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Halonium-Initiated C–O Bond Formation via Umpolung of α-Carbon to the Carbonyl: Efficient Access to 5-Amino-3(2*H*)-furanones

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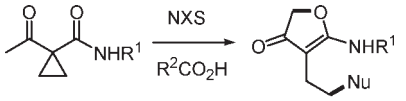
ABSTRACT



R^1 = alkyl; R^2 = H, alkyl, aryl
X = Cl, Br, I; Nu = OR, O_2CR, X

Highly efficient C–O bond formation has been developed via carboxylic acid catalyzed reaction of 1-acetylcyclopropanecarboxamides with *N*-halosuccinimide (NXS), which provides strategically novel and atom-economic access to biologically important 5-amino-3(2*H*)-furanones. The mechanism of halonium-initiated tandem oxa-cyclization and ring opening of cyclopropane was proposed. A variety of nucleophiles were found to open the cyclopropane.

The 3(2*H*)-furanone is a core structural unit in a number of natural products such as bullatenon,[1] jatrophone,[2] pseurotin A,[3] and eremantholide A.[4] They have a wide range of applications in medicine and biology, including antitumor, antiulcer, and antiallergic activities.[5] Various methods have been developed for the construction of this five-membered ring system.[6] However, most of the current approaches suffer from (i) limited substrate scope or the lack of readily available precursors, and (ii) tedious synthetic procedures. Therefore, further development of efficient methods that allow the facile assembly of highly functionalized

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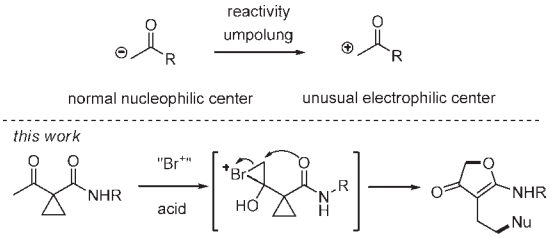
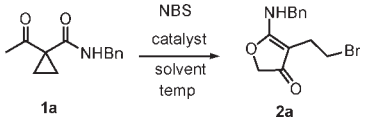
Scheme 1. Umpolung Strategy via Bromonium Ion Intermediate Generated in Situ



3(2*H*)-furanones from readily available and simple starting materials is still required.

The α-carbon to the carbonyl group is generally regarded as a nucleophilic center. The reversal of this prime reactivity (umpolung[7]), that is, making the α-carbon of the carbonyl electrophilic, would be of significant synthetic utility and provide a complementary strategy to access derivatives that are otherwise difficult to prepare conventionally. In our research on the synthetic potential of *β*-ketoamides toward various carbo- and heterocycles,[8] we have developed a convenient and economic route for intramolecular C−O coupling of 1-acetylcyclopropanecarboxamides via an umpolung strategy. The reactivity of the α-carbon to the carbonyl group is converted from originally nucelophilic to electrophilic via an in situ formed halonium ion intermediate (Scheme 1).[9] The sequential amide oxa-cyclization[10] and ring opening of cyclopropane[11] represents a new strategy toward substituted 5-amino-3(2*H*)-furanones.

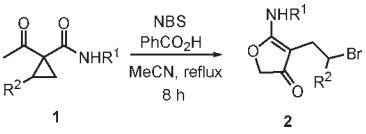
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	—	DMF	80	12	n.r.
2	$Cu(OAc)_2$	DMF	80	12	32
3	$Cu(OAc)_2$	DCE	80	12	30
4	$Cu(OAc)_2$	MeCN	reflux	12	34
5	CuBr	MeCN	reflux	12	65
6	TsOH	MeCN	reflux	8	96
7	TFA	MeCN	reflux	8	94
8	HCO_2H	MeCN	reflux	8	89[c]
9	$PhCO_2H$	MeCN	reflux	8	93

[a] Reactions were carried out with **1a** (1.0 mmol), NBS (1.2 mmol), and catalyst (5% loading amount for Lewis acid; 0.2 equiv for Brønsted acid) in solvent (2.0 mL). [b] Isolated yield. [c] With trace amount of **2i** (5%).

