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Temperature controlled condensation of nitriles: efficient and convenient synthesis of β -enaminonitriles, 4-aminopyrimidines and 4-amidinopyrimidines in one system†

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A series of β -enaminonitriles, 4-aminopyrimidines and 4-amidinopyrimidines were synthesized by condensation of organonitriles in one system. A wide variety of compounds were obtained in good to excellent yields by simply controlling the reaction temperature. The base-induced transformation process is easy for production. The scope and versatility of the method have been successfully demonstrated with 72 examples. The flexible and diversified characteristics of nitriles were introduced based on electronic effect, steric effect, position of substituted groups and intermolecular hydrogen bonding. An updated reaction mechanism is proposed based on the study of the stoichiometric reaction conditions at variable temperature, and on the investigation of products with *cis-trans* configuration transformation.

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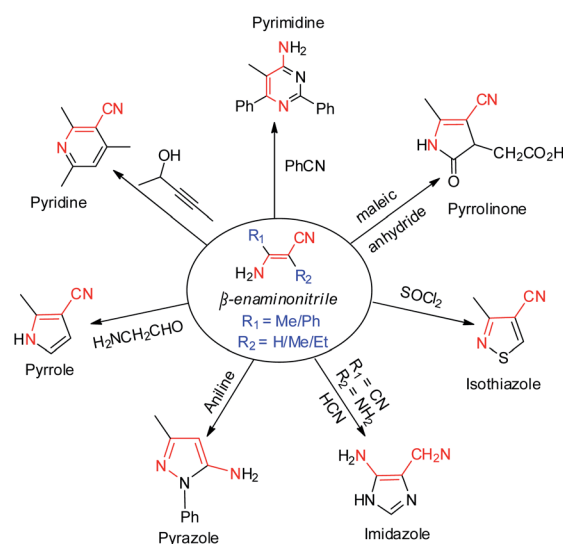
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Introduction

As a versatile and designable building block, β -enaminonitrile plays an important role in the synthesis of pharmaceuticals, fungicides, dyes and biological pesticides.^{1,2} Many heterocyclic compounds, *e.g.* pyrimidine,³ pyridine,⁴ pyrrole,⁵ pyrazole,⁶ imidazole,⁷ isothiazole⁸ and pyrrolinone⁹ are proposed to be synthesized from β -enaminonitriles (Scheme 1). The great significance of them in synthetic chemistry has consistently stimulated the development of new methods for their preparation. Meanwhile, the base-facilitated alkylation of stabilized carbanions, directed by functional groups, has been extensively employed in the construction of small molecule precursors for organic synthesis.¹⁰ Among which, the alkylation of deprotonated nitrile anions occupies a unique position as being powerful nucleophiles, ideally suited for transformation into a variety of functional groups.¹¹ The challenging issues lie ahead in controlling selectivity and efficiency of transformation, from the viewpoints of practicality in laboratory synthesis and industrial applications.

β -Enaminonitriles were commonly synthesized by condensation of two functional amide/nitrile molecules under high temperature and/or strong base conditions (Scheme 2a and b),^{1,12,13} Other methods were also developed to obtain β -enaminonitriles, including the refluxing of methylenecarbonitriles with triethyl orthoformate and amine (Scheme 2c),¹⁴ the metal-catalysed condensation of active nitriles with isocyanides or cyclopropanes (Scheme 2d and e),^{15,16} the cyclization of chloromethyl *p*-tolyl sulfoxide with cyanomethyl lithium and (Scheme 2f),¹⁷ and the



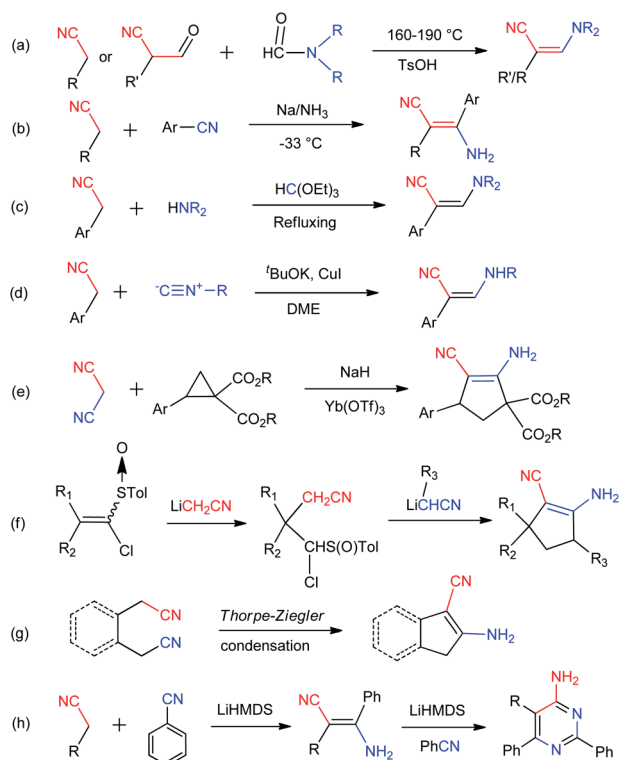
Scheme 1 Synthesis of diverse heterocycles from β -enaminonitriles.

