ORGANIC LETTERS

2011
Vol. 13, No. 9
2322–2325

Mild Decarboxylative Activation of Malonic Acid Derivatives by 1,1′-Carbonyldiimidazole

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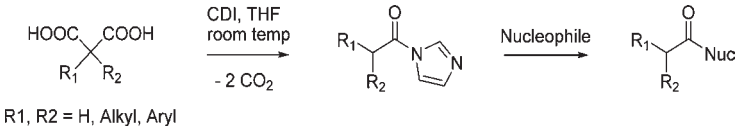
Received March 3, 2011

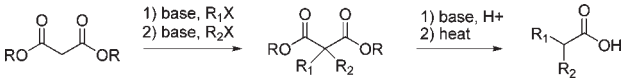
ABSTRACT



Malonic acid derivatives undergo unusually mild decarboxylation when treated with *N,N′*-carbonyldiimidazole (CDI) at room temperature to generate the carbonyl imidazole moiety in high yield, which can be reacted further with a variety of nucleophiles in an efficient one-pot process.

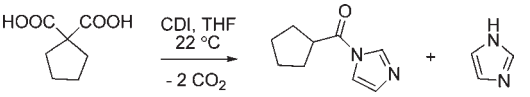
The synthesis of carboxylic acid derivatives via malonic ester alkylation, hydrolysis, and subsequent decarboxylation is a well established method for carbon−carbon bond formation (Scheme 1).[1] The decarboxylation step is usually performed under harsh thermal conditions (up to 200 °C) using conventional[2] or microwave[3] heating. A milder copper catalyzed decarboxylation of malonic acid derivatives was reported to proceed in refluxing acetonitrile, but it was later established that copper had no actual impact on the rate of carbon dioxide extrusion.[4] In addition to the thermal methods, decarboxylase enzymes can also be used for specific substrates at room temperature.[5]

Scheme 1. Conversion of Malonic Ester to Carboxylic Acids



During our investigation of cost-effective synthetic methods for the preparation of cyclopentanecarboxylic acid, we observed that the treatment of cyclopentane-1,1-dicarboxylic acid with 1 equivalent of 1-1′-carbonyldiimidazole at room temperature resulted in the clean and quantitative formation to the monocarbonylimidazole within 30 min (Scheme 2),[6] implying that the decarboxylation step was proceeding rapidly under *unusually mild conditions*. The carbonyl imidazole prepared can then be treated with a basic aqueous solution followed by an acidic workup to generate the carboxylic acid, or with a variety of nucleophiles, taking advantage of the direct activation of the carbonyl position. We report herein our synthetic studies of this reaction and its application toward a variety of malonic acid derivatives.[7]

Scheme 2. Cyclopentane Carbonyl Imidazole Formation



(1) Carey, F. A., Sunberg, R. J. In *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; pp 12−13 and references cited therein.

(2) (a) Oniciu, D. C.; Dasseux, J. L. *J. Med. Chem.* **2006**, *49*, 334. (b) Chow, H.; Ng, K. *Org. Lett.* **2006**, *8*, 471. (c) Brace, N. O. *J. Fluorine Chem.* **2005**, *126*, 7. (d) Wu, Z.; Minhas, G. S. *J. Med. Chem.* **2004**, *47*, 3281. (e) Dahan, A.; Portnoy, M. *J. Org. Chem.* **2001**, *66*, 6484.

(3) (a) Zara, C. L.; Jin, T. *Synth. Commun.* **2000**, *30*, 2099. (b) Hubbs, J. L. U.S. Patent 7 834 034, 2006.

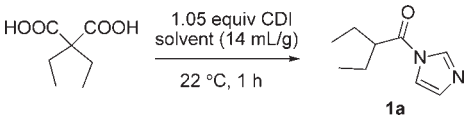
(4) Cu_2O is acting as a base catalyst in the thermal decarboxylation: Blanchet, J.; Baudoux, J. *Eur. J. Org. Chem.* **2008**, 5493 and references cited therein.

(5) (a) Okrasa, K.; Levy, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4691. (b) Miyamato, K.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 4077.

