Efficient three-component one-pot synthesis of fully substituted pyridin-2(1*H*)-ones *via* tandem Knoevenagel condensation–ring-opening of cyclopropane–intramolecular cyclization†

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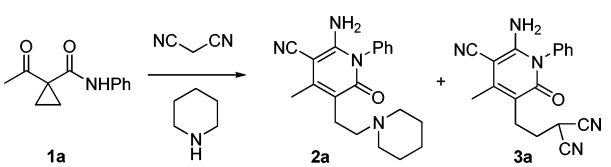
An efficient synthesis of fully substituted pyridin-2(1*H*)-ones was developed *via* three-component one-pot reactions of readily available 1-acetyl-1-carbamoyl cyclopropanes, malononitrile and cyclic secondary amines.

The utility of cyclopropane derivatives in organic synthesis has been recognized due to their well-known "unsaturated" character, which can lead to a variety of ring-opening reactions under the influence of a wide range of reactive species, such as electrophiles, nucleophiles, and radicals.[1] In our previous work, the ring-opening/ring closure reactions of 1-acetyl-1-carbamoyl cyclopropanes were developed for the synthesis of furoquinolines[2a] under metal catalyst, and halogenated pyridin-2(1*H*)-ones under Vilsmeier conditions.[2b] In conjunction with these studies and our continued interest regarding the synthetic potential of double EWGs (electron-withdrawing groups) activated cyclopropanes towards various carbo- and heterocycles,[3] we explored the Knoevenagel reaction[4] of 1-acetyl-1-carbamoyl cyclopropanes and malononitrile[5] in the presence of piperidine. As a result of the research, we developed a straightforward and efficient synthesis of fully functionalized pyridin-2(1*H*)-ones[6] of types **2** and **3** *via* a one-pot three-component tandem reaction. Multicomponent reactions (MCRs) have been refined in recent years as powerful and useful tools in synthetic chemistry and have attracted increasing attention due to the advantages of greater efficiency, atom economy and structural complexity.[7] The development of three-component reactions on appropriately substituted cyclopropanes has been reported by separate groups.[8] Herein, we wish to communicate our preliminary results.

The substrates, 1-acetyl-1-carbamoyl cyclopropanes **1**, were prepared following the procedure described by our group.[2] With substrates **1** in hand, we selected 1-acetyl-*N*-phenylcyclopropanecarboxamide **1a** as the model compound to examine the three-component reaction. The mixture comprising **1a**, malononitrile (2.0 equiv.) and piperidine (2.0 equiv.) was stirred in anhydrous DMF solution (5.0 mL) at room temperature. As indicated by TLC, the reaction proceeded smoothly and the two products **2a** and **3a** were successfully isolated after work-up and column chromatography gave these in 32% and 28% yield, respectively. The structures of **2a** and **2b** were characterized as fully substituted pyridin-2(1*H*)-ones on the basis of their spectra and analytical data (Scheme 1). Clearly, both piperidine and malononitrile take part in the ring-opening reaction of the cyclopropane, leading to different pendant groups on the pyridin-2(1*H*)-one framework. It was reasonable to believe that either **2a** or **2b** may be achieved as the main product after optimization of the reaction.

With this idea in mind, we modified the reaction in Scheme 1 by varying of the amount of malononitrile and piperidine in the reaction system. Upon treatment of **1a** with malononitrile (1.1 equiv.) and piperidine (2.0 equiv.), the reaction exclusively afforded **2a** in 68% yield (Table 1, entry 1). In the following work, a variety of 1-acetyl-1-carbamoyl cyclopropanes **1** were subjected to the reactions under identical conditions (Table 1). It was observed that cyclopropane substrates **1b–d** bearing a variety of amide groups were efficient for the three-component reaction, giving the corresponding pyridin-2(1*H*)-ones **2b–d** in high yields (entries 2–4). When the R^1 group on substrates **1** was changed to methyl, the desired cyclization product could not be attained (entry 5). In the case of cyclopropane substrate **1e** with a methyl substituent on the cyclopropyl ring, the reaction proceeded smoothly to furnish pyridin-2(1*H*)-one **2f** as a single regioisomer in 58% yield (entry 6). Such a regioselective ring-opening is in accordance with the results observed in similar ring-enlargement reactions.[2,9] In order to determine the scope with respect to the amine component, and to prepare multisubstituted pyridin-2(1*H*)-ones with different amine group, morpholine and pyrrolidine were selected. To our delight, the reactions of **1a**, **1d** and **1g** with morpholine and malononitrile, under identical conditions afforded the desired pyridin-2(1*H*)-ones **2g–i** in 60–65% yield (entries 7–9). Similarly, the reaction of **1d** with pyrrolidine and malononitrile also gave a satisfactory result and 2-amino-4-methyl-6-oxo-1-phenyl-5-(2-(pyrrolidin-1-yl)ethyl)-1,6-dihydropyridine-3-carbonitrile **2j** was obtained in 66% yield



Scheme 1 Reaction of **1a** with malononitrile in the presence of piperidine.

