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Aza−Oxy−Carbanion Relay via Non-Brook Rearrangement: Efficient Synthesis of Furo[3,2-*c*]pyridinones

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Supporting Information

ABSTRACT: An aza−oxy−carbanion relay via tandem Michael addition/ring opening of cyclopropane and recyclization/carbanion migration/electrophile trapping has been developed by the utilization of 1-cinnamoylcyclopropanecarboxamides to react with various electrophiles. This represents the first example of anion relay chemistry via non-Brook rearrangement. This novel protocol has been applied in the facile and efficient synthesis of biologically active bicyclic furo[3,2-*c*]pyridinone compounds.

Since first exploited in 1979 by Matsuda,[1a] anion relay chemistry (ARC) has attracted considerable attention as an effective tactic for diversity-oriented synthesis of architecturally complex natural and unnatural products.[1] However, almost all of the anion relays reported to date have been established by virtue of the Brook rearrangement.[1] Development of ARC via non-Brook rearrangement by exploring new chemical building blocks is of great significance and still remains a challenge.

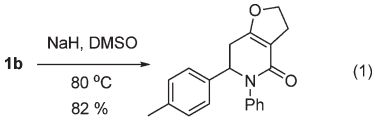
In our research on the synthetic potential of β-ketoamides[2] bearing both electrophilic and nucleophilic centers toward various carbo- and heterocycles,[3] we envisioned that under appropriate conditions, a tandem aza−oxy−carbanion relay may be realized by the utilization of 1-cinnamoylcyclopropanecarboxamides **1** as starting materials (Scheme 1). With this idea in mind, the reactions of a series of electrophiles with substrates **1** were investigated. Consequently, bicyclic furo[3,2-*c*]pyridinones were efficiently attained. Furo[3,2-*c*]pyridinone alkaloids are widespread among the Rutaceae family of plants and display important biological activities.[4] Although a few synthetic approaches for the construction of this kind of heterocycle have been reported, most of them may suffer from tedious steps, low yields, and poor regioselectivity.[5] Our present work has provided not only an efficient route to the structurally interesting and biologically significant *N*,*O*-bicyclic furo[3,2-*c*]pyridinone skeleton from readily available starting materials in a single step but also a new protocol for an anion relay cascade that involves a tandem aza-Michael addition/ring opening of cyclopropane and recyclization/carbanion migration/electrophile trapping.[6]

Initially, the model reaction of 1-cinnamoyl-*N*-phenylcyclopropanecarboxamide (**1a**) with phenylaldehyde (**2a**) was examined under basic conditions (Table 1). The reaction in NaOH/EtOH at reflux gave compound **4** in 77% yield (entry 1).[3f] The same result was observed in the cases using NaH as the base, whether in THF at reflux or DMF at 80 °C (entries 2 and 3). When the reaction was performed using *t*-BuOK in *t*-BuOH at 80 °C, compound **5** with an intact cyclopropane ring was produced via aza-Michael addition and aldol condensation (entry 4). To our delight, when the reaction was conducted using NaH in DMSO at 80 °C, the expected 7-benzylidene-5,6-diphenyl-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-one **3a** was obtained in 85% yield (entry 5). The reaction between **1a** and **2a** did not occur when Et_3N or DBU was employed as the base (entries 6 and 7).

Under the optimized conditions (Table 1, entry 5), a range of reactions was carried out with various substrates **1** and aldehydes **2** (Table 2). All of the reactions proceeded smoothly to afford the corresponding substituted 2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **3a**−**j** in good to excellent yields (entries 1−10). The aryl substituents Ar^1 and/or Ar^2 on substrates **1** may be either electron-rich or electron-deficient (entries 1−5). The scope of aldehydes **2** was also broad, including an electron-rich aryl aldehyde (entry 6), an electron-deficient aryl aldehyde (entry 7), heteroaryl aldehydes (entries 8 and 9), and an alkenyl aldehyde (entry 10). However, the reaction with an aliphatic aldehyde such as 3-phenylpropionaldehyde led to a complex mixture (entry 11). The structures of **3g** and **3j** and their stereochemistries were confirmed by single-crystal X-ray diffraction (Figure S1 in the Supporting Information).[7] All of the above results indicate the efficiency of the anion relay cascade reactions reported here.

Next, under conditions identical to those above, we examined the scope of the anion relay reactions by replacing the aldehyde with other electrophiles (Scheme 2).[8] The reaction of substrate **1b** with 1.1 equiv of α,β-unsaturated enones bearing different Ar^3 groups (phenyl, 4-chlorophenyl, and 2-furyl) as the Michael acceptor gave high yields of the corresponding expected products **6a**−**c** with three contiguous stereogenic centers.