10.1021/ol200575c
Published on Web 04/13/2011

The volume of CO_2 produced in a pilot reaction using 1 g of diethylmalonic acid as the reference starting material was measured at 146 mL, in accordance with the calculated volume expected for 2 mol of CO_2 (150 mL)[8] being produced. Using the same reaction conditions (1.05 mol equiv of CDI at room temperature), we next conducted the decarboxylative activation of diethylmalonic acid in different solvents and looked at the in situ yield by GCMS after 1 h (Table 1). The reaction works equally well in all solvent screened except for toluene, which resulted in a more sluggish conversion. This is likely caused by poor solubility of this specific substrate in toluene.

Table 1. Solvent Screen Study



1a

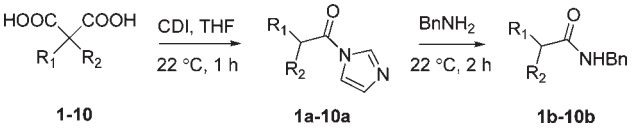
entry	solvent	conv[a] (%)
1	THF	95
2	DCM	92
3	Acetonitrile	96
4	Toluene	71[b]
5	EtOAc	95
6	DMF	88

[a] In situ conversion measured by GCMS. [b] Precipitate forms in toluene upon CDI addition.

As expected from reported *N*-acylimidazole stability studies,[9] the carbonyl imidazole **1a** was found to be relatively stable under neutral or slightly acidic aqueous conditions, while hydrolyzing rapidly under basic conditions. Compound **1a** was successfully isolated in good yield (80%) and purity (98% by GCMS) as a light yellow oil after an aqueous citric acid workup followed by extraction with ethyl acetate. However, the isolated product appears to degrade rapidly when left on the bench at room temperature, the light yellow oil turning to a dark brown color overnight. The decomposition may not be due to hydrolysis and could rather be the results of photodegradation.[10] Given the limited stability of the isolated carbonyl imidazole and the reactive nature of this activated carbonyl, we decided to trap the intermediate formed in situ with benzyl amine in order to obtain an accurate isolated yield for this process (Table 2). Other nucleophiles were also used with diethylmalonic acid as the starting material to synthesize a variety of functionalized end products in an efficient one-pot reaction (Table 3).

We were pleased to observe that the reaction proceeds smoothly across a range of alkyl-, alkyl(aryl)-, aryl-, and

Table 2. Malonic Acid Derivatives Screen



1-10 **1a-10a** **1b-10b**

malonic acid	1a-10a (%)[a]	product	yield (%)[b]
1	95	1b	90
2	93	2b	98
3	96	3b	100
4	97	4b	92
5	98	5b	83
6	98	6b	85
7	94	7b	89
8	-	8b	0[c]
9	93	-	(n/a)[d]
10	-	10b	19[e]

[a] In situ conversion measured by GCMS referenced against residual malonic acid. [b] Isolated yield. [c] Only a mixture of bis-carbonyl imidazole and 1-carboxylate-1′-carbonylimidazole was observed. [d] An attempt to trap **9a** with benzyl amine yielded a mixture of desired product and competitive Michael adduct side product. [e] Isolated pure product separated by chromatography. Alternative reaction conditions were not investigated.

(6) ^{1}H NMR tube reaction.

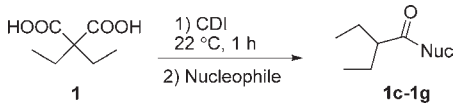
(7) To the best of our knowledge, there is only one report of this reaction in the literature, but no details or comments are provided for this specific step: Connolly, T. J. U.S. Patent 0 269 342, 2008.

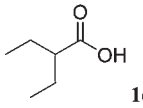
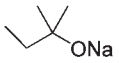
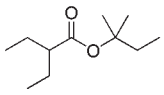
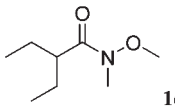
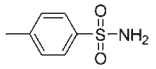
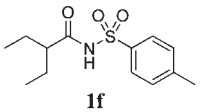
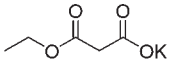
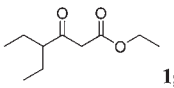
(8) An inverted graduated cylinder in a water bath was used. Pressure stabilizes after 90 min. Parameters: n = 6.24 mmol, T = 292.5 K, p = 101.3 Kpa.

(9) Zamarella, S.; Stromberg, R. *Eur. J. Org. Chem.* **2002**, *15*, 2663.

(10) Iwasaki, S. *Helv. Chim. Acta* **1976**, *59*, 2753.

