ChemInform Abstract: Ring-Enlargement of Dimethylaminopropenoyl Cyclopropanes: An Efficient Route to Substituted 2,3-Dihydrofurans

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · OCTOBER 2008

Impact Factor: 4.72 · DOI: 10.1021/jo801289p · Source: PubMed

JOC*Note*

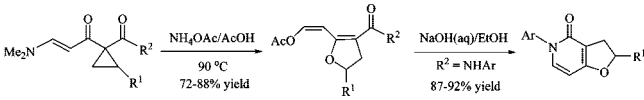
Ring-Enlargement of Dimethylaminopropenoyl Cyclopropanes: An Efficient Route to Substituted 2,3-Dihydrofurans

Rui Zhang,[†] Yongjiu Liang,[†] Guangyuan Zhou,[†] Kewei Wang,[‡] and Dewen Dong*,[†,‡]

Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, China, and Department of Chemistry, Northeast Normal University, Changchun, 130024, China

dwdong@ciac.jl.cn

Received June 16, 2008



A convenient and efficient synthesis of substituted dihydrofurans is developed via ring-enlargement of 1-dimethylaminopropenoyl-1-carbamoyl/benzoyl cyclopropanes catalyzed by ammonium acetate in acetic acid with high regio- and stereoselectivity. Some of the newly synthesized substituted dihydrofurans are subjected to further synthetic transformation in the presence of NaOH (aq) in ethanol to afford the corresponding 5-aryl-2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones in high yields.

The vast number of bioactive natural products as well as medicinally important unnatural compounds based on the 2,3-dihydrofuran ring system, such as aflatoxin B_1 and clerodin, are very important in the area of natural product and pharmaceutical chemistry.[1,2] In addition, the utility of 2,3-dihydrofuran derivatives as organic intermediates in the synthesis of an array of highly functionalized tetrahydrofurans with good stereoselectivity is well recognized.[3] The development of efficient synthetic approaches for 2,3-dihydrofurans has been the focus of intense research for decades, and continues to be an active area of research today. Extensive work has generated a variety of synthetic approaches, including ionic or radical [3 + 2] annulations of 1,3-dicarbonyl compounds with appropriate olefins,[4,5] formal [3 + 2] annulations of β-ketosulfides/β-ketosulfones with aldehydes,[6] and the transition metal-catalyzed [4 + 1] cycloaddition of enones with diazo compounds.[7]

SCHEME 1. Ring-Enlargement of Cyclopropyl Ketones

On the other hand, cyclopropanes are extremely versatile synthetic intermediates for their ready accessibility and good reactivity.[8,9] Their well-known "unsaturated" character can lead to a variety of ring-opening reactions under the influence of electrophiles, nucleophiles, and radicals, or external physical forces such as heat and light. Since the pioneering work on the ring-enlargement of cyclopropylketones was first reported by Cloke in 1929 (Scheme 1),[10] this type of transformation became a notable approach for the synthesis of 2,3-dihydrofurans and was widely studied by employing varied catalysts, such as Lewis acids, metal, or strong oxidizing agents.[11] Recently, Zhang and

[†] Chinese Academy of Sciences.
[‡] Northeast Normal University.

(1) (a) Meyers, A. I. *Heterocycles in Organic Synthesis*; John Wiley & Sons: New York, 1974. (b) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1982; Vol. 30, pp 167−238. (c) Dean, F. M.; Sargent, M. V. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon: New York, 1984; Vol. 4, Part 3, pp 531−598. (d) Vernin, G. *The Chemistry of Heterocyclic Flavoring and Aroma Compounds*; Ellis Horwood: Chichester, UK, 1982.

(2) (a) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, 4929–4949. (b) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095–12096. (c) Danheiser, R. L.; Stoner, E. J.; Kojama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407–4413. (d) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217–241. (e) Merrit, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243–287. (f) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.

(3) (a) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2005**, *17*, 142–171. (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301–2323. (c) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2473. (d) Mueller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Grass, S. *Synlett* **2005**, 1397–1400. (e) Ishitani, H.; Achiwa, K. *Heterocycles* **1997**, *46*, 153–156.

