Microwave-Assisted Aqueous Krapcho Decarboxylation

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Abstract: The Krapcho decarboxylation of alkyl malonate derivatives has been adapted to aqueous microwave conditions. Various salt additives were examined, and both the cation and the anion impacted the facility of the reaction. A strong correlation was found between the pKa of the anion and the reaction rate, suggesting a straightforward base-catalyzed hydrolysis. Lithium sulfate gave the best results, obviating the need for DMSO co-solvent.

Key words: cleavage, esters, hydrolysis, lithium, solvent effects

The Krapcho decarboxylation is a convenient protocol for the removal of an ester moiety from an electron-deficient carbon under mild conditions. First reported in 1967 as the cyanide-mediated decarbethoxylation of monoalkyl malonate derivatives (e.g., $1a \rightarrow 2a$),¹ the Krapcho protocol was later modified to a system of wet DMSO without the need for cyanide² (Scheme 1). More than 40 years after the first example, the Krapcho conditions still have currency in the literature.³



Scheme 1 Original Krapcho conditions

Our interest in this reaction arose from the nexus of two research projects, one involving methodology for the synthesis of 2,4-disubstituted furans⁴ requiring convenient access to β -dicarbonyls, and the other centering about our ongoing interest in adapting workhorse synthetic methods to sealed-tube microwave conditions.⁵

Previous investigators have carried out the Krapcho decarboxylation using microwave acceleration, as seen in Kerr's synthesis of mersicarpine⁶ and Jung's enantiospecific formal total synthesis of (+)-Fawcettimine.⁷ Both routes adapt conditions previously reported by Curran involving wet DMF as a solvent.⁸

For our particular synthetic application, we required access to β -diketones in which one substituent was a methyl

SYNLETT 2013, 24, 1391–1394 Advanced online publication: 08.05.2013 DOI: 10.1055/s-0033-1338701; Art ID: ST-2013-R0260-L © Georg Thieme Verlag Stuttgart · New York group (e.g., 4). To that end, Krückert had reported a straightforward procedure that involved treating an acyl chloride with ethyl acetoacetate in the presence of magnesium chloride to produce a diketoester (e.g., 3), which was decarbethoxylated by refluxing for 12 hours with sodium chloride in aqueous DMSO.⁹

In adapting Krückert's conditions to a sealed-tube microwave reactor, we found that the use of DMSO could be avoided, and that very good isolated yields could be achieved by heating in water containing 1.2 equivalents of sodium chloride for five minutes at 185 °C (Scheme 2). Remarkably, good yields could also be obtained by brief heating in water alone.



Scheme 2 Decarboxylation of a diactivated system

Intrigued by the facility of this reaction, we sought to expand its scope by turning our attention to the much less reactive malonate derivatives, with an eye toward parsing

Table 1 Cation Effects

Ph OEt	salt (1 equiv) H ₂ O 210 °C 15 min	Ph
1b		2b

Entry	Salt	Conversion (%) ^a
1	none	8
2	NaCl	17
3	LiCl	69
4	KCl	7
5	MgCl ₂ ^b	7
6	NH₄Cl	17

^a Determined by HPLC.

^b Amount of MgCl₂ used was 0.5 equiv (1 equiv chloride).

out the factors impacting the efficiency of the reaction. We began with a survey of common cations (Table 1), which showed lithium to be the most effective cation by far. One rationale for this outcome could be the differential coordination of the cation with the carbonyl oxygen, which in turn would be dependent upon hard–soft acid–base (HSAB) parameters. Indeed, the facility of the decarboxylation using alkali metal cations correlates strongly to their absolute hardness (η) values¹⁰ (Figure 1).



Figure 1 Conversion as a function of cation absolute hardness

In light of this trend, it is somewhat surprising that magnesium cation is so ineffective in catalyzing the reaction, since its hardness value is quite high. This anomaly might be explained by the tendency of magnesium cation to form a stabilized enolate chelate, which would be resistant to hydrolysis (Scheme 3). For example, Rathke and Cowan¹¹ demonstrated through NMR studies that diethyl malonate was not significantly deprotonated by triethyl-amine ($pK_a = 10$) in acetonitrile solution, an unsurprising result given the substrate has a pK_a of 14. However, in the presence of one equivalent of magnesium chloride, even pyridine ($pK_a = 5$) effected practically quantitative deprotonation.



