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A mild, chemoselective, one-pot synthesis of δ-keto α-cyano esters by organocatalysis

Gang Liu, Yingcai Wang *

Department of Therapeutic Discovery, Amgen Inc., 1120 Veterans Blvd., South San Francisco, CA 94080, USA

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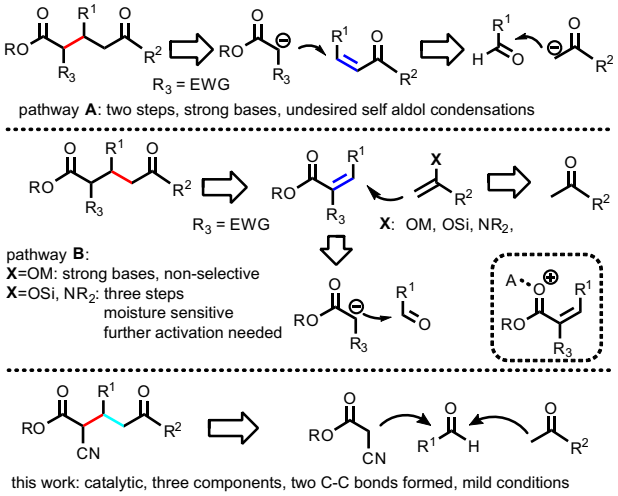
ABSTRACT

A sequential condensation of α-cyano esters, aldehydes, and ketones with catalytic amount of pyrrolidine/HOAc at room temperature has been developed. This method offers a chemoselective, one-pot cascade access to δ-keto α-cyano esters with moderate to good yields under mild conditions.

δ-Keto esters, as a class of 1,5-dicarbonyl compounds, are very common, yet important synthetic intermediates, especially in terpenoid synthesis and δ-lactone/lactam preparation.[1] The classic synthetic pathway (Scheme 1, pathway A) entails the disconnection leading to a malonate type synthon that functions as a highly reactive nucleophile under basic conditions, and an α,β unsaturated ketone as the corresponding electrophile.[2] Retrosynthetically, the latter usually goes further back to an aldehyde and a ketone by Claisen–Schmidt condensation.[3,4]

Another logically reasonable disconnection (Scheme 1, pathway B) is the Michael addition of a ketone enolate, or the equivalent thereof, to an alkylidene malonate type conjugate electrophile. The principal challenge of pathway B lies in the generation of a reactive yet selective nucleophile from ketones under mild conditions. Formation of a ketone enolate (X = OM) normally requires a strong base. This type of nucleophiles is highly reactive but not selective. The 1,4 addition to conjugate electrophiles is complicated with the addition to carbonyl groups of the conjugated system (1,2 addition) and further addition to the keto groups of the initial 1,4 addition products. Vinyl silyl ether or enamine formation in a stoichiometric fashion is an alternative, mild way to activate the ketones (X = OSi, NR_2),[5] however, it requires an extra step to prepare these compounds from the corresponding ketones in addition to the preparation of the conjugate electrophile.

In the past decade, organocatalysis has been brought to the attention of synthetic chemists and has profoundly diversified the bond disconnection strategies in organic synthesis design.[6] Enamine catalysis, as one of the major models of activation in organocatalysis, provides a reversible and mild way to activate the α-position of carbonyl compounds. Amine catalyzed Michael addition, particularly, has attracted considerable attention recently.[7] The Michael acceptors are often confined to highly reactive conjugated systems such as nitroalkenes and alkylidene malonates. The Michael donors are mainly aldehydes and specific



Scheme 1. Pathways to δ-keto ester synthesis.

* Corresponding author. Tel.: +1 650 244 2231; fax: +1 650 837 9369.
E-mail address: yingcaiw@amgen.com (Y. Wang).

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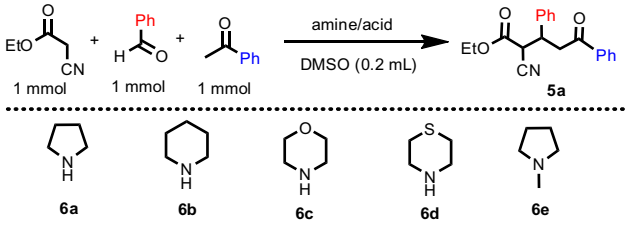
ketones, that is cyclic aliphatic ketones and acetone.[8] High levels of enantioselectivity (up to 99% ee) have been reported on conjugate addition of aldehydes or ketones to β-dimethyl(phenyl)silylmethylene malonate and trifluoroethylidene malonates.[9]

Along with our studies in multicomponent reactions to prepare pyridones,[10] we became interested to explore the preparation of δ-keto esters through a one-pot, three-component condensation of ketones, aldehydes, and malonates (Scheme 1). Barbas's group reported that (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine catalyzed three-component reaction of diethyl malonate, acetone, and benzaldehydes in moderate enantioselectivities.[8c] List and Castello reported that L-proline is efficient in catalyzing a three-component reaction between Meldrum's acid, acetone (or cyclic ketones), and a range of aldehydes.[11] Herein we describe a pyrrolidine catalyzed three component condensation of α-cyano ethyl acetate with a wide range of aldehydes and ketones.[12]