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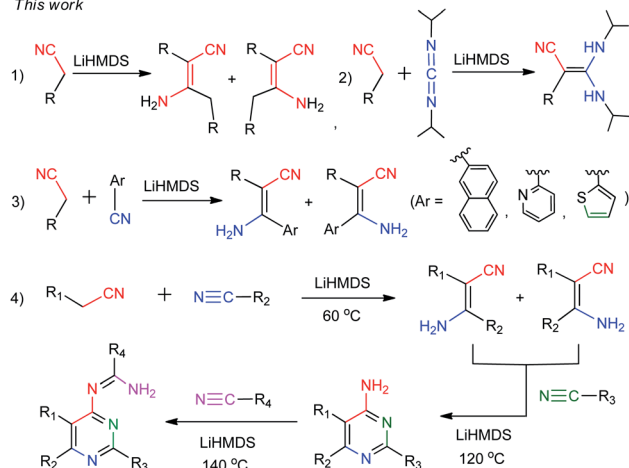
† Electronic supplementary information (ESI) available: Characterization of compounds; X-ray crystal structures of compounds 2j, 4a and 5e; synthesis and characterization of 2,3,3-triphenylacrylonitrile. CCDC 1956320–1956327, 1969352. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra10866a



Previous work



This work



Scheme 2 Methods and routines for the synthesis of β -enaminonitriles and its related 4-aminopyrimidines, 4-amidinopyrimidines.

Thorpe-Ziegler condensation of aliphatic nitriles (Scheme 2g).¹⁸ However, all these reactions show limited tolerance for the synthesis of various enaminonitriles due to the rigorous reaction conditions and/or limited reaction substrates.^{1,12-18} Thus, the utilization of β -enaminonitriles for the synthesis of different substituted 4-aminopyrimidines is rarely described. 4-Aminopyrimidines and their derivatives are an important building blocks found in the molecules of natural products.¹⁹ The biochemical activity of them has been discovered and explored for the treatment of diseases such as T cell-mediated autoimmune and inflammatory disorders,²⁰ external injuries²¹ and cancer.²² An

efficient method is desired for the synthesis of various β -enaminonitriles, 4-aminopyrimidines and their derivatives, consistent with the development of heterocyclic chemistry and its related medical synthetic chemistry.

Organonitriles possess versatile chemical properties,²³ and the nitrile group can be easily transformed into a variety of heterocyclic groups such as amines, amides, amidines, tetrazoles, triazoles, oxazoles and thiazoles.²⁴ The employment of nitriles as nitrogen source has become a scientific interest in the construction of nitrogenous substances and heterocyclic compounds.^{1,25} We recently reported a simple and catalyst-free method for the synthesis of β -enaminonitriles and 4-aminopyrimidines by using aliphatic nitriles as electron donors and benzonitriles as electron acceptor (Scheme 2h).²⁶ However, the application of aliphatic nitriles and other types of aromatic nitriles (e.g. naphthyl, pyridyl, thienyl) as electron acceptors has not been concerned. Also, the condensation of aliphatic nitriles only and the discussion of the *cis-trans* isomerization of β -enaminonitriles was not involved in that paper. Herein, we introduce the method for the synthesis of β -enaminonitriles by self-condensation of aliphatic nitriles, as well as reaction of aliphatic nitriles with *N,N'*-diisopropylcarbodiimide (DIC) and various aromatic nitriles. The discussion of *cis-trans* isomerization of β -enaminonitriles is concluded based on the results of condensation of various nitriles. Furthermore, the formation of 4-aminopyrimidines with various types of nitriles is examined, and a new type condensation of four-component nitriles is developed for the construction of novel multi-substituted 4-amidinopyrimidines.

