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Proline-catalyzed aldol reactions of acyl cyanides with acetone: an efficient and convenient synthesis of 1,3-diketones

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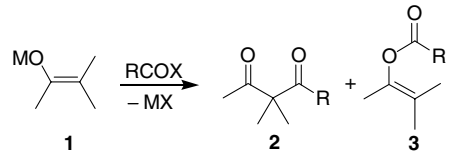
Abstract—The aldol-type addition of acetone towards (un)substituted benzoyl, heteroarylcarbonyl or α,β-unsaturated acyl cyanides was efficiently catalyzed by L-proline (30 mol %) to give 2-hydroxy-4-oxo-2-substituted pentanenitriles. Upon the treatment with sodium hydroxide, the adducts transformed to 1,3-diketones in good-to-excellent yield, furnishing an efficient and convenient method for the regioselective synthesis of 1,3-diketones.

1,3-Diketones are one of the most synthetically important classes of compounds.

One of the familiar syntheses of 1,3-diketones is the C-acylation of simple ketones via their metal enolates, enamines or silyl enol ethers, using acyl chlorides or cyanides as the acylating reagent, with or without catalysts. Since the ketone anions (**1**) are ambident, such acylating reaction often results in the formation of a mixture of C-acylated product (**2**) and O-acylated product (**3**), which are difficult to separate (Scheme 1). Although some methods such as the reaction of ketone metal enolates with acyl chlorides[1] or acyl cyanides,[2] the acylation of enamines,[3] the direct BF_3 acylation of ketones,[4] and the C-acylation of silyl enol ethers,[5] had been reported as reactions, which preferentially lead to C-acylated ketones, the 1,3-diketones obtained are usually contaminated with variable amounts of O-acylated products. In



1 2 3

Scheme 1. Formation of C- and O-acylated products.

Keywords: 1,3-Diketones; Proline; Acyl cyanides; Acetone; Addition.
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2002, Stephen J. Haswell reported the C-acylation of lithium enolate or silyl enol ether with acyl cyanide, which excluded the formation of O-acylated product. However, the ketone must be converted to its enolate by using LiHMDS, an expensive reagent, or a silyl enol ether must be prepared beforehand.[6]

The second familiar synthesis of 1,3-diketones is the C-acylation of acetylacetone or its derivatives by acyl halides or esters followed by base-promoted cleavage of a carbonyl group. The C-acylation of acetylacetone using acyl chloride in the presence of a base, also suffered from the competition of O-acylation. For example, under phase-transfer conditions, acylation of acetylacetone and of ethyl acetoacetate with acetyl chloride and benzoyl chloride yielded O-acylated enol esters predominantly.[7] The chemoselectivity of such acylations depends on the nature of the solvent, electrophile, metal counterion, reaction temperature and structure of the substrate. Alan R. Katritzky reported a novel method for the preparation of 1,3-diketones from acetylacetone using the strategy of acylation–deacylation, in which, 1-acylbenzotriazoles were employed as the acylating reagents.[8] However, to improve the yield of this reaction is still necessary.

As a versatile organocatalyst, proline has drawn much attention in recent years.[9] We were interested in broadening the scope of proline-catalyzed asymmetric aldol-type addition. In the view of electron effects, the electron-withdrawing cyano group in an acyl cyanide molecule

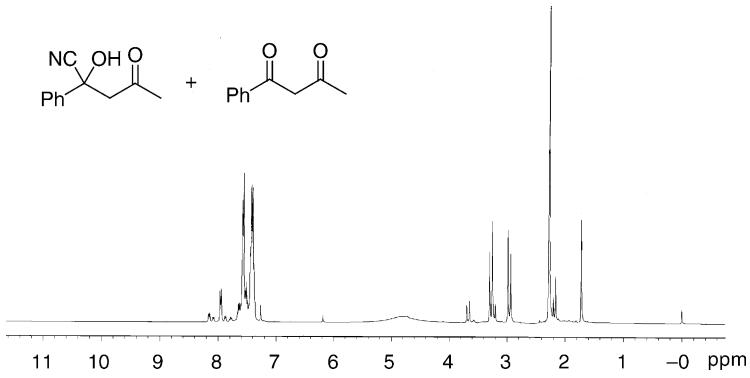
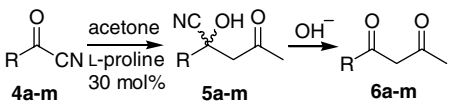


