ORGANIC LETTERS

2005
Vol. 7, No. 11
2125−2127

Unexpected Reaction of Dimethyl Acetylenedicarboxylate with in Situ Generated Arylketenes Catalyzed by 1-Methylimidazole

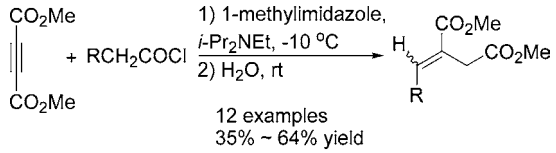
Hanfeng Ding, Cheng Ma,* Yewei Yang, and Yanguang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

mcorg@zju.edu.cn; orgwyg@zju.edu.cn

Received March 8, 2005

ABSTRACT



R = substituted phenyl and naphthyl groups

An unexpected 1-methylimidazole-catalyzed reaction of dimethyl acetylenedicarboxylate (DMAD) with in situ generated arylketenes leading to the synthesis of dimethyl 2-arylidenesuccinates under mild conditions is described. A plausible mechanism has been proposed.

The reaction of nucleophiles with activated acetylenes for C−C bond formation is of great significance in organic synthesis.[1] In these reaction processes, zwitterionic species are known to arise from the addition of nucleophiles such as triphenylphosphine,[1c,2] pyridine,[1d,3] and a wide range of tertiary amines[2d,4] to activated acetylenes such as dimethyl acetylenedicarboxylate (DMAD).[5] Then, these intermediates can be trapped by suitable substrates (such as dioxide,[6] isocyanate,[7] and carbonyl compounds[3c−e]), and this interception can either be a two-component reaction or a multicomponent reaction. However, to the best of our knowledge, no attempts have been made to trap the zwitterionic intermediates with ketene.[8,9] Here, the preliminary results of the 1-methylimidazole-catalyzed reaction of DMAD with in situ generated aryl ketenes are reported.

Our studies were initiated by the reaction of *p*-nitrophenylacetyl chloride with DMAD in the presence of 1-meth-

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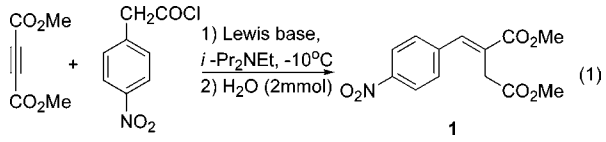
(8) For [2 + 2] cycloaddition of ketene equivalents with electrophilic acetylenes promoted by Lewis acid, see selected references: (a) Semmelhack, M. F.; Tomada, S. *J. Am. Chem. Soc.* **1981**, *103*, 2427. (b) Semmelhack, M. F.; Tomada, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 747. (c) Quendo, A.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 6443. (d) Quendo, A.; Ali, S. M.; Rousseau, G. *J. Org. Chem.* **1992**, *57*, 689.

(9) For uncatalyzed [2 + 2] cycloaddition of ketenetrimethylsilyl-acetates with electrophilic acetylenes, see: (a) Misesch, M.; Wendling, F.; Franck-Neumann, M. *Tetrahedron Lett.* **1999**, *40*, 839. (b) Misesch, M.; Wendling, F. *Eur. J. Org. Chem.* **2000**, 3381.

10.1021/ol050492q CCC: $30.25
Published on Web 04/30/2005

ylimidazole and *i*-Pr_2NEt[10] in CH_2Cl_2 at −10 °C to room temperature for 2 days. To our surprise, (*E*)-dimethyl 2-(4-nitrobenzylidene)succinate **1** was isolated from the reaction mixture (eq 1). Intrigued by this result, we carried the reaction under various conditions, and the results are shown in Table 1. In the presence of stoichiometric amounts of

Table 1. Reaction of *p*-Nitrophenylacetyl Chloride (2 mmol) with DMAD (2 mmol) Catalyzed by Nitrogen Lewis Bases under Various Conditions



1

entry	Lewis base[a]	solvent	*T* (°C)	time[b] (h)	yield[c] (%)
1	1-methylimidazole[d]	DCM	−10 to +20	48	26
2	1-methylimidazole	DCM	−10 to +20	48	65
3	1-methylimidazole	THF	−10 to +20	48	62
4	1-methylimidazole	toluene	−10 to +20	48	34
5	1-methylimidazole	THF	−10 to +80	12	61
6	pyridine	DCM	−10 to +20	48	trace
7	DBU	DCM	−10 to +20	50	trace
8	*i*-Pr_2NEt	DCM	−10 to +20	60	trace

[a] Unless otherwise specified, all of the reactions were carried out in the presence of 100 mol % Lewis base. [b] Reaction time for consuming all of the starting materials. [c] Isolated yield. [d] 20 mol %.

