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[5C + 1N] Annulations: Two Novel Routes to Substituted Dihydrofuro[3,2-*c*]pyridines

Peng Huang, Rui Zhang, Yongjiu Liang, and Dewen Dong*

Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, China

dwdong@ciac.jl.cn

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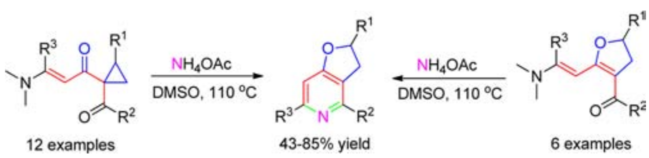
ABSTRACT



Two novel routes based on [5C + 1N] annulations for the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridines are described. Ammonium acetate (NH_4OAc) is used as an ammonia source in both routes. The first route utilizes 1-acyl-1-[(dimethylamino)alkenoyl]cyclopropanes as a five-carbon 1,5-bielectrophilic species and combines the [5C + 1N] annulation and regioselective ring-enlargement of cyclopropyl ketone into one pot, whereas the second route utilizes 3-acyl-2-[(dimethylamino)alkenyl]-4,5-dihydrofurans as the five-carbon synthons, which involves a sequential intermolecular aza-addition, intramolecular aza-nucleophilic addition/elimination, and dehydration reaction.

Furo[3,2-*c*]pyridines play an important role in organic chemistry for their presence in numerous natural products and synthetic organic compounds along with diverse bio-, physio-, and pharmacological activities.[1,2] In addition, furo[3,2-*c*]pyridines are common organic ligands in transition metal complexes.[3] Extensive work has generated many synthetic approaches to furo[3,2-*c*]pyridine derivatives,[4] starting either from preformed furans or pyridines.[5,6] However, most of the existing methods require multistep procedures to generate the pyridine and furan rings individually, and suffer from limited substrate scope and harsh reaction conditions. So far, there are only very few methods reported on the synthesis of furo[3,2-*c*]pyridines by construction of the furan and pyridine nuclei in a single step.[7] Therefore, to match the increasing scientific and pharmaceutical demands, it is still of continued interest and great importance to develop facile and efficient

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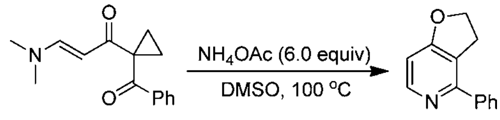
approaches for the preparation of furo[3,2-*c*]pyridines from readily available and simple starting materials.

On the other hand, cyclopropanes are extremely versatile synthetic intermediates due to their ready accessibility and good reactivity.[8,9] During the course of our studies on the chemistry of cyclopropanes,[10] we developed an efficient synthesis of 2,3-dihydrofurans via ring-enlargment of 1-benzoyl/carbamoyl-1-dimethylaminoalkenoyl cyclopropanes[11] in which a dual role of dimethylamino group in the transformation was noted as (i) a strong electron-donating group to direct the ring-enlargement reaction of cyclopropyl ketone and (ii) a good leaving group when subjected to a nucleophilic vinylic substitution (S_NV) reaction. In light of these findings, we recently achieved divergent synthesis of 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones and 2,3-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-ones from 1-carbamoyl-1-[(dimethylamino)alkenoyl]cyclopropanes in the presence of Vilsmeier-type reagent (Tf_2O/DMF) and Lawesson's reagent, respectively.[12] Inspired by these results and as a continuation of our interest in the synthesis of highly valuable heterocycles from cyclopropanes, we envisioned that 1-acyl-1-dimethylaminoalkenoyl cyclopropanes **1** might serve as a five-carbon 1,5-bielectrophilic species and undergo a formal [5C + 1N] annulation[13] with ammonia, and their cyclopropane ring might open new pathways for further and useful synthetic elaborations of the pyridinone skeleton. We report herewith the results on the synthesis of furo[3,2-*c*]pyridines based on the formal [5C + 1N] annulations.