Table 2. Halonium-Induced Intramolecular C−O Bond Formation of 1-Acetylcyclopropanecarboxamides **2**[a]



entry	**1**	R^1	R^2	**2**	yield (%)[b]
1	**1a**	Bn	H	**2a**	93
2	**1b**	2-Cl-$C_6H_4CH_2$	H	**2b**	90
3	**1c**	4-Me$C_6H_4CH_2$	H	**2c**	94
4	**1d**	$BnCH_2$	H	**2d**	92
5	**1e**	Ph	H	**2e**	0
6	**1f**	Bn	Me	**2f**	90

[a] Reactions were carried out with **1** (1.0 mmol), NBS (1.2 mmol), and $PhCO_2H$ (0.2 mmol) in MeCN (2.0 mL). [b] Isolated yield.

Initially, the model reaction of 1-acetyl-*N*-benzylcyclopropanecarboxamide (**1a**) with NBS was examined under acidic conditions (Table 1). No reaction occurred in the absence of an acid catalyst (entry 1). The reaction with Lewis acid catalysts like $Cu(OAc)_2$ and CuBr (5% loading amount) at 80 °C gave an amide oxa-cyclized and cyclopropane ring-opened product, 5-(benzylamino)-4-(2-bromoethyl)furan-3(2*H*)-one (**2a**) in 32−65% yields (entries 2−5). The reaction with Brønsted acids such as TsOH or TFA as the catalyst exhibited higher efficiency, giving **2a** in 94−96% yields (entries 6 and 7). When formic acid was introduced as the catalyst, product **2a** was obtained in 89% yield, along with

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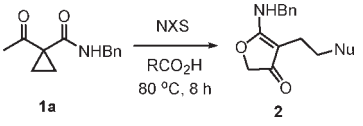
the separation of side product **2i** in 5% yield (entry 8). Benzoic acid, as an easily available, cheap, safe, and environmentally benign organic carboxylic acid, was finally examined. To our delight, the reaction afforded the desired product **2a** in 93% yield (entry 9).[12]

Then, a range of reactions were carried out with various substrates **1** in the presence of NBS and $PhCO_2H$ (Table 2). The amide scope was examined first. All of the reactions based on *N*-alkylamide substrates **1a**–**d**, NBS (1.2 equiv), and $PhCO_2H$ (0.2 equiv) in MeCN proceeded efficiently, affording 5-amino-3(2*H*)-furanones **2a**–**d**, in excellent yields (entries 1–4). Nevertheless, no reaction occurred with *N*-aryl counterpart **1e** as the substrate (entry 5).[13] For 1-acetylcyclopropanecarboxamide **1f** bearing a methyl group on the cyclopropane ring, the reaction proceeded smoothly to furnish the corresponding 5-amino-3(2*H*)-furanone **2f** in 90% yield (entry 6).[14]

In the following work, we further examined the scope of the reaction, mainly through the variation of NXS, carboxylic acids, and solvents (Table 3). Similar to NBS, reactions with NCS or NIS gave 5-amino-3(2*H*)-furanones **2g** and **2h** in excellent yields (entries 1–2). Aliphatic carboxylic acids including HCO_2H, CH_3CO_2H, and $CH_3CH_2CO_2H$ proved to be suitable, affording **2i**–**k**, respectively, in high yields (entries 3–5). Alcoholic solvents such as methanol and ethanol are also efficient in the explored reactions, giving the corresponding products **2l** and **2m** in good yields (entries 6–7). Interestingly, when the reaction was conducted in DMF, product **2i** was produced in 85% yield (entry 8). In this case, DMF acts as an external nucleophile to participate in the reaction.[15] Obviously, a variety of nucleophiles may be used to open the cyclopropane.

Table 3. Exploration the Scope of Nu[a]



entry	X	R	solvent	Nu	**2**	yield (%)[b]
1	Cl	Ph	MeCN	Cl	**2g**	93
2	I	Ph	MeCN	I	**2h**	94
3	Br	H	HCO_2H	O_2CH	**2i**	92
4	Br	Me	$MeCO_2H$	O_2CMe	**2j**	87
5	Br	Et	$EtCO_2H$	O_2CEt	**2k**	85
6	Br	Ph	HOMe	OMe	**2l**	73
7	Br	Ph	HOEt	OEt	**2m**	79
8	Br	Ph	DMF	O_2CH	**2i**	85

[a] Reactions were carried out with **1** (1.0 mmol), NXS (1.2 mmol), RCO_2H (0.2 mmol) in the solvent (2.0 mL). [b] Isolated yield.

