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Claisen-Type Condensation of Vinylogous Acyl Triflates

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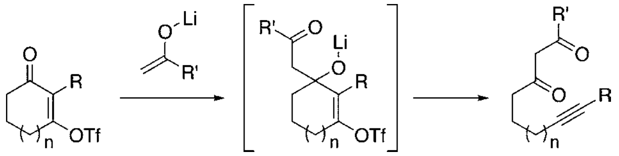
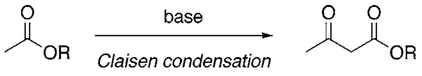
ABSTRACT



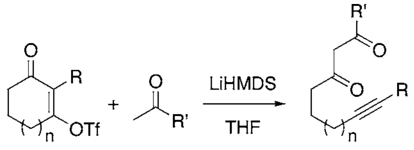
The Claisen-type condensation reaction of cyclic vinylogous carboxylic acid triflates with lithium enolates and their analogues produces acyclic alkynes bearing a 1,3-diketone-type moiety. The present transformation is proposed to proceed via a 1,2-addition of the enolate to the vinylogous acyl triflate, followed by fragmentation of the aldolate intermediate.

The Claisen condensation is one of the hallmark reactions of organic chemistry.[1] The first report on the Claisen condensation dates back more than a century and describes the homocoupling reaction of esters in the presence of an excess amount of base to yield 1,3-ketoesters (eq 1). This mechanistic pathway extends to the cross-coupling reactions of esters with a variety of enolates and enolate analogues.



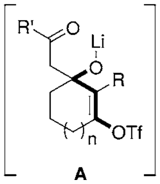
(1)

During the course of our investigations on the reaction between cyclic vinylogous acyl triflates (**1**) and organolithium reagents,[2] we found that the cross-coupling reaction of **1** with lithium enolates derived from **2** proceeds to give **3**, β-dicarbonyls tethered to alkynes (eq 2). This reaction appears to be a direct mechanistic analogue of the Claisen condensation using a vinylogous carboxylic acid ester as a starting material.



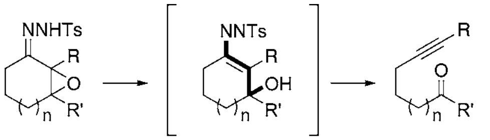
(2)

1 **2** **3**



A

The fragmentation event also calls to mind the process developed by Eschenmoser and Tanabe (eq 3),[3,4] although the reaction protocols are distinctly different (vide infra).



(3)

Eschenmoser-Tanabe fragmentation

Herein, we report a Claisen-type condensation of vinylogous acyl triflates, which appears to proceed via a fragmentation pathway and is, to the best of our knowledge, unprecedented.

We chose triflate **1a** (R = Me, n = 1 in eq 2) and the lithium enolate of acetophenone (**2a**, R′ = Ph in eq 2) as

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[1] For reviews on the Claisen condensation, see: (a) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795−863. (b) Hauser, C. R.; Hudson, D. E. *Org. React.* **1942**, *1*, 266. (c) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. For a review on the Dieckman condensation, see: (d) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1.

[2] (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028.

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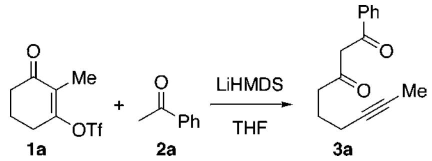
the prototype, and we screened to find optimal conditions for the formation of the acyclic alkynyl-1,3-diketone **3a**. The reaction stoichiometry had a significant effect on the yield of **3a** (Table 1). The reaction of triflate **1a** with 1.4 equiv of **2a** and 1.2 equiv of LiHMDS (lithium hexamethyldisilazide) gave **3a** in 56% yield along with recovered **1a** (entry 1). Treatment of **1a** with 2.4 equiv of **2a** and 2.2 equiv of LiHMDS furnished the product (**3a**) in 85% isolated yield (entry 2). When **1a** was treated with 1.2 equiv of **2a** and 2.2 equiv of LiHMDS, **3a** was obtained in 70% yield (entry 3). This stoichiometric requirement is consistent with the traditional Claisen condensation, wherein the relatively acidic dicarbonyl product consumes 1 equiv of base as it is formed.