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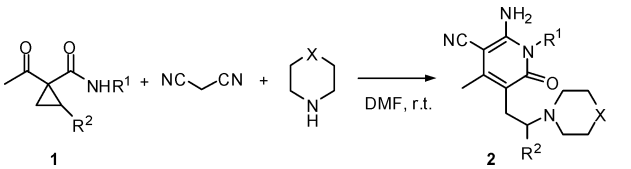
† Electronic supplementary information (ESI) available: Experimental details and characterization for all new compounds. CCDC 714333 (**4b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b905742k

Table 1 Three-component one-pot reactions leading to multi-substituted pyridin-2(1*H*)-ones **2**[a]



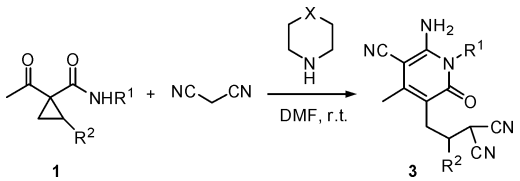
Entry	1	R^1	R^2	X	Time/h	2	Yield[b] (%)
1	**1a**	Ph	H	CH_2	2.5	**2a**	68
2	**1b**	4-ClPh	H	CH_2	2.0	**2b**	78
3	**1c**	4-MePh	H	CH_2	2.5	**2c**	65
4	**1d**	2,4-Me_2Ph	H	CH_2	3.5	**2d**	64
5	**1e**	Me	H	CH_2	8.0	**2e**	n.r.
6	**1f**	Ph	Me	CH_2	3.0	**2f**	58
7	**1a**	Ph	H	O	2.5	**2g**	60
8	**1d**	2,4-Me_2Ph	H	O	2.5	**2h**	61
9	**1g**	2-Cl	H	O	2.5	**2i**	65
10	**1d**	2,4-Me_2Ph	H	nil	3.0	**2j**	66

[a] **1** : malononitrile : amine = 1 : 1.1 : 2.0. [b] Isolated yields after purification by recrystallization in ethanol.

(entry 10). It is noteworthy that all the crude products **2** could be purified simply by recrystallization from ethanol.

Next, with the aim to make product **3a** in Scheme 1 to be the main product, we increased the amount of malononitrile and decreased that of piperidine simultaneously. After several trials, we found that when the feed ratio of **1a**–malononitrile–piperidine was 1 : 2.1 : 0.2, product **3a** could be obtained in a yield of 64% (Table 2, entry 1). Further decrease in the amount of piperidine to 0.1 equiv. was not enough to drive the reaction to completion. Under the optimized conditions mentioned above, a series of 1-acetyl-1-carbamoyl cyclopropanes **1b–d** and **1f** were reacted with malononitrile (2.1 equiv.) in the presence of piperidine (0.2 equiv.). The multi-component reactions proved to be efficient, affording the corresponding highly substituted pyridin-2(1*H*)-ones **3b–e** in

Table 2 Three-component one-pot reactions leading to multi-substituted pyridin-2(1*H*)-ones **3**[a]



Entry	1	R^1	R^2	X	Time/h	3	Yield[b] (%)
1	**1a**	Ph	H	CH_2	2.5	**3a**	64
2	**1b**	4-ClPh	H	CH_2	2.5	**3b**	83
3	**1c**	4-MePh	H	CH_2	3.5	**3c**	60
4	**1d**	2,4-Me_2Ph	H	CH_2	3.5	**3d**	65
5	**1f**	Ph	Me	CH_2	2.5	**3e**	66
6	**1a**	Ph	H	O	3.0	**3a**	72
7	**1g**	2-Cl	H	O	3.0	**3f**	76
8	**1a**	Ph	H	nil	3.5	**3a**	62
9	**1d**	2,4-Me_2Ph	H	nil	4.0	**3d**	64

[a] **1** : malononitrile : amine = 1 : 2.1 : 0.2. [b] Isolated yields after purification by recrystalization in ethanol.

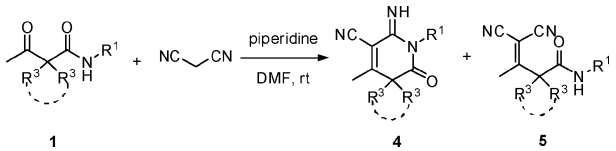
60–83% yield (entries 2–5). Likewise, other secondary amines such as morpholine and pyrrolidine were also subjected to reaction sequences. Consequently, in the reactions of **1a** or **1g** with malononitrile and morpholine, pyridin-2(1*H*)-ones **3a** and **3f** were obtained in 72 and 76% yield, respectively (entries 6 and 7). Pyrrolidine also proved to be effective in the reactions of **1a** or **1d** with malononitrile, giving **3a** in 62% yield and **3d** in 64% yield (entries 8 and 9). From the above one can see that the formation of either **2** or **3** as the main product was dependent on the feed ratio between the amine and malononitrile used in the reaction. The pyridin-2(1*H*)-ones of types **2** and **3** with molecular versatility and multi-substitutions indicated the efficiency of the three-component one-pot reaction. Furthermore, the functional groups on the framework and the flexible placement of the latent functionalities in these products make them extremely versatile intermediates in further synthetic transformations.

