Synthesis of 3,4-Disubstituted Pyridines Starting from Baylis-Hillman Adducts Using Schweizer Reaction

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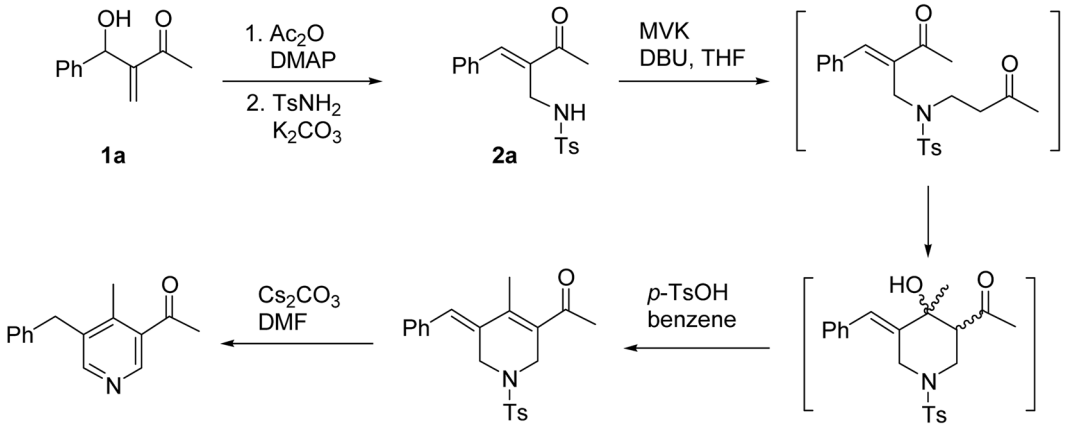
Received December 4, 2005

Key Words : Pyridines, Baylis-Hillman adducts, Schweizer reaction, Vinyltriphenylphosphonium bromide

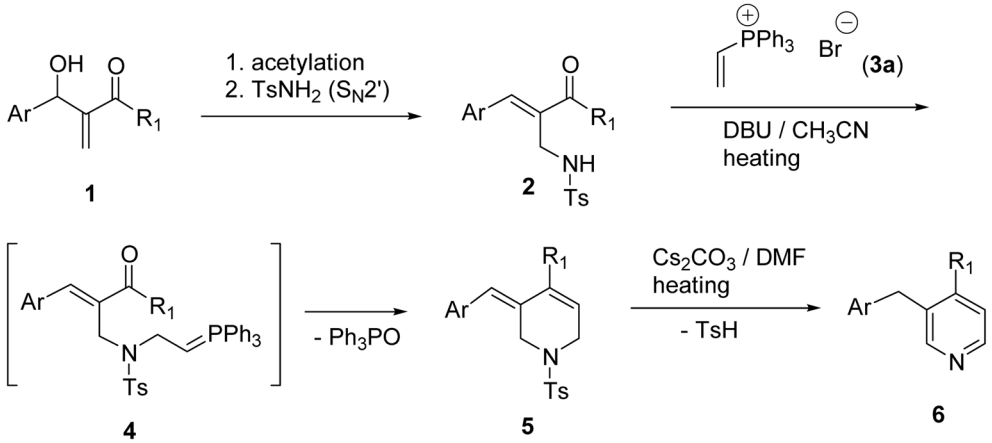
Recently, we have reported the facile synthesis of polysubstituted pyridine derivatives from the Baylis-Hillman adducts.[1] As shown in Scheme 1, the Baylis-Hillman adducts of alkyl vinyl ketone **1a** could be converted easily into their tosylamide derivatives **2a**. Sequential Michael addition of **2a** to the appropriate Michael acceptor, aldol type cyclization, dehydration, elimination of *p*-toluenesulfinic acid, and the final isomerization afforded polysubstituted pyridines.[1] In the reaction, compound **2a** served three-carbons and one-nitrogen atom for the final pyridine while the Michael acceptor served two-carbon atoms.