Table 3. Trapping of the Carbonyl Imidazole Intermediate with Various Nucleophiles



entry	nucleophile	product	yield (%)[a]
1	NaOH	 **1c**	90
2		 **1d**	91
3		 **1e**	85
4		 **1f**	79
5		 **1g**	67

[a] In situ conversion measured by GCMS.

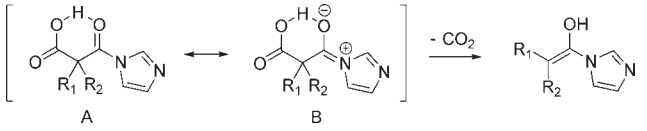
cycloalkylmalonic acid derivatives (Table 2, entries 1–7). To our surprise, the rate of the key decarboxylation step is independent of the nature of the malonic acid structure at room temperature. For example, the first-order rate constant for the thermal decarboxylation of phenylmalonic acid in water compared to malonic acid is approximately 100 times higher.[11] Despite numerous attempts to carry out the decarboxylative activation of cyclopropane dicarboxylic acid (Table 2, entry 8), we were unable to detect the presence of the carbonyl imidazole product or the trapped benzyl amine product, even at slightly higher temperature (45 °C). Cinnamylidenemalonic acid (Table 2, entry 9) was found to decarboxylate smoothly under the reaction conditions to generate 93% in situ yield of the corresponding carbonyl imidazole. Fluoromalonic acid (Table 2, entry 10) did produce the desired product in low yield as a mixture with a *N*-*N*′-dibenzylurea side product, which could be explained by the poor solubility of the intermediates in THF.[12] We believe that as the reaction progresses, the free base imidazole generated during the process forms a salt with the unreacted malonic acid that precipitates and prevent full reaction conversion. This leaves unreacted CDI that gets trapped by benzyl amine to generate the urea side product.

(11) Gelles, E. *J. Am. Chem. Soc.* **1954**, *75*, 6199.

Diethylmalonic acid **1** was converted easily (Table 3) to the carboxylic acid (entry 1), *tert*-amyl ester (entry 2), Weinreb amide (entry 3), sulfonamide (entry 4), and β-keto ester (entry 5) using a variety of conditions in a practical one-pot process.

We initially postulated a simple reaction mechanism ressembling the known decarboxylation mechanism of malonic acid derivatives,[13] where an intermediate enolate is formed through an intramolecular proton transfer. In the case of the carbonyl imidazole, resonance stabilization from the imidazole moiety could have explained the faster rate compared to malonic acids (Scheme 3).

Scheme 3. Intramolecular Proton Transfer



However, when the bis-carbonyl imidazole of diethylmalonic acid (prepared from treatment of diethylmalonyl dichloride with imidazole) was hydrolyzed under different conditions (acidic, neutral and basic), only the diethylmalonic acid was recovered and no decarboxylated product was formed. This suggested that monoactivation of one carboxylic acid group to the carbonyl imidazole, followed by a decarboxylation step as depicted in Scheme 3, was not the actual mechanism of the reaction. In addition, the resonance interaction from N-1 to the carbonyl carbon (Scheme 3, structure B) has been shown to be very weak,[14] with the imidazole group having a net negative charge on the N-3 atom. These findings are also supported by a recent report[15] presenting the synthesis of malonic monocarbonyl (alkyl)imidazole and benzimidazole (similar to structure A in Scheme 3) that were isolated in good yields without degrading via decarboxylation to the activated carboxylic acid. To account for the results obtained for the bis-carbonyl imidazole control reactions, as well as the decarboxylation rate observed when using a variety of malonic acid starting materials (Table 2), we propose a mechanism that involves the formation of a ketene intermediate that is quickly trapped by the imidazole free base to form the carbonyl imidazole **15** (Scheme 4). Considering that ketene exhibits a strong characteristic IR signal around 2100 cm^{-1}, we attempted to detect the ketene intermediate by monitoring a reaction using ReactIR. Although we were unable to directly observe the ketene peak, we postulated that this intermediate would be trapped as it forms by the free imidazole, which would prevent it from accumulating in

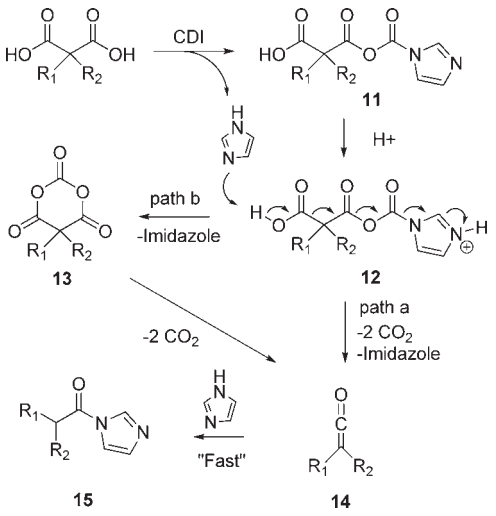
(12) The reaction was also tried in DCM and DMF, but the yield remains moderate. Factors other than solubility could be involved.