In order to explore the effect of α-substituent(s) of acetamides on the reactions, noncyclopropane substrates **1h**–**j** and **3a**–**b** were subjected to the reaction sequences (Figure 1 and Scheme 2). As a result, *N*-benzyl-2-methyl-3-oxobutanamide (**1i**) gave desired product **2n** in 88% yield, while *N*-benzyl-2,2-dimethyl-3-oxobutanamide (**1h**) gave no reaction and *N*-benzyl-3-oxobutanamide (**1j**) gave a complex mixture. Surprisingly, 4,4′-(phenylmethylene) difuran-3(2*H*)-ones **4a** and **4b** were successfully obtained in high yields from *N*-benzyl-2-benzylidene-3-oxobutanamides **3a** and **3b**, respectively, via double oxa-cyclization (Scheme 2). The structure of **4a** was confirmed unambiguously by X-ray single crystal diffraction (Figure 2).[16]

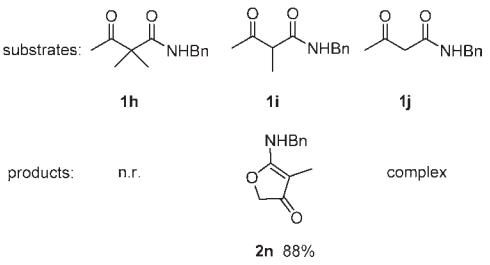
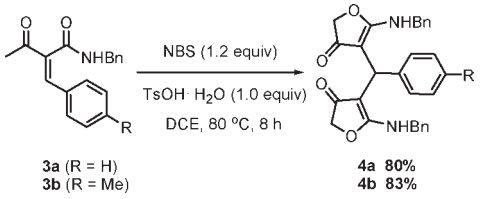


Figure 1. Effect of α-substituent(s) on the substrates.

Scheme 2. Reaction of Benzylidene-Substituted β-Ketoamides **3**



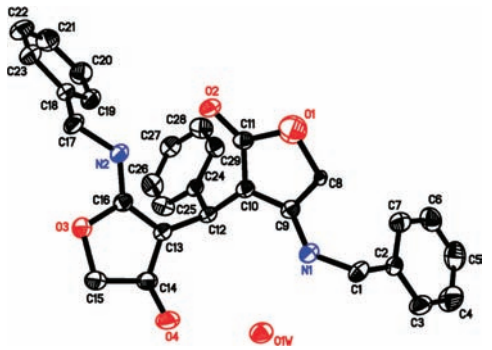
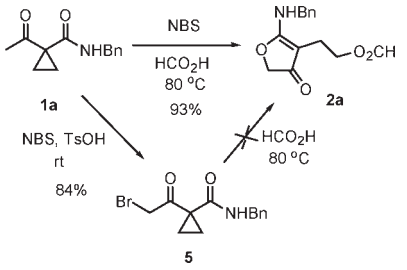


Figure 2. ORTEP drawing of **4a**.

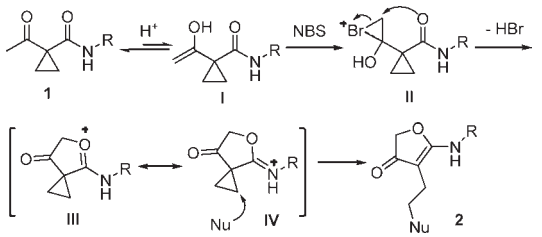
To clarify the proposed halonium ion initiated C–O bond formation involved in the reaction leading to 5-amino-3(2*H*)-furanones (Tables 2 and 3), we performed a control reaction

(12) Different from formic acid (Table 1, entry 8 and Table 3, entries 3–5), benzoic acid is incapable of ring opening the cyclopropane, due to the weak nucleophilicity.