1-methylimidazole, **1** could be obtained in 26−65% yields with (*E*)-selectivity in various solvents (entries 2−4). While using other Lewis base such as pyridine, DBU, or *i*-Pr_2NEt as catalyst, only a trace of **1** is formed (entries 6−8). Moreover, the catalyst loading below 100 mol % afforded a significantly reduced yield of **1** (entry 1).

The structure of **1** was characterized by spectroscopic analysis. In the ^1H NMR spectrum, the olefinic proton resonated at δ 7.92.[11] The ^{13}C NMR signals for the two ester carbonyls of **1** were seen at δ 167.2 and 171.2. Finally, the structure and stereochemistry of **1** were established unambiguously by X-ray analysis (Figure 1).

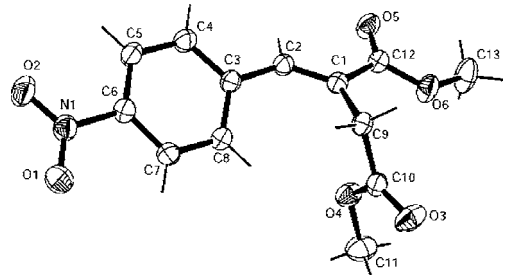
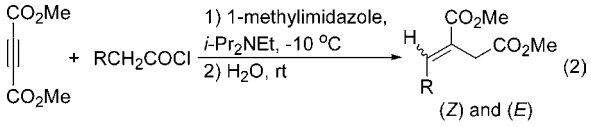


Figure 1. X-ray crystal structure of **1**.

The reaction was found to be applicable to a number of other arylacetyl chlorides and gave the dimethyl 2-arylidenesuccinates **3a**−**k** as a pair of (*Z*)- and (*E*)-isomers in moderate to good yields (Table 2, eq 2).[12,13] It is interesting

Table 2. Reaction of in Situ Generated Ketenes with DMAD Catalyzed by 1-Methylimidazole (100 mol %)



2a-k **3a-k**

entry	R	time[a] (h)	product	yield[b] (%)	*Z*/*E* ratio[c]
1	Ph	48	**3a**	58	79:21
2	4-ClC_6H_4	48	**3b**	52	87:13
3	2-ClC_6H_4	60	**3c**	38	69:31
4	3-ClC_6H_4	48	**3d**	46	81:19
5	1-naphthyl	48	**3e**	55	60:40
6	4-FC_6H_4	48	**3f**	53	79:21
7	2-FC_6H_4	48	**3g**	41	72:28
8	2,4-dichlorophenyl	48	**3h**	63	72:28
9	3,4-dichlorophenyl	48	**3i**	64	72:28
10	4-MeC_6H_4	60	**3j**	37	76:24
11	2-MeC_6H_4	60	**3k**	35	57:43

[a] Reaction time for consuming all of the starting materials. [b] Isolated yields. [c] Determined by GC−MS analysis and verified by isolated yields.

that the products **3a**−**k** were obtained with dominant (*Z*)-selectivity.[14]

To explore the mechanism of the 1-methylimidazole-catalyzed reaction, one further experiment was performed under the same conditions but using D_2O in place of H_2O with phenylacetyl chloride as substrate (Scheme 1). The isolated product (*Z*)-**4** was determined by ^1H NMR (see the Supporting Information). It is shown that only the two protons connected to the α-C of product (*Z*)-**4** were deuterated.

On the basis of our results, we propose the following mechanism for the 1-methylimidazole-catalyzed reaction of

(10) *i*-Pr_2NEt was used as additional base to form the corresponding ketene in situ.

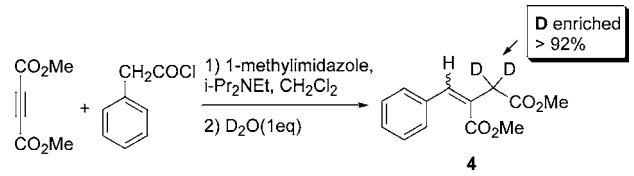
(11) The chemical shift of the vinyl proton in *E*-isomer of substituted 3-alkoxycarbonyl-β,γ-unsaturated esters has been reported in the range of δ = 7.83−8.00; see: McCombie, S. W.; Luchaco, C. A. *Tetrahedron Lett.* **1997**, *38*, 5775.