Scheme 3 Complexation of malonate derivatives with Mg²⁺

We next turned our attention to the effect of the anion (Table 2). In examining an array of common sodium salts, we found that not only were yields widely divergent, but so too was the propensity of the initial ester (**2b**) to undergo further hydrolysis to the corresponding acid (**5**). The most effective sodium salts were sodium fluoride (entry 2) and sodium sulfate (entry 12). A synergistic effect was obTable 2 Anion Effects

1b	salt (1 equiv) H ₂ O, 210 °C 15 min	OEt + Ph	ОН
		2b	5
Entry	Salt	Conv. (%) ^a	Ratio 2b/5
1	none	8	6:1
2	NaF	89	15:1
3	NaCl	17	5:1
4	NaBr	16	5:1
5	NaI	26	5:1
6	NaOAc	91	9:1
7	NaNO ₃	41	8:1
8	NaH ₂ PO ₄	68	11:1
9	Na ₂ HPO ₄	95	2:1
10	$Na_2C_2O_4$	86	12:1
11	NaHSO ₄	25	1:1
12	Na_2SO_4	75	16:1
13	Li ₂ SO ₄	86	17:1

^a Determined by HPLC.

served when a good anion was combined with a harder cation, such as lithium (entry 13).

Interesting mechanistic insight is revealed when the conversions are plotted against the pK_a values of the respective anions (Figure 2). In short, the facility of the Krapcho decarboxylation correlates very strongly to the basicity of the anion. Thus, it would appear that one important role of the salt additive is to modulate the pH of the reaction medium, at least under the conditions of this study.



Figure 2 Conversion as a function of anion pK_a

Finally, the effects of reaction time, salt equivalency, and co-solvent were studied (Table 3). Increasing the salt concentration enhances conversion (entry 3), but with a slight negative impact on hydrolysis selectivity. Longer reaction times (entry 4) also lead to higher conversions, and the same trend with increased salt concentration is observed (entry 5). Adding DMSO as a co-solvent (entries 6-8) makes the decarboxylation both more rapid and more selective, especially at very high DMSO-water ratios. However, DMSO alone is insufficient, as removing the salt, even in a 9:1 DMSO-water medium, hobbles the reaction (entry 9).

Table 3 Effects of Other Parameters

1b Na ₂ 210	SO₄ °C Ph		+ Ph	ОН	
		2b		5	
Entry	Na ₂ SO ₄ (equiv)	Time (min)	DMSO (vol%)	Conv. (%) ^a	Ratio 2b/5
1	0	15	0	8	6:1
2	1	15	0	75	16:1
3	2	15	0	87	13:1
4	1	30	0	94	14:1
5	2	30	0	97	11:1
6	1	15	10	80 ^b	20:1
7	1	15	50	88 ^b	20:1
8	1	15	90	90 ^b	90:1
9	0	15	90	32 ^b	7:1

^a Unless otherwise denoted, determined by HPLC.

^b Determined by NMR.

In sum, these data suggest a mechanism for the Krapcho decarboxylation that proceeds through a BAC2-type mechanism (Scheme 4). Thus, initial coordination of the ester moiety to the cation activates the carbonyl toward attack of hydroxide, which is generated by the mild basicity of the anion present. Once the half-acid is formed, thermal elimination of carbon dioxide provides the monoester.

To demonstrate the generality of the procedure, a series of monoalkyl malonate derivatives was subjected to optimized conditions (Table 4). Lithium sulfate was selected as the salt additive, as it combines the best chelating properties of the cation and an optimum pH profile of the anion. We also preferred to avoid a DMSO co-solvent to simplify workup and to achieve a greener solvent system. Isolated yields are generally good, with the exception of the *tert*-butyldimethylsilyl derivative (entry 7), which suffers significant deprotection under the conditions.

In summary, we have developed a convenient and rapid microwave-accelerated Krapcho decarboxylation of



Scheme 4 Mechanism of the Krapcho decarboxylation

Table 4 Optimized Conditions



^a Isolated yield.

^b Deprotected alcohol was obtained in 38% yield.

malonate derivatives in an entirely aqueous medium using lithium sulfate as a catalyst.¹² This methodology realizes a useful confluence of green reaction solvent and short conversion times, and is therefore advantageous for highthroughput synthesis techniques.

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- (12) **Experimental Procedure**: To a 2–5 mL microwave vial were added the diethyl alkyl malonate (1.5 mmol), lithium sulfate (166 mg, 1.5 mmol), and deionized H_2O (3.0 mL). The vial was sealed and heated at 210 °C for 30 min (see ref. 13) after which the contents were poured into sat. NaHCO₃ (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic phases were washed sequentially with NaHCO₃ (15 mL) and brine (15 mL), dried over Na₂SO₄, and concentrated in vacuo to yield a crude oil, which was purified by column chromatography.
- (13) Since carbon dioxide is liberated during the reaction, 3–4 atm of residual pressure remains after the vial is cooled. The manufacturer's instructions for releasing this pressure should be carefully followed before opening the vial for aqueous workup.

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