Scheme 3. Control Experiment



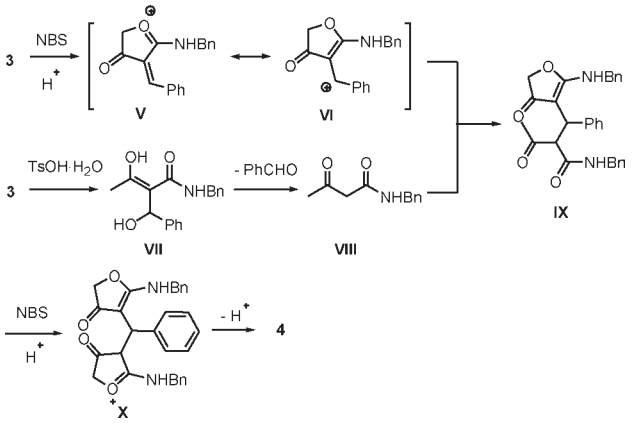
Scheme 4. Possible Mechanism for the Formation of 3(2*H*)-Furanones **2**



of α-bromonated counterpart **5** in HCO_2H at 80 °C (Scheme 3). As a result, no reaction took place.[17]

Based on all the results described, a possible mechanism for the efficient one-pot transformation into 5-amino-3(2*H*)-furanones **2** was proposed, as depicted in Scheme 4. First, acid-induced enolization of 1-cyclopropylethanone **1** produces enolate **I**. Second, in the presence of NXS, halonium ion **II** is supposed to generate in situ, which is directly captured by the amide oxygen, giving the oxonium intermediate **III** and its resonance structure, iminium ion **IV**.[18] Finally, triggered by an external nucleophile, ring opening of the cyclopropane takes place, furnishing the 5-amino-3(2*H*)-furanone product **2**.[19]

Scheme 5. Possible Mechanism for the Formation of 4,4′-Methylene-3(2*H*)-furanones **4**



The possible mechanism for the formation of **4** was illustrated in Scheme 5, which involves the coupling of carbocation **VI** and β-ketoamide **VIII**.[20]

In conclusion, we have developed a practical and efficient protocol for the production of highly functionalized 5-amino-3(2*H*)-furanones by the reactions of 1-acetylcyclopropanecarboxamides with NXS. Through in situ generated halonium ion intermediates, the reactivity of the α-carbon to the carbonyl group was converted from originally nucleophilic into electrophilic, leading to the formation of a C−O bond with an amide oxygen atom.[21] Further work on the synthetic application of the reactivity umpolung is ongoing in our laboratory.

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Supporting Information Available. Experimental details and characterization for all new compounds and crystal structure data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

(13) An *N*-alkyl substituted amide oxygen atom has stronger nucleophilicity than an *N*-aryl counterpart, due to the greater electron-donating ability of the alkylamino group vs the arylamino group.

(14) Reactions with β-ketoesters, such as ethyl 1-acetyl-cyclopropanecarboxylate, and 1,3-diketones, such as 1,1-diacetylcyclopropane, as the substrates were also examined but proved to be inefficient.

(15) With DMF as a nucleophile, see: (a) Dakanali, M.; Tsikalas, G. K.; Krautscheid, H.; Katerinopoulos, H. E. *Tetrahedron Lett.* **2008**, *49*, 1648. (b) Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

(16) See the Supporting Information.

(17) No α-bromonated ketone **5** was observed during the transformation from **1** to **2** (Tables 1−3).

(18) The efficient C−O bond formation may indicate that the formation of 3(2*H*)-furanones **2** via oxa-cyclization is predominant compared to the generally observed α-bromonation of ketones leading to **5**.

(19) In this case, cyclopropanes appear to be highly sensitive to external nucleophiles, which can be attributed to (i) inherent strain; (ii) spiro structure; and (iii) activation by a strongly electron-withdrawing oxonium or iminium ion. For recent examples of cyclopropyl iminium, oxonium, or phosphonium activation, see: ref 11k−11m.

(20) Intermediate **VIII** in Scheme 5 was presumably produced from **3**. In a separate reaction of substrate **3a** and $TsOH·H_2O$, benzaldehyde was observed clearly on a TLC plate.

(21) For recent papers on α C−H functionalization of ketones, see: (a) Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738. (b) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (c) Gandeepan, P.; Parthasarathy, K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8569. (d) He, C.; Guo, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273. (e) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181.

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