Selective Stobbe condensation under solvent-free conditions

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Solvent-free condensation of cyclohexanone (**1**) and diethyl succinate (**2**) in the presence of Bu^{t}OK at room temperature gives cyclohexylidenesuccinic acid (**3**), while heating a mixture of **1**, **2** and Bu^{t}OK at 80 °C gives only cyclohexenylsuccinic acid (**4**).

Introduction

Stobbe condensation is an important C–C bond forming reaction.[1] Stobbe condensation reactions of ketones and diethyl succinate to monoesters of alkylidenesuccinic acid have been carried out under refluxing the alcoholic solution in the presence of a strong base such as sodium hydride or potassium *tert*-butoxide. This reaction, however, yields complex mixtures, both of stereoisomers and of regioisomers in which the double bond can occupy several positions.[2] We have now found that the Stobbe condensation reaction proceeds efficiently in the absence of solvent. Very interestingly, solvent-free Stobbe condensation reaction of cyclohexanone (**1**) and diethyl succinate (**2**) in the presence of Bu^{t}OK at room temperature and at 80 °C gave cyclohexlidenesuccinic acid (**3**) and cyclohexenylsuccinic acid (**4**), respectively.

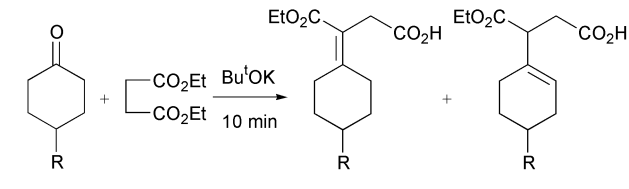
Results and discussion

To a equivalent mixture of **1a** and **2** was added powdered Bu^{t}OK (1.2 equiv.) in a mortar. The mixture was ground at room temperature for 10 min. The reaction was exposed to the air. Then, the reaction mixture was neutralized with dil. HCl and the crystals formed were isolated by filtration to give cyclohexylidenesuccinic acid (**3a**) in 75% yield. In contrast, when the reaction was carried out at 80 °C, cyclohexenylsuccinic acid (**4a**) was obtained in 92% yield. Interestingly, the yield of **4a** was increased as the reaction temperature was raised (Table 1). This method is very useful because both structural isomers (**3a** and **4a**) can be prepared selectively simply by changing the reaction temperature. Similar treatment of **1b** with **2** in the presence of Bu^{t}OK for 10 min at room temperature and at 80 °C gave **3b** and **4b** in 55 and 85% yields, respectively (Table 1).

We also found that paraconic acid derivatives (**5a** and **5b**) can be prepared efficiently in a one-pot reaction. For example, a mixture of **1a**, **2** and Bu^{t}OK was mixed and ground using a mortar and pestle for 10 min and then heated 80 °C in conc. HCl for 1 h to give γ,γ-pentamethyleneparaconic acid (**5a**)[2] in 92% yield. Similarly, **5b** was also obtained in 92% yield from the reaction between **1b** and **2** in a one-pot reaction (Scheme 1).

Solvent-free Stobbe condensation reactions of alkyl phenyl ketones (**6**) and diethyl succinate (**2**) were also found to proceed more efficiently and more selectively than those in solution. For example, a mixture of **6a**, **2** and Bu^{t}OK was mixed and ground using a mortar and pestle for 10 min at room temperature. The reaction mixture was neutralized with dil. HCl and then the crystalline product was isolated by filtration to give only **7a** (E:Z = 10:90) in 93% yield. The E:Z ratio was determined by ^{1}H NMR and the major isomer of **7a** was determined to be Z by comparison of its melting point with an authentic sample.[4] In contrast, the reaction under refluxing in Bu^{t}OH gave a 90:10 mixture of **7a** and **8a**, and the E:Z ratio of **7a** was 65:34.[2]

Table 1 Stobbe condensation of **1** and **2**



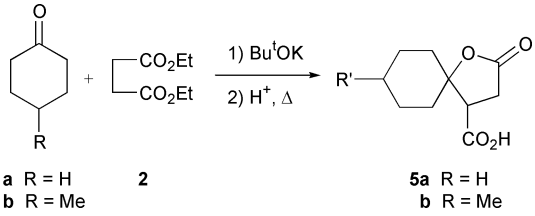
1a R = H **b** R = Me **2** **3a** R = H **b** R = Me **4a** R = H **b** R = Me

Cyclohexanone **1**	Solvent	T/°C	Yield(%)	**3**:**4**[a]
a	Bu^{t}OH	reflux	84	27:73[b]
a	None	rt	75	100:0
a	None	40	88	65:35
a	None	60	81	10:90
a	None	80	92	0:100
b	None	rt	55	95:5
b	None	80	85	0:100

[a] Determined by ^{1}H NMR.

