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Electrochemical Oxidative Decarboxylation of Malonic Acid Derivatives: A Method for the Synthesis of Ketals and Ketones

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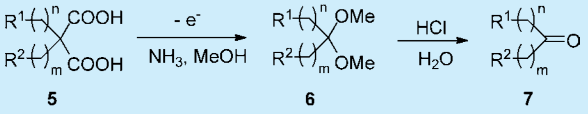
Ⓢ *Supporting Information*



ABSTRACT: A novel electrochemical oxidative decarboxylation of disubstituted malonic acids leading to dimethoxy ketals is described. In the presence of NH_3, a wide range of disubstituted malonic acids was transformed into the corresponding ketals in good to excellent yields under electrochemical conditions. When the crude reaction mixture, obtained after electrolysis, was directly treated with 1 M aq HCl, the initially generated ketals were smoothly transformed into the corresponding ketones in a single vessel operation.

Ketones are among the most versatile and valuable functional groups in organic synthesis.[1] Not only are they extensively found in a wide range of natural products, man-made compounds, and fine chemicals, but they are also key chemical partners in numerous important synthetic transformations such as the aldol reaction.[2] Moreover, ketones can be further converted into a plethora of other useful functionalities, such as alcohols, amines, amides, alkenes, and esters, to cite but a few.[3]

Despite their synthetic importance, access to ketones, especially unsymmetrical ones, usually requires multistep sequences. Most popular among these are (1) the addition of an organometallic reagent to an aldehyde followed by a subsequent oxidation, (2) the α-alkylation of a pre-existing ketone, and (3) the double alkylation of a carbonyl dianion equivalent, such as a dithiane.[4] More recently, the sequential nucleophilic addition of organolithium or magnesium species to electrophilic carbonyl equivalents has received sustained attention.[5]

In this context, we wish to report on a novel methodology for the synthesis of symmetrical and unsymmetrical ketones **1** and ketals **3** from the corresponding malonic acids **2**. In our approach, disubstituted malonic acids **2** are considered as 1,1-dicationic synthetic equivalents **4** (Figure 1).

Malonic acid derivatives have been used extensively in organic synthesis, and conditions have been developed for the selective mono- and dialkylation of malonic esters. These alkylated products have been subsequently employed for the preparation of a wide range of substituted acetic acids.[6] Condensations of malonic acids form the basis of several well-known processes, such as the Knoevenagel reaction[7] and the barbituric acid synthesis.[8]

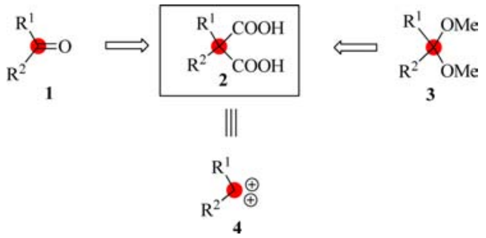


Figure 1. Malonic acids as ketones and ketals equivalents.

While numerous transformations of disubstituted malonic acid derivatives have been reported, their conversion into the corresponding ketones by double-oxidative decarboxylation has been little investigated so far, and long synthetic sequences are typically required. For example, Meinwald and co-workers reported a five-step procedure to prepare *trans*-bicyclo[3.2.0]-heptan-3-one from the corresponding malonic acid derivative.[9]

A major breakthrough was accomplished by Tufariello,[10] who showed that treatment of disubstituted malonic acids **2** with lead tetraacetate afforded the corresponding 1,1-diacetates in moderate to good yields. Basic or acidic hydrolysis then generated the expected ketones **1** (Scheme 1, eq 1). However, the conditions are quite harsh, and the reaction appears to be limited to cases in which both substituents are relatively simple. Moreover, an excess of the fairly toxic $Pb(OAc)_4$ is required for the double decarboxylation to reach completion.

In 1979, a particularly interesting, though essentially unnoticed, contribution was reported by the group of Nokami,[11] who disclosed that passing an electric current through a basic aqueous solution containing a disubstituted malonic acid salt led to the corresponding ketone **1** (Scheme 1, eq 2). Unfortunately, only three examples using simple substrates were reported, the reaction conditions were rather severe, and moderate yields were obtained.