In this paper we wish to report the application of another two-carbon unit, vinyltriphenylphosphonium bromide (**3a**, Schweizer reagent),[2] for the synthesis of 3,4-disubstituted pyridines. Extensive efforts have been devoted to the synthesis of 3,4-disubstituted pyridine derivatives due to their biological importance and the usefulness as synthetic intermediates.[3]

As shown in Scheme 2 and in Table 1, the reaction of **2a** and **3a** in CH_3CN in the presence of DBU at 40-50 °C for 16 h afforded **5a** in 72% yield. Benzylidene derivative **5a** must be formed *via* the successive Michael-Wittig reaction (Schweizer reaction). We could prepare 3-benzyl-4-methylpyridine (**6a**) from the reaction of **5a** under K_2CO_3/DMF

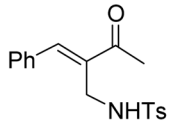
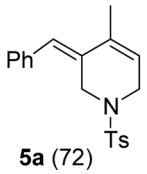
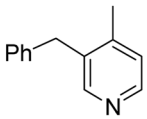
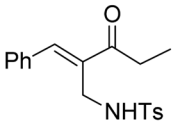
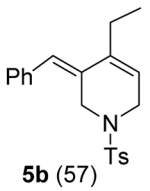
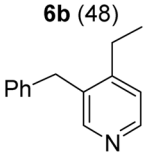
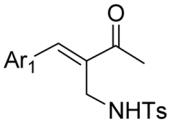
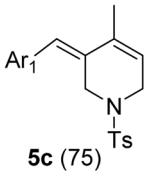
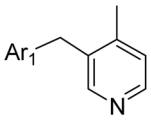
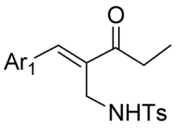
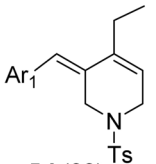
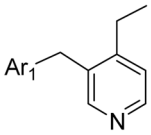
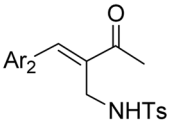
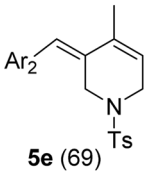
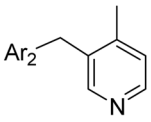
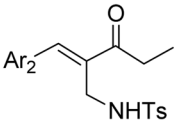
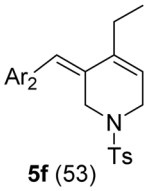
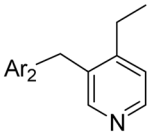