Figure 1. ^{1}H NMR spectrum of 2-hydroxy-4-oxo-2-phenyl-pentane-nitrile containing 1-phenyl-butane-1,3-dione as impurity.

would enhance the reactivity of the adjacent carbonyl carbon atom so that a proline-catalyzed aldol-type addition of acetone to acyl cyanide may occur. Indeed, benzoyl cyanide, when stirred with proline in acetone at room temperature, gave a new compound, which was identified as the expected aldol-type adduct (**5a**). This adduct was found labile and eliminated HCN to form 1,3-diketone during chromatographic purification or storage at room temperature. From the ^{1}H NMR spectrum of the crude 2-hydroxy-4-oxo-2-phenyl-pentanenitrile (Fig. 1) one can find the presence of 1-phenyl-butane-1,3-dione (**6a**), formed from the adduct by elimination of a hydrogen cyanide molecule. However, analogue **5g** was found so stable that it could be purified by column chromatography and characterized by NMR.[10] Also, evidence for the formation of the adduct **5a** has been received from its acetylation and characterization of the resulting compound.[11]

After evaporation of the excess acetone, the treatment of the crude adduct **5a** with base, afforded C-acylated acetone **6a** in excellent yield, without any detectable formation of O-acylated or diacylated product. This proline-catalyzed aldol-type addition furnished an efficient, convenient and regio-specific method for the C-acylation of acetone, affording 1,3-diketones after a base-promoted elimination of hydrogen cyanide (Scheme 2).

Encouraged by this success, a variety of acyl cyanides, including substituted benzoyl, cinnamoyl, furan-2-carbonyl cyanide were then tested. The results are summarized in Table 1.



a: R = Ph;
b: R = 4-CH_3-C_6H_4;
c: R = 2-CH_3-C_6H_4;
d: R = 4-CH_3O-C_6H_4;
e: R = 2-F-C_6H_4;
f: R = 4-F-C_6H_4;
g: R = 2-Cl-C_6H_4;
h: R = 4-Cl-C_6H_4;
i: R = 2-Br-C_6H_4;
j: R = 4-Br-C_6H_4;
k: R = 4-NO_2-C_6H_4;
l: R = Ph-CH=CH;
m: R = furan-2-yl

Scheme 2. L-Proline-catalyzed acylation of acetone with acyl cyanides as the acylating reagents.

Table 1. Syntheses of 1,3-diketones from acyl cyanides and acetone[12]

Entry	R	Cat (mol %)	Product	*t* (h)	Yield % (Conv %)
1	Ph	30	**6a**	30	93
2	4-Me-C_6H_4	60	**6b**	72	75
3	2-Me-C_6H_4	60	**6c**	96	<10 (16.7)
4	4-MeO-C_6H_4	60	**6d**	96	71
5	2-F-C_6H_4	30	**6e**	11	92
6	4-F-C_6H_4	30	**6f**	10	93
7	2-Cl-C_6H_4	30	**6g**	12	94
8	4-Cl-C_6H_4	30	**6h**	10	92
9	2-Br-C_6H_4	30	**6i**	15	87
10	4-Br-C_6H_4	30	**6j**	10	90
11	4-NO_2-C_6H_4	30	**6k**	7	88
12	Ph-CH=CH	30	**6l**	18	89
13	Furan-2-yl	30	**6m**	60	82

