Microwave Heating Effects Rapid and Selective Decarboalkoxylation of Mono-Alkylated Malonates and β-Ketoesters

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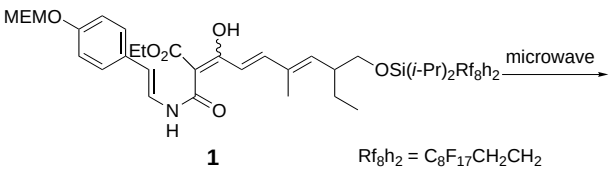
Received: November 21, 2002; Accepted: December 27, 2002

Abstract: Brief microwave irradiation of mono-alkylated malonates and β-ketoesters at 160–200 °C in wet DMF induces smooth and selective decarboalkoxylation. Observations suggest that this reaction occurs by nucleophilic attack of water at the ester carbonyl carbon (hydrolysis) followed by decarboxylation of the resulting acid. The process occurs despite the absence of traditional acid, base or nucleophile catalysts or reagents.

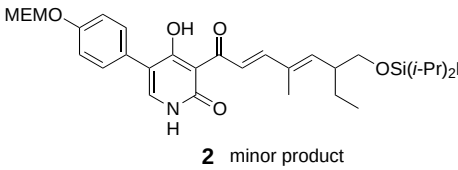
Keywords: acetoacetic ester synthesis; decarboalkoxylation; hydrolysis; malonic ester synthesis; microwave heating

The alkylation of malonate esters, β-ketoesters and related molecules followed by decarboalkoxylation is a proven strategy for regioselective alkylation adjacent to carbonyl groups.[1] Limitations in this process reside mainly in the decarboalkoxylation reaction. Classical methods call for exposure of substrates to strong acid,[2] strong base[3] or both, and hydrolysis and decarboxylation are often accomplished in two distinct steps. Direct decarboalkoxylations promoted by nucleophiles or metal salts (for example, the Krapcho reaction[4]) have replaced classical methods for many applications, but long reaction times at high temperatures are still needed. Recent reports of microwave-promoted[5] decarboxylations reduce reaction times but still employ acids, bases or metal salts to promote the reaction.[6] Here we report new conditions for decarboalkoxylation that are the essence of simplicity: decarboalkoxylation takes place upon microwave irradiation of a substrate in wet DMF with no added reagents or catalysts. The reaction is selective for mono-alkylated malonates and β-ketoesters.

The discovery of this microwave-induced decarboalkoxylation emanated from a failed experiment. We have previously reported that thermal cyclization of enamide **1** to pyridone **2** (Equation 1a) occurred in a modest 50% yield by heating in diphenyl ether at 250 °C (bath temperature) for 8 min.[7] There was little room to maneuver in optimizing the yield since shorter times or lower temperatures reduced the conversion while longer times or higher temperatures resulted in extensive decomposition.

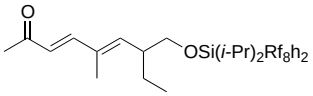


1 $Rf_8h_2 = C_8F_{17}CH_2CH_2$

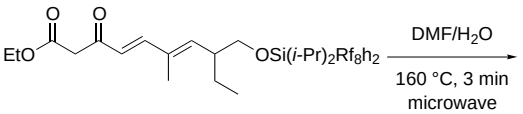


(1a)

2 minor product

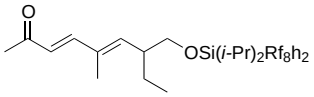


3a major product



4a $Rf_8h_2 = C_8F_{17}CH_2CH_2$

(1b)



3a

In an attempt to improve this transformation, we irradiated **1** in a microwave reactor under several different conditions varying time, temperature and solvent. Most reactions were not especially clean and pyridone **2** was a

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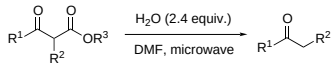
minor product at best. However, under several conditions, a new product was formed and this was readily isolated and identified as ketone **3a**. Speculating that this ketone might arise by retro-Claisen reaction of **1** to give ketoester **4a** followed by decarboalkoxylation, we heated authentic **4a** in a microwave reactor and indeed found that **3** was formed (Equation 1b). After a brief optimization of solvent, temperature and time, we found that microwave heating of **4a** in a sealed tube in wet DMF at 160 °C for 3 min cleanly provided ketone **3a**, which was isolated in 89% yield after flash chromatography.

