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Journal Name

ARTICLE

Acid-promoted rapid solvent-free access to substituted 1,4-dihydropyridines from β-ketothioamides

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β-Ketothioamides (KTAs) have been used as building blocks with aldehydes and β-enaminonitriles for synthesis of 1,4-dihydropyridines in the presence of AcOH under solvent-free conditions within 5 min. This new strategy exhibits remarkable features such as high chemoselectivity, mild reaction conditions, easily available substrates, and good yields.

Introduction

1,4-Dihydropyridines (DHPs) are an important class of *N*-heterocyclic scaffold with low molecular weight in medicinal field, which provide important ligands for biological and pharmacological receptors.[1] DHPs are widely used as antitumor,[2] antiasthmatic,[3] anticonvulsant,[4] analgesic,[5] insecticide,[6] anti-HIV drugs,[7] and antimicrobial and antioxidant.[8] Many examples of clinically-used calcium channel antagonist (such as nifedipine and benidipine)[9] and calcium agonists (such as BAY K 8644)[10] also have DHP scaffolds. Furthermore, DHPs have been used in organic syntheses because of their reducing ability.[11]

As a result, the synthesis of multisubstituted DHPs has attracted increasing attention, and a number of procedures have been established.[12] The traditional method for the construction of DHPs was the classical Hantzsch synthesis, a multicomponent condensation involving β-ketoesters, aldehydes and ammonia.[13] Coutinho and coworkers[2] synthesized multisubstituted DHPs by using β-enaminonitriles[14] and acrylamides. Although these reported approaches remain widely used protocols to access DHP derivatives, most of them suffer from significant limitations such as complex operations, long reaction times, multistep synthesis, or difficult purification. Thus, development of a more general, efficient, rapid, and viable route for their preparation is desired.

Recently, β-ketothioamides (KTAs)[15] have received much attention as versatile building blocks in organic synthesis, which have been extensively used in various carbon-carbon and carbon-heteroatom bond-forming reactions for construction of heterocycles. An extensive literature survey revealed that the base-catalyzed reactions of KTAs were most common, and numerous reports have been disclosed (Fig. 1, types A, B, and C). However, acid-promoted reactions of KTAs have rarely been reported (Fig. 1, type D).

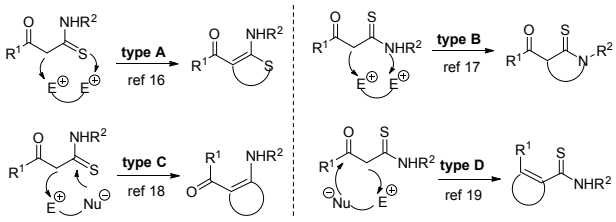
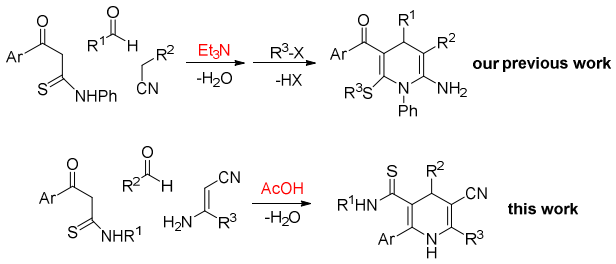


Fig. 1 Some reaction types of β-ketothioamides.

Our group[20] reported the method for the synthesis of DHPs using KTAs as synthons in the presence of Et_3N (Scheme 1). As a continuation of our ongoing research interest in the synthesis of heterocycles by utilizing KTAs as synthons,[21] and with the purpose of developing new methods to form DHP skeleton with the easy introduction of different substituents, herein, we report a facile solvent-free three-component reaction for the synthesis of DHPs in the presence of AcOH from KTAs, aldehydes, and β-enaminonitriles.



Scheme 1 Strategies for the synthesis of DHPs.

