Hz, 3H), 1.26-1.45 (m, 6H), 1.61-1.71 (m, 2H), 2.54 (t, J = 7.2 Hz, 2H), 7.48-7.58 (m, 3H), 7.98 (s, 1H), 8.20-8.25 (m, 2H), 12.86 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.09, 22.65, 27.58, 28.22, 29.17, 31.65, 127.03, 127.34, 128.88, 131.64, 132.14, 152.23, 155.16, 164.74.

Compound **3e**: 84%; white solid, mp 269-271 °C (dec.); IR (film) 3377, 2917, 2850, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.02 (s, 2H), 7.41-7.55 (m, 6H), 7.72-7.81 (m, 4H), 7.98 (s, 1H), 8.06-8.08 (m, 2H), 11.57 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.77, 125.38, 126.03, 126.60, 127.36, 127.45, 127.46, 127.50, 127.55, 127.56, 127.76, 128.61, 131.40, 131.69, 133.09, 137.15, 151.53, 155.94, 163.04.

Compound **3f**: 53%; white solid, mp 68-69 °C; IR (film) 3030, 2923, 1574, 1541, 1426 cm^{-1}; ^1H NMR ($CDCl_3$, 300

MHz) δ 2.49 (s, 3H), 3.99 (s, 2H), 7.12-7.15 (m, 2H), 7.20-7.33 (m, 3H), 7.44-7.51 (m, 3H), 8.41-8.46 (m, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.40, 35.87, 126.66, 127.93, 128.49, 128.53, 128.75, 129.45, 130.27, 137.73, 138.15, 157.22, 162.73, 166.13.

Compound **3g**: 30%; colorless oil; IR (film) 3042, 2926, 1581, 1556, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 2.68 (s, 3H), 3.94 (s, 2H), 7.08-7.11 (m, 2H), 7.20-7.33 (m, 3H), 8.32 (s, 1H) ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.09, 25.62, 35.68, 126.64, 128.42, 128.45, 128.73, 138.15, 157.02, 165.86, 165.93.

Compound **3h**: 27%; white solid, mp 176-178 °C; IR (film) 3481, 3286, 3066, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 2H), 4.79 (br s, 2H), 7.19-7.24 (m, 2H), 7.25-7.36 (m, 3H), 7.41-7.46 (m, 3H), 8.24 (s, 1H), 8.31-8.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.78, 113.71, 127.10, 127.81, 128.28, 128.33, 129.03, 130.08, 137.09, 137.93, 156.18, 161.83, 163.31.

Compound **3i**: 56%; yellow solid, mp 160-162 °C; IR (film) 3431, 2254, 2127, 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.80 (d, J = 1.8 Hz, 2H), 6.86 (br s, 2H), 7.01-7.06 (m, 1H), 7.26-7.31 (m, 5H), 7.37-7.44 (m, 7H), 7.57 (br s, 1H), 7.87 (s, 1H). We took the ^{13}C NMR spectrum of compound **3i**, however, we could not assign the peaks definitely due to line broadening. Thus we prepared *N*-allyl derivative (**3i**, allyl bromide, K_2CO_3, DMF, rt, 2 h, 66%) and confirmed the structure of **3i**, and the spectroscopic data of *N*-allyl derivative of **3i** are as follows: 66%; pale yellow oil; IR (film) 1627, 1589, 1493, 1417, 1377 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.61 (d, J = 1.5 Hz, 2H), 4.84 (d, J = 5.4 Hz, 2H), 5.26 (dd, J = 10.2 and 1.5 Hz, 1H), 5.38 (dd, J = 17.1 and 1.5 Hz, 1H), 6.06-6.20 (m, 1H), 6.53-6.56 (m, 2H), 6.61-6.66 (m, 1H), 6.72-6.81 (m, 3H), 6.86-7.00 (m, 4H), 7.12-7.15 (m, 2H), 7.30-7.32 (m, 3H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.83, 49.50, 116.87, 121.58, 121.79, 124.32, 124.39, 125.29, 127.95, 128.60, 128.66, 129.10, 129.41, 133.48, 134.27, 137.51, 144.01, 144.63, 147.51, 164.77.

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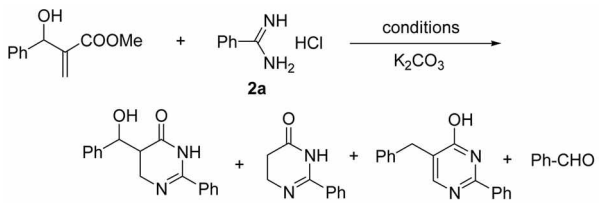
7. The reaction of Baylis-Hillman adduct itself and **2a** is summarized in Scheme 2. The reaction in *tert*-butanol in the presence of K_2CO_3 showed the formation of diastereomeric mixture of **4** (58%, 1:1), dihydropyrimidine **5** (15%),[8] and benzaldehyde **6** (13%). Dihydropyrimidine **5** and benzaldehyde **6** might be produced by retro-Baylis-Hillman process from **4**. When we carried out the reaction in ethanol we observed rapid decomposition of initially formed **4** into intractable polar compounds. The compound **4** could be transformed into product **3a** by dehydration (*p*-TsOH, toluene, reflux, 1 h) and the following isomerization (K_2CO_3, *tert*-butanol, reflux, 1 h) in 35% yield.



tert-butanol, reflux, 3 h	**4** (58%)	**5** (15%)	**3a** (not formed)	**6** (13%)
EtOH, reflux, 1 h	**4** (10%)	**5** (20%)	**3a** (not formed)	**6** (15%)

Scheme 2

8. (a) Weis, A. L.; Zamir, D. *J. Org. Chem.* **1987**, *52*, 3421-3425. (b) Einsiedel, J.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 851-854.