The reaction of 1-benzoyl-1-[(dimethylamino)alkenoyl]-cyclopropane **1a** with NH_4OAc (6.0 equiv) was initially tested in dimethyl sulfoxide (DMSO) at 100 °C, which proceeded as indicated by TLC (Scheme 1). A main product was obtained in 36% yield and characterized as 4-phenyl-2,3-dihydrofuro[3,2-*c*]pyridine **2a**.[14]

Scheme 1. Reaction of **1a** with NH_4OAc in DMSO



The above result encouraged us to optimize the reaction conditions, including the ratio of NH_4OAc to **1a**, reaction temperature, and solvents. It was observed that **2a** could be obtained in 50% yield by raising the ratio of NH_4OAc/**1a** to 10:1, but a further increase of the amount of NH_4OAc had no significant effect on the reaction. Higher temperature, for example, 120 °C, would result in lower yield. The reaction could proceed in other reaction media, such as *N,N*-dimethylformamide, toluene, and glycerol, but the yield of **2a** was lower than in DMSO. Other ammonia sources, such as $NH_3 \cdot H_2O$, NH_3/ethanol, and NH_4Cl, were investigated in the reaction; however, no efficient result was achieved. A series of experiments revealed that the optimal results were obtained when the reaction of **1a** and 10.0 equiv of NH_4OAc was performed in DMSO at 110 °C for 3.0 h, whereby the yield of **2a** reached 55% (Table 1, entry 1).

Having established the optimal conditions for the 2,3-dihydrofuro[3,2-*c*]pyridine synthesis, we intended to determine its scope and limitation. Thus, a series of reaction of 1-acyl-1-[(dimethylamino)alkenoyl]cyclopropanes **1** and NH_4OAc were carried out under the conditions as for entry 1, Table 1. All the reactions of cyclopropanes **1b**–**i** bearing varied R^1 and R^2 groups proceeded smoothly to afford the corresponding 2,3-dihydrofuro[3,2-*c*]pyridines **2b**–**i** in moderate to good yields (Table 1, entries 2–9). The efficiency of the 2,3-dihydrofuro[3,2-*c*]pyridine synthesis was evaluated by subjecting cyclopropanes **1j**–**l** with R^3 as methyl group to the above conditions, and the corresponding **2j**–**l** were obtained, but in lower yields (Table 1, entries 10–12). It is worth noting that the ring-enlargement reaction of substrates **1** containing an additional R^1 substituent on the cyclopropane ring occurred in a highly regioselective manner (Table 1, entries 2–8, 11, and 12). Aactually, such regioselectivity was observed in the previous work achieved by us[11,12] and other researchers[9b] on the ring-enlargement reactions of cyclopropane. Therefore, we provide here a novel route for the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridines that combines the construction of furan and pyridine ring in a single step.

On the basis of the above experimental results together with some literature reported, a plausible mechanism for the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridines **2** from cyclopropanes **1** is proposed as depicted in Scheme 2. The attack of ammonia on the carbon–carbon double

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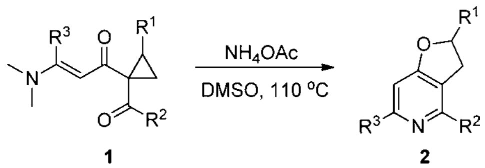
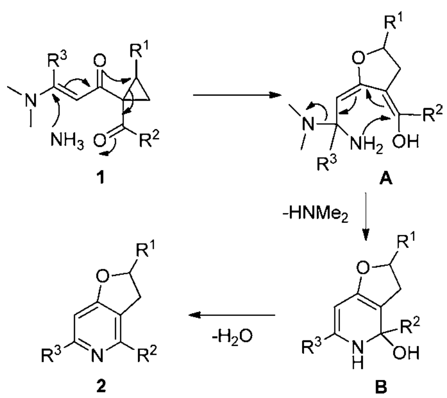
Table 1. Synthesis of 2,3-Dihydrofuro[3,2-*c*]pyridines **2** from 1-Acyl-1-[(dimethylamino)alkenoyl]cyclopropanes **1**[a]



entry	1	R[1]	R[2]	R[3]	2	yield[b] (%)
1	**1a**	H	Ph	H	**2a**	55
2	**1b**	Ph	Ph	H	**2b**	57
3	**1c**	4-ClC$_6$H$_4$	Ph	H	**2c**	52
4	**1d**	4-MeC$_6$H$_4$	Ph	H	**2d**	53
5	**1e**	Ph	Me	H	**2e**	61
6	**1f**	4-MeC$_6$H$_4$	Me	H	**2f**	64
7	**1g**	4-*t*-BuC$_6$H$_4$	Me	H	**2g**	56
8	**1h**	Ph	styryl	H	**2h**	50
9	**1i**	H	cyclopropyl	H	**2i**	58
10	**1j**	H	Ph	Me	**2j**	46
11	**1k**	Ph	Ph	Me	**2k**	43
12	**1l**	Ph	Me	Me	**2l**	45