(4) (a) Aso, M.; Ojida, A.; Yang, G.; Cha, O. J.; Osawa, E.; Kamematsu, K. *J. Org. Chem.* **1993**, *58*, 3960–3968. (b) Antonioletti, R.; Righi, G.; Oliveri, L.; Bovicelli, P. *Tetrahedron Lett.* **2000**, *41*, 10127–10130. (c) Antonioletti, R.; Bovicelli, P.; Malancona, S. *Tetrahedron* **2002**, *58*, 589–596. (d) Lee, Y. R.; Suk, J. Y. *Tetrahedron* **2002**, *58*, 2359–2367.

(5) (a) Ichikawa, K.; Uemura, S. *J. Org. Chem.* **1967**, *32*, 493–495. (b) Nishino, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1922–1927. (c) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *J. Org. Chem.* **1985**, *50*, 3467–3473. (d) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1991**, *56*, 4772–4778. (e) Yamada, T.; Iwahara, Y.; Nishino, H.; Korp, J. D.; Kurosawa, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 609–616. (f) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952–6953. (g) Roy, S. C.; Mandal, P. K *Tetrahedron* **1996**, *52*, 2193–2198. (h) Alonso, I.; Carretero, J. C.; Garrido, J. L.; Magro, V.; Pedregal, C. *J. Org. Chem.* **1997**, *62*, 5682–5683. (i) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406–9413. (j) Lee, Y. R.; Kim, B. S.; Kim, D. H. *Tetrahedron* **2000**, *56*, 8845–8853. (k) Zhang, Y.; Raines, A. J.; Flowers, R. A. *Org. Lett.* **2003**, *5*, 2363–2365.

(6) (a) Calo, V.; Scordari, F.; Nacci, A.; Schingaro, E.; D'Accolti, L.; Monopoli, A. *J. Org. Chem.* **2003**, *68*, 4406–4409. (b) Xing, C.; Zhu, S. *J. Org. Chem.* **2004**, *69*, 6486–6488.

(7) (a) Spencer, T. A.; Villarica, R. M.; Storm, D. L.; Weaver, T. D.; Friary, R. J.; Posler, J.; Shafer, P. R. *J. Am. Chem. Soc.* **1967**, *89*, 5497–5499. (b) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 9739–9742. (c) Anac, O.; Ozdemir, A. D.; Sezer, O. *Helv. Chim. Acta* **2003**, *86*, 290–298. (d) Jiang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1033–1038. (e) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046–1047.

(8) (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (c) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150. (d) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603–1624. (e) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (f) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (g) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (h) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493–4537.

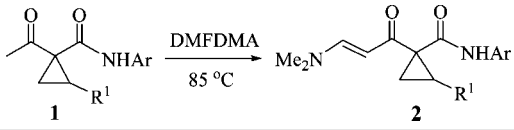
(9) (a) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 183–187. (b) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565–4568. (c) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350–5351. (d) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348–5349.

(10) Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174–1187.

(11) (a) Alonso, M. E.; Morales, A. *J. Org. Chem.* **1980**, *45*, 4530–4532. (b) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717–2719. (c) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573–576. (d) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565–4568. (e) Lee, P. H.; Kim, J. S.; Kim, S. *Tetrahedron Lett.* **1993**, *34*, 7583–7586. (f) Nakajima, T.; Segi, M.; Mituoka, T.; Fukute, Y.; Honda, M.; Naitou, K. *Tetrahedron Lett.* **1995**, *36*, 1667–1670. (g) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573–576.

10.1021/jo801289p CCC: $40.75
Published on Web 09/18/2008

TABLE 1. Synthesis of Doubly Activated Cyclopropanes 2[a]



1 **2**

entry	**1**	Ar	R^1	**2**	yield (%)[b]
1	**1a**	4-MeC_6H_4	H	**2a**	88
2	**1b**	C_6H_5	H	**2b**	81
3	**1c**	2-MeC_6H_4	H	**2c**	85
4	**1d**	2,4-$Me_2C_6H_3$	H	**2d**	83
5	**1e**	4-$MeOC_6H_4$	H	**2e**	89
6	**1f**	2-$MeOC_6H_4$	H	**2f**	91
7	**1g**	2-ClC_6H_4	H	**2g**	78
8	**1h**	2-MeO-5-ClC_6H_3	H	**2h**	86
9	**1i**	4-MeC_6H_4	C_6H_5	**2i**	83