Nevertheless, despite its shortcomings, this seminal contribution attracted our interest, and we decided to revisit it in order to delineate its scope and limitations. In this paper, we report some of our results concerning the establishment of an

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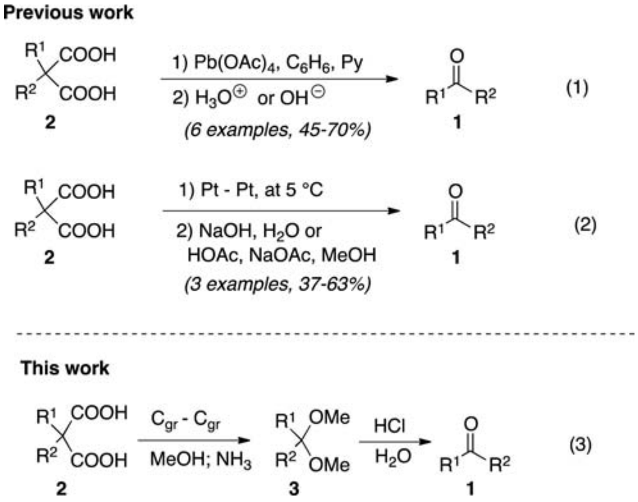
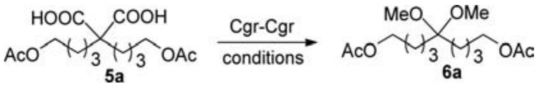
Scheme 1. Decarboxylation of disubstituted malonic acid derivatives



efficient and chemoselective electrochemical oxidative methodology for the conversion of malonic acids **2** into ketals **3** and ketones **1** under mild conditions and in good to excellent yields (Scheme 1, eq 3).

Our investigation began with the study of the electrochemical oxidative decarboxylation of the disubstituted malonic acid **5a**. Compound **5a** can be easily prepared by the double alkylation of di-*tert*-butyl malonate with 1-iodo-4-acetoxybutane followed by the removal of the two *tert*-butyl groups in the presence of TFA. With compound **5a** in hand, various reaction conditions were screened. Some salient results are compiled in Table 1.

Table 1. Optimization of the Reaction Conditions[a]



entry	current (mA)	base (equiv)	time (h)	yield[b] (%)
1	30	NaOMe in MeOH (2.2)	6.0	31
2	30	NaOMe in MeOH (1.1)	4.0	74
3	30	NaOMe in MeOH (0.1)	5.5	71
4	30	NH_3 in MeOH (42)	4.5	60
5	30	NH_3 in MeOH (42)	7.0	77
6	60	NH_3 in MeOH (42)	3.0	69
7	90	NH_3 in MeOH (42)	3.0	72
8[c]	30	none (0)	6.5	69
9	30	NH_3 in MeOH (2.1)	8.0	76
10	60	NH_3 in MeOH (2.1)	4.5	80
11	30	NH_3 in MeOH (0.2)	8.0	0

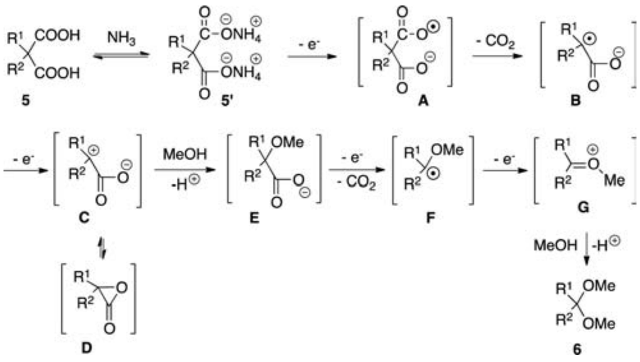
[a] All reactions were carried out using 0.5 mmol of disubstituted malonic acid **5a** as starting material. The surface of the electrodes was always 3 cm^2. [b] Isolated yield. [c] The corresponding amnonium salt was used.

Based upon our previous experience on the Kolbe-type reactions of monocarboxylic acids,[12] the electrolysis of malonic acid **5a** was initially performed in the presence of sodium methoxide (2.2 equiv) in MeOH. Since a double Hofer−Moest[13] process was to take place, carbon graphite (Cgr) electrodes were thought to be the most appropriate (Table 1, entry 1). Disappointingly, despite full conversion of **5a**, only poor yields of the desired ketal **6a** were obtained. Lowering the amount of NaOMe by half significantly improved the yield (Table 1, entry 2). Finally, when 0.1 equiv of sodium methoxide was used, the desired product could be isolated in 71% yield (Table 1, entry 3). While this protocol gave us ketal **6a** in good yield, alternative conditions employing milder bases, and hence more tolerant toward other functionalities and protecting groups, were also investigated.