Scheme 1



Scheme 2

Table 1. Synthesis of 3,4-disubstituted pyridine derivatives

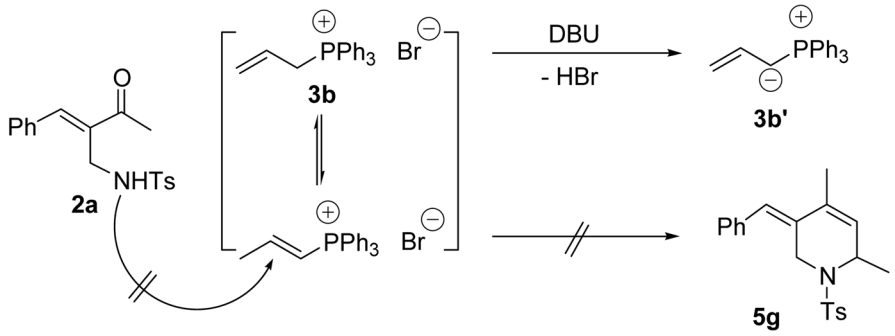
Entry	Compound **2**[a]	Conditions	Compound **5**	Conditions	Product **6** (%)
1	 **2a**	**3a** (1.3 equiv) DBU (3.0 equiv) CH_3CN 40-50 °C, 16 h	 **5a** (72)	K_2CO_3 (3.0 equiv) DMF 70-80 °C, 24 h Cs_2CO_3 (3.0 equiv) DMF 120-130 °C, 2 h	**6a** (55)  **6a** (75)
2	 **2b**	**3a** (1.3 equiv) DBU (3.0 equiv) CH_3CN 40-50 °C, 26 h	 **5b** (57)	K_2CO_3 (3.0 equiv) DMF 70-80 °C, 72 h Cs_2CO_3 (3.0 equiv) DMF 120-130 °C, 2 h	**6b** (48)  **6b** (71)
3	 **2c**	**3a** (1.3 equiv) DBU (3.0 equiv) CH_3CN 40-50 °C, 11 h	 **5c** (75)	Cs_2CO_3 (3.0 equiv) DMF 120-130 °C, 2 h	 **6c** (81)
4	 **2d**	**3a** (1.4 equiv) DBU (3.0 equiv) CH_3CN 40-50 °C, 12 h	 **5d** (66)	Cs_2CO_3 (3.0 equiv) DMF 120-130 °C, 2 h	 **6d** (73)
5	 **2e**	**3a** (1.3 equiv) DBU (2.0 equiv) CH_3CN 40-50 °C, 16 h	 **5e** (69)	Cs_2CO_3 (3.0 equiv) DMF 120-130 °C, 1 h	 **6e** (70)
6	 **2f**	**3a** (1.4 equiv) DBU (3.0 equiv) CH_3CN 40-50 °C, 12 h	 **5f** (53)	Cs_2CO_3 (3.0 equiv) DMF 120-130 °C, 1 h	 **6f** (74)

[a]Ar_1 is 4-methylphenyl and Ar_2 is 4-chlorophenyl.

(70-80 °C, 24 h) conditions in 55% yield *via* the elimination of *p*-toluenesulfinic acid and the following 1,3-H shift (entry 1). When we used Cs_2CO_3 instead of K_2CO_3 at elevated temperature we could obtain **6a** in an improved yield (75%) in short time (entry 1). Encouraged by the results we prepared 3,4-disubstituted pyridine derivatives **6b-f** by using similar method and the results are summarized in Table 1.

As shown in Table 1, various kinds of starting materials **2b-f** showed similar reactivity to form the corresponding benzylidene compounds **5b-f** in moderate yields. The final 3,4-disubstituted pyridine derivatives **6b-f** were also synthesized in good yields under the same reaction conditions. However, unfortunately, the use of allyltriphenylphosphonium bromide (**3b**) in order to synthesize **5g** failed completely (Scheme 3). It was known that **3b** could be isomerized easily into 2-propenyltriphenylphosphonium bromide in the presence of weak base such as pyridine.[2c] However, the nitrogen atom of **2a** did not attack **3b** due to its low nucleophilicity. Instead, **3b** must be converted into the corresponding ylide **3b'** with the aid of relatively strong base, DBU, as reported.[4] Actually, the reaction mixture of **2a** and **3b** showed very complex intractable mixtures on TLC.

In summary, we disclosed the facile synthesis of 3,4-disubstituted pyridines starting from the Baylis-Hillman adducts[5] *via* the sequential introduction of tosylamide, Schweizer reaction with vinyltriphenylphosphonium bromide,



Scheme 3

elimination of *p*-toluenesulfinic acid, and the final 1,3-proton shift process.

Experimental Section

The starting materials **2a-c** and **2e** were synthesized as reported.[1] Compound **2d** and **2f** were prepared analogously in moderate yields.[1]

Compound **2d**: 71%; white solid, mp 106-107 °C; IR (film) 3278, 1662, 1331, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, J = 7.2 Hz, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 2.68 (q, J = 7.2 Hz, 2H), 3.90 (d, J = 6.6 Hz, 2H), 5.24 (t, J = 6.6 Hz, NH, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.56 (s, 1H), 7.67 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.32, 21.41, 21.48, 30.21, 40.37, 127.22, 129.57, 129.60, 129.69, 131.04, 134.41, 136.51, 140.10, 143.06, 143.32, 203.10.