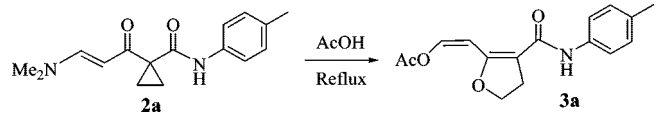
[a] Reagents and conditions: **1** (5.0 mmol), DMFDMA (6.0 mmol), DMF (15 mL), 85 °C, 5.0−6.0 h. [b] Isolated yields.

co-workers achieved the synthesis of furoquinolines through $SnCl_4$-mediated tandem ring-opening/recyclization reaction of 1-acyl-1-carbamoylcyclopropanes.[12] From the same precursors, we developed a facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones under Vilsmeier conditions.[13] Furthermore, we achieved divergent synthesis of fully substituted 1*H*-pyrazoles and isoxazoles from the oximes of 1-acyl-1-carbamoylcyclopropanes in the presence of $POCl_3$/DMF (Vilsmeier reagent) and $POCl_3/CH_2Cl_2$, respectively.[14] In connection with these studies and our continuing interest in the utility of β-oxo amide derivatives in the synthesis of carbo- and heterocycles,[15] we prepared a series of 1-dimethylaminopropenoyl-1-carbamoyl/benzoylcyclopropanes **2** and explored their synthetic potential. As a result, we wish to describe herein a strategy for performing metal-free, mild rearrangements of the doubly activated cyclopropanes **2** to substituted dihydrofurans **3**, and their further synthetic transformation to substituted 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **4**.

The substrates, 1-acyl-1-carbamoylcyclopropanes **1a**−**i**, were synthesized from commercially available β-oxo amides, 1,2-dibromoethane/1-phenyl-1,2-dibromoethane in very high yields following the reported procedure.[12,13,16] Upon treatment of compounds **1** with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) in DMF at 85 °C for 5.0−6.0 h, a series of condensation adducts **2a**−**i** was synthesized in high yields (Table 1).

With the doubly activated cyclopropanes **1** and **2** in hand, we selected **1a** and **2a** as model compounds to examine their reaction behaviors. In contrast with the studies on the reactions of **1** with Lewis acid or Vilsmeier reagent,[12,13] in the present work we envisage the reactions of **1** in the presence of organic acid. Thus, **1a** was treated in acetic acid at room temperature for 10.0 h, but no reaction was observed as indicated by TLC. After the mixture was heated to reflux, the reaction proceeded,

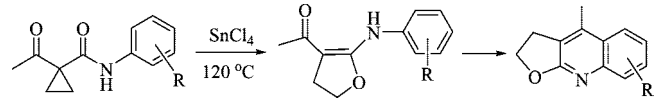
SCHEME 2. Ring-Enlargement of 1-Alkenoyl-1-carbamoylcyclopropane 2a



2a **3a**

and a major product was obtained and characterized as *N*-tolylacetamide, indicating the cleavage of **1a** under the employed acidic conditions. When **2a** was subjected to acetic acid under reflux, the reaction furnished a white solid, which was characterized as 2-(3-(*p*-tolylcarbamoyl)-4,5-dihydrofuran-2-yl)vinyl acetate **3a** (73% yield) on the basis of its spectral and analytical data (Scheme 2).

