Self Condensation of β-Acylpyruvates and *in situ* Complexation with Some Amine Bases

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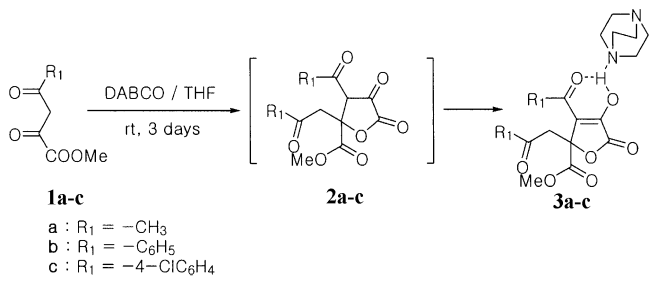
Recently we have reported the self-condensation reaction of methyl acetopyruvate (**1a**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO).[1] In the reaction, self condensation of **1a** followed by intramolecular esterification afforded **2a** as reported.[1] The initially formed product, 4,5,5-trisubstituted tetrahydrofuran-2,3-dione **2a**, has acidic proton at the 4-position and forms 1 : 1 acid-base complex with DABCO to give **3a** as an isolable solid.

As a continuous study of previous report, we describe here further results on the reaction of some β-acylpyruvates in the presence of DABCO or similar amine bases. In the reactions of **1b** and **1c**, we could obtain the similar complex **3b** and **3c** in 39% and 59% respectively. In addition, we could detect acetophenone (from **1b**) or 4'-chloroacetophenone (from **1c**) in trace amounts (<5%) which might be generated *via* the DABCO catalyzed demethoxycarbonylation and decarbonylation.[2]

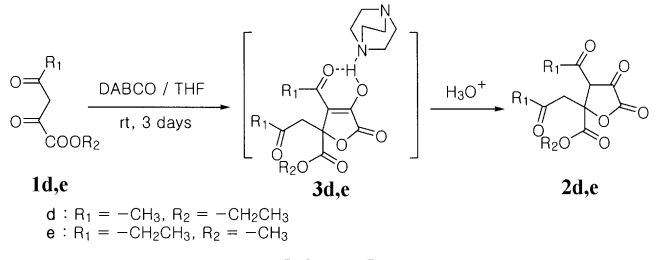
However, isolation of DABCO complex **3d** and **3e** as solids was not successful in the cases of **1d** and **1e** (Scheme 2). The reason seems to be the increased solubility of the complex in tetrahydrofuran and contamination of some side products (*vide infra*). Thus, in these cases we isolated the corresponding DABCO-free tetrahydrofuran-2,3-dione derivatives **2d** and **2e** in 74% and 97% respectively by simply treating the reaction mixture with aqueous HCl as shown in Scheme 2. In the reactions of **1d** and **1e**, some phenol derivatives **4d** and **4e** (3-5%) were obtained.[3] These compounds **4d** and **4e** might be generated from **2d** and **2e** *via* consecutive aldol reaction, dehydration, decarboxylation, decarbonylation, and finally tautomerization as shown in Scheme 3.

This type of self condensation of β-acylpyruvates occurred in the presence of other amine bases such as hexamethylenetetramine (methenamine) or *N,N*-dimethylaminopyridine (DMAP). As an example, in the case of methyl acetopyruvate (**1a**), DMAP or methenamine gave the corresponding complex **5** and **6** as solids effectively in 68% and 32% respectively as shown in Scheme 4. The results are summarized in Table 1.

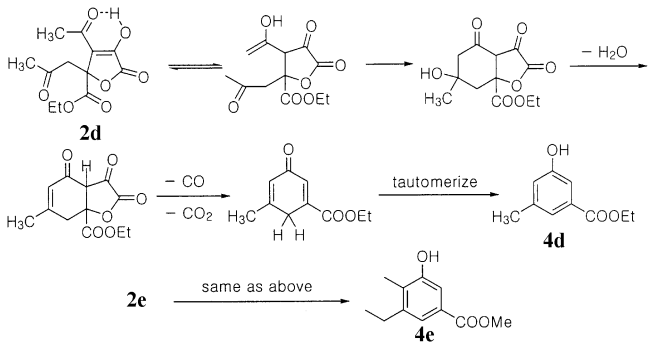
In summary, 4,5,5-trisubstituted tetrahydrofuran-2,3-dione