In order to elucidate the possible mechanism, the reaction of substrate **1b** in the absence of additional electrophile was carried out, and 5-phenyl-6-*p*-tolyl-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-one (**7**) was isolated in 82% yield (eq 1):



(1)

7

Obviously, the control experiment gave support to the proposed aza−oxy−carbanion relay cascade starting from **1** (Scheme 1). In particular, with NaH as the base, amide anion is produced. Upon initiation by intramolecular aza-Michael addition, enolate intermediate **II** is formed.[9] Next, an oxyanion-triggered 1,3-sigmatropic carbon rearrangement takes place,[10] giving bicyclic

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Scheme 1. Proposed Strategy for the Aza−Oxy−Carbanion Relay Cascade

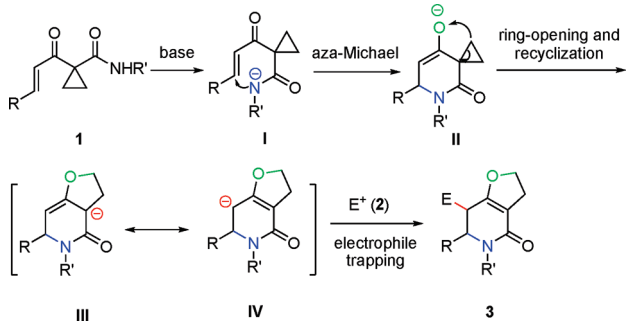
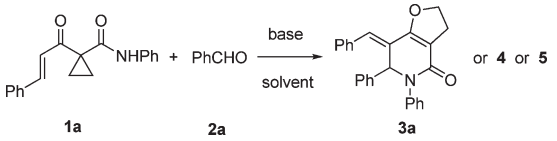
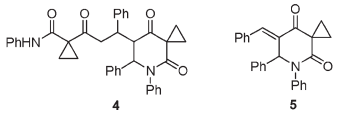


Table 1. Optimization of the Reaction Conditions[a]

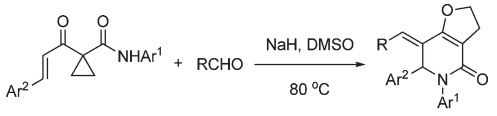


entry	base	solvent	t (°C)	time (h)	product (yield, %)[b]
1	NaOH	EtOH	reflux	5	**4** (77)
2	NaH	THF	reflux	5	**4** (35)
3	NaH	DMF	80	10	**4** (70)
4	*t*-BuOK	*t*-BuOH	80	6	**5** (81)
5	**NaH**	**DMSO**	**80**	**2**	**3a (85)**
6	DBU	CH_3CN	reflux	8	—
7	Et_3N	DMF	80	12	—



[a] Reactions were carried out on a 1.0 mmol scale in 5.0 mL of solvent with **2a** (1.1 equiv) and a base (1.1 equiv). [b] Yield of isolated product.

Table 2. Reactions of Substrates 1 with Aldehydes 2[a]

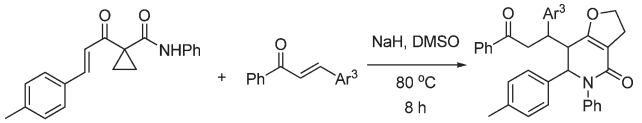


entry	Ar^1	Ar^2	R	3	yield (%)[b]
1	Ph	Ph	Ph	**3a**	85
2	Ph	4-ClC_6H_4	Ph	**3b**	88
3	Ph	4-MeC_6H_4	Ph	**3c**	81
4	2-MeC_6H_4	4-MeC_6H_4	Ph	**3d**	79
5	4-ClC_6H_4	4-MeC_6H_4	Ph	**3e**	88
6	Ph	4-MeC_6H_4	4-MeC_6H_4	**3f**	87
7	Ph	4-MeC_6H_4	4-$NO_2C_6H_4$	**3g**	91
8	Ph	4-MeC_6H_4	2-thienyl	**3h**	86
9	Ph	4-MeC_6H_4	2-furyl	**3i**	92
10	Ph	4-MeC_6H_4	PhCH=CH	**3j**	83
11	Ph	4-MeC_6H_4	$PhCH_2CH_2$	**3k**	complex

[a] Reactions were carried out on a 1.0 mmol scale in DMSO (5.0 mL) with **2** (1.1 equiv) and NaH (1.1 equiv). [b] Yield of isolated product.

intermediate **III** (with a tertiary carbanion, which is stabilized by the adjacent double bonds) and its resonance structure **IV**. Direct electrophile capture of secondary carbanion **IV** leads to the final product **2** or **6**.[11] In the cascade reactions of anions, tandem C−N, C−O, and C−C bonds were established successfully.

Scheme 2. Scope Extension



6a: Ar^3 = Ph (88%) **6b:** Ar^3 = 4-ClPh (85%) **6c:** Ar^3 = 2-furyl (81%)

In conclusion, an effective aza−oxy−carbanion relay via non-Brook rearrangement has been developed for the first time by judicious selection of 1-cinnamoylcyclopropanecarboxamides as precursors. The protocol provides a convenient and efficient one-pot entry to biologically important furo[3,2-*c*]pyridinones in an atom-economic manner. Further work to extend the anion relay chemistry is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data, and crystal structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) See the Supporting Information for details.

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(9) For a minireview of conjugate-addition-triggered tandem transformations, see: Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366. For a recent review of organocatalytic asymmetric aza-Michael additions, see: Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058.

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