SCHEME 3. Ring-Enlargement of 1-Acyl-1-carbamoylcyclopropanes



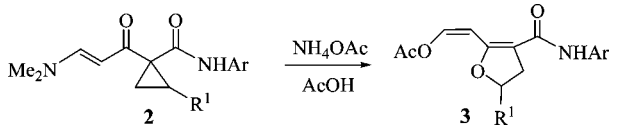
In Zhang's recent work on the ring-opening/recyclization of cyclopropanes **1** in the presence of $SnCl_4 \cdot H_2O$, 4-acyl-5-arylamino-2,3-dihydrofurans were obtained as the key intermediates (Scheme 3).[12] Their studies and our results suggest that both the nature of substituents on cyclopropanes and the reaction conditions employed have a great effect on the selectivity of the ring-enlargement on the different carbonyl groups of the doubly activated cyclopropanes. Moreover, it is worth noting that the ring-enlargement reaction of **2a** proceeded to afford **3a** along with an unexpected reversal of the configuration of its C=C bond as determined by ^{1}H NMR spectra. Two doublet peaks with resonances at δ 4.70 and 7.72 in the ^{1}H NMR spectra of **2a** are assigned to the two neighboring protons of the C=C bond. Their coupling constant (J = 12.5 Hz) reveals that **2a** is an *E*-isomer. In contrast, **3a** displays two doublet peaks at δ 6.06 and 7.39, respectively, in its ^{1}H NMR spectra, and their coupling constant (J = 8.0 Hz) indicates that **3a** is formed in the *Z*-configuration. We could not isolate the *E*-isomer, which might be present in trace amounts in the reaction mixture.

The optimization of the reaction conditions, including reaction temperature and solvents, was then investigated. It was noted that variation of the reaction temperature in the range of 80−120 °C had no significant influence on the reaction, but the reaction required prolonged reaction time along with low conversion when performed at temperatures below 80 °C. Interestingly, the addition of a small amount of ammonium salt such as NH_4OAc could accelerate the reaction. By employing DMF as the solvent instead of acetic acid, the reaction resulted in a complex mixture. Subjecting **2a** to acetic anhydride at 100 °C for 24 h, no reaction was observed as monitored by TLC. With the addition of several drops of water, the reaction proceeded and produced a mixture containing **3a**. The results suggest that the existence of acetate anion in the reaction system might play an important role in the ring-enlargement process. After a series of experiments, the optimal results were achieved when the reaction of **2a** was performed with NH_4OAc (0.1 equiv) in acetic acid at 90 °C for 4.0 h, whereby the yield of **3a** reached 85% (Table 2, entry 1). It is worth mentioning that **3a** can be obtained in pure form by the nonchromatography purification method, namely washing the crude product with water and cold acetone.

Having established the optimal conditions for the ring-enlargement reaction, we aimed to determine its scope with

(12) Zhang, Z.; Zhang, Q.; Sun, S.; Xiong, T.; Liu, Q. *Angew. Chem., Int. Ed.* **2007**, *46*, 1726–1729.
(13) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421–2423.
(14) Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. *Org. Lett.* **2008**, *10*, 1691–1694.
(15) (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579. (b) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580–3582. (c) Wang, Y.; Dong, D.; Yang, Y.; Huang, J.; Ouyang, Y.; Liu, Q. *Tetrahedron* **2007**, *63*, 2724–2728. (d) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593–8596.
(16) White, D. A. *Synth. Commun.* **1977**, *7*, 559–568.

TABLE 2. Synthesis of Substituted Dihydrofurans 3 from Doubly Activated Cyclopropanes 2[a]

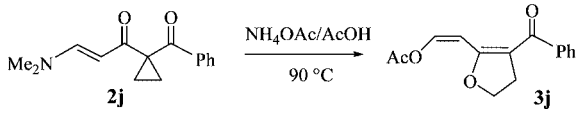


entry	2	Ar	R^1	3	yield[b]
1	**2a**	4-MeC_6H_4	H	**3a**	85
2	**2b**	C_6H_5	H	**3b**	82
3	**2c**	2-MeC_6H_4	H	**3c**	80
4	**2d**	2,4-$Me_2C_6H_3$	H	**3d**	83
5	**2e**	4-$MeOC_6H_4$	H	**3e**	88
6	**2f**	2-$MeOC_6H_4$	H	**3f**	87
7	**2g**	2-ClC_6H_4	H	**3g**	81
8	**2h**	2-MeO,5-ClC_6H_3	H	**3h**	85
9	**2i**	4-MeC_6H_4	C_6H_5	**3i**	87

[a] Reagents and conditions: **2** (2.0 mmol), NH_4OAc (0.2 mmol), AcOH (15 mL), 90 °C, 2.5−5.0 h. [b] Isolated yields.

