Modified Friedländer Synthesis of Quinolines from *N*-Phenyl Cyclic Enaminones

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Friedländer synthesis of quinolines has been used extensively for the synthesis of a variety of quinoline derivatives due to the versatility and its simplicity of the reaction.[1-3] Friedländer synthesis required the use of aniline derivatives with carbonyl substituent at the *ortho* position. However, the requisite starting materials were hardly accessible.[1-3] Friedländer synthesis of quinolines is schematically represented as in Scheme 1.

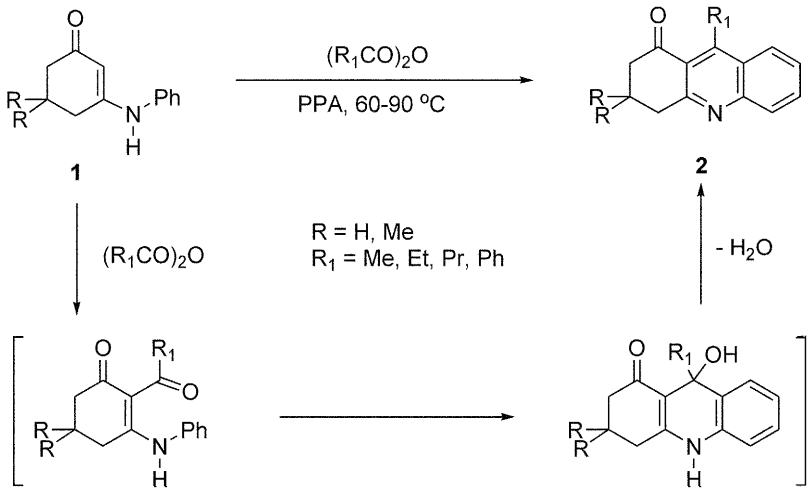
During the investigation regarding enaminone chemistry including iodination of enaminones[4a] and synthesis of vinamidinium salts,[4b] and regarding the synthesis of quinoline derivatives from Baylis-Hillman adducts,[5] we reasoned that we could prepare quinoline derivatives from the easily available *N*-phenyl cyclic enaminones[4] by following the Scheme 2. Acylation of enaminone at the α-position with carboxylic acid anhydride under appropriate conditions[6] followed by intramolecular Friedel-Crafts type reaction and dehydration could afford the desired quinoline derivatives (Scheme 2).

Based on the literature survey,[6] we reasoned that acylation of enaminone **1** at the α-position could be carried out easily and the following Friedel-Crafts type reaction and dehydration might occur simultaneously under suitable conditions in one-pot. Thus, we examined various reaction conditions, and finally found an effective reaction conditions for the one-pot conversion of *N*-phenyl cyclic enaminones **1** into quinolines **2**.

The reaction of enaminone **1a** and acetic anhydride (5 equiv.) in polyphosphoric acid (PPA) afforded the desired quinoline **2a** at 60-70 °C for 5 h in good yield (79%). When we used other carboxylic acid anhydride, the corresponding quinolines, **2b-d**, were obtained similarly in moderate yields (57-64%) as shown in Table 1. The reaction mechanism can be proposed as shown in Scheme 2: acylation at the α-position of enaminones, cyclization, and the following dehydration. The whole reactions occurred successively in one-pot effectively and gave excellent yields of the corresponding quinoline derivatives.

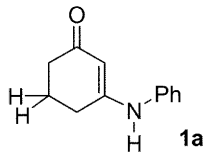
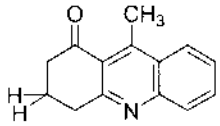
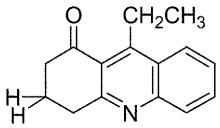
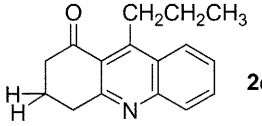
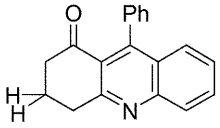
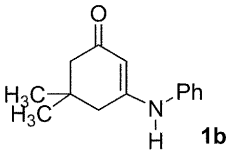
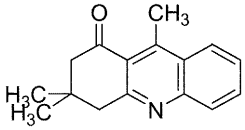
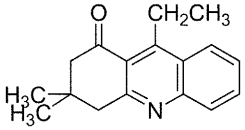
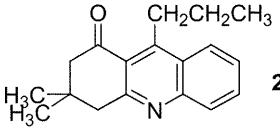
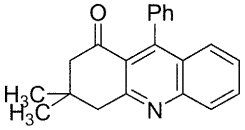
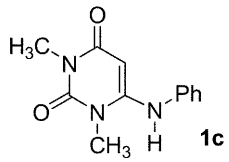
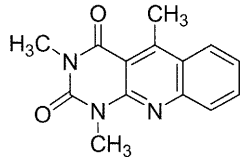
The reaction of enaminone **1b** and four carboxylic acid anhydrides afforded the corresponding quinolines **2e-h** similarly in high yields (63-87%). The enaminone **1c**, which was made from 6-chloro-1,3-dimethyluracil,[7] gave **2i** in