Compound **2f**: 60%; white solid, mp 120-121 °C; IR (film) 3275, 1666, 1327, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 2.71 (q, J = 7.2 Hz, 2H), 3.82 (d, J = 6.6 Hz, 2H), 5.22 (t, J = 6.6 Hz, NH, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.41 (s, 4H), 7.55 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.22, 21.49, 30.31, 40.20, 127.21, 129.11, 129.68, 130.89, 132.32, 135.70, 135.78, 136.28, 141.40, 143.53, 202.85.

Typical procedure for the synthesis of 3-benzyl-4-methylpyridine (6a): To a stirred solution of **2a** (658 mg, 2.0 mmol) and vinyltriphenylphosphonium bromide (**3a**, 960 mg, 2.6 mmol) in CH_3CN (5 mL) was added DBU (912 mg, 6.0 mmol) and the reaction mixture was heated to 40-50 °C for 16 h. After the usual workup and column chromatographic purification process (hexanes/ether, 7 : 1) we obtained **5a** as a white solid, 489 mg (72%). A solution of **5a** (339 mg, 1.0 mmol) and Cs_2CO_3 (978 mg, 3.0 mmol) in DMF (5 mL) was heated to 120-130 °C for 2 h. After the usual workup and column chromatographic purification process (hexanes/EtOAc, 4 : 1) we obtained **6a** as clear oil, 138 mg (75%). The other compounds **5b-f** and **6b-f** were synthesized analogously and the spectroscopic data are as follows.

Compound **5a**: 72%; white solid, mp 113-114 °C; IR (KBr) 1343, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78 (d, J = 1.5 Hz, 3H), 2.39 (s, 3H), 3.79-3.81 (m, 2H), 4.12 (d, J = 1.5 Hz, 2H), 5.56 (t, J = 3.0 Hz, 1H), 6.44 (s, 1H), 7.15-7.39 (m, 7H), 7.56 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.09, 21.35, 44.80, 45.27, 122.07, 125.43, 127.03, 127.61, 128.32, 128.86, 129.28, 131.72, 132.51, 133.82, 136.22, 143.32.

Compound **5b**: 57%; white solid, mp 74-76 °C; IR (KBr) 1346, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J = 7.5 Hz, 3H), 2.18 (q, J = 7.5 Hz, 2H), 2.40 (s, 3H), 3.85-3.86 (m, 2H), 4.13 (d, J = 1.2 Hz, 2H), 5.55 (t, J = 3.9 Hz, 1H), 6.50 (s, 1H), 7.16-7.20 (m, 2H), 7.22-7.29 (m, 3H), 7.35-7.40 (m, 2H), 7.54-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.74, 21.41, 24.87, 44.94, 45.47, 120.29, 124.91, 127.08, 127.69, 128.40, 128.94, 129.33, 130.69, 134.09, 136.38, 137.98, 143.35.

Compound **5c**: 75%; white solid, mp 141-142 °C; IR (film) 1454, 1346, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78 (s, 3H), 2.37 (s, 3H), 2.40 (s, 3H), 3.80 (s, 2H), 4.13 (s, 2H), 5.54 (s, 1H), 6.41 (s, 1H), 7.07 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.18, 21.15, 21.43, 44.93, 45.33, 121.67, 125.53, 127.71, 128.86, 129.12, 129.31, 131.16, 132.68, 133.38, 133.96, 136.91, 143.30.

Compound **5d**: 66%; white solid, mp 122-124 °C; IR (KBr) 1454, 1346, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, J = 7.5 Hz, 3H), 2.17 (q, J = 7.5 Hz, 2H), 2.37 (s, 3H), 2.40 (s, 3H), 3.85 (s, 2H), 4.13 (s, 2H), 5.53 (s, 1H), 6.47 (s, 1H), 7.07 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.78, 21.17, 21.43, 24.90, 45.01, 45.48, 119.86, 124.93, 127.71, 128.88, 129.13, 129.31, 130.06, 133.46, 134.11, 136.90, 138.07, 143.30.