respect to the amide moiety. Thus, a series of reactions of 1-alkenoyl-1-carbamoyl cyclopropanes **2** were carried out under the optimal conditions. As shown in Table 2, the ring-enlargement reaction proved to be suitable for **2b**−**h** bearing varied amide groups, affording the corresponding 2-[3-(aryl-carbamoyl)-4,5-dihydrofuran-2-yl]vinyl acetates **3b**−**h** in high yields (Table 2, entries 2−8). In the case of cyclopropane **2i** bearing a 2-substituted phenyl group, the reaction proceeds smoothly to furnish the corresponding dihydrofuran **3i** as a single regioisomer in high yield (Table 2, entry 9); such regioselective ring opening is in accordance with the results achieved in similar ring-enlargement reactions.[11a−d,12] It is significant to note that, in all cases of **3a**−**i**, only *Z*-isomeric products are isolated, revealing a high stereoselectivity.

SCHEME 4. Ring-Enlargement of 1-Alkenoyl-1-benzoylcyclopropane 2j

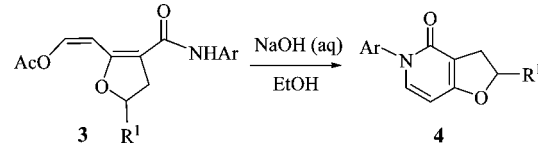


The versatility of this dihydrofuran synthesis was also evaluated by using 1-alkenoyl-1-benzoylcyclopropane **2j** under the identical conditions. The reaction proceeded smoothly to give the corresponding dihydrofuran **3j** in 72% yield (Scheme 4). From the ^1H NMR spectra of **3j**, it is noteworthy that the coupling constant of the two neighboring protons of the C=C bond is 6.0 Hz, indicating the formation of a *Z*-isomeric product, too.

On the basis of the obtained results, a plausible mechanism for the ring-enlargement of cyclopropanes **2** is presented in Scheme 5. The transformation might commence from a nucleophilic vinylic substitution (S_NV) reaction of **2** in acetic acid.[17] The *N*-protonation of **2** and the hydrogen bonding interaction between **2** and ammonium acetate (or acetic acid) leads to the formation of **A**.[18] The strong electron-attracting effect of dimethylaminium and carbonyl groups on the vinyl moiety of **A** makes it liable to undergo tandem oxa-Michael addition to the unsaturated β-carbon and elimination reaction of dimethylamine to generate intermediate **C** in the *Z*-configuration via a transition state **B**.[19] Under the acidic conditions, the carbonyl group bearing the R^2 group of **C** is protonated to afford oxonium ion **D**, followed by a regioselective ring expansion to give oxonium ion **E**,[20] which is finally converted into the substituted dihydrofuran of type **3**.

It should be noted that the vinyl acetate moiety of **3** can be regarded as a potential formyl group, which may lead to further synthetic transformations under appropriate conditions. Inspired by this, we selected **3a** as a model compound to examine its behavior under basic conditions. Thus, **3a** was subjected to NaOH (aq, 1.5 equiv) in ethanol at room temperature for 2.0 h. The reaction furnished a white solid, which was characterized as 5-phenyl-2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one **4a** (84% yield) on the basis of its spectral and analytical data. With the increase of the amount of NaOH to 2.0 equiv, the reaction completed within 30 min and the yield of **4a** reached 92% (Table 3, entry 1). Under the identical conditions, some of the newly synthesized 2-(3-(carbamoyl)-4,5-dihydrofuran-2-yl)vinyl acetates **3** were converted into the corresponding substituted 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **4** in excellent yields (Table 3, entries 2−7). It is assumed that the vinyl acetate of **3** undergoes hydrolysis reaction mediated by NaOH (aq) in ethanol to give the corresponding aldehyde and which upon intramolecular cyclization with amide group followed by dehydration furnishes the 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one of type **4**.