Results and discussion

All the reactions were carried out under N_2 atmosphere in Teflon screw-cap sealed tubes. The condensation of phenylacetone nitrile (**1a**) was selected as a model reaction and optimized by changing reagents or reaction conditions to find out the most suitable condition (Table 1). Based on the experimental results obtained, it is concluded that the reaction of substrates **1a** (0.4 mmol) and lithium hexamethyldisilazide (LiHMDS, 0.2 mmol) in dimethoxyethane (DME) at $120^\circ C$ for 24 h gives the best result with the production of compound **2a** in yield up to 86% (entry 6). The LiHMDS salt works as a highly efficient base in deprotonation of the α -H of **1a**, and it was added in stoichiometric ratio for a completed reaction. Other alkali salts and/or organic bases of *t*BuOK, EtONa, CS_2CO_3 , 4-dimethylaminopyridine (DMAP) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) afforded the product of **2a** in lower yields (entry 1–2) or without yield (entry 3–5). Meanwhile, the type of solvent was important for the formation of **2a** (entry 6–11). Less polar solvents such as DME, anisole and THF would help to increase the reaction yield, among which the DME is the best choice (entry 6). In contrast, more polar solvents would be unfavourable for the generation of product with the decline of yield to trace in DMF (entry 11). The existence of hydrogen bonding interaction between solvent and intermediate imine/amine is suggested to be responsible for the inaction of the self-condensation reaction in more polar solvent system.



Table 1 Optimization of the formation of compound 2a^a

En	Base	Solvent	Temp (°C)	T (h)	Yield ^b (%)
1	^t BuOK	DME	120	24	12
2	EtONa	DME	120	24	26
3	CS ₂ CO ₃	DME	120	24	None
4	DMAP	DME	120	24	None
5	DBU	DME	120	24	None
6	LiHMDS	DME	120	24	86
7	LiHMDS	Anisole	120	24	55
8	LiHMDS	THF	120	24	45
9	LiHMDS	Dioxane	120	24	None
10	LiHMDS	DCE	120	24	None
11	LiHMDS	DMF	120	24	None
12	LiHMDS	DME	60	24	3
13	LiHMDS	DME	100	24	22
14	LiHMDS	DME	140	24	61
15	LiHMDS	DME	120	12	67
16	LiHMDS	DME	120	36	71


^a Reaction conditions: **1a** (0.4 mmol), base (0.20 mmol), solvent (1 mL), N₂. ^b Isolated yield. DME = dimethoxyethane, DMAP = 4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran, DCE = dichloroethane, DMF = *N,N*-dimethylformamide.

The percent conversion of nitrile was examined in a temperature range of 60–140 °C (entry 6, 12–14), and the temperature of 120 °C was determined as standard condition according to the transformation efficiency of compound **2a**. Lower temperature would decrease the yield dramatically down to 3% at 60 °C (entry 12), and higher temperature might not help to improve the efficiency of production (entry 14). In addition, the influence of reaction time on the production of **2a** was monitored at points of 12 h, 24 h and 36 h (entry 6, 15–16). It was found that 24 h would be a right time for the achievement of reaction. Shorter or longer time would be disadvantageous for the transformation of **1a** to **2a** with yields decreased to 67% at 12 h and 71% at 36 h, respectively.


Encouraged by the above results, we started to examine the scope of the reaction system as to other nitrile substrates (Table 2). A total of 29 organonitriles were chosen for analysis of the implication of reaction, including aliphatic nitriles, aromatic nitriles, heteroaromatic nitriles, dinitriles. The reactions produced 37 β-enaminonitrile compounds in the same way as phenylacetone nitrile (**1a**) worked. The yield distribution and production efficiency of β-enaminonitriles were discussed based on the electronic effect, steric effect and the synergic effect of functional groups on the nitriles. It was found that all the aliphatic nitriles could work both as electron donors and electron acceptors in the above reaction system, by means of deprotonation of the α-H of nitriles and polarization of the carbon atom on the CN triple bond. By contrast, the aromatic nitriles could only work as electron acceptors owing to the absence of α-H. Firstly, 25 alkyl organonitriles (**2a–2y**) were deprotonated and performed to study the electronic

Table 2 Scope of nitriles with respect to β-enaminonitriles^a


$$\begin{array}{c}
 \text{R}_1\text{---CH}_2\text{---CN} + \text{R}_1\text{---CH(R}_2\text{)---CN or R}_2\text{CN} \\
 \text{1} \qquad \qquad \qquad \text{1'}
 \end{array}
 \xrightarrow[120^\circ\text{C, 24 h}]{\text{LiHMDS, DME}}
 \begin{array}{c}
 \text{H}_2\text{N---CH=CH---R}_1 \\
 \text{R}_1\text{---CN} \\
 \text{2}
 \end{array}
 \text{ or }
 \begin{array}{c}
 \text{H}_2\text{N---CH(R}_2\text{)---CN} \\
 \text{R}_1\text{---CN} \\
 \text{3}
 \end{array}$$