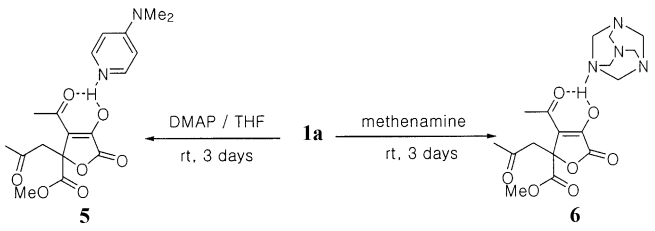
Scheme 1



Scheme 2



Scheme 3



Scheme 4

Table 1. Self condensation of β-acylpyruvates and *in situ* complexation

entry	β-acylpyruvate	amine base	product	yield (%)
1	**1b**	DABCO	**3b**	39
2	**1c**	DABCO	**3c**	59
3[a]	**1d**	DABCO	**2d**	74
4[a]	**1e**	DABCO	**2e**	97
5	**1a**	DMAP	**5**	68
6	**1a**	methenamine	**6**	32

[a] The yield represent DABCO free self condensed product.

derivatives could be generated from β-acylpyruvates *via* the self condensation-cyclization process with the aid of amine bases. The products could form insoluble acid-base complex in tetrahydrofuran in certain cases.

Experimental Section

The starting materials **1a-e** were prepared from the reaction of diethyl oxalate and acetone, acetophenone, 4'-chloroacetophenone, or 2-butanone in the presence of sodium methoxide or sodium ethoxide according to the literature method.[4]

Synthesis of DABCO complex 3b and 3c. To a stirred solution of **1b** and **1c** (10 mmol) in dry tetrahydrofuran (10 mL) was added DABCO (560 mg, 5 mmol) and stirred at room temperature for 3 days. The solids thus formed were filtered and washed with small amounts of tetrahydrofuran to give analytically pure **3b** and **3c**.

3b: 960 mg (39%); ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 12H, DABCO), 3.69 (s, 3H), 3.94 (d, J = 17.5 Hz, 1H), 4.19 (d, J = 17.5 Hz, 1H), 7.15-7.90 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 40.50, 44.99 (DABCO), 52.94, 83.77, 114.78, 127.22, 128.11, 128.41, 129.26, 131.07, 132.94, 137.38, 139.27, 158.97, 170.40, 173.98, 189.06, 196.49; Mass (70 eV) *m z* (rel intensity) 77 (63), 105 (100), 112 (7, DABCO), 229 (22), 306 (13), 334 (2), 380 (M$^+$, 1).

3c: 1.65 g (59%) ^{1}H NMR (DMSO-d_6) δ 3.09 (s, 12H, DABCO), 3.60 (s, 3H), 3.86 (d, J = 16.0 Hz, 1H), 3.94 (d, J = 16.0 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 40.39, 44.93 (DABCO), 53.06, 83.77, 114.28, 127.46, 128.78, 129.62, 130.84, 135.72, 137.12, 137.50, 139.49, 159.34, 170.25, 173.83, 187.48, 195.38; Mass (70 eV) *m z* (rel intensity) 70 (40), 111 (38), 113 (46), 139 (100), 141 (30), 448 (M$^+$, 1).

Synthesis of DABCO-free 2d and 2e. To a stirred solution of **1d** and **1e** (10 mmol) in dry tetrahydrofuran (10 mL) was added DABCO (560 mg, 5 mmol) and stirred at room temperature for 3 days. To the reaction mixture was added dilute aqueous hydrochloric acid (30 mL), and extracted with ether (2 × 30 mL). The organic layers were dried, and the pure products **2d** and **2e** were obtained by flash column chromatography (ethyl acetate/ethyl alcohol, 40 : 1).

2d: 1.0 g (74%) ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 2.17 (s, 3H), 2.51 (s, 3H), 3.30 (d, J = 17.7 Hz, 1H), 3.67 (d, J = 17.7 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H).