From the data listed in Table 1, we found that for most acyl cyanide tested, diketone was obtained in good to excellent yield when the reaction was carried out at room temperature. The substitution effects were obvious: the introduction of an electron-withdrawing substituent accelerated the reaction while electron-donating substituents retarded the reaction. For example, the shortest reaction time was found in the reaction of 4-nitrobenzoyl cyanide, which has a typical electron-withdrawing substituent NO_2 in the molecule (entry 11); reaction of substrates with electron-donating substituent, such as methyl or methoxy group, gave relatively low yield and need longer reaction time than benzoyl cyanide itself, even with 60 mol % of L-proline. Also, regular stereo effects were observed. All *ortho*-substituted substrates had some-lower reaction rate compared to the corresponding *para*-substituted congener. Especially, the reaction of 2-methylbenzoyl cyanide was too slow to be practically employed for the preparation of the corresponding 1,3-diketone.

From the data listed in Table 2, we noticed that under the reaction conditions, proline itself could be acylated and lost in catalytic activity.[13] Employment of proline much less than 30 mol % (10 mol %, for example) was proved disadvantageous (entry 2) probably because the lowered catalyst amount decreased the reaction rate, resulting in a prolonged reaction time, which offered a chance of proline N-acylation, which decreases the reaction rate further and the reaction could not be completed in fact.

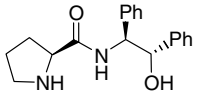
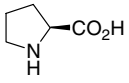
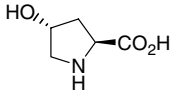
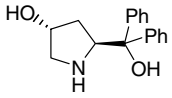
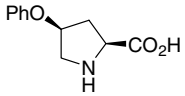
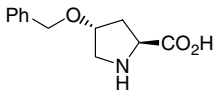
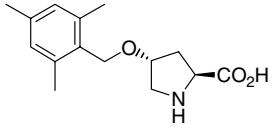
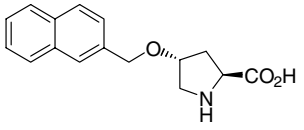
Table 2. Effects of temperature and amount of the catalyst

Entry	R	Cat (mol %)	T (°C)	Product	t (h)	Yield % (Conv %)
1	Ph	30	rt	**6a**	30	93
2	Ph	10	rt	**6a**	72	61
3	Ph	30	−25	**6a**	32	90
4	Ph	30	−78	**6a**	72	6.3 (6.6)
5	4-MeC_6H_4	60	rt	**6b**	72	75
6	4-MeC_6H_4	60	−25	**6b**	72	74
7	4-MeC_6H_4	60	−78	**6b**	72	8.6 (9.2)

With the reactions conducted at −25 °C, no significant changes in reaction time and yield were found (entries 3 and 6), probably because the N-acylation of proline was restricted at this temperature. At −78 °C, the reaction proceeded very slowly (entries 4 and 7).

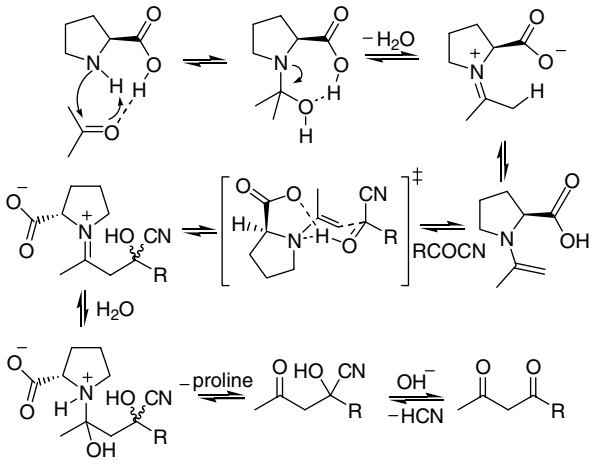
A variety of proline derivatives were also tested as catalysts for this reaction under standard conditions (Table 3). To our surprise, (4*R*)-hydroxy-(*S*)-proline did not show any catalytic activity, although it was reported to catalyze intermolecular aldol reaction between acetone and aldehydes enantioselectively.[14] However, the O-alkylated or arylated hydroxyprolines were found to be effective catalysts for this reaction (entries 5, 6, 7, and 8). Among them, (4*S*)-phenoxy-(*S*)-proline and (4*R*)-phenyl-methoxy-(*S*)-proline showed catalytic activities similar to that of proline itself, while proline derivatives with steric hindered substituents showed lower activities. Aminoalcohols did not show any catalytic activity (entries 1 and 4), although (*S*)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)pyrrolidine-2-carboxamide showed an excellent catalytic activity for the intermolecular aldol additions between acetone and substituted benzaldehydes.[15]