(12) **Representative Experimental Procedure.** A mixture of DMAD (2 mmol) and phenylacetyl chloride (2 mmol) in DCM (3 mL) was added dropwise to the solution of 1-methylimidazole (2 mmol) and *i*-Pr_2NEt (3 mmol) in dry DCM (5 mL) under a nitrogen atmosphere at −10 °C, and the resulting solution was stirred for 6 h. Then, the reaction solution was allowed to warm to rt, and water (2 mmol) was added. After an additional 2 days at this temperature, the solvent was then removed under vacuum, and the residue was chromatographed on a silica gel column with a hexanes−ethyl acetate mixture (7:1) to afford (*Z*)-**3a** and (*E*)-**3a**. GC−MS analysis: (*Z*)-**3a** (t_R = 6.19 min); (*E*)-**3a** (t_R = 6.42 min).

(13) The stereochemistry of **3** is determined by the chemical shift of vinyl proton in ^1H NMR spectra. We assigned the chemical shift in the range of δ 7.79−8.41 as the (*E*)-isomer, while that in the range of δ 6.77−7.01 was assigned as the (*Z*)-isomer. See Shen, Y.-C.; Zhang, Y.-M. *Heteroatom Chem.* **2003**, *14*, 276.

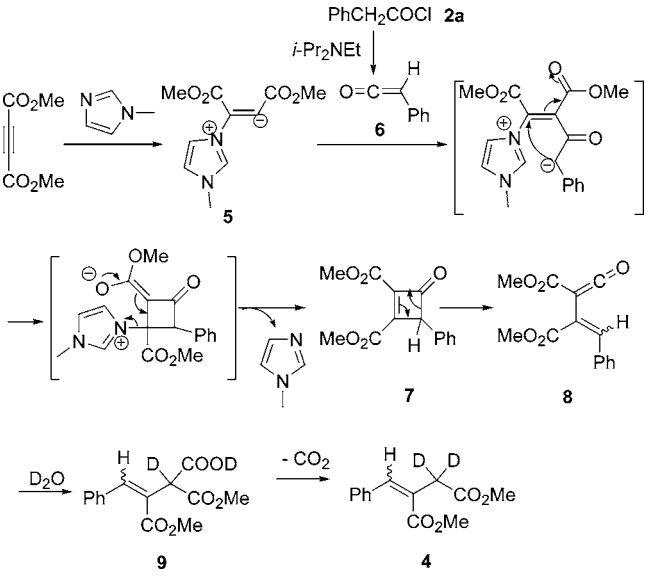
(14) The consecutive reaction of bis[2,2,2-trifluoroethyl] with sodium hydride, dimethyl maleate, and aldehydes gives 3-alkoxycarbonyl-β,γ-unsaturated esters with *Z*-selectivity was reported; see ref 13.

Scheme 1



DMAD with in situ generated arylketenes (Scheme 2). Thus, the formal [2 + 2] cycloaddition of the zwitterion **5** to the

Scheme 2. Plausible Reaction Mechanism in the Reaction of Arylketenes with DMAD Catalyzed by 1-Methylimidazole



ketene **6** affords cyclobutenone **7**, followed by electrocyclic ring opening under basic condition to give unstable vinylketene **8**.[15,16] The latter intermediate is trapped by nucleophilic addition of D_2O to afford β-ester acid derivative **9**. Finally, spontaneous decarboxylation of **9** generates the product **4**.[17]

It is noteworthy that 3-alkoxycarbonyl-β,γ-unsaturated esters are useful intermediates for the synthesis of substituted tetrahydrofurans and therefore have attracted much interest in recent years.[18] Although several methods have been reported for the synthesis of these compounds, most of them suffer from drawbacks such as the use of harsh conditions and employment of strong base and/or tedious procedures.[19]

In conclusion, we have described a novel 1-methylimidazole-catalyzed reaction of DMAD with in situ generated arylketenes leading to the synthesis of dimethyl 2-arylidenesuccinates under mild conditions. Further investigations are underway to elucidate the mechanistic details and to disclose the scope and limitations of this reaction.

Acknowledgment. We thank Dr. J.-M. Gu for X-ray diffraction analysis.

Supporting Information Available: Crystallographic information files (CIF) for **1** and experimental procedures and characterization data of **1**, **3ak**, and (*Z*)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The reaction of acyclic ketenetrimethylsilylacetals with DMAD afforded ring opening products of [2 + 2] cycloadduct in the presence of catalytic amounts of $ZrCl_4$. See: Mitani, M.; Sudoh, T.; Koyama, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1683.

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