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A convenient synthesis of 2-methyl-3-oxoheptane-1,7-dicarboxylic esters and amides

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Abstract—A range of simple derivatives of 2-methyl-3-oxoheptane-1,7-dicarboxylic acid have been prepared by Birch reduction/methylation of 2,6-dimethoxybenzoic acid derivatives followed by solvolysis.

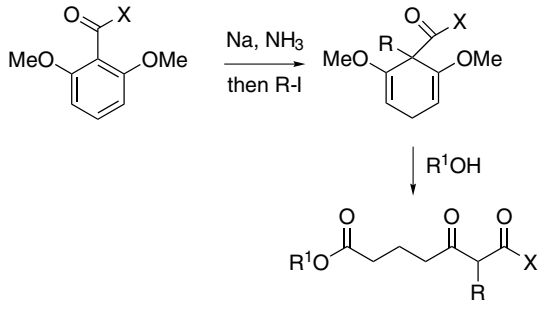
1. Introduction

Derivatives of 3-oxoheptane-1,7-dioic acid have been prepared a number of times, mostly using Claisen or dianion chemistry.[1] These compounds are of interest as synthetic intermediates,[2] and the corresponding amides have been shown to have activity as inhibitors of human dihydrorotate dehydrogenase.[3]

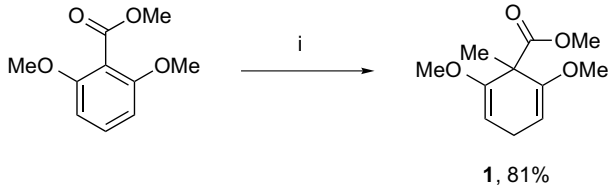
The formation of differentiated dicarbonyl compounds is of general synthetic interest, especially in the case of similar carbonyls such as the carboxylic acids in the present case.[4] We now report a convenient synthesis of the title compounds based on the hydrolytic and solvolytic ring-opening of Birch reduction products as shown in the general Scheme 1.

The Birch reduction/alkylation of benzoic acid derivatives, largely developed by Mander[5] and Schultz[6] and their respective co-workers, has been used numerous times over the last 30 years.[7]

In our hands, the reductive alkylation of methyl 2,6-dimethoxybenzoate initially proved problematic, and it was only when we first distilled the supposedly anhydrous liquid ammonia from sodium that we were able to isolate compound **1** in good yield (Scheme 2). The preparation of the corresponding amides by this method failed, although we were able to carry out normal Birch reductions to give **2** and **3** with no problems (Scheme 3). In the attempted reductive alkylations, variable amounts of the same compounds were formed.



Scheme 1.



Scheme 2. Reagents and conditions: (i) K, NH_3, THF, *t*-BuOH then MeI.

With ester **1** in hand, the simplest way to access the required amides was by reaction with the corresponding lithium amides. This worked well for the anilide **4** but was less effective for *n*-propylamide **5** (Scheme 4).

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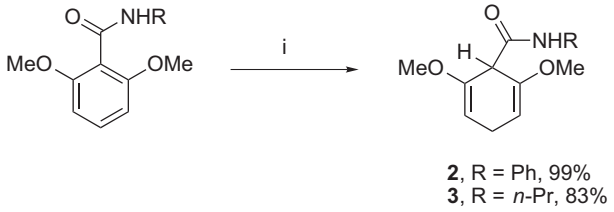
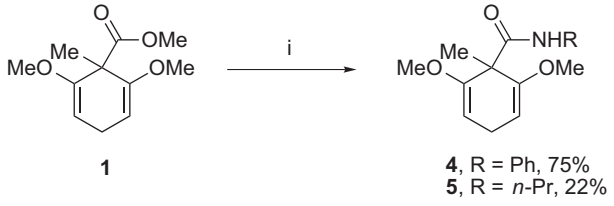


Scheme 3. Reagents and conditions: (i) K, NH_3, THF, *t*-BuOH then NH_4Cl.

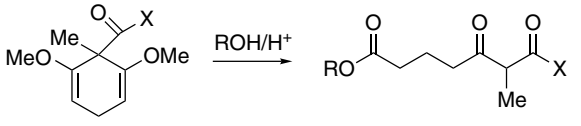


Scheme 4. Reagents and conditions: (i) RNH_2, *n*-BuLi, THF, 0 °C then **1**, 0–25 °C.

Nevertheless, we were able to prepare sufficient quantities of the amides to carry out hydrolysis studies.

Compounds **1**, **4** and **5** were subjected to solvolysis under a range of conditions. The results are summarised in Table 1. Stirring compounds **1**, **4** or **5** in THF with concentrated hydrochloric acid gave compounds **6a–c** in variable yields (entries 1–3). The lower yields in entries 2 and 5 are probably not representative. For example, compound **6b** was prepared in 80% yield by addition of a dichloromethane solution of boron tribromide to compound **4** in the same solvent. After 48 h the product was isolated by normal aqueous work-up. Reaction of the same substrates with methanol and ethanol were also straightforward (entries 4–9). In these cases the alcohol was used as solvent, again with the addition of a small amount of concentrated hydrochloric acid as

Table 1. Solvolysis reactions of compounds **1**, **4** and **5**

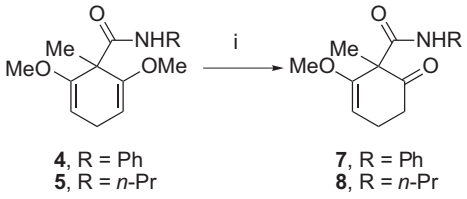


1, **4**, **5** **6a - 6i**

Entry	X	R	Product	Time (h)	Yield (%)[a]
1	OMe	H	**6a**	2	84
2	NHPh	H	**6b**	2	31 (80)[b]
3[b]	NH*n*-Pr	H	**6c**	3	83
4	OMe	Me	**6d**	6	98
5	NHPh	Me	**6e**	2	42
6	NH*n*-Pr	Me	**6f**	15	88
7	OMe	Et	**6g**	36	94
8	NHPh	Et	**6h**	5	92
9	NH*n*-Pr	Et	**6i**	15	92

[a] Refers to isolated yield. Most experiments were conducted only once, so these results are not optimised.