[a] Reagents and conditions: **1** (1.0 mmol), NH$_4$OAc (10.0 mmol), DMSO (4.0 mL), 110 °C, 2.5–4.0 h. [b] Isolated yield.

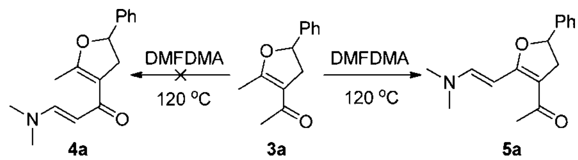
Scheme 2. Plausible Mechanism for the Reaction of **1** with NH$_4$OAc



bond of **1** at high temperature triggers the transformation[13e] and induces a regioselective ring-enlargement to generate intermediate **A**,[11,12b] followed by an intramolecular aza-nucleophilic addition and elimination to form bicyclic intermediate **B**,[15] which then undergoes dehydration reaction to give rise to the final product 2,3-dihydrofuro-[3,2-*c*]pyridine of type **2**. It should be noted that the added cyclopropane ring of **1** makes it possible to construct pyridine skeleton in the presence of amonia in this work, which is different from the traditional formal [5C + 1N] annulation of 1,5-dicarbonyl compounds and their equivalents with ammonia, Guareschi–Thorpe condensation, or Hantzsch reaction.[16]

The above successful expansion of the formal [5C + 1N] synthetic strategy to fused heterobicyclic systems[17] and our continued interest in exploring novel [5 + 1] annulation reaction prompted us to search for new five-carbon precursors. One system that attracted our atention is 3-[(dimethylamino)alkenoyl]-4,5-dihydrofurans, which is analogous to α-alkenoyl ketene-*S,S*-acetals used in our previously reported [5 + 1] annulations as five-carbon 1,5-bielectrophilic species.[18]

Scheme 3. Reaction of **3a** with DMFDMA



Thus, the condensation reaction of easily accessible 3-acetyl-2-methyl-5-phenyl-4,5-dihydrofuran **3a**[19] and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) at 120 °C was conducted.[11,12] The reaction furnished a product in 80% isolated yield, which was characterized as 3-acetyl-2-dimethylaminovinyl-5-phenyl-4,5-dihydrofuran **5a** instead of 3-[(dimethylamino)alkenoyl]-2-methyl-5-phenyl-4,5-dihydrofuran **4a** based on its analytical and spectra data (Scheme 3). Comparison of the ^{13}C NMR spectra between **3a** and **5a** let us establish the structure of **5a** without difficulty. In the ^{13}C NMR spectra, **3a** displayed two peaks at δ 14.9 and 29.4 ppm, which were assigned to the carbon signals of 2-methyl of dihydrofuran ring and the methyl group of 3-acetyl, respectively. The disappearance of peak at δ 14.9 ppm along with appearance of two peaks at δ 85.8 and 149.3 ppm in the ^{13}C NMR spectra of **5a** indicated that the 2-methyl is more reactive than acetyl group of **3a** in its condensation with DMFDMA.[20]

