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Michael Addition of Allenoates to Electron-Deficient Olefins: Facile Synthesis of 2-Alkynyl-Substituted Glutaric Acid Derivatives

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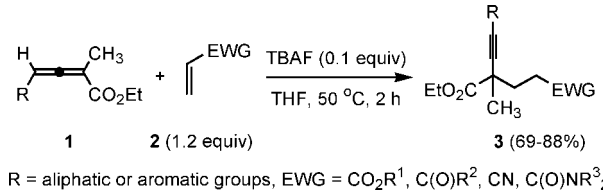
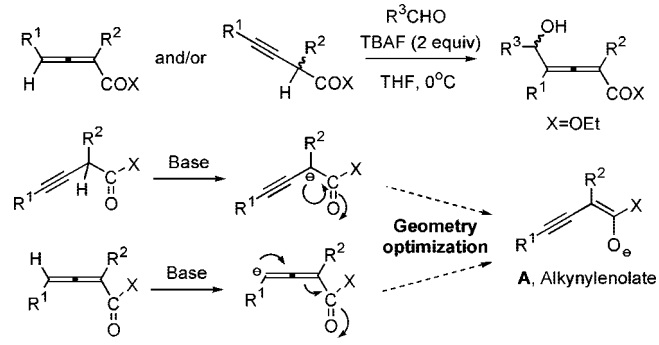
ABSTRACT



A Michael addition of allenoates to electron-deficient olefins was mediated efficiently by a catalytic amount of commercial tetra-*n*-butylammonium fluoride (TBAF) under mild conditions. And 2-alkynyl substituted glutaric acid derivatives, which may be potential building blocks in organic synthesis, were obtained in good to excellent yields from these reactions. The mechanism for the Michael addition reaction may involve the formation of an alkynylenolate intermediate.

The Michael addition reaction is one of the most powerful methods for the generation of 1,5-dicarbonyl compounds, which are of general synthetic interest in organic synthesis. Enolates or stabilized carbanions could be regarded as proper nucleophiles for conjugate addition reactions.[1] Recently, we reported an aldol reaction of allenoates or propargylic esters that we regarded to occur via a common alkynylenolate intermediate **A** (Scheme 1).[2] When the intermediate **A**—generated by the action of tetra-*n*-butylammonium fluoride (TBAF)—reacted with an aldehyde, the reaction favored exclusively the thermodynamically preferred γ-product, namely the carbinol allenoate shown in Scheme 1 (top right). To probe further the reactivity of this alkynylenolate intermediate **A**, we decided to investigate the reaction of the allenoates—which are suitable precursors of intermediate **A**[3] and easily prepared using textbook methodologies[4]—with

Scheme 1. Aldol Reaction of Allenoates or Propargylic Esters



(1) For selected recent reviews on conjugate addition reactions, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1992. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (d) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393–401. (e) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (f) Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188. (g) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135.

(2) Xu, B.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 689–692.

(3) For the generation and reaction of allenyl/propargyl anions, see: (a) Marshall, J. A.; Gung, B. W.; Grachan, M. L. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapter 9. (b) Back, T. G. *Tetrahedron* **2001**, *57*, 5263–5301. (c) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805–2827.

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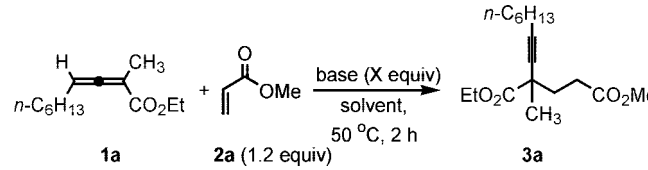
Michael acceptors such as alkyl acrylate, methyl vinyl ketone, acrylonitrile, and *N*,*N*-dimethyl acrylamide. Herein, we wish to report a highly attractive Michael addition of allenoates[5] to electron-deficient carbon−carbon double bonds that provides a convenient entry into 2-alkynyl-substituted glutaric acid derivatives. Although glutaric acid derivatives have been used extensively in organic synthesis,[6] the synthetically more useful 2-alkynyl-substituted glutaric acid derivatives rarely have been reported in the literature.[7]