Thus, the oxidative decarboxylation of **5a** was carried out in the presence of excess ammonia (7.0 M in MeOH) under otherwise similar conditions. Much to our delight, the desired ketal **6a** could be obtained in 60% yield after 4.5 h (Table 1, entry 4) and up to 77% yield after 7 h (Table 1, entry 5). Increasing the current density from 30 to 90 mA reduced significantly the reaction time without affecting the yield (Table 1, entries 6 and 7). Though these results looked promising, complete consumption of the starting material was never observed.

In order to better understand the influence of ammonia in this process, the corresponding bis-ammonium salt **5a′** (Scheme 2) was independently prepared[14] and submitted to the electrochemical oxidation in pure MeOH. Gratifyingly, complete conversion ensued and the ketal product **6a** could be isolated in 69% yield (Table 1, entry 8). This result strongly suggested that a large excess of ammonia had a negative impact on the reaction. In order to simplify the protocol and avoid the independent generation of the malonate bis-ammonium salt, the electrolysis was repeated after addition of malonic acid **5a** to 2.1 equiv of NH_3 in MeOH. Using a current density of 10 mA/cm^2, substrate **5a** disappeared within 8 h and the ketal product **6a** was obtained in 76% yield (Table 1, entry 9). Increasing the current density to 20 mA/cm^2 led to complete conversion of **6a** within 4.5 h, and ketal **6a** could be isolated in 80% yield (Table 1, entry 10). Finally, attempts to use catalytic amounts of ammonia proved to be unsuccessful as no conversion was observed (Table 1, entry 11).[15]

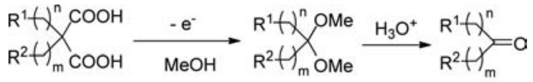
Scheme 2. Proposed Reaction Mechanism



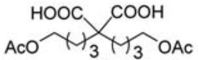
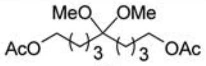
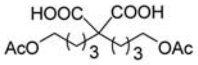
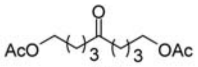
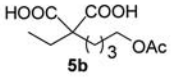
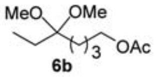
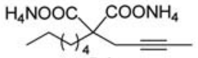
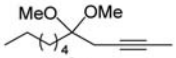
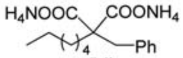
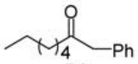
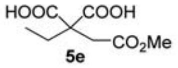
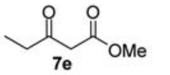
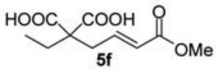
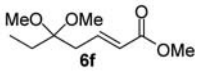
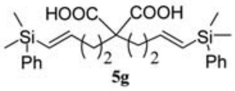
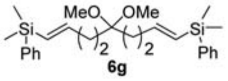
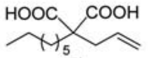
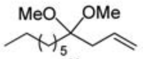
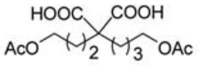
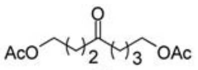
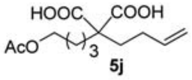
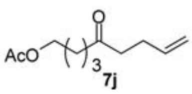
Careful optimization thus provided us with two sets of conditions appropriate for the transformation of malonic acid **5a** into the corresponding ketal **6a** in good to excellent yield (Table 1, entries 3 and 10). In order to evaluate the scope and limitations of this oxidative process, we selected the most convenient reaction conditions, i.e., 2.1 equiv of NH_3 in MeOH, MeOH as the solvent, and 20 mA/cm^2 current density, at room temperature, for 4.5 to 5 h (Faradaic efficiency = 5.03).

Some of our results are summarized in Table 2. As can be seen, various symmetrical and unsymmetrical alkyl-substituted ketals could be obtained in good yields by the electrochemical oxidative decarboxylation of the corresponding disubstituted

Table 2. Scope of the Reaction[a]



5 6 7

entry	starting material	product	yield[b] (%)
1	 5a	 6a	80
2	 5a	 7a	78
3	 5b	 6b	85
4	 5c'	 6c	78
5	 5d'	 7d	50
6	 5e	 7e	75
7	 5f	 6f	82
8	 5g	 6g	59
9	 5h	 6h	56
10	 5i	 7i	82
11	 5j	 7j	72

[a] All reactions were carried out using 0.5 mmol of starting material with 2.1 equiv of NH_3 (7.0 M in MeOH) in MeOH at room temperature for 4–4.5 h. [b] Isolated yield (Faradaic efficiency = 5.03).