Results and discussion

The reactions of KTAs (**1**) with aldehydes (**2**) and β-enaminonitriles (**3**) might occur in two different modes (Scheme 2). In mode 1 (type D), the intermediates **7** would

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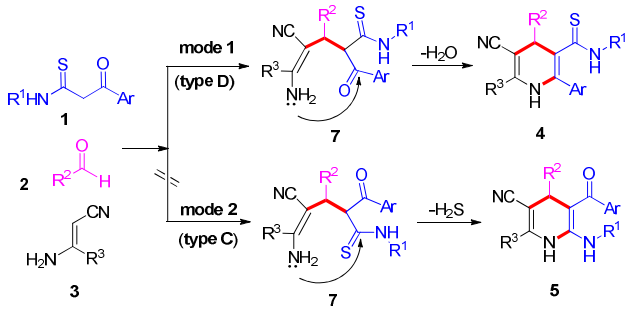
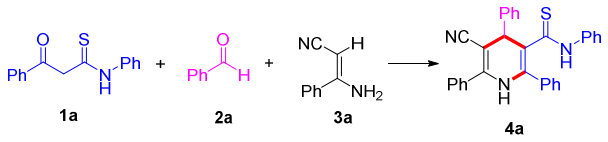
undergo the intramolecular *N*-cyclization of NH_2 group in β-enaminonitriles attacking C=O leading to **4**. In mode 2 (type C), the product **5** would be produced by intramolecular *N*-cyclisation of the NH_2 group of β-enaminonitriles on the C=S bond. Fortunately, we obtained a single crystal (Figure S1 in ESI) of the product **4b** (Table 2), and the X-ray diffraction analysis of **4b** revealed that the obtained product was compound **4** instead of **5**, which demonstrated that the three-component reaction occurred with high chemoselectivity of the ketone versus the thioamide.



Scheme 2 Chemoselectivity of the reaction.

Optimization of the reaction conditions was carried out with 3-oxo-*N*,3-diphenylpropanethioamide (**1a**), benzaldehyde (**2a**), and 3-amino-3-phenylacrylonitrile (**3a**) as model substrates, and the results are collected in Table 1.

Table 1 Optimization of reaction conditions[a]



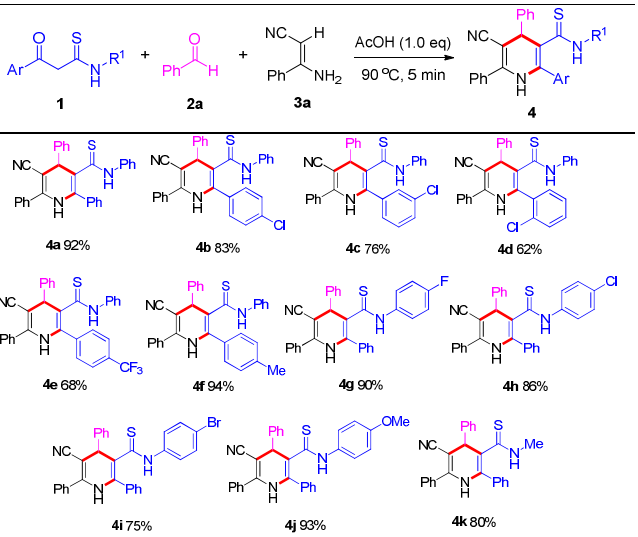
Entry	Promoter (equiv)	Temp (°C)	Solvent	Time (min)	Yield (%)[b]
1	Et_3N (2.0)	90	none	6 h	mixture
2	DABCO (2.0)	90	none	6 h	mixture
3	Na_2CO_3 (2.0)	90	none	6 h	mixture
4		82	MeCN	7 h	50
5		90	none	5	43
6	**AcOH (1.0)**	**90**	**none**	**5**	**92**
7	AcOH (0.5)	90	none	5	83
8	AcOH (2.0)	90	none	5	92
9	AcOH (1.0)	80	none	5	87
10	AcOH (1.0)	100	none	5	84
11	CF_3COOH (1.0)	90	none	5	86
12	PhCOOH (1.0)	90	none	5	91
13	HCl (1.0)[c]	90	none	5	76
14	$InCl_3$ (1.0)	90	none	5	78

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.2 mmol) and solvent (1.0 mL). [b] Isolated yield. [c] Conc. HCl (12 M), 0.017 mL.