2e: 1.38 g (97%) ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 2.35 (qt, J = 7.5 and 2.7 Hz, 2H), 2.53-2.79 (m, 2H), 3.03 (d, J = 16.8 Hz, 1H), 3.55 (s, 3H), 3.57 (d, J = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.27, 7.66, 35.80, 37.06, 43.16, 53.70, 83.22, 123.25, 148.84, 167.73, 168.31, 197.28, 206.76; Mass (70 eV) *m z* (rel intensity) 57 (100), 69 (5), 84 (21), 86 (12), 151 (4), 181 (4), 183 (6), 207 (4), 284 (M$^+$, 1).

Synthesis of DMAP complex 5. To a stirred solution of **1a** (1.44 g, 10 mmol) in dry tetrahydrofuran (10 mL) was added DMAP (610 mg, 5 mmol) and stirred at room temperature for 3 days. The solids thus formed were filtered and washed with small amounts of tetrahydrofuran to give analytically pure **5**.

5: 1.29 g (68%) ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.48 (s, 3H), 3.15 (d, J = 17.4 Hz, 1H), 3.21 (s, 6H), 3.66 (s, 3H), 3.83 (d, J = 17.4 Hz, 1H), 6.69 (d, J = 7.3 Hz, 2H), 8.28 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.93, 30.93, 39.95, 46.21, 52.71, 82.57, 106.43, 115.27, 140.47, 157.02, 161.86, 170.27, 173.40, 192.60, 204.76; Mass (70 eV) *m z* (rel intensity) 43 (100), 85 (17), 121 (62), 122 (50, DMAP), 127 (23), 169 (32), 180 (18), 256 (M$^+$, 1).

Synthesis of hexamethylenetetramine complex 6. To a stirred solution of **1a** (1.44 g, 10 mmol) in dry tetrahydrofuran (10 mL) was added hexamethylenetetramine (700 mg, 5 mmol) and stirred at room temperature for 3 days. The solids thus formed were filtered and washed with small amounts of tetrahydrofuran to afford analytically pure **6**.

6: 634 mg (32%) ^{1}H NMR (DMSO-d_6) δ 1.99 (s, 3H), 2.16 (s, 3H), 2.95 (d, J = 16.9 Hz, 1H), 3.51 (s, 3H), 3.61 (d, J = 16.9 Hz, 1H), 4.78 (s, 12H); Mass (70 eV) *m z* (rel intensity) 43 (100), 66 (56), 84 (71), 86 (23), 140 (18, hexamethylenetetramine), 169 (6), 256 (M$^+$, 1).

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References

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2. (a) Huang, B.-S.; Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1974**, *39*, 2647. (b) Miles, D. H.; Huang, B.-S. *J. Org. Chem.* **1976**, *41*, 208.
3. During isolation of **2d** and **2e**, we could isolate 3-5% yields of phenol derivatives **4d** and **4e**. Ethyl 3-hydroxy-5-methylbenzoate (**4d**) from **2d**: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 8.4 Hz, 3H), 2.35 (s, 3H), 4.35 (q, J = 8.4 Hz, 2H), 6.86 (m, 1H), 7.31 (m, 1H), 7.44 (m, 1H); Mass (70 eV) *m z* (rel intensity) 43 (15), 55 (12), 57 (11), 77 (29), 107 (40), 135 (100), 149 (28), 152 (25), 180 (M$^+$, 34). Methyl 3-hydroxy-4-methyl-5-ethylbenzoate (**4e**) from **2e**: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.6 Hz, 3H), 2.24 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 3.89 (s, 3H), 5.35 (brs, 1H), 7.34 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.43, 14.52, 26.62, 52.03, 113.35, 121.96, 128.06, 144.34, 153.79, 167.28; Mass (70 eV) *m z* (rel intensity) 91 (15), 135 (29), 163 (96), 164 (11), 179 (48), 194 (M$^+$, 100).
4. Kim, J. N.; Ryu, E. K. *Heterocycles* **1990**, *31*, 663, and further references cited therein.