2a (86% for E)
E:Z = 10:1




2b (85% for E)
E:Z = 12:1




2c (74% for E)
E:Z = 8:1




2d (71% for E)
E:Z = 7:1




2e (70% for E)
E:Z = 7:1




2f (73% for E)
E:Z = 12:1




2g (72% for E)
E:Z = 10:1




2h (63% for E)
E:Z = 14:1




2i (71% for E)
E:Z = 7:1




2j (67% for E)
E:Z = 7:1




2k (62% for E)
E:Z = 8:1




2l (51% for E)
E:Z = 6:1




2m (55% for E)
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
2n (47% for E)
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
2o (34% for E)
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
2p (72% for E)
E:Z = 26:1




2q (70% for E)
E:Z = 20:1




2r (78% for E)
E:Z = 15:1




2s (77% for E)
E:Z = 15:1




2t (78% for E)
E:Z = 28:1




2u (65% for E)
E:Z = 23:1




2v (76% for E)
E:Z = 27:1




2w (62%)^b




2x (72% for E)




2y (41% for E)
E:Z = 9:11




3a (88% for E)^c
E:Z = 11:1




3b (89% for E)^c
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
3c (90% for E)^d




3d (86% for E)^e




3e (85% for E)^c




3f (83% for E)^d




3g (62% for E)^c
E:Z = 8:1




3h (60% for E)^c
E:Z = 12:1




3i (73% for E)^d



3j (61% for E)^c
E:Z = 6:1



3k (65% for E)^c
E:Z = 4:1



3l (71% for E)^d

^a Reaction conditions: (1) **1** (0.40 mmol), LiHMDS (0.20 mmol), 120 °C, 24 h, N₂; (2) **1** (0.20 mmol), **1'** (0.20 mmol), LiHMDS (0.20 mmol), 120 °C, 24 h, N₂; (3) isolated yield. ^b LiHMDS (0.4 mmol). ^c 60 °C. ^d 140 °C. The absence of E/Z ratio means that no Z-form of product was found.

effect of functional groups in manner of self-condensation. The experimental results showed that electronic effect of substituted groups on the aliphatic nitriles had a significant impact on the production of β-enaminonitriles. The reaction of phenylacetone nitrile derivatives with electron-donating groups and weak electron-withdrawing substituted groups on the *para*-position of phenyl ring afforded the product of β-enaminonitriles in high yields (**2a–2g**, 70–86%). The electron-withdrawing fluoro group would offer the product in lower yield (**2h**, 63%) compared to its analogous bromo and chloro groups (**2f**, **2g**). No product of β-enaminonitrile could be isolated when the strong electron-



withdrawing groups (nitro and/or trifluoromethyl) substituted phenylacetonitrile derivatives were used for reaction. This point of view was consistent with the results presented in the formation of compounds **2p–2w**, in which the reaction of naphthyl groups and various alkyl groups substituted nitriles generated the products in yields 62–78%. Secondly, the steric hindrance to the reaction was studied by employment of methoxyl group (**2e**, **2j**), fluoro group (**2h**, **2k**, **2m**) and methyl group (**2c**, **2i**, **2l**) in the *para*-, *meta*- and *ortho*-positions, respectively. The result showed that the yields of reaction decreased dramatically from the substitution of *para*-position (**2c**, **2h**) to *ortho*-position (**2l**, **2m**), and no self-condensation product was found when the methoxyl group was employed in the *ortho*-position of the phenyl ring of phenylacetonitrile. This conclusion was in accordance with the fact that the dimethyl groups substituted nitriles (**2n**, **2o**) provided the products in much lower yields (47% and 34%). Finally, the condensation reaction was examined with mixed nitriles by using the deprotonated *n*-butyronitrile, 3-phenylpropionitrile, 2-pyridylacetonitrile as electron donors and benzonitrile, 2-cyanopyridine, 2-thiophenecarbonitrile, 2-naphthonitrile as electron acceptors (**3a–3l**). All the reactions were carried out at 60 °C and the products were obtained in good to excellent yields, except for those reactions using 2-pyridylacetonitrile as electron donor. The experiments of 2-pyridylacetonitrile were run at 140 °C for a complete transformation of starting materials to compounds (**3c**, **3f**, **3i**, **3l**) with the yields above 70%. It is supposed that the interaction of hydrogen bonding between the pyridine group of starting material and the amine group of product decreased the free degree of molecules, which would lead to the difficulty in the molecular collision at lower temperature.