Initially, we envisioned the synthesis of multisubstituted DHPs by a straightforward one-pot three-component reaction in the presence of Et_3N at 90 °C under solvent-free conditions. Unfortunately, the reaction system became a complex mixture (Table 1, entry 1). Next, other bases such as DABCO and Na_2CO_3 were screened and also led to mixtures (entries 2 and 3). When the reaction was carried out in MeCN without any additive at 90 °C, only 50% yield of **4a** was obtained even after 7 h (entry 4). When the model reaction was conducted in the absence of solvent and additive at 90 °C, 43% yield of **4a** was afforded, however, the reaction time was significantly shortened to 5 min (entry 5). This result promoted us to explore acidic solvent-free conditions. Then the reaction was performed in a stoichiometric amount of AcOH at 90 °C, delightedly, the yield of **4a** was improved to 92% within 5 min (entry 6). The amount of AcOH was also investigated (entries 7 and 8), the results showed increasing or decreasing the amount of AcOH did not improve the yield of **4a**. Changing the reaction temperature failed to improve the yield of **4a** (entries 9 and 10). Other Bronsted acids such as CF_3COOH, PhCOOH, and HCl, and Lewis acid such as $InCl_3$ were also tested. However, compared to AcOH, they could not provide better results (entries 12-14). It is clear that the optimum reaction conditions are AcOH (1.0 equiv) as promoter without any solvent at 90 °C.

With the optimal conditions in hand, we commenced exploring the substrate scope.

Table 2 Substrate scope of KTAs **1**[a,b]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), **3a** (0.5 mmol), and AcOH (0.5 mmol). [b] Isolated yields.

First, we tested the scope of substrates **1** (Table 2). KTAs bearing either electron-donating or electron-withdrawing substituents on aroyl group (Ar) could be accommodated, and reacted efficiently with **2a** and **3a** to yield the desired products. KTAs with a substituent at 3- or 4-positions on Ar could provide good to excellent yields. However, when the substituent on the aroyl group of KTAs was at 2-position such

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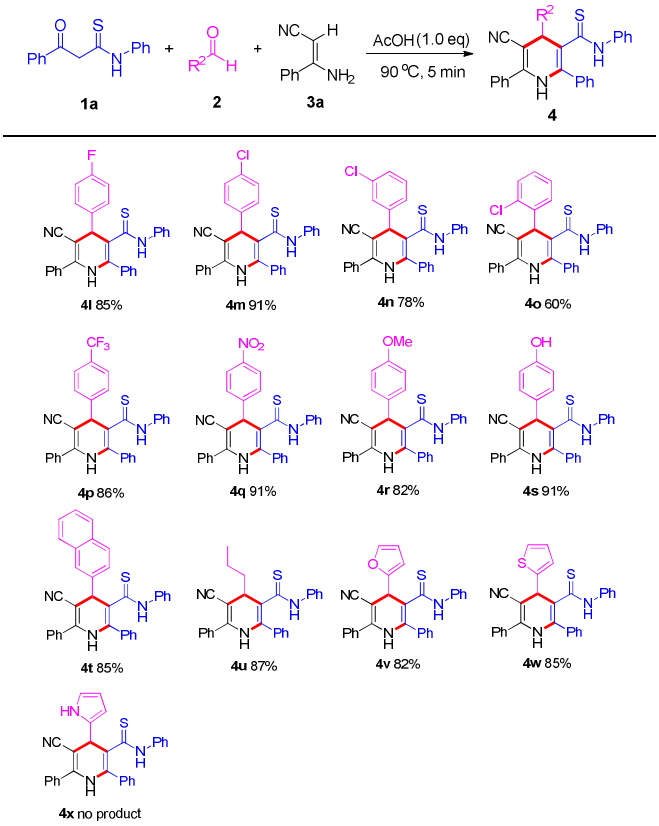
as *ortho*-Cl, the yield was relatively low, which might be due to steric hindrance. Additionally, compound **4d** was provided two rotational isomers contributed by the *o*-chlorine atom.[22] When R^1 is an alkyl substituent such as methyl, the corresponding DHP was hard to purify and compound **4k** was obtained by MPLC.