malonic acids.[16] The functional group tolerance of this method proved to be quite broad. Indeed, the electrolysis can be successfully accomplished in the presence of esters (Table 2, entries 1–3, 6, 7, and 10), alkenes (Table 2, entries 9 and 11), conjugate alkenes (Table 2, entry 7), vinylsilanes (Table 2, entry 8), alkynes (Table 2, entry 4), and aromatic group (Table 2, entry 5). In all these cases, the corresponding ketal products could be obtained in good to excellent yields. It is noteworthy that the electron-rich vinylsilane **5g**, relatively prone toward oxidation, underwent side reactions resulting in lower yields of **6g**. Interestingly, if the crude electrolysis mixture was directly treated, in the same reaction vessel, with 1 M aq HCl, the corresponding ketones **7** could be isolated in good yields (Table 2, entries 2, 5, 6, 10, and 11). Noteworthy among these is the preparation of β-keto ester **7e** (Table 2, entry 6), which offers an alternative synthetic route toward these useful building blocks.

Based upon our previous work on radical generation under electrolytic conditions,[17] a plausible reaction mechanism can be proposed (Scheme 2). At the onset, NH_3 reacts with the malonic acid **5** to form the corresponding ammonium carboxylate **5′**. Loss of an electron from **5′** then produces the unstable radical intermediate **A**. Elimination of CO_2 ensues, leading to the carboxy-stabilized radical **B**. This electron-deficient species is oxidized further, in what is most probably the rate-determining step of the sequence, generating as a transient intermediate the zwitterionic species **C**,[18] which can be captured in an intramolecular manner by the proximal carboxylate function, leading to the α-lactone **D**. Reversible ring opening of lactone **D** in the presence of MeOH delivers the α-methoxy-substituted carboxylic acid derivative **E**.

Carboxylic acids bearing an electron-donating substituent at the α-position are particularly prone to undergo Hofer–Moest reactions.[19] It is therefore not surprising that **E** experienced swift loss of an electron, followed by the release of CO_2, generating radical **F**, which is rapidly oxidized to the corresponding oxonium cation **G**. Addition of MeOH to **G** ultimately delivers the desired ketal product **6**.

In summary, we have developed a simple, efficient, and convenient methodology for the synthesis of ketals and ketones by the electrochemical oxidative decarboxylation of disubstituted malonic acid ammonium salts. Advantages of our approach include the use of simple, cheap, and readily available malonic acid derivatives as substrates, environmentally friendly electro-organic conditions, mild reaction protocol, and excellent tolerance toward a large range of functional groups. We believe that our approach might open new vistas for the construction of a wide variety of symmetrical and unsymmetrical ketals and ketones bearing various substitution patterns. The application of our method to the synthesis of more complex molecules, including the total synthesis of natural products, is currently under investigation in our laboratories, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02084.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(14) The salt was prepared by dissolving the malonic acid **5a** in methanol containing excess ammonia, followed by removal of the solvent and amine and washing the solid with diethyl ether (see the Supporting Information).

(15) Essentially no current went through this solution, indicating that the amount of ions was too low for the current to pass.

(16) Compounds **5a−j** were assembled by sequential alkylation of di-*tert*-butyl malonate or dimethyl malonate. The *tert*-butyl groups were selected in order to offer orthogonal protection and enable chemoselective deprotection when required.

(17) (a) Lam, K.; Markó, I. E. *Synlett* **2012**, *23*, 1235−1239. (b) Lam, K.; Markó, I. E. *Org. Lett.* **2011**, *13*, 406−409. (c) Lam, K.; Markó, I. E. *Tetrahedron* **2009**, *65*, 10930−10940. (d) Lam, K.; Markó, I. E. *Org. Lett.* **2009**, *11*, 2752−2755. (e) Lam, K.; Markó, I. E. *Chem. Commun.* **2009**, 95−97. (f) Bastug, G.; Eviolitte, C.; Markó, I. E. *Org. Lett.* **2012**, *14*, 3502−3505.

(18) Support in favor of the passage from **D** to **C** and subsequent capture of **C** has been provided in the literature: (a) Adam, W.; Rucktaeschel, R. *J. Am. Chem. Soc.* **1971**, *93*, 557−559. (b) Crandall, J. K.; Sojka, S. A.; Komin, J. B. *J. Org. Chem.* **1974**, *39*, 2172−2175. We are grateful to a reviewer for providing us with these highly valuable references. It is also conceivable that the zwitterionic species **C** may not be formed initially under these conditions. Indeed, removal of the single electron of radical **B** might be assisted by the neighboring carboxylate function, and a direct collapse of **B** to the α-lactone **D** is a possible pathway. Ring opening of **D** to **C** then ensues.

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