In addition, it was found that the *cis*–*trans* isomerization was less evident in the formation of β -enaminonitriles in our reaction, since all the reactions produced *trans* isomers as main products. The yields of (*Z*)- β -enaminonitriles was less than 10% in the condensation of aliphatic nitriles only (worked as both electron donor and electron acceptor). The proportion of *cis* isomers turned out to be higher in the reaction of aliphatic nitriles (electron donors) with aromatic nitriles (electron acceptors). The yields could reach 16% in the formation of compound **3k**. It is thought that the aryl group on the aromatic nitriles decreased the energy barrier of C \equiv N bond cleavage, which would lead to decreasing energy consumption for C–C bonding again steric hindrance for the generation of *cis*-form products. Beyond that, no *cis*-form compounds was found in the formation of pyridyl group contained β -enaminonitriles. The strong intramolecular hydrogen bonding would bring the reaction to the generation of (*E*)- β -enaminonitriles during this process (Fig. 1). There was a special case: the condensation of acetonitrile in our conditions afforded *cis*–*trans* isomers of 3-aminocrotononitrile (**2y**) in a ratio of about 1 : 1, which could be due to the similar steric effect of methyl group and amine group to the cyanide group on the other carbon atom.

Our condensation reaction also demonstrates good reactivity and stability towards the formation of functional β -enaminonitriles with N=C=N type substrates (Table 3 and Fig. S1†). The reaction of phenylacetonitrile with *N,N'*-diisopropylcarbodiimide (DIC) in THF (60 °C, 6 h) afforded compound **4a** in yield

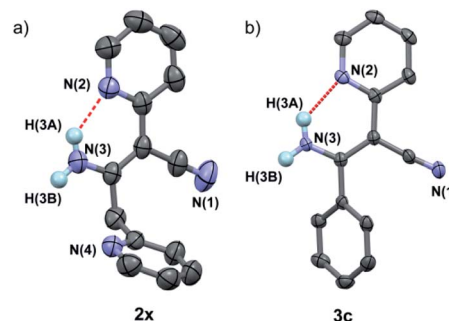
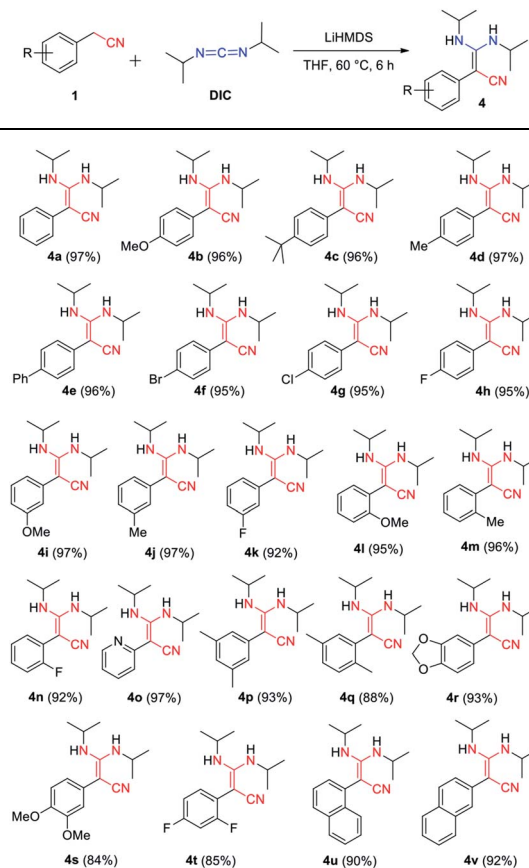


Fig. 1 Crystal structures of compounds **2x** (CCDC number: 1969352) (a) and **3c** (1956321) (b), showing the strong intermolecular hydrogen bondings between amine and pyridine groups ($N_2 \cdots H-N_3 = 1.998$ Å for compound **2x** and 2.010 Å for compound **3c**).

97% (Table 3). The scope of phenylacetonitriles substrates was explored by changing functional groups on the phenyl ring, including electron donating groups (MeO^- , tBu^- , Me^- ; **4b–4d**), electron withdrawing groups (Ph^- , Br^- , Cl^- , F^- ; **4e–4h**), difunctional groups (dimethyl, dimethoxyl, dioxolane, difluoro;