For the substrates **2**, we employed various aromatic, aliphatic, and heterocyclic aldehydes (Table 3). Aromatic aldehydes with either electron-donating or electron-withdrawing groups showed similar reactivities. However, compared to 3- and 4-positions, the substituents at 2-position on the phenyl ring gave relatively lower yields, which might be due to steric hindrance. Aliphatic aldehydes such as *n*-butyl aldehyde and heterocyclic aldehydes such as 2-furaldehyde, and 2-thienyl aldehyde were well accommodated in the reaction. Unfortunately, when 2-pyrrol aldehyde was used, the reaction system became a dark brown complex mixture and did not give the desired product **4x**. This may be considered as a limitation for practical achievement in this reaction.

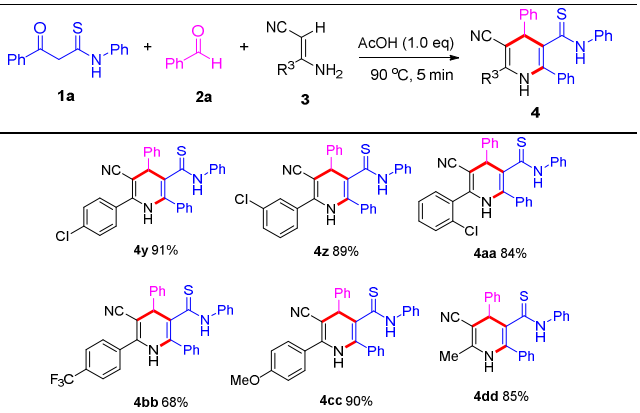
Table 3 Substrate scope of aldehydes **2**[a,b]



[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), **3a** (0.5 mmol), and AcOH (0.5 mmol). [b] Isolated yields.

Efforts were also made to expand the scope of substrates **3** (Table 4). As one can see from Table 4, both aromatic and aliphatic β-enaminonitriles **3** could smoothly react with **1a** and **2a**, yielding the corresponding DHP derivatives **4y**-**4dd** in good to excellent yields. Adding the substituent group at different positions on the aryl ring had no obvious influence on the yield.

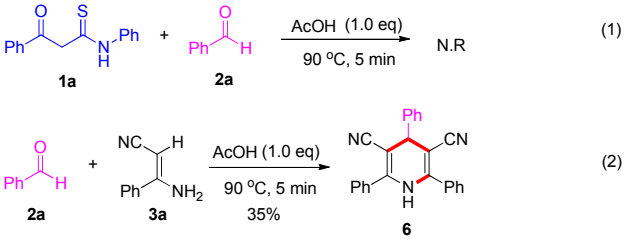
Table 4 Substrate scope of β-enaminonitriles **3**[a,b]



[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **3** (0.5 mmol), and AcOH (0.5 mmol). [b] Isolated yields.

The structures of all new compounds **4** were identified by their ^{1}H NMR, ^{13}C NMR, HRMS spectra, and ascertained by the single-crystal X-ray diffraction analysis of compound **4b**.

It is noteworthy that all of the products only need washing with dichloromethane (DCM) rather than column chromatography or recrystallization. This easy purification makes this methodology facile, practical, and rapid to execute.



Scheme 3 Control experiments

In order to explore the reaction mechanism, several control experiments were conducted (Scheme 3). **1a** (0.2 mmol) did not react with **2a** (0.3 mmol) under the standard conditions (eq 1); whereas the reaction of **2a** (0.3 mmol) with **3a** (0.2 mmol) under same conditions provided compound 6[23] (eq 2). These results indicate that β-enaminonitriles **3** could firstly react with aldehydes **2** in this reaction under acidic conditions.

On the basis of the above results, a possible mechanism for the tandem reaction leading to the synthesis of multisubstituted DHPs **4** is depicted in Scheme 4. First, the reaction of aldehydes **2** with β-enaminonitriles **3** results in the formation of adducts **A**. KTAs **1** undergo a rapid keto-enol tautomerization and then take place the Michael addition to **A** to generate intermediates **7**. Due to the easy protonation of the oxygen atom of C=O group by AcOH, **7** undergo intramolecular *N*-cyclization of NH_2 group from β-