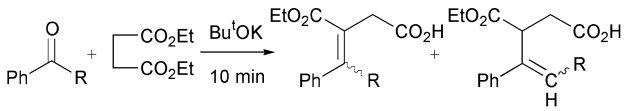
Green Context

The development of solvent free processes is an important area of activity and many studies have been carried out, mostly using solid catalysts and microwave irradiation. Many such reactions proceed well, but use solvents to separate the product and catalyst at the end, making them not truly solvent free. This paper describes the use of solvent free processes in the Stobbe condensation, normally carried out with metal alkoxides in refluxing alcohols. Here, the solvent is omitted and the reaction proceeds smoothly. The base is neutralised, causing the product to crystallise, allowing solvent free isolation and a genuinely solvent free process with only salt waste being formed. Also of interest is the excellent selectivity of the reaction—at room temperature one isomer is exclusively formed; heating the reaction leads to the exclusive formation of a different isomer. ***DJM***



Scheme 1

Table 2 Stobbe condensation of **5** and **2**



Ketone **6**	Solvent	*T*/°C	Yield(%)	**7**:**8**[a]	*E*:*Z* ratio of **7**
a	Bu^{t}OH	reflux	71	90:10	65:35
a	None	rt	93	100:0	10:90
a	None	80	82	90:10	55:45
a	None	120	82	85:15	55:45
b	Bu^{t}OH	reflux	18	90:10	25:75
b	None	rt	59	90:10	10:90
b	None	80	87	35:65	45:55
b	None	120	79	30:70	45:55

Similarly, Stobbe condensation reaction of **6b** and **2** in the absence of solvent gave a 90:10 mixture of **7b** and **8b** in 68% yield with high *E*/*Z* selectivity (Table 2). However, the selective formation of **8** was not completely accomplished when the reaction was carried out even at 120 °C (Table 2).

In conclusion, we have developed a solvent-free procedure[5] for the selective Stobbe condensation reaction. This provides a simple, stereoselective and environmentally friendly organic synthetic method.

Experimental

Solvent-free Stobbe condensation reaction of 1a and 2 in the presence of Bu^{t}OK at room temperature

To a mixture of **1a** (1.0 g, 10.2 mmol) and **2** (1.78 g, 10.2 mmol) was added powdered Bu^{t}OK (1.37 g, 12.3 mmol) in a mortar which was well ground with a pestle at room temperature for 10 min. The reaction was exposed to the air. The reaction mixture was neutralized with dil. HCl and then the crystals formed were isolated by filtration to give β-carbethoxy-β-cyclohexylidenepropionic acid **3a** (colorless plates, 1.73 g) in 75% yield after recrystallization from acetone. Data for **3a**: mp 59–61 °C; ν(C=O) 1718, 1700 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.21 (2H, q, *J* 7.2 Hz), 3.42 (2H, s), 2.45 (2H, br s), 2.25 (2H, br s), 1.62 (6H, br s), 1.29 (3H, t, *J* 7.2 Hz).

Solvent-free Stobbe condensation reaction of 1a and 2 in the presence of Bu^{t}OK at 80 °C

A neat mixture of **1a** (1.0 g, 10.2 mmol), **2** (1.78 g, 10.2 mmol) and powdered Bu^{t}OK (1.37 g, 12.3 mmol) was heated at 80 °C for 10 min. The reaction has been exposed to the air. The reaction mixture was decomposed by adding dil. HCl and extracted with ether to give β-carbethoxy-β-cyclohexenylpropionic acid **4a** (2.13 g) in 92% yield as an oil. Data for **4a**: bp 150–155 °C (0.5 mmHg); ν(C=O) 1733, 1708 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.63 (1H, s), 4.16 (2H, q, *J* 7.1 Hz), 3.38 (1H, dd, *J* 5.1 and 9.9 Hz), 2.97 (1H, dd, *J* 9.9 and 16.8 Hz), 2.50 (1H, dd, *J* 5.1 and 16.8 Hz), 1.52–2.09 (8H, m), 1.27 (3H, t, *J* 7.1 Hz).

One-pot preparation of γ,γ-pentamethyleneparaconic acid (5a)

A mixture of **1a** (1.0 g, 10.2 mmol), **2** (1.78 g, 10.2 mmol) and Bu^{t}OK (1.37 g, 12.3 mmol) was mixed and ground using a mortar and pestle for 10 min, followed by heating the reaction mixture at 80 °C in conc. HCl (10 ml) for 1 h. After cooling to room temperature, the crystals formed were isolated by filtration to give γ,γ-pentamethyleneparaconic acid **5a**[2] (colorless plates, 1.98 g) in 92% yield after recrystallization from MeOH–toluene (1:1). Data for **5a**: mp 185–186 °C; ν(C=O) 1734, 1717 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.69–2.78 (1H, m), 3.00–3.18 (2H, m), 1.25–1.85 (10H, m).

Solvent-free Stobbe condensation reaction of 6a and 2 in the presence of Bu^{t}OK at room temperature

To a mixture of **6a** (1.23 g, 10.2 mmol) and **2** (1.78 g, 10.2 mmol) was added powdered Bu^{t}OK (1.37 g, 12.3 mmol) in a mortar and well ground with pestle at room temperature for 10 min. The reaction was exposed to the air. The reaction mixture was neutralized with dil. HCl and then the crude crystals formed were isolated by filtration to give 2-(1-phenylethylidene)-succinic acid 1-ethylester **7a** (2.35 g) in 93% yield. Recrystallization of crude crystals from acetone gave pure (*Z*)-**7a**[4] (2.1 g, 83%). Data for (*Z*)-**7a**: mp 110–112 °C; ν(C=O) 1720, 1692 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.12–7.35 (5H, m), 3.86 (2H, q, *J* 7.2 Hz), 3.57 (2H, s), 2.17 (3H, s), 0.79 (3H, t, *J* 7.2 Hz). Distillation of the solvent from the mother liquor of (*Z*)-**7a** gave (*E*)-**7a** as a viscous oil (0.2 g, 8%). Data for (*E*)-**7a**; ν(C=O) 1720, 1692 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.12–7.35 (5H, m), 4.27 (2H, q, *J* 7.2 Hz), 3.24 (2H, s), 2.43 (3H, s), 1.31 (3H, t, *J* 7.2 Hz).

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