Table 3 Scope of nitriles with respect to compound **4^a**

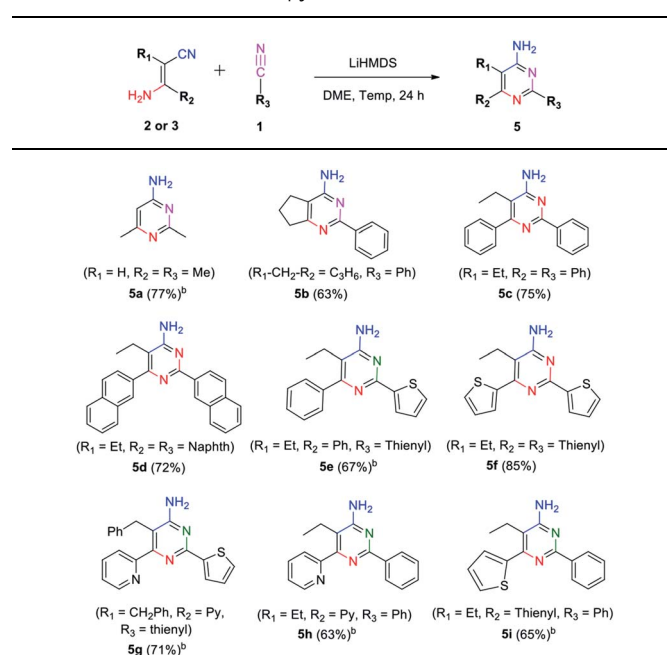


^a Reaction conditions: **1** (0.20 mmol), DIC (0.20 mmol), LiHMDS (0.20 mmol), 60 °C, 6 h, N_2 , isolated yield. DIC = *N,N'*-diisopropylcarbodiimide.

4p–4t) and aromatic groups (pyridyl, naphthyl; **4o**, **4u** and **4v**). All the reactions showed high production efficiency with the yields obtained from 84% to 97%, this result indicated that the above electron groups had weak impacts on the yield of the reaction. The difunctional substituted groups such as 3,5-dimethyl (**4p**), 2,5-dimethyl (**4q**), 2,4-difluoro (**4t**) and 3,4-dimethoxyl (**4s**) could reduce the generation of product by *ca.* 10%. Larger substituted group might be disadvantageous for the production of compound **4** and its derivative. Meanwhile, the reaction of DIC with 2-pyridylacetonitrile (**4o**), 1-naphthylacetonitrile (**4u**) and 2-naphthylacetonitrile (**4v**) gave the target products in good yields of 97%, 90% and 92%, respectively. It shows that our reaction have a good tolerance in the transformation of various aryl acetonitriles to β -enaminonitriles. The reactivity of nitrile in our system was also examined by reaction of phenylacetonitrile with benzophenone. The reaction afforded the product of 2,3,3-triphenylacrylonitrile in yield 80% after dehydroxylation (Fig. S2†). In addition, the synthetic utility of our reaction was also examined by running the experiments on gram scale. The self-condensation of phenylacetonitrile (**1a**) or cross-coupling of **1a** with DIC on 5 gram scale yielded the products of **2a** and **4a** in high overall yields of 80% and 95% (Scheme 3), respectively.

In order to explore the application of β -enaminonitriles for the construction of various substituted 4-aminopyrimidines, the condensation of β -enaminonitrile with another portion of nitrile was examined under base condition (Table 4). The reactions were carried out at 120 °C and 140 °C for the condensation of two-species (**5b–5d**, **5f**) and three-species organonitriles (**5e**, **5g–5i**) respectively. The self-condensation of acetonitrile was also completed at a temperature of 140 °C (**5a**). Nine types of 4-aminopyrimidines were obtained in yields 63–77%, which reflected that the reaction had a wide range of application in the synthesis of nitrogen containing heterocycles. Higher temperature was required for the achievement of multi-substituted 4-aminopyrimidines. It showed that the condensation of multi-components of nitriles was more difficult than that of fewer-components. Also, the electrophilicity of nitrile has an impact on the formation of 4-aminopyrimidine. The CN groups of aliphatic nitriles possess less electrophilicity to be attacked than aromatic nitriles, and the condensation of aliphatic nitriles for the synthesis of 4-aminopyrimidines needs higher temperature (≥ 140 °C). Furthermore, it was found that the component of 2-pyridylacetonitrile might not be suitable for the building of pyrimidine core, since the reactions of pyridylacetonitrile-contained β -enaminonitriles (**2w**, **3c**, **3f**, **3i**,

Table 4 Investigation of β -enaminonitriles for the construction of variable substituted 4-aminopyrimidines^a



^a Reaction conditions: **1** (0.20 mmol), **2** or **3** (0.20 mmol), LiHMDS (0.22 mmol), 120 °C, 24 h, N₂, isolated yield. ^b 140 °C.

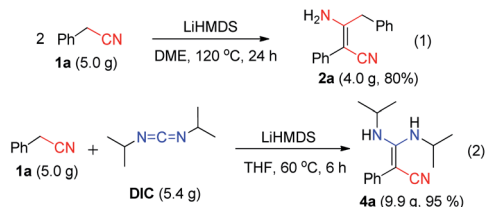
3l) with aromatic nitriles did not yield the target products under the same conditions. It is thought that the strong hydrogen bonding between the pyridine and amine group in the molecule limits the change of conformation from 'trans' to 'cis' (Fig. 1). The inversion of configuration is critical for the construction of pyrimidine core through cycloaddition with another portion of nitrile.

Interestingly, our method also provides an efficient way to synthesize 4-amidinopyrimidines by further condensation of 4-aminopyrimidines with a fourth portion of nitriles (Scheme 4).