To realize the preparation of δ-keto esters by amine catalyzed addition of ketones to conjugated system, the choice of suitable α,β unsaturated ester as the Michael acceptor is critical. The acceptor must be electrophilic enough to ensure the reactivity, yet the electrophilicity must also be maintained at a certain level so that the amine catalyst would not be quenched by an azo-Michael addition to the Michael acceptor. At the outset of our study, failure was encountered when alkylidenemalonate **1** was used as the substrate with pyrrolidine/acetate salt as the catalysts in DMSO (Scheme 2). Unsaturated ketone **4** was obtained as the major product, arising from the retro Knoevenagel reaction and subsequent aldol-condensation of benzyl ketone and benzaldehyde. Another candidate, alkylidenemalononitrile **2**, gave a very complex mixture, though previously reported as a suitable Michael acceptor in a primary amine catalyzed Michael addition reaction.[8g] Pleasingly, desired product **5a** was obtained when **3** was used as the Michael acceptor. Furthermore, cyanoacrylate **3** could be prepared in situ, making this process an attractive method by which an aldehyde, an α-cyano ester, and a ketone are condensed sequentially to give the desired δ-ketoester with the formation of two C–C bonds under mild conditions in a catalytic fashion.

Thus, when an equimolar mixture of α-cyano ethyl acetate, benzaldehyde, and acetophenone was added with 0.3 equiv of pyrrolidine and followed by 0.3 equiv of acetic acid, desired δ-keto product **5a** was obtained with good yield (Table 1, entry 1). Further screening of the amines showed that other secondary amines

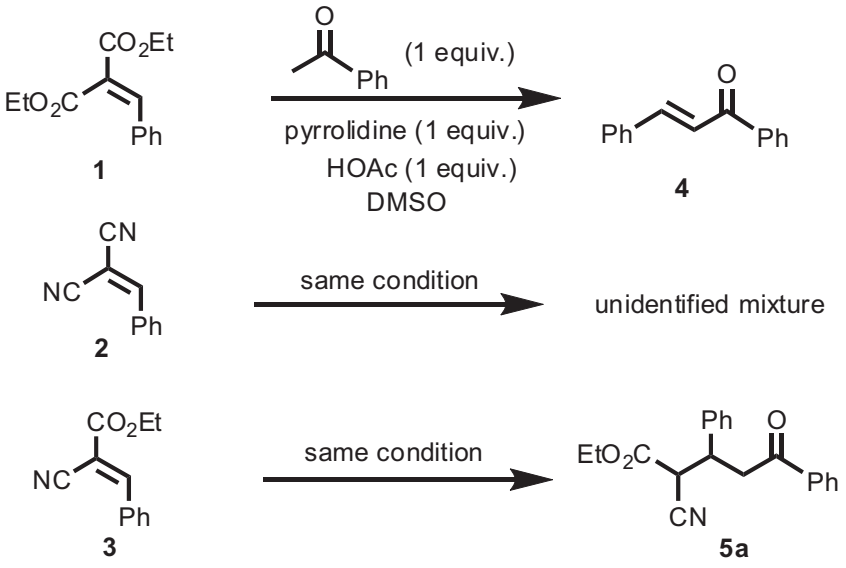
Table 1
Optimization of the reaction conditions



Entry[a]	Amine (equiv)	Acid (equiv)	*T* (h)	Yield[b] (%)
1	**6a** (0.3)	HOAc (0.3)	24	76
2	**6b** (0.3)	HOAc (0.3)	24	55
3	**6c** (0.3)	HOAc (0.3)	24	32
4	**6d** (0.3)	HOAc (0.3)	24	5
5	**6e** (0.3)	HOAc (0.3)	24	—[c]
6	**6a** (0.3)	No acids	24	—[c]
7	**6a** (0.3)	TFA (0.3)	24	45
8	**6a** (0.3)	HOAc (0.3)	24	69[d]
9	**6a** (0.3)	HOAc (0.3)	24	80[e]
10	**6a** (0.3)	HOAc (0.3)	24	53[f]
11	**6a** (0.3)	HOAc (0.3)	72	85[e]
12	**6a** (0.2)	HOAc (0.2)	48	88[e]
13	**6a** (0.2)	HOAc (0.2)	48	92[e,g]