To gain insight into the mechanism of the multi-component reaction of 1-acetyl-1-carbamoyl cyclopropanes, malononitrile and piperidine, reactions based on acetylacetamides containing a 2,2-diethyl or cyclopentyl group[2,3a] with malononitrile and piperidine were conducted under otherwise identical conditions (Table 3). However, the reaction with 2,2-diethyl-3-oxo-*N*-phenylbutanamide **1h** gave none of the expected cyclization product **4a**. Instead, a Knoevenagel condensation product **5a** was obtained in high yield (entry 1). As for their cyclopentyl counterparts **1i** and **1j**, the corresponding pyridin-2(1*H*)-ones **4b** and **4c** could be obtained, but in fairly low yield (18% for **4b** and 20% for **4c**, entries 2 and 3) and prolonged reaction time (24 h).[10] The structure of **4b** was confirmed by single-crystal X-ray analysis (Fig. 1). The Knoevenagal condensation products **5b** and **5c** were demonstrated as the main products.[11]

On the basis of all the results mentioned above, a possible mechanism for the synthesis of substituted pyridin-2(1*H*)-ones of type **2** was proposed, as depicted in Scheme 2. The overall transformation involves tandem Knoevenagel condensation of **1** and malononitrile with piperidine as the base, ring-opening reaction of cyclopropane with piperidine as the nucleophile and intramolecular cyclization sequences. Interestingly, piperidine plays dual roles of both a base (twice) and a nucleophile (once) in the explored reactions. Similarly, when malononitrile acts as a nucleophile to fragment the cyclopropane moiety, the corresponding pyridin-2(1*H*)-ones **3** would be produced. The experimental results presented in Tables 1–3 demonstrate that the formation of the allene-type imino intermediate **II** *via* the ring-opening of cyclopropane, is favorable for the formation of fully substituted pyridin-2(1*H*)-ones.

In summary, an efficient and divergent synthesis of fully substituted pyridin-2(1*H*)-ones **2** and **3** has been developed based on the three-component one-pot reaction of readily available 1-acetyl-1-carbamoyl cyclopropanes **1**, malononitrile and secondary amines such as piperidine, morpholine or pyrrolidine. The overall transformation involves tandem Knoevenagel condensation of **1** with malononitrile, ring-opening reaction of activated cyclopropane towards a C–N nucleophile and intramolecular cyclization sequences. This protocol is associated with readily available starting materials, mild conditions, dense and flexible substitution patterns,

Table 3 Reactions of acetylacetamides containing a 2,2-diethyl or cyclopentyl group with malononitrile and piperidine[a]



Entry	1	R^1	R^3 or (R^3,R^3)	Time/h	4 (yield, %)[b]	5 (yield, %)[b]
1	1h	Ph	Et	24	4a (0%)	5a (85%)
2	1i	4-ClPh	$(CH_2)_4$	24	4b (18%)	5b (74%)
3	1j	4-OMePh	$(CH_2)_4$	24	4c (20%)	5c (70%)

[a] *Reagents and conditions*: **1** (1.0 mmol), malononitrile (2.0 mmol), piperidine (2.0 mmol), room temperature. [b] Isolated yields.

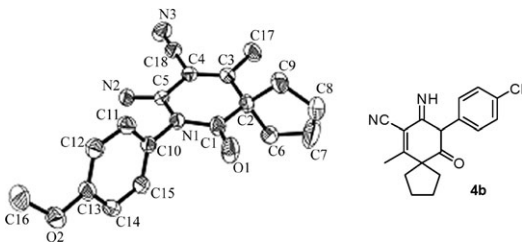
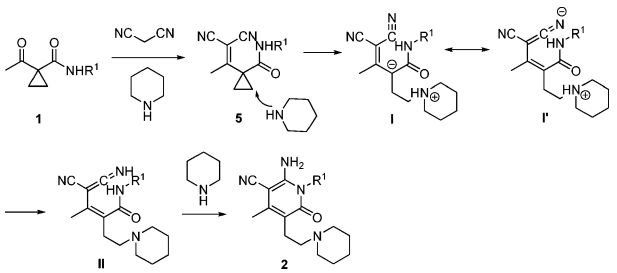


Fig. 1 ORTEP drawing of **4b**.



Scheme 2 Possible mechanism for the three-component reaction leading to fully substituted pyridin-2(1*H*)-ones **2**.

potential synthetic utility of the final products, and easy control of the reaction orientation by reaction conditions selection. Further research is ongoing in our laboratory.

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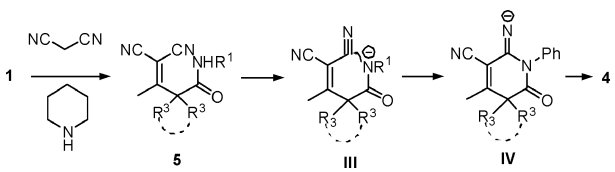

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