(13) Bach, R. D.; Canepa, C. *J. Org. Chem.* **1996**, *61*, 6346.

(14) Fife, T. H.; Natarajan, R. *J. Org. Chem.* **1987**, *52*, 740 and references cited therein.

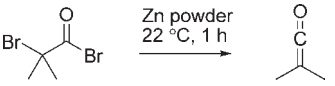
(15) Chatterjee, S.; Charles, G. Y. *Tetrahedron Lett.* **2010**, *51*, 1139.

Scheme 4. Proposed Reaction Mechanism



the reactor and generating a strong signal. This assumption was confirmed by preparing dimethyl ketene (Scheme 5) using a known method[16] and reacting it with 1 mol equiv of imidazole in THF at room temperature. The sharp peak at 2120 cm^{-1} was completely consumed in less than 2 min.

Scheme 5. Dimethyl Ketene Formation



The quick trapping of the ketene intermediate as it forms is also consistent with the fact that none of the side products typically associated with ketene formation, such as ketene dimer or trimer,[17] are formed in this reaction. Interestingly, the ReactIR results for the reaction of diethylmalonic acid with CDI suggest that the reaction is completed in less than 5 min at room temperature, as both starting materials get completely consumed and the formation of free imidazole (1330 cm^{-1}) and CO_2 gas (2340 cm^{-1}) are leveling out within this short period of time.[18]

The ketene intermediate **14** (Scheme 4) can be formed via two different paths. In path a, intermediate **12** would undergo a cascade type decarboxylation that would sequentially generate 2 mol equiv of carbon dioxide and 1 mol equiv of imidazole. Such a mechanism is similar to the ketene formation from 2-bromoisobutyryl bromide (Scheme 5), where the enolate species generated from bromide reduction is unstable and driven to the ketene product by the leaving group expulsion from the carbonyl. In path b, an intramolecular cyclization of **12** could take place to generate the cyclotrione intermediate **13**,[19] which would then undergo a concerted bis-decarboxylation directly to the ketene intermediate. A similar mechanism was postulated to account for the formation of a related imino ketene intermediate,[20] presumably formed by pyrolytic concerted expulsion of acetone and CO_2 from a Meldrum's acid hydrazone derivative. Finally, the seemingly sharp difference in reactivity between **7** and **8** could be explained by the known propensity of the cyclobutane system to stabilize exocyclic enolate, due to the α-carbon having intermediate sp^2/sp^3 hybridization.[21]

In summary, we have developed a novel decarboxylative activation of malonic acid derivatives with CDI that proceeds in near quantitative yield under unusually mild conditions. The carbonyl imidazole thus formed can be trapped with a variety of nucleophiles in an efficient one-pot process. Although we could not directly observe the ketene intermediate postulated, cumulative observations suggest a mechanism going through this key intermediate.

Acknowledgment. The authors thank the following Pfizer colleagues: Juan Colberg and Stephane Caron for helpful suggestions and discussions, and the SEG group for analytical support.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Baigrie, L. M.; Lenoir, D. *J. Org. Chem.* **1985**, *50*, 2105.
(17) Hoffmann, M. R.; Eggert, U. *J. Org. Chem.* **1989**, *54*, 6096.
(18) Carbon dioxide concentration gets lower as off-gasing takes place over a period of about 90 min.
(19) 1,3-Dioxane-2,4,6-triones are an unstable species that have only been reported in theoretical studies as a hydrogen bond acceptor: Zue, L.; Teng, Q. *Chin. J. Struct. Chem.* **2006**, *25* (2), 143.
(20) Briehl, H.; Lukosch, A. *J. Org. Chem.* **1984**, *49*, 2772.
(21) Eames, J.; Coumbarides, G. S. *Eur. J. Org. Chem.* **2003**, 634.