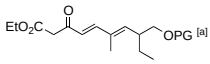
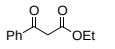
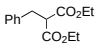
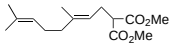
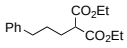
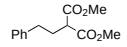
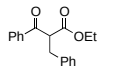
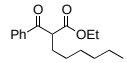
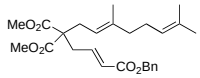
The generality of the procedure was tested by microwaving a variety of malonates and β-ketoesters **4b** – **i** in wet DMF at temperatures varying from 160 to 200 °C for 3 – 30 min. The results of this series of experiments are summarized in Table 1. The indicated yields of **3a** – **h** are after flash chromatographic isolation, but in most cases the crude product after simple aqueous work-up to remove the DMF was sufficiently clean (> 90% by GC analysis) for further use. The reaction showed good generality for unsubstituted and monosubstituted malonates and ketoesters. However, the time and temperature depend significantly on the substitution pattern. The unalkylated ketoester **4b** in entry 2 suffers decarboalkoxylation over 3 min at 160 °C while its monoalkylated derivatives **4g** and **4h** (entries 7 and 8) require 20 min at 200 °C. A simple control experiment showed the importance of microwave heating. When a mixture of **4c** in wet DMF was heated at 160 °C for 25 min in an oil bath, only 5% conversion to ketoester **3c** was observed by GC. Contrast this to the microwave experiment (entry 3), where complete conversion was observed in 20 min.

These reaction conditions are not effective for dialkylated ketoesters and malonates. For example, heating of **4i** (entry 9) for 20 min at 160 °C returned mostly starting material along with some decomposition products. Under comparable conditions, monoalkylated malonates **4c** and **4d** (entries 3 and 4) gave clean products. As these results imply, it is indeed possible to conduct a selective decarboalkoxylation of a monoalkylated malonate in the presence of a dialkylated malonate.[8] For example, microwaving a 1/1 mixture of **4e** and its dialkylated analogue $\{[Ph(CH_2)_3]_2C(CO_2Et)_2\}$ at 180 °C for 30 min resulted in 94% conversion (GC) of monalkylated **4e** to **3e** while the dialkylated precursor was largely unchanged.

Scheme 1 shows the three mechanistic pathways that we have considered for this transformation:[9] ester hydrolysis by nucleophilic attack of water on the carboxy carbon of the ester, ester dealkylation by nucleophilic attack of water on the alcohol carbon of the ester, and alcohol elimination to form an acylketene followed by nucleophilic attack of water. In both the hydrolysis and dealkylation mechanisms, activation by enol formation and intramolecular hydrogen bonding[10] is proposed because of the difference in reactivity between mono- and dialkylated substrates. However, direct (or water-promoted) attack of water on the keto form cannot be ruled out. The ketene mechanism[11] is unusual but was considered because of the low reactivity of the dialkylated substrates (these cannot form ketenes). In all three pathways, thermal decarboxylation of the intermediate β-carbonyl acid completes the transformation.

Table 1. Microwave-promoted dealkoxylcarbonylation in wet DMF.