Compound **5e**: 69%; white solid, mp 93-95 °C; IR (KBr) 1597, 1489, 1346, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 2.41 (s, 3H), 3.80 (s, 2H), 4.06 (s, 2H), 5.60 (s, 1H), 6.38 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.11, 21.44, 44.70, 45.30, 122.59, 124.17, 127.64, 128.58, 129.39, 130.18, 132.39, 132.48, 132.88, 133.69, 134.75, 143.49; ESIMS (*m/z*) 354 (M^++H).

Compound **5f**: 53%; white solid, mp 93-95 °C; IR (KBr) 1489, 1346, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, J = 7.5 Hz, 3H), 2.19 (q, J = 7.5 Hz, 2H), 2.41 (s, 3H), 3.85 (s, 2H), 4.06 (s, 2H), 5.59 (s, 1H), 6.45 (s, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

12.73, 21.48, 24.86, 44.84, 45.50, 120.81, 123.63, 127.73, 128.67, 129.43, 130.25, 131.52, 132.99, 134.01, 134.88, 137.85, 143.50.

Compound **6a**[6]: 75%; clear oil; IR (KBr) 2924, 1593, 1493, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 3.99 (s, 2H), 7.06-7.12 (m, 3H), 7.16-7.30 (m, 3H), 8.37 (br s, 2H); ESIMS (*m/z*) 184 (M^++H).

Compound **6b**: 71%; clear oil; IR (KBr) 2970, 1666, 1593, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, J = 7.5 Hz, 3H), 2.56 (q, J = 7.5 Hz, 2H), 4.01 (s, 2H), 7.08-7.30 (m, 6H), 8.36 (s, 1H), 8.41 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.43, 24.93, 36.12, 123.11, 126.25, 128.45, 128.50, 133.86, 139.58, 148.22, 150.91, 151.31; ESIMS (*m/z*) 198 (M^++H).

Compound **6c**: 81%; clear oil; IR (film) 1658, 1593, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 2.30 (s, 3H), 3.93 (s, 2H), 6.99 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 4.5 Hz, 1H), 7.07 (d, J = 8.1 Hz, 2H), 8.35 (d, J = 4.5 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.00, 20.89, 36.15, 125.25, 128.31, 129.15, 134.80, 135.72, 135.96, 145.82, 147.85, 150.48; ESIMS (*m/z*) 198 (M^++H).

Compound **6d**: 73%; clear oil; IR (film) 2970, 1593, 1512, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, J = 7.5 Hz, 3H), 2.30 (s, 3H), 2.56 (q, J = 7.5 Hz, 2H), 3.96 (s, 2H), 6.98 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 4.5 Hz, 1H), 8.36 (s, 1H), 8.41 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.39, 20.88, 24.86, 35.64, 123.01, 128.27, 129.13, 134.04, 135.69, 136.43, 148.11, 150.84, 151.18; ESIMS (*m/z*) 212 (M^++H).

Compound **6e**: 70%; clear oil; IR (film) 1593, 1493, 1408, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (s, 3H), 3.94 (s, 2H), 7.03 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 4.8 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 8.35 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.97, 35.94, 125.37, 128.60, 129.73, 132.05, 134.04, 137.56, 145.79, 148.21, 150.47; ESIMS (*m/z*) 218 (M^++H).

Compound **6f**: 74%; clear oil; IR (film) 2970, 1593, 1489, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, J = 7.5 Hz, 3H), 2.54 (q, J = 7.5 Hz, 2H), 3.97 (s, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 4.5 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 8.35 (s, 1H), 8.43 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.41, 24.90, 35.49, 123.18, 128.62, 129.73, 132.08, 133.35, 138.07, 148.47, 150.81, 151.26; ESIMS (*m/z*) 232 (M^++H).

Acknowledgments. This work was supported by the grant (R-05-2003-000-10042-0) from the Basic Research Program of the Korea Science and Engineering Foundation (Now controlled under the authority of Korea Research Foundation). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

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