TABLE 3. Intramolecular Annulation Reactions of Dihydrofurans 3[a]



entry	3	Ar	R^1	4	yield[b]
1	**3a**	4-MeC_6H_4	H	**4a**	92
2	**3b**	C_6H_5	H	**4b**	91
3	**3c**	2-MeC_6H_4	H	**4c**	93
4	**3d**	2,4-$Me_2C_6H_3$	H	**4d**	90
5	**3e**	4-$MeOC_6H_4$	H	**4e**	91
6	**3h**	2-MeO-5-ClC_6H_3	H	**4h**	94
7	**3i**	4-MeC_6H_4	C_6H_5	**4i**	87

[a] Reagents and conditions: **3** (2.0 mmol), NaOH (aq, 4.0 mmol), EtOH, rt, 0.5−1.0 h. [b] Isolated yields.

Dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one alkaloids are widely distributed in the Rutaceae family of plants along with useful bioactivities.[21] To date, some synthetic approaches for the synthesis of this kind of heterocycles have been reported, such as the oxidative cycloaddition or photoinduced cycloaddition

(17) (a) Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 2719–2725. (b) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017–4090. (c) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7461–7468.

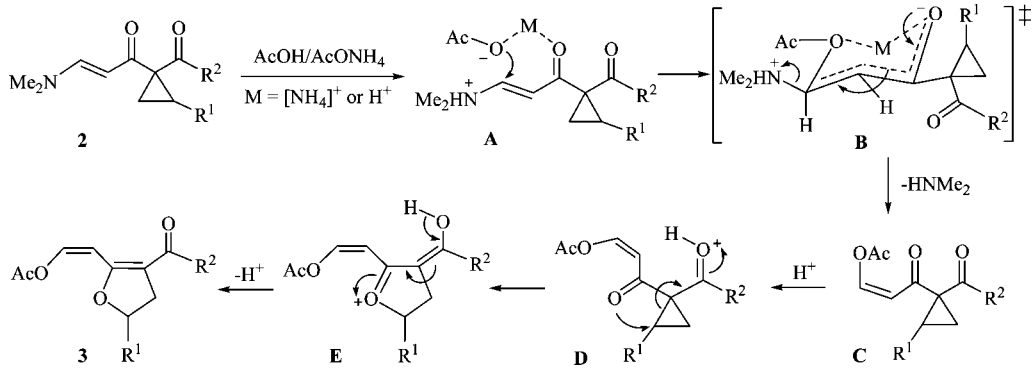
(18) (a) Shirakawa, S.; Shimizu, S. *Synlett* **2007**, 3160–3164. (b) Yang, Y.; Xiang, D.; Zhao, X.; Liang, Y.; Huang, J.; Dong, D. *Tetrahedron* **2008**, *64*, 4959–4966.

(19) (a) Basavaiah, D.; Pandiaraju, S.; Krishnamacharyulu, M. *Synlett* **1996**, 747–748. (b) Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis* **2000**, 545–548. (c) Ollevier, T.; Mwene-Mbeja, T. M. *Tetrahedron* **2008**, *64*, 5150–5155.

(20) Pittman, C. U., Jr.; MacManus, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 5915–5918.

(21) (a) Scheuer, P. J. In *Chemistry of Alkaloids*; Pelletier, S. W., Ed.; van Nostrand Reinhold: New York, 1970; p 355. (b) Grundon, M. F. *Nat. Prod. Rep.* **1990**, *7*, 131–138. (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605–618. (d) Basco, L. K.; Mitaku, S.; Skaltsounis, A. L.; Ravelomanantsoa, N.; Tillequin, F.; Koch, M.; Le Bras, J. *Antimicrob. Agents Chemother.* **1994**, *38*, 1169–1171. (e) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650–668.

SCHEME 5. Plausible Mechanism of Ring-Enlargement of 2



of 4-hydroxypyridin-2(1*H*)-one derivatives with olefins.[22] Our present work provided an alternative and novel route to the synthesis of substituted dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones from commercially available β-oxo amides.

In summary, a facile and efficient synthesis of substituted 2,3-dihydrofurans **3** is developed from cyclopropanes **2** catalyzed by NH_4OAc in acetic acid involving stereoselective S_NV, regioselective ring-enlargement reactions. Some of the newly synthesized substituted dihydrofurans **3** bearing an amide group are subjected to further transformation in the presence of NaOH (aq) in ethanol to afford the corresponding 5-aryl-2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **4** in high yields. This protocol is associated with readily available starting materials, mild conditions, high yields, and potential utility of the products.