[b] Yield in parentheses refers to hydrolysis using BBr_3/H_2O.



Scheme 5. Reagents and conditions: (i) THF, H_2O, 2 M HCl, 2 h.

catalyst. Reactions were generally complete within 2 h, although for convenience the reaction could be left longer with no loss in isolated yield. In most cases the crude products were essentially pure, and satisfactory spectroscopic data were obtained directly.

Various modified protocols were investigated with the aim of forming more hindered esters, particularly *t*-butyl. These were unsuccessful, with the acids **6a–c** being obtained in these cases as sole products. Similarly, use of ammonium chloride failed to give the corresponding unsymmetrical amides. However, these reactions were only briefly investigated.

We considered the possibility that hydrolysis of compounds **1**, **4** and **5** might give rise to the cyclic 1,3-dicarbonyl compounds under suitably mild conditions. Although this proved not to be the case, we were able to accomplish the partial hydrolysis of compounds **4** and **5** by addition of dilute hydrochloric acid (2 M) to give compounds **7** and **8** in aqueous THF solution (Scheme 5). After stirring for 2 h, monitoring the disappearance of starting material by TLC analysis, the desired compounds were obtained in good yields (Scheme 5).

Typical experimental procedures and selected data are as follows.[8]

2. Methyl-7-anilino-6-methyl-5,7-dioxoheptanoate 6e

2,6-Dimethoxy-1-methyl-*N*-phenylcyclohexa-2,5-diene-1-carboxamide (0.1 g, 0.37 mmol) was dissolved in MeOH (3 mL). To this was added concentrated hydrochloric acid (0.5 mL). The flask contents were then stirred for 2 h. Following the addition of water (10 mL), the organic materials were extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (1:1 hexane/ether) gave the title compound (0.41 g, 42%) as a colourless solid, mp 62–64 °C (Found: C, 65.28; H, 7.22; N, 5.15%. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%.) ν_{max} (Nujol mull)/cm^{-1} 1728 and 1680; δ_H (400 MHz; d_6-DMSO) 8.32 (1H, br s, N*H*) 7.53 (2H, d, *J* 7.9, phenyl 2-*H* and 6-*H*), 7.33 (2H, apparent t, *J* 7.9, phenyl 3-*H* and 5-*H*), 7.12 (1H, t, *J* 7.4, phenyl 4-*H*), 3.66 (3H, s, OCH_3), 3.57 (1H, q, *J* 7.2, $HCCH_3$), 2.71 (2H, t, *J* 7.0, $OCCH_2$), 2.36 (2H, t, *J* 7.1, MeO_2CCH_2), 1.93 (2H, apparent quintet, *J* 7.1, $CH_2CH_2CH_2$) and 1.51 (3H, d, *J* 7.2, H_3C).

3. 2-Methoxy-1-methyl-6-oxo-*N*-phenylcyclohex-2-ene-1-carboxamide 7

2,6-Dimethoxy-1-methyl-*N*-phenylcyclohexa-2,5-diene-1-carboxamide (0.17 g, 0.62 mmol) was dissolved in THF (10 mL). Water (15 mL) was added followed by 2 M hydrochloric acid (3 mL). The reaction was allowed to stir for 2 h after which the reaction was seen to be complete by TLC analysis (Et_2O solvent system). Following the addition of saturated aqueous sodium bicarbonate solution, the product was extracted into ethyl acetate and the organic layer separated and dried over sodium sulfate. Following filtration the solvent was removed in vacuo. The product was recrystallised from 2:1 hexane/Et_2O to yield the pure title compound, (0.11 g, 68%) as a colourless solid, mp 90–92 °C. $\nu_{max.}$ (Nujol mull)/cm^{-1} 3380, 1731 and 1684; δ_H (400 MHz; $CDCl_3$) 8.00 (1H, br s, N-*H*), 7.47 (2H, d, *J* 7.7, phenyl 2-*H* and 6-*H*), 7.31 (2H, apparent t, *J* 8.0, phenyl 3-*H* and 5-*H*), 7.10 (1H, t, *J* 7.5, phenyl 4-*H*), 5.10 (1H, dd, J_1 5.2, J_2 3.2, C*H*), 3.71 (3H, s, CH_3O), 2.78 (1H, m, OCHC*H*) 2.52 (2H, m, $HCCH_2$), 2.36 (1H, m, OC*H*CH) and 1.59 (3H, s, CH_3).

In summary, we have developed a convenient approach to the title compounds by Birch reduction/alkylation of 2,6-dimethoxybenzoic acid derivatives followed by solvolysis. The approach appears to be reasonably general, although some limitations have been highlighted.

Acknowledgements

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8. All new compounds were characterised by a combination of proton and ^{13}C NMR spectroscopy, infrared spectroscopy and mass spectrometry.