We next examined the Claisen-type condensation of the vinylogous acyl triflate **1a** with various nucleophiles derived from analogues of **2** (Table 2). As mentioned above, the reaction between triflate **1a** and acetophenone (**2a**, pretreated with LiHMDS) in THF afforded acyclic alkynyl-1,3-diketone **3a**[5] in 85% yield (entry 1). The lithium enolate derived from acetone gave diketone **3b** in moderate yield (entry 2). The ethyl acetate enolate produced ketoester **3c** in 88% yield (entry 3). The anion of dimethyl sulfone (**2d**) reacted with **1a** to furnish β-ketosulfone **3d** in moderate yield (entry 4), along with a small amount of the diyne **3d′**. A similar reaction using dimethyl methylphosphonate (**2e**) provided β-ketophosphonate **3e** in low yield (entry 5).

We then explored the Claisen-type condensation using various triflates **1** and the lithium enolate of acetophenone (Table 3). Triflate **1b** afforded the corresponding diketone

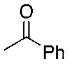
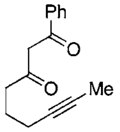
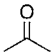
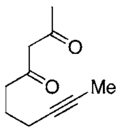
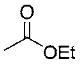
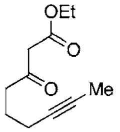
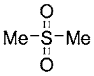
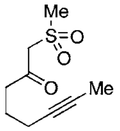
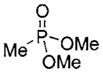
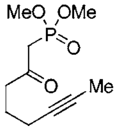
Table 1. Claisen-Type Condensation of the Vinylogous Acyl Triflate **1a** with Nucleophilic Derivatives of **2a**[a]



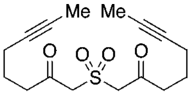
entry	triflate **1a**, equiv	acetophenone **2a**, equiv	LiHMDS, equiv	yield, %[b]
1	1.0	1.4	1.2	56[c]
2	1.0	2.4	2.2	85[d]
3	1.0	1.2	2.2	70

[a] The triflate **1a** was reacted with acetophenone **2a** (pretreated with LiHMDS) in THF at −78 to 60 °C within 80 min. [b] ^{1}H NMR yield using anisole as an internal standard unless otherwise noted. [c] The recovery of **1a** was observed. [d] Isolated yield.

Table 2. Claisen-Type Condensation of the Vinylogous Acyl Triflate **1a** with Nucleophilic Derivatives[a]

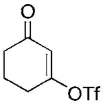
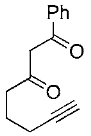
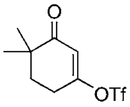
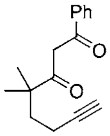
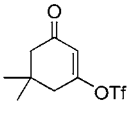
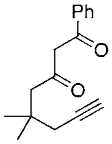
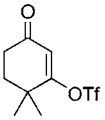
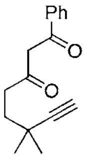
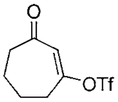
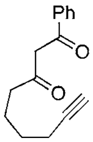
entry	pre-nucleophile (analogue of **2**)	product (analogue of **3**)	**3**	yield, %[b]
1	 **2a**		**3a**	85
2	 **2b**		**3b**	42
3	 **2c**		**3c**	88
4[c]	 **2d**		**3d**	53[d]
5[c]	 **2e**		**3e**	21

[a] Triflate **1a** (0.5 mmol) was reacted with the pre-nucleophile (1.2 mmol, pretreated with 1.1 mmol of LiHMDS) in 2 mL of THF at −78 to 60 °C within 80 min. [b] Isolated yield. [c] *n*-BuLi was used instead of LiHMDS. [d] Diyne **3d′** was obtained in 8.4% yield.