To our best knowledge, the synthesis of 4-amidinopyrimidine was rarely reported, and the only example of (2,6-dimethyl-4-acetamidine)-pyrimidine was obtained as a by product in the condensation of acetonitrile under pressure of a few thousand atmosphere.²⁷ The preparation of different component 4-amidinopyrimidine has not been reported so far. In our lab, the reactions run smoothly with four typical type of 4-amidinopyrimidines and the products were obtained in yields over 76%. All the compounds were characterized by ¹H NMR, ¹³C NMR, mass spectra and X-ray crystallography (Fig. 2).

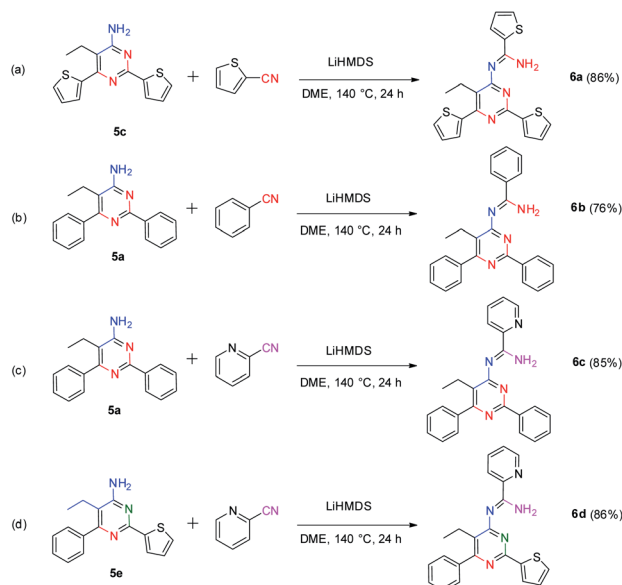
The bond lengths and bond angles of heterocyclic rings are comparable to those presented in the analogous compounds,²⁶ indicating the formation of pyrimidine cores and peripheral amidine function groups.

Based on the above experimental results, an updated mechanism is proposed in Scheme 5. One of hydrogen atoms on the methylene group of aliphatic nitrile is deprotonated by

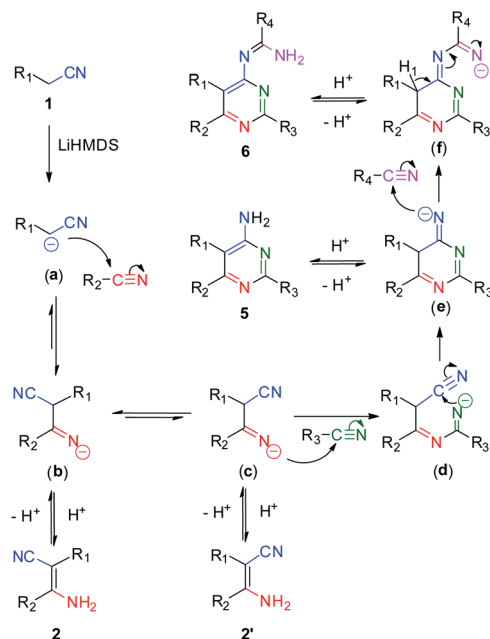


Scheme 3 Studies of the synthetic utility of β -enaminonitriles.



Scheme 4 Studies of the synthetic utility of β -enaminonitriles.

LiHMDS to form a cyanoalkylide anion (**a**). The anion attacks an adjacent nitrile molecule on the carbon atom of cyanide group to generate an intermediate imine species (**b**) and (**c**). The species (**c**) attacks another nitrile molecule to produce the imine species (**d**), following by an intramolecular cycloaddition reaction to form the intermediate (**e**). The imine species (**e**) attacks a fourth nitrile molecule to form the four-component intermediate (**f**). The chemical shift of hydrogen atom (H_A) and the electron transfer of C–H bond to the terminal imine nitrogen affords the product of **6** spontaneously. In addition, the intermediates (**b**), (**c**) and (**e**) would transform to compounds **2**, **2'** and **5** by controlling the addition of nitriles and the reaction temperature.



Scheme 5 Plausible mechanism of the condensation of various nitriles under base conditions.

Conclusions

In summary, we have described a simple and efficient method for the synthesis of β -enaminonitriles, 4-aminopyrimidines and 4-amidinopyrimidines in a total of 72 samples by means of condensation of organonitriles. The products can be obtained gradually by simply controlling the reaction temperature and the addition of nitrile substrates. The presence of various products in one system indicates the flexible and diversified characteristics of nitriles as electron donor and/or electron acceptor under base conditions. The extra reactivity and stability were studied based on electronic effect, steric effect, position of substituted groups and intermolecular hydrogen bonding. The employment of easily available reagents and mild reaction condition makes this method useful for synthesis chemistry. This work is superior in simple reaction condition, low-cost materials, broad substrate applicability and wide adaptability of production. It might provide a clue to synthesize various multi-substituted 4-aminopyrimidines and/or 4-amidinopyrimidines in favour of the development of biological chemistry, pharmaceutical chemistry and pesticide chemistry.