Using ethyl α-methyl-γ-(*n*-hexyl)-allenoate **1a** as the substrate, we studied its Michael addition to methyl acrylate **2a** under similar conditions employed for the γ-selective aldol reaction.[2] We were pleased to observe that the reaction proceeded smoothly at rt in 12 h yielding exclusively the α-selective adduct[8] **3a** in 55% yield (Table 1, entry 1). When conducted at higher temperature (50 °C), the reaction could be completed in 2 h and gave a much higher yield (Table 1, entry 2). Water did not prevent the reaction from occurring since a very good yield of **3a** was obtained when using TBAF trihydrate as the base (Table 1, entry 3). Other bases, either inorganic or organic, were also examined in this reaction, but the yields of product dropped sharply. In most of these cases, only traces of the product were found by TLC and most of the starting material remained (Table 1, entries 4−13). Solvent effects were also investigated. We found that compound **3a** could be isolated in very good yields in toluene (Table 1, entry 14), but when 1,2-dichloroethane (DCE), dichloromethane (DCM), and diethyl ether were employed, the reaction was severely retarded (Table 1, entries 15−17). The reaction could also take place in polar aprotic solvents such as acetonitrile, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) and the product **3a** could be obtained in moderate to good isolated yields (Table 1, entries 18−20). Reducing the amount of TBAF to as low as 0.1 equiv of the allenoate did not decrease the yield of the product (Table 1, entries 21−24). This clearly marked a substantial improvement to our methodology.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** (1.2 equiv) **3a**

entry	base	*X* (equiv)	solvent	yield[b] (%)
1[c]	TBAF[d]	2.0	THF	55
2	TBAF[d]	2.0	THF	80
3	TABF·3H_2O	2.0	THF	82
4	(*n*-Bu_4N^+)$^-$OAc	2.0	THF	trace
5	(*n*-Bu_4N^+)$^-$Br	2.0	THF	no reaction
6	K_2CO_3	2.0	THF	trace
7	Cs_2CO_3	2.0	THF	trace
8	CsF	2.0	THF	trace
9	KO^{t}Bu	2.0	THF	complex mixture
10	NaOAc	2.0	THF	trace
11	Et_3N	2.0	THF	trace
12	PyH	2.0	THF	trace
13	DBU	2.0	THF	complex mixture
14	TBAF·3H_2O	2.0	toluene	81
15	TBAF·3H_2O	2.0	DCE	trace
16	TBAF·3H_2O	2.0	DCM	trace
17	TBAF·3H_2O	2.0	Et_2O	trace
18	TBAF·3H_2O	2.0	CH_3CN	84
19	TBAF·3H_2O	2.0	DMF	42
20	TBAF·3H_2O	2.0	DMSO	59
21	TBAF[d]	1.0	THF	79
22	TBAF[d]	0.5	THF	81
23	TBAF[d]	0.2	THF	77
24	TBAF[d]	0.1	THF	83

[a] Reaction conditions: allenoate **1a** (0.3 mmol), methyl acrylate **2a** (0.36 mmol), solvent (2.0 mL). [b] Isolated yields; [c] Conducted at rt for 12 h. [d] 1.0 M solution in THF.

With optimal reaction conditions in hand, we explored the scope of this Michael reaction. By using allenoate **1a** as a fixed substrate, we carried out the reactions with various types of olefins bearing an electron-withdrawing group (EWG); the results are outlined in Table 2. EWG could be esters (Table 2, entries 1−3), ketone (Table 2, entry 4), nitrile (Table 2, entry 5), or amide (Table 2, entry 6). In all these cases we found that the corresponding products could be obtained in good yields. When using acrylates having a methyl group substituted at α- or β-positions, such as methyl methacrylate (Table 2, entry 7) and methyl crotonate (Table 2, entry 8), higher temperatures and prolonged times were needed for the reactions to occur and lower yields were obtained. This clearly indicated that the reaction was susceptible to steric effects.

We then proceeded to examine the Michael addition reactions of various allenoates with methyl acrylate; the results are summarized in Table 3. As can be seen from this table, aromatic and aliphatic substituted allenoates reacted with methyl acrylate smoothly and the corresponding products were isolated, again in very good yields. For the aromatic group-substituted substrates (Table 3, entries 1−3), either an electron-donating or electron-withdrawing group

(4) For preparation of allenoates, see: Lang, R. W.; Hansen, H.-J. *Org. Synth., Collect.* **1990**, *7*, 232.

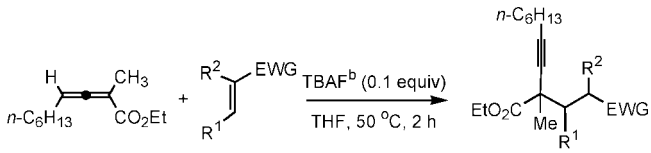
(5) Selected recent papers on allenoates, see: (a) Elsner, P.; Bernardi, L.; Dela Salla, G.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897–4905. (b) Singh, L.; Ishar, M. P. S.; Elango, M.; Subramaniam, V.; Gupta, V.; Kanwal, P. *J. Org. Chem.* **2008**, *73*, 2224–2233. (c) Shi, M.; Tang, X.-Y.; Yang, Y.-H. *Org. Lett.* **2007**, *9*, 4017–4020. (d) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989. (e) Li, C.-Y.; Sun, X.-L.; Jing, Q.; Tang, Y. *Chem. Commun.* **2006**, 2980–2982. (f) Klein, A.; Miesch, M. *Synthesis* **2006**, 2613–2617.