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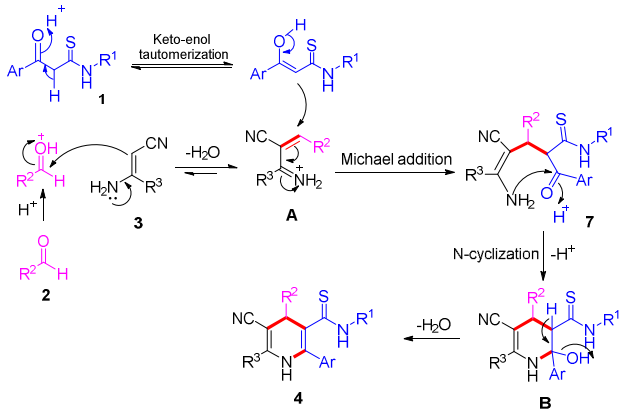
enaminonitrile moiety attacking C=O to give intermediates **B**, which eliminate a molecule of H_2O to provide products **4**.



Scheme 4 Plausible mechanism for the formation of **4**.

Conclusions

In summary, we have successfully developed a novel, operationally simple one-pot three-component reaction promoted by AcOH to synthesize novel multisubstituted DHPs. The high efficiency and chemoselectivity, short reaction time (within 5 min), free solvents, good functional compatibility, and broad substrate scope render this reaction particularly valuable for organic synthesis. This novel method not only extends the application of KTAs in organic synthesis but also provides an access to structurally diverse DHPs.

Experimental section

General information

Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. Melting points were recorded on a RY-1 microscopic melting apparatus and were uncorrected. ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra were recorded at 125 MHz by using a Bruker Avance 500 spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). HRMS was performed on an Ultima Global spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on Saturn 724+ instrument. The medium pressure liquid chromatography (MPLC) purification was performed by the Swiss company Büchi with reversed-phase column prepacked with C-18 silica gel, mobile phase: MeOH-H_2O 1:1 (v/v), flow rate 2.5 mL/min. The substrate KTAs were prepared according to a reported procedure.[24]

General procedure

Synthesis of β-enaminonitriles (3a for example). Benzylcyanide (5 mmol), acetonitrile (5 mmol) in toluene (30 mL) was stirred in a flask in oil bath, then powdered *t*BuOK (14 mmol) was added to the stirring solution. The mixture was stirred for 10 min at 40 °C. Water (50 mL) was added and the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to 5 mL under reduced pressure. Petroleum ether was added to the organic layers and kept at room temperature to give the pure product **3a** as crystal in the yield of 90%.

Synthesis of DHPs 4. KTAs **1** (0.5 mmol), aldehydes **2** (0.75 mmol), β-enaminonitriles **3** (0.5 mmol), and AcOH (0.5 mmol) were placed into a flask and the mixture was stirred for 5 min at 90 °C in oil bath until **3** were completely consumed. After completion of the reaction as indicated by TLC (petroleum ether/EtOAc, 4:1 v/v), the mixture was cooled to room temperature, and the solid mixture was washed with DCM to give the pure products **4**. Specially, compound **4k** was obtained by MPLC.

Acknowledgements

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Graphical abstract

Acid-promoted rapid solvent-free access to substituted 1,4-dihydropyridines from β-ketothioamides

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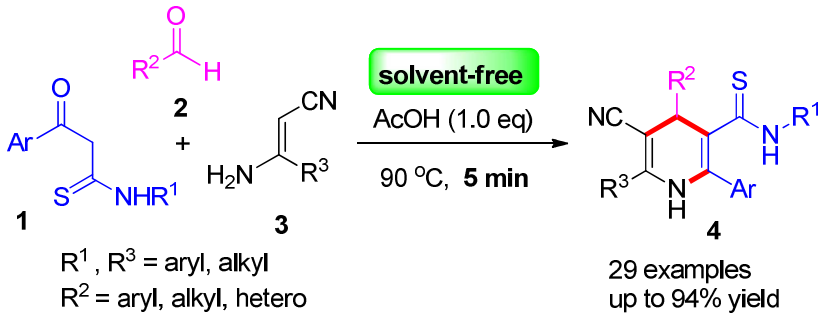

1,4-Dihydropyridines were synthesized via a tandem reaction of *β*-ketothioamides with aldehydes and *β*-enaminonitriles by AcOH as promoter within 5 min.