3d'

Table 3. Claisen-Type Condensation of Triflates **1** with Acetophenone[a]

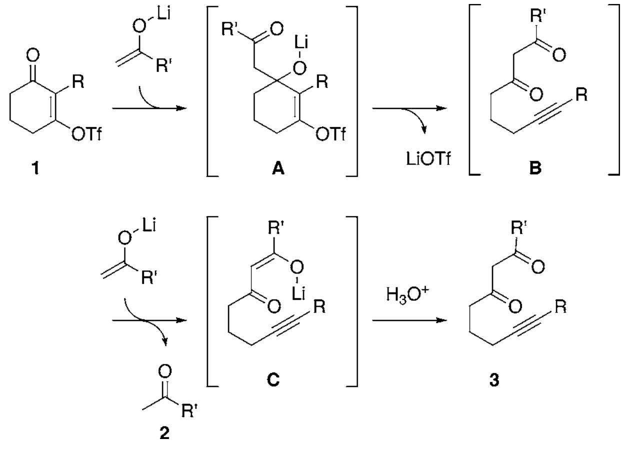
entry	triflate	**1**	product	**3**	yield, %[b]
1		**1b**		**3f**	95
2		**1c**		**3g**	–[c]
3		**1d**		**3h**	45
4		**1e**		**3i**	79
5		**1f**		**3j**	90

[a] Triflate **1** (0.5 mmol) was reacted with acetophenone (**2a**, 1.2 mmol, pretreated with 1.1 mmol of LiHMDS) in 2 mL of THF at −78 to 60 °C within 80 min. [b] Isolated yield. [c] Decomposition of **1c**.

3f in excellent yield (entry 1). The six-membered triflates **1c**−**e** bearing a geminal dimethyl group were next examined. The reaction of triflate **1c**, which bears a sterically congested quaternary center α to the carbonyl group, resulted in decomposition; no desired product (**3g**) was obtained (entry 2). On the other hand, the triflates such as **1d** and **1e**, in which the carbonyl groups are progressively less hindered, furnished the corresponding products **3h** and **3i** in 45% and 80% yield, respectively (entries 3 and 4). Accordingly, the reaction seemed to be sensitive to the steric demands of the substrates.[6] The seven-membered triflate **1f** gave the desired product **3j** in high yield (entry 5).

The mechanistic pathway for this novel Claisen-type condensation of vinylogous acyl triflates **1** with lithium enolates generated from **2** is proposed as shown in Scheme 1. Initially, 1,2-addition of the lithium enolate to the carbonyl group of triflate **1** generates intermediate **A**. Steric congestion around the reacting site would retard this addition process, and the prolonged exposure of triflate **1** to the reaction conditions would lead to its decomposition. The Grob-type fragmentation effects C−C bond cleavage along with extrusion of LiOTf to give intermediate **B**.[2] Subsequently, a second equivalent of the enolate abstracts a proton from the newly formed active methylene moiety to furnish intermediate **C**, which yields **3** upon aqueous workup.[7]

Scheme 1. Proposed Mechanistic Pathway for the Claisen-Type Condensation of Vinylogous Acyl Triflates **1** with Lithium Enolates



In summary, we describe the first examples of the Claisen-type condensation reaction of vinylogous acyl triflates (**1**) with lithium enolates and their analogues to form acyclic alkynes bearing a 1,3-diketone-type moiety (**3**). The present transformation contains an intriguing C−C bond cleavage process initiated by the nucleophilic addition of the lithium enolates to the carbonyl group of triflates **1**.

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Supporting Information Available: Experimental procedures, characterization data for products **3**, and details of a deuterium-labeling experiment in support of the mechanism proposed in Scheme 1. This material is available free of charge via the Internet at http://pub.acs.org.

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(3) (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. (b) Felix, D.; Shreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896. (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943. (d) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739.

(4) (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254. (d) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 1041−1070.

(5) 1,3-Diketones **3a**, **3b**, **3f**, and **3h**−**k** exist predominantly in the enol form in $CDCl_3$. See Supporting Information for details.

(6) The reactions of enolates derived from more hindered esters such as ethyl valerate and ethyl isobutyrate with triflate **1a** did not proceed well. In the former case, we could detect the corresponding product in the crude mixture by mass spectrometry (ESI, $C_{14}H_{22}0_3Na$; $M^+ = 261.1$); however, the yield was quite low and we could not isolate the desired product in acceptable purity. In the latter case, the reaction resulted in decomposition of triflate **1a**, and a significant amount of ethyl isobutyrate was recovered.

(7) An alternative pathway, enolization of **1** and fragmentation to provide a ketene intermediate, is inconsistent with a deuterium-labeling experiment. See the Supporting Information for details.