(6) For selected recent papers on glutaric acid derivatives, see: (a) Yan, J.; Travis, B. R.; Borhan, B. *J. Org. Chem.* **2004**, *69*, 9299–9302. (b) Tagat, J. R.; McCombie, S. W.; Nazareno, D. V.; Boyle, C. D.; Kozlowski, J. A.; Chackalamannil, S.; Josien, H.; Wang, Y.; Zhou, G. *J. Org. Chem.* **2002**, *67*, 1171–1177. (c) Vera, M.; Almontassir, A.; Rodríguez-Galán, A.; Puiggalí, J. *Macromolecules* **2003**, *36*, 9784–9796. For glutaric acid derivatives used in total synthesis, see: (d) Nayyar, N. K.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982–991. (e) Colobert, F.; Mazery, R. D.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723–1725. (f) Zhu, C.; Tang, P.; Yu, B. *J. Am. Chem. Soc.* **2008**, *130*, 5872–5873.

(7) To the best of our knowledge, there is only one report on 2-alkynyl-substituted glutaric acid derivatives, see:Casara, P.; Metcalf, B. W. *Tetrahedron Lett.* **1978**, *19*, 1581–1584.

(8) For a recent example of alkynyl-substituted cyclization products from sulfonylallene derivatives by base treatment, see: (a) Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett.* **2007**, *9*, 2549−2552, and references cited therein. For a palladium-catalyzed alkylation of vinyl oxiranes with allenoates, see: (b) Nanayakkara, P.; Alper, H. *J. Org. Chem.* **2004**, *69*, 4686–4691.

Table 2. Michael Addition Reactions of Allenoate **1a** with Various Michael Acceptors **2**[a]



1a **2** (1.2 equiv) **3**

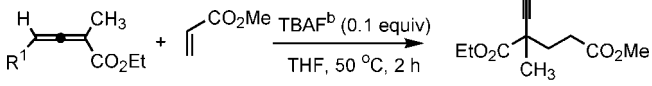
entry	R^1/R^2	EWG	**3**, yield[c] (%)
1	H/H	$CO_2{}^nBu$ (**2b**)	**3b**, 81
2	H/H	$CO_2{}^tBu$ (**2c**)	**3c**, 78
3	H/H	CO_2Allyl (**2d**)	**3d**, 72
4	H/H	$COCH_3$ (**2e**)	**3e**, 70
5	H/H	CN (**2f**)	**3f**, 84
6	H/H	$CON(CH_3)_2$ (**2g**)	**3g**, 69
7[d]	H/Me	CO_2Me (**2h**)	**3h**, 58[e]
8[d]	Me/H	CO_2Me (**2i**)	**3i**, 36[e]

[a] Reaction conditions: allenoate **1a** (0.3 mmol), Michael acceptor **2** (0.36 mmol), THF (2.0 mL). [b] 1.0 M solution in THF. [c] Isolated yields. [d] Conducted under reflux for 6 h. [e] Total yield of two diastereoisomers.

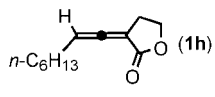
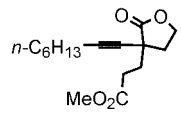
on the aromatic ring did not affect the reaction significantly. For the aliphatic group-substituted substrates (Table 3, entries 4−6), steric hindrance did not prevent the reaction from taking place, even when an isopropyl-substituted allenoate was used as the substrate (Table 3, entry 5). An allenic lactone **1h** was also employed in this reaction and the corresponding α-alkynyl-substituted lactone **3p** was obtained in 73% yield.