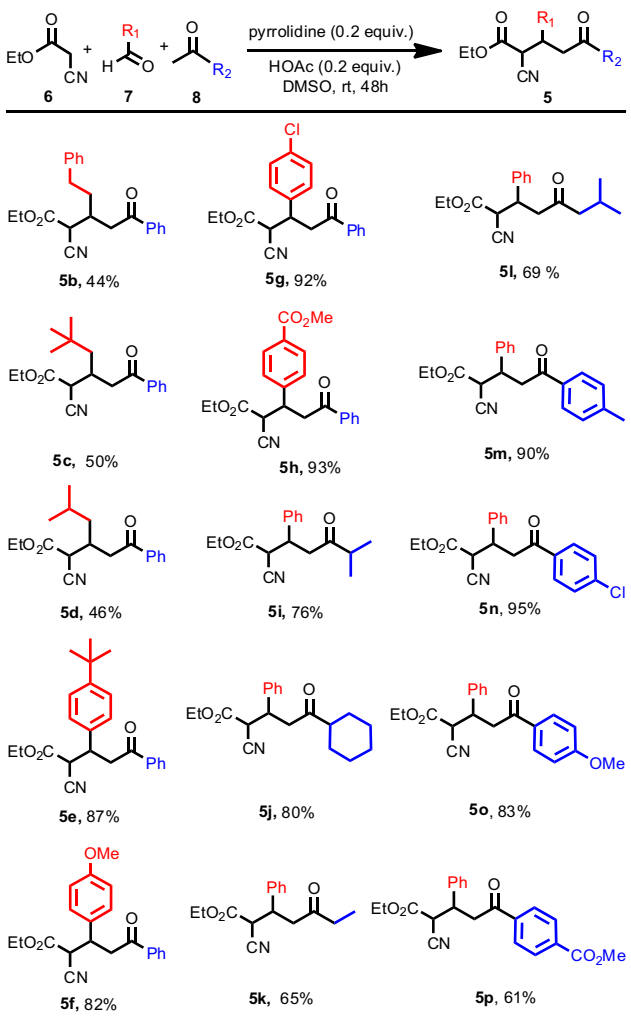
[a] Condition: 1 mmol scale in 0.2 mL DMSO; amine was added slowly followed by HOAc.
[b] Values refer to isolated yields after column chromatography.
[c] No desired product observed.
[d] 0.4 mL DMSO.
[e] 0.1 mL DMSO.
[f] Neat condition.
[g] 2 equiv ketone was used.

(**6b**–**6d**) are inferior to pyrrolidine (entries 2–4). Tertiary amine **6e** was not capable of catalyzing this reaction at all (entry 5), producing only ethyl 2-cyano-3-phenylacrylate as the Knoevenagel condensation product along with unreacted acetophenone. The absence of an acid counterpart did not produce desired product (entry 6), and a stronger acid (TFA) did not help to improve the yield (entry 7). Performing the reaction under more dilute conditions led to decreased yield (entry 8), while running the reaction neat gave only modest yield (entry 10). The optimal concentration was

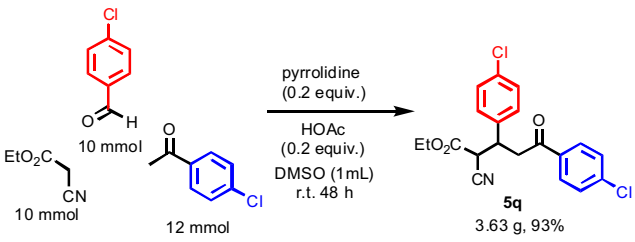


Scheme 2. Identification of suitable Michael acceptors.

Table 2
Synthesis of α-cyano δ-keto esters[a,b]



[a] Condition: 1 mmol scale, pyrrolidine (0.2 equiv) was added followed by HOAc (0.2 equiv), DMSO (0.1 mL), room temperature, 48 h.



Scheme 3. Gram scale synthesis of **5q**.

highly concentrated to maintain the reaction a homogeneous mixture (entry 9). After a brief survey of the reaction time and catalyst loading, the optimal condition was identified (entry 12). It is noteworthy that under this condition, an equimolar mixture of the three components gave excellent yield, and two equivalents of ketone gave only slightly higher yield under the optimized condition (entry 13), which implies no large excess of ketone is needed to drive the reaction to completion.

With the optimized condition we then investigated the generality of this method by expanding the substrate scope to both aliphatic and aromatic aldehydes and ketones (Table 2).

Aliphatic aldehydes are applicable to this method with modest yields (**5b**–**5d**), while aromatic aldehyde gave excellent yields, independent of the electronic nature of the substituents (**5e**–**5h**). Aliphatic ketones with various substitutions also worked well (**5i**–**5l**). When aromatic ketones were examined, it was found that strong electron withdrawing substituent (**5p**) lowered the yield considerably comparing to the electron donating substituents (**5m**, **5o**).

To demonstrate the scalability of this method, a gram scale synthesis of ketoester **5q** was executed (Scheme 3). A mixture of α-cyano ester, 4-chloro benzaldehyde, and slightly excessive 4-chloro acetophenone in DMSO was sequentially treated with a catalytic amount of pyrrolidine and acetic acid. After stirring at ambient temperature for 48 h, a clean product was obtained with excellent yield following purification by Flash chromatography.[13]

In summary, a catalytic, three-component condensation of an α-cyano ester, an aldehyde, and a ketone has been realized by a sequential Knoevenagel–Michael reaction under very mild conditions. This method provides versatile access to δ-keto α-cyano esters in a single step from simple, commercially available materials.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.145. These data include MOL files and InChiKeys of the most important compounds described in this article.

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