Scheme 1



Scheme 2

Table 1. Synthesis of Quinolines **2a-i**

Entry	Ensminones **1**	Conditions	Quinolins **2** (% yield)
1	 **1a**	$(CH_3CO)_2O$ (5 equiv.) PPA, 60-70 °C, 5 h	 **2a** (79)
2	**1a**	$(CH_3CH_2CO)_2O$ (2 equiv.) PPA, 70-80 °C, 2 h	 **2b** (63)
3	**1a**	$(CH_3CH_2CH_2CO)_2O$ (2 equiv.) PPA, 70-80 °C, 2 h	 **2c** (64)
4	**1a**	$(PhCO)_2O$ (2 equiv.) PPA, 70-80 °C, 3 h	 **2d** (57)
5	 **1b**	$(CH_3CO)_2O$ (5 equiv.) PPA, 80-90 °C, 6 h	 **2e** (87)
6	**1b**	$(CH_3CH_2CO)_2O$ (3 equiv.) PPA, 80-90 °C, 5 h	 **2f** (86)
7	**1b**	$(CH_3CH_2CH_2CO)_2O$ (3 equiv.) PPA, 80-90 °C, 3 h	 **2g** (87)
8	**1b**	$(PhCO)_2O$ (3 equiv.) PPA, 80-90 °C, 4 h	 **2h** (63)
9	 **1c**	$(CH_3CO)_2O$ (4 equiv.) PPA, 80-90 °C, 4 h	 **2i** (55)

55% yield. Unfortunately, the reaction of **1a** and trifluoroacetic anhydride failed completely under the same reaction conditions.

In summary, we disclosed the facile synthesis of various quinolines from the easily available enaminones and carboxylic acid anhydrides in PPA in one-pot. Currently, the studies on the oxidation of **2a-d** toward acridine derivatives are underway.

Experimental Section

Typical procedure for the synthesis of 2a: To a solution of enaminone **1a** (120 mg, 0.64 mmol) in PPA (2-3 g) was added acetic anhydride (328 mg, 3.21 mmol) and heated to 60-70 °C for 5 h. After cooling to room temperature, the reaction mixture was poured into cold water, extracted with ethyl acetate, washed successively with $NaHCO_3$ solution, dried with $MgSO_4$, removal of solvent, and column chromatographic purification (hexanes/EtOAc, 2 : 1) afforded the desired compound **2a** as a yellow solid, 106 mg (79%). The spectroscopic data of prepared compounds are as follows.

2a: 79%, yellow solid, mp 55-57 °C; IR (KBr) 1682, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (quintet, J = 6.6 Hz, 2H), 2.81 (t, J = 6.6 Hz, 2H), 3.04 (s, 3H), 3.27 (t, J = 6.6 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H); ^{13}C NMR

($CDCl_3$) δ 16.26, 21.55, 35.01, 41.31, 125.62, 125.69, 126.56, 127.93, 129.40, 131.71, 148.17, 150.16, 162.34, 200.85; Mass (70 eV) *m/z* (rel. intensity) 154 (29), 183 (100), 211 (M^+, 43).

2b: 63%, yellow oil; IR (KBr) 1682, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3H), 2.20 (quintet, J = 6.6 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 3.27 (t, J = 6.6 Hz, 2H), 3.52 (q, J = 7.5 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.27, 21.42, 22.39, 34.97, 41.31, 124.57, 125.37, 126.53, 126.80, 129.45, 131.53, 148.44, 155.68, 162.47, 200.15.