Experimental section

General information

Unless otherwise stated, the loading of starting materials were completed in a glove box. The sealed Teflon screw-cap tube (50 mL) was moved out of glove box, and heated to react under N₂ atmosphere. All the liquid nitriles were distilled before use. Other commercial-grade chemicals were used without further purification. DME was distilled over Na and degassed before use. Flash chromatography was performed on silica gel (200–

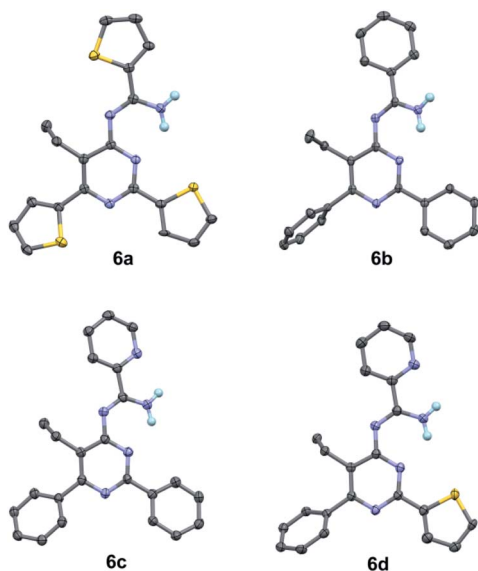


Fig. 2 Crystal structures of compounds **6a–6d** (CCDC number: 1956324–1956327).

300 mesh). The single crystal data of compounds were collected by a Cu-K α rotating anode source at 100 K, using a Supernova diffractometer with the ω -scan method. ESI-MS were obtained using a Bruker Impact II quadrupole time-of-flight mass spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III (400 MHz) and chemical shifts were expressed in δ ppm values with reference to tetramethylsilane (TMS) as internal standard. The NMR spectra were recorded in solvent of CDCl_3 (*Safety Note: along with standard practice (eye protection, fume hood, laboratory coat) the use of LiHMDS requires no water, far away from the environment of fire source and training for the operator.*).

General experimental procedures

Synthesis of compounds 2 or 3. Nitrile **1** (0.40 mmol) (**1/1'** = 0.20/0.20 mmol for **3**), lithium bis(trimethylsilyl)-amide (0.20 mmol) and dried DME (1 mL) were mixed in a 50 mL Teflon screw-cap sealed tube. The tube was charged with N_2 (1 atm) and the mixture was vigorously stirred at 60–120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a pad of silica gel and concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with petroleum ether/acetone (4 : 1 v/v) to afford β -enaminonitriles in yields up to 90% (**3c**).

Synthesis of compounds 4. Phenylacetonitrile (0.20 mmol), N,N' -diisopropylcarbodiimide (0.2 mmol), lithium bis(trimethylsilyl)amide (0.20 mmol) and dried THF (1 mL) were mixed in a 50 mL Teflon screw-cap sealed tube. The tube was charged with N_2 (1 atm) and the mixture was stirred at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a pad of silica gel and concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with petroleum ether/acetone (4 : 1 v/v) to afford compound **4** in yields up to 97% (**4a**).

Synthesis of compounds 5. β -Enaminonitrile (0.20 mmol), aromatic nitrile (0.2 mmol), lithium bis(trimethylsilyl)amide (0.20 mmol) and dried DME (1 mL) were mixed in a 50 mL Teflon screw-cap sealed tube. The tube was charged with N_2 (1 atm) and the mixture was stirred at 120–140 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a pad of silica gel and concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with petroleum ether/acetone (4 : 1 v/v) to afford compound **5** in yields up to 85% (**5f**).

Synthesis of compounds 6. 4-Aminopyrimidine (0.20 mmol), aromatic nitrile (0.2 mmol), lithium bis(trimethylsilyl)amide (0.20 mmol) and dried DME (1 mL) were mixed in a 50 mL Teflon screw-cap sealed tube. The tube was charged with N_2 (1 atm) and the mixture was stirred at 140 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a pad of silica gel and concentrated under reduced pressure. The crude product was purified on a silica gel column eluted with

petroleum ether/acetone (4 : 1 v/v) to afford compound **6** in yields up to 86% (**6a**).

Conflicts of interest

There are no conflicts to declare.

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