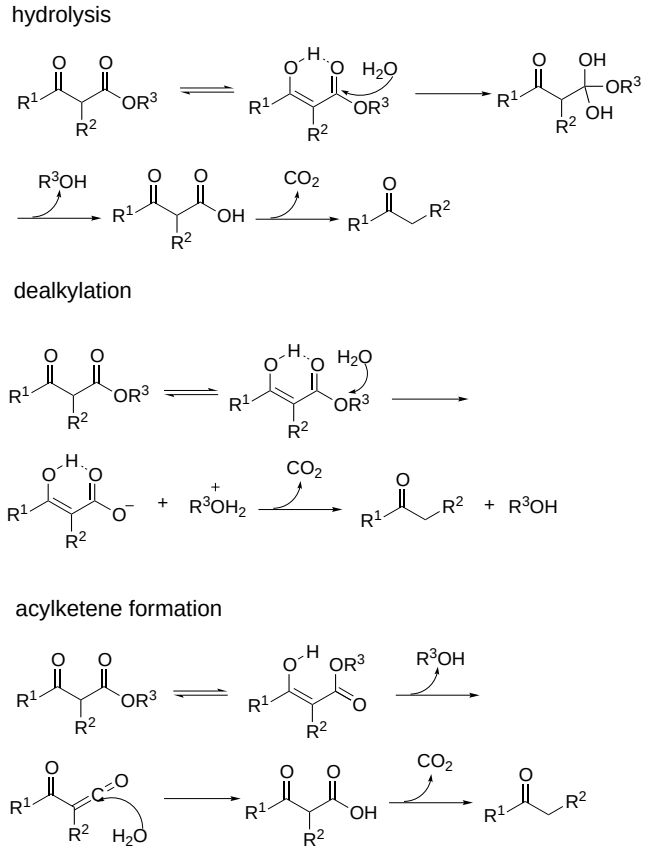


Entry	Substrate		Temperature [°C]	Time [min]	Product	Yield [%]
1		**4a**	160	3	**3a**	89%
2		**4b**	160	3	**3b**	82%
3		**4c**	160	20	**3c**	92%
4		**4d**	160	20	**3d**	84%
5		**4e**	180	30	**3e**	96%
6		**4f**	180	30	**3f**	95%
7		**4g**	200	20	**3g**	91%
8		**4h**	200	20	**3h**	84%
9		**4i**	160	20	**4i** + decomposition	—

[a] PG = Si(*i*-Pr)$_2$($CH_2CH_2C_8F_{17}$).

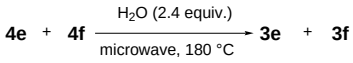
Two lines of evidence suggest that the ketene pathway is not operating. First, water is required for substrate conversion; **4c** was recovered largely unchanged after heating in rigorously dry DMF under the conditions in Table 1. Second, heating of **4c** in dry DMF in the presence of dihydropyran or cyclohexanone to trap intermediate ketenes again returned starting material. Both experiments also gave traces of decarboalkoxylated product **3c**, which we presume arose by reaction with adventitious water.

To differentiate between the hydrolysis and dealkylation mechanisms, we conducted a competition experiment on a mixture of diethyl malonate **4e** and dimethyl malonate **4f**. If hydrolysis is occurring, then these two substrates will be consumed at similar rates. However, the ethyl ester **4e** should be considerably less reactive than the methyl ester **4f** if dealkylation is the path. We mixed **4e** and **4f** in a 1/1 ratio in wet DMF and microwaved the mixture at 180 °C. The conversion of both precursors was followed by GC as a function of time, and the results are shown in Table 2. The dimethyl



Scheme 1.

Table 2. Effects of the alkoxy substituent on the rate of dealkoxylcarbonylation reaction.



Time [min] at 180 °C	Conversion [%] 4e	4f	4f/4e
0[a]	25.9	26.8	1.03
2	27.8	31.5	1.13
4	34.9	44.8	1.28
20	68.5	75.6	1.11

[a] The time (about 45 seconds) for the mixture to reach 180 °C is not counted. However, entry 1 shows that significant conversion occurs during this period.

malonate **4f** is only marginally (about 1.1 times) more reactive than the diethyl malonate **4e**. The diesters were consumed not only by decarboalkoxylation but also by transesterificaton to make the mixed diester (not shown). These observations are consistent with the hydrolysis mechanism, not the dealkylation mechanism.

In summary, malonic esters and β-ketoesters are decarboxylated by brief microwave heating in wet DMF in the absence of traditional reagents or catalysts. The reaction occurs readily with monoalkylated derivatives but not with dialkylated derivatives. Several lines of evidence suggest that standard hydrolysis of the substrate (possibly in its enol form) by water is followed by thermal decarboxylation of the resulting acid. These reactions are convenient and atom economical, and the mild conditions suggest the potential for broad scope.

Experimental Section

Typical Experimental Procedure

Diethyl benzylmalonate **4c** (25.0 mg, 0.1 mmol), H_2O (4.3 mg, 0.24 mmol) and DMF (2 mL) were heated in a sealed tube at 160 °C with stirring for 20 min in a CEM Discover microwave reactor. The reaction mixture was then cooled to room temperature and diluted with ether (20 mL) and water (5 mL). The layers were separated and the ether layer was further washed with H_2O (2 mL × 3), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexanes/Et_2O = 5:1) on silica gel to afford **3c** as a colorless oil; yield: 16.4 mg (92%).

Acknowledgements

*We thank the National Institutes of Health for funding this work. We are especially grateful to the CEM Corporation for providing the microwave reactor. We thank Mr. Jonathan Tripp for providing compounds **4d** and **4i**.*

References and Notes

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