2c: 64%, yellow oil; IR (KBr) 1682, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3H), 1.73 (m, 2H), 2.20 (quintet, J = 6.6 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.47 (t, J = 7.8 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.98, 21.50, 24.72, 31.10, 35.12, 41.44, 124.80, 125.62, 126.54, 127.20, 129.51, 131.62, 148.52, 154.45, 162.56, 200.36.

2d: 57%, yellow solid, mp 156-158 °C (lit.,[2f,2g,2n,3g] mp 156 °C); IR (KBr) 1685, 1554 cm^{-1}; Mass (70 eV) *m/z* (rel. intensity) 136 (34), 189 (33), 216 (51), 244 (85), 273 (M^+, 100).

Typical procedure for the synthesis of 2e: To a solution of enaminone **1b** (180 mg, 0.84 mmol) in PPA (2-3 g) was added acetic anhydride (427 mg, 4.18 mmol) and heated to 80-90 °C for 6 h. After cooling to room temperature, the reaction mixture was poured into cold water, extracted with ethyl acetate, washed successively with $NaHCO_3$ solution, dried with $MgSO_4$, removal of solvent, and column chromatographic purification (hexanes/EtOAc, 4 : 1) afforded the desired compound **2e** as a white solid, 174 mg (87%). The spectroscopic data of prepared compounds are as follows.

2e: 87%, white solid, mp 105-107 °C; IR (KBr) 1678, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 6H), 2.67 (s, 2H), 3.07 (s, 3H), 3.18 (s, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.16, 28.51, 32.31, 48.82, 55.08, 124.38, 125.73, 126.57, 127.86, 129.44, 131.63, 148.53, 149.86, 161.30, 200.87; Mass (70 eV) *m/z* (rel. intensity) 154 (43), 183 (100), 211 (51), 239 (M^+, 45).

2f: 86%, white solid, mp 114-115 °C; IR (KBr) 1685, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 6H), 1.38 (t, J = 7.5 Hz, 3H), 2.67 (s, 2H), 3.18 (s, 2H), 3.57 (q, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.36, 22.34, 28.55, 32.27, 48.96, 55.17, 123.47, 125.56, 126.68, 126.89, 129.64, 131.61, 148.95, 155.61, 161.59, 200.34.

2g: 87%, white solid, mp 83-85 °C; IR (KBr) 1674, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 6H), 1.16 (t, J = 7.2 Hz, 3H), 1.66-1.78 (m, 2H), 2.66 (s, 2H), 3.18 (s, 2H), 3.49-3.54 (m, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.97, 24.74, 28.51, 30.89, 32.21, 48.92, 55.18, 123.58, 125.67, 126.58, 127.16, 129.53, 131.59, 148.86, 154.27, 161.54, 200.39.

2h: 63%, white solid, mp 195-197 °C (lit.,[2g,2n] mp 195 °C); IR (KBr) 1685, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 6H), 2.57 (s, 2H), 3.28 (s, 2H), 7.15-7.20 (m, 2H), 7.38-7.54 (m, 5H), 7.76 (t, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.56, 32.47, 48.63, 54.45, 122.94, 126.66, 127.65, 127.75, 128.27, 128.34, 128.48, 128.74, 131.87, 137.82, 149.24, 151.25, 161.38, 198.19; Mass (70 eV) *m/z* (rel. intensity) 217 (47), 245 (55), 272 (59), 301 (M^+, 100).

Typical procedure for the synthesis of 2i: To a solution of enaminone **1c** (80 mg, 0.34 mmol) in PPA (2 g) was added acetic anhydride (141 mg, 1.38 mmol) and heated to 80-90 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into cold water, extracted with ethyl acetate, washed successively with $NaHCO_3$ solution, dried with $MgSO_4$, removal of solvent, and column chromatographic purification (hexanes/CH_2Cl_2, 1 : 6) afforded the desired compound **2i** as a white solid, 48 mg (55%). The spectroscopic data of prepared compound are as follows.

2i: 55%, white solid, mp 231-233 °C; IR (KBr) 1705, 1666, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (s, 3H), 3.48 (s, 3H), 3.79 (s, 3H), 7.50 (t, J = 7.5 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.32, 28.70, 30.19, 108.94, 125.40, 125.57, 125.58, 128.95, 132.64, 148.35, 148.81, 151.53, 154.08, 162.53; Mass (70 eV) *m/z* (rel. intensity) 143 (100), 226 (84), 240 934), 255 (M^-, 89).

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References and Notes

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