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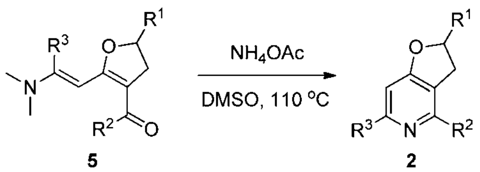
Actually, 3-acetyl-2-dimethylaminovinyl-5-phenyl-4,5-dihydrofuran **5a** can also be regarded as a five-carbon 1,5-bielectrophilic species.[21] Then, the reaction of **5a** and NH_4OAc (10.0 equiv) was attempted in DMSO at 110 °C. To our delight, the reaction proceeded smoothly as indicated by TLC and furnished a product which was characterized as 4-methyl-2-phenyl-2,3-dihydrofuro[3,2-*c*]pyridine (Table 2, entry 1). In the same fashion, a range of reactions of selected 3-acyl-2-[(dimethylamino)alkenyl]-4,5-dihydrofurans **5b**–**e** bearing varied R^1 and R^2 substituents on the dihydrofuran ring were carried out, and the corresponding 2,3-dihydrofuro[3,2-*c*]pyridines **2** were obtained in good to high yields (Table 2, entries 2–5). It should be noted that the cyclization proved to be suitable for substrate **5f** with R^3 as methyl group to afford the corresponding 2,3-dihydrofuro[3,2-*c*]pyridine **2o** in moderate yield (Table 2, entry 6). The results shown above have demonstrated the efficiency and synthetic interest of the formal [5C + 1N] annulation for the synthesis of 2,3-dihydrofuro-[3,2-*c*]pyridines **2** with respect to the five-carbon precursors **5** bearing variable substituted groups, i.e., R^1, R^2, and R^3. Thus, we provided an alternative route to the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridine of type **2**.

Table 2. Synthesis of 2.3-Dihydrofuro[3,2-*c*]pyridines **2** from 3-Acyl-2-[(dimethylamino)alkenyl]-4,5-dihydrofurans **5**[a]

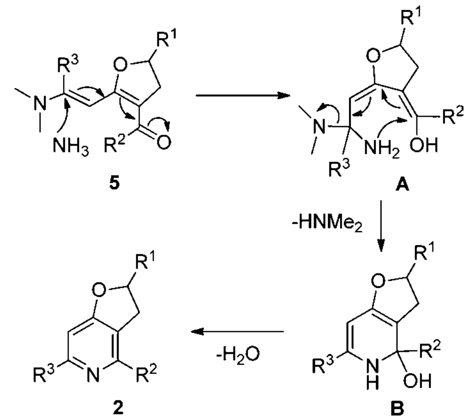


entry	5	R^1	R^2	R^3	2	yield[b] (%)
1	**5a**	Ph	Me	H	**2e**	83
2	**5b**	4-MeC_6H_4	Me	H	**2f**	85
3	**5c**	4-*t*-BuC_6H_4	Me	H	**2g**	80
4	**5d**	4-ClC_6H_4	Me	H	**2m**	81
5	**5e**	Ph	CF_3	H	**2n**	70
6	**5f**	Ph	CF_3	Me	**2o**	63

[a] Reagents and conditions: **3** (1.0 mmol), NH_4OAc (10.0 mmol), DMSO (4.0 mL), 110 °C, 3.0–4.0 h. [b] Isolated yield.

Based on the above results, a mechanism for the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridines **2** from 3-acyl-2-[(dimethylamino)alkenyl]-4,5-dihydrofurans **5** is proposed. As shown in Scheme 4, the reaction commences from the 1,6-addition of ammonia to **5** at high temperature,[5d,13e,21] followed by intramolecular tandem aza-nucleophilic addition and elimination reactions to afford the product 2,3-dihydrofuro[3,2-*c*]pyridine of type **2**.[15]

Scheme 4. Plausible Mechanism for the Reaction of **5** with NH_4OAc



In summary, two novel routes for the synthesis of 2,3-dihydrofuro[3,2-*c*]pyridine of type **2** based on the formal [5C + 1N] annulations are developed. The first route uses 1-acyl-1-dimethylaminoalkenoylcyclopropanes as a five-carbon 1,5-bielectrophilic species, which involves intermolecular addition of ammonia, regioselective ring-enlargement of cyclopropylketone, intramolecular aza-addition/elimination, and dehydration reactions. The second route utilizes 3-acyl-2-[(dimethylamino)alkenyl]-4,5-dihydrofurans as the five-carbon synthons, which involves a sequential intermolecular 1,6-addition of ammonia, intramolecular aza-addition/elimination, and dehydration reaction. Both routes allow the construction of the fused heterobicyclic system in a single step, and are associated with readily available starting materials, mild conditions, and flexible substitution patterns. Further work on the utilization and extension of the scope of the protocols is currently under investigation in our laboratory.

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Supporting Information Available. Experimental details, full characterization data, and copies of NMR spectra for new compounds **1**–**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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