Table 3. Catalytic activity of various proline derivatives

Entry	Cat[a]	t (h)	Yield (%)[b]
1		—	—
2		30	93
3		—	—
4		—	—
5		25	94
6		24	94
7		48	88
8		50	87

[a]All reactions were carried out at room temperature, employing 30 mol % of the catalyst.

[b]Chemical yields are given on the isolated products and all products are determined by IR, ^{1}H NMR, ^{13}C NMR, HRMS, etc.



Scheme 3. A proposed mechanism.

A mechanism, similar to that proposed by Carlos F. Barbas III[14] for the aldol addition of acetone to aldehyde, was proposed, as shown in Scheme 3. We supposed that acetone was activated by formation of an enamine with proline. An acyl cyanide molecule was pulled close to the enamine by the proline hydroxyl group through hydrogen-bonding interaction. The enamine attacked the carbonyl group of the acyl cyanide acceptor, forming the key intermediate, which then eliminated HCN on treating with sodium hydroxide to afford the 1,3-diketone.

In summary, we have shown that the aldol-type addition of acetone towards (un)substituted benzoyl, heteroarylcarbonyl, and α,β-unsaturated acyl cyanides was efficiently catalyzed by L-proline (30 mol %), to give 2-hydroxy-4-oxo-2-substituted-pentanenitriles in good-to-excellent yields. On treating with sodium hydroxide, the adducts eliminated HCN, furnishing an efficient and convenient method for regioselective synthesis of 1,3-diketones.

Acknowledgements

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10. ^{1}H NMR of **5g** (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.85 (d, $J = 18.4$ Hz, 1H), 3.93 (d, $J = 18.4$ Hz, 1H), 5.83 (s, 1H), 7.33–7.40 (m, 2H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 7.6$ Hz, 1H).
11. ^{1}H NMR of acetylated **5a** (400 MHz, $CDCl_3$): δ 2.13–2.15 (m, 6H), 3.25 (d, $J = 17.2$ Hz, 1H), 3.45 (d, $J = 17.2$ Hz, 1H), 7.38–7.44 (m, 3H), 7.54 (d, $J = 7.6$ Hz, 2H).
12. A typical procedure for the reaction of acyl cyanides with acetone is as follows: L-proline (70 mg, 0.6 mmol) was stirred in acetone (10 mL) for 30 min. To this was added acyl cyanide (2.0 mmol) at room temperature while stirring for the desired time given in Table 1 (checked by TLC, ether/ethyl acetate = 4:1, v/v). The solid was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was stirred in a mixture of CH_2Cl_2 (10 mL) and 5% NaOH (5 mL) for 30 min, extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1, v/v) yielding the 1,3-diketone in the yields given in Table 1. All diketones obtained were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy.
13. This had been demonstrated by the separation of *N*-benzoyl-(*S*)-proline from the reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87–1.94 (m, 1H), 2.00–2.09 (m, 1H), 2.23–2.29 (m, 1H), 2.33–2.39 (m, 1H), 3.59 (t, $J = 6.8$ Hz, 2H), 4.56 (br s, 1H), 4.76 (dd, $J = 7.6$, 4.8 Hz, 1H), 7.38–7.58 (m, 5H).
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