Experimental Section

Typical Procedure for the Preparation of Substituted Cyclopropanes 2 (2a as an example). To a 50 mL round-bottomed flask was added DMFDMA (6.0 mmol), 1-acetyl-*N*-phenylcyclopropanecarboxamide **1a** (5.0 mmol), and DMF (15 mL). Then the mixture was heated and stirred at 85 °C for 4.0 h, then cooled to room temperature. The resulting mixture was slowly poured into saturated aqueous NaCl (100 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (silica gel, petroleum ether:ethyl acetate 2:1) to give 88% yield of **2a**: white solid; mp 181−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (q, J = 3.5 Hz, 2H), 1.81 (q, J = 3.5 Hz, 2H), 2.28 (s, 3H), 2.79 (s, 3H), 3.09 (s, 3H), 4.71 (d, J = 12.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 12.5 Hz, 1H), 11.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 20.8, 31.6, 37.2, 45.1, 88.5, 120.0, 129.2, 132.9, 136.2, 154.5, 169.0, 196.6. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.31; H, 7.47; N, 10.13.

Typical Procedure for the Preparation of Substituted Dihydrofurans 3 (3a as an example). To a 50 mL round-bottomed flask was added **2a** (2.0 mmol), NH_4OAc (0.2 mmol), and acetic acid (15 mL). The mixture was heated and stirred at 90 °C for 4.0 h, then cooled to room temperature. The solvent was removed under reduced pressure. The residue was neutralized with saturated aqueous $NaHCO_3$. The precipitated solid was washed with water (3 × 30 mL) and cold acetone (2 × 20 mL), and dried in vacuum to give 85% yield of **3a**: white solid; mp 196−198 °C; ^{1}H NMR (400 MHz, DMSO) δ 1.97 (s, 3H), 2.35 (s, 3H), 2.72 (t, J = 7.5 Hz, 2H), 4.04 (t, J = 7.5 Hz, 2H), 6.06 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 7.5 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 10.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 21.3, 21.5, 23.7, 62.5, 100.3, 106.9, 127.3, 129.9, 137.6, 137.8, 139.3, 163.3, 164.0, 171.0. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.75; H, 6.01; N, 4.85.

Typical Procedure for the Synthesis of Substituted Dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones 4 (4a as an example). To a 50 mL round-bottomed flask was added **3a** (2.0 mmol), aqueous NaOH (30%, 4.0 mmol), and EtOH (10 mL). The mixture was stirred at room temperature for 30 min, then poured into saturated aqueous NaCl (50 mL) and neutralized with aqueous HCl (10%). The resulting mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum to give 92% yield of **4a**: white solid; mp 208−210 °C; ^{1}H NMR (500 MHz, DMSO) δ 2.32 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 3.41 (t, J = 7.5 Hz, 2H), 6.08 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 21.3, 28.1, 60.3, 100.7, 108.5, 127.3, 129.9, 137.0, 137.7, 139.5, 163.7, 163.8. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.07; H, 5.72; N, 6.21.

Acknowledgment. Financial support of this research by the National Natural Science Foundation of China (20572013 and 20711130229), the Ministry of Education of China (105061), and the Department of Science and Technology of Jilin Province (20050309) is greatly acknowledged.

Supporting Information Available: Analytical data and NMR spectra for **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801289P

(22) (a) Lee, Y. R.; Kim, B. S.; Kweon, H. I. *Tetrahedron* **2000**, *56*, 3867–3874. (b) Barr, S. A.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1994**, 153–154. (c) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642–3649. (d) Senboku, H.; Takashima, M.; Suzuki, M.; Kobayashi, K.; Suginome, H. *Tetrahedron* **1996**, *52*, 6125–6138. (e) Suginome, H.; Kobayashi, K.; Itoh, M.; Seko, S.; Furusaki, A. *J. Org. Chem.* **1990**, *55*, 4933–4943. (f) Suginome, H.; Seko, S.; Konishi, A.; Kobayashi, K. *Tetrahedron Lett.* **1991**, *38*, 5115–5118.