When using ethyl γ-methylallenoate **1i** as the substrate, the reaction with methyl acrylate did not gave the 2-alkynyl-

Table 3. Michael addition reactions of allenoates **1** with methyl acrylate **2a**[a]



1 **2a** (1.2 equiv) **3**

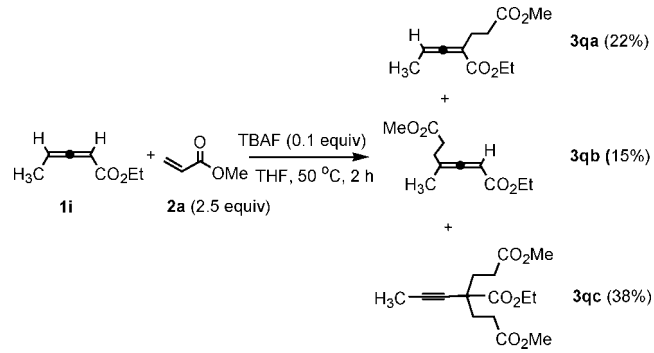
entry	R^1	**3**, yield %[c]
1	C_6H_5 (**1b**)	**3j**, 88
2	p-$CH_3OC_6H_4$ (**1c**)	**3k**, 85
3	p-ClC_6H_4 (**1d**)	**3l**, 79
4	$C_6H_5CH_2$ (**1e**)	**3m**, 83
5	$(CH_3)_2CH$ (**1f**)	**3n**, 82
6	CH_3 (**1g**)	**3o**, 77
7	 (**1h**)	 **3p**, 73

[b,c]

[a] Reaction conditions: allenoate **1** (0.3 mmol), methyl acrylate **2a** (0.36 mmol), THF (2.0 mL). [b] 1.0 M solution in THF. [c] Isolated yields.

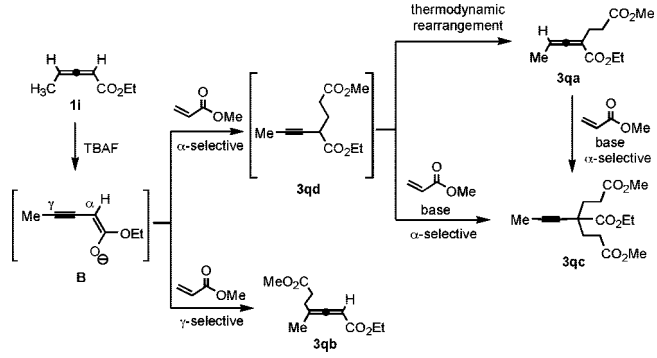
substituted glutaric acid derivatives **3qd** but afforded instead **3qa**, **3qb**, and **3qc** as the only products (Scheme 2).

Scheme 2. Michael Addition Reaction of Allenoate **1i** with Methyl Acrylate **2a** under Optimized Conditions



A proposed mechanism for the formation of these products is depicted in Scheme 3. Alkynylenolate intermediate[2,9] **B**,

Scheme 3. Proposed Mechanism for the Formation of Compounds **3qa**, **3qb**,and **3qc**



which was formed from substrate **1i** under the mediation of TBAF, added to the carbon−carbon double bond of methyl acrylate with α-selectivity to give intermediate **3qd**. However, under the reaction conditions, this intermediate rearranged to the thermodynamically more stable product **3qa**.[10] Intermediate **3qd** could be deprotonated once more, reacting with another molecule of methyl acrylate to give the double addition product **3qc**. An alternative route to **3qc** could involve the reaction of **3qa** with methyl acrylate in a similar

(9) (a) Lepore, S. D.; He, Y.; Damisse, P. *J. Org. Chem.* **2004**, *69*, 9171–9175. (b) Petasis, N. A.; Teets, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 10328–10334.

(10) It is well-known that allenic and propargylic esters tend to interconvert to each other in the presence of base through a prototropic rearrangement, see: (a) Sleeman, M. J.; Meehan, G. V. *Tetrahedron Lett.* **1989**, *30*, 3345–3348. (b) Clinet, J. C.; Linstrumelle, G. *Synthesis* **1981**, 875–877. (c) Croudace, M. C.; Schore, N. E. *J. Org. Chem.* **1981**, *46*, 5357–5363.

manner.[11] Likewise, intermediate **B** added to methyl acrylate with γ-selectivity to give the product **3qb**.

In surmmary, we found that allenoates react with various types of Michael acceptors under the mediation of catalytic amounts of a commercial solution of TBAF and mild conditions. And the exclusive α-selective products, 2-alkynyl substituted glutaric acid derivatives, which may have potential application in organic synthesis, were obtained in very good yields. The broader applications of this reaction in organic synthesis, including its asymmetric variant, are currently under investigation.

(11) Compound **3qa** was isolated and subjected to the reaction with methyl acrylate under the same conditions, and compound **3qc** was obtained in 76% isolated yield as the only product.

Acknowledgment. We are grateful to the National Science Foundation for financial support (CHE-0809683).

Supporting Information Available: ^{1}H, ^{13}C NMR spectroscopic data, MS, and analytic data of the compounds shown in Tables 1–3 and Schemes 1–3, and detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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