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Halonium-initiated electrophilic cascades of 1-alkenoylcyclopropane carboxamides: efficient access to dihydrofuropyridinones and 3(2*H*)-furanones†

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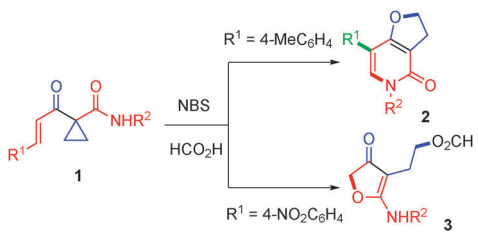
Halonium-initiated cascade reaction of 1-alkenoylcyclopropane carboxamides was developed, which leads to the production of dihydrofuropyridinones and 3(2*H*)-furanones, respectively, depending on the property of substituents on the enone moiety.

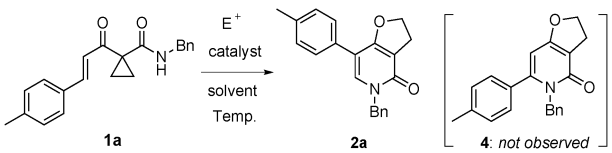
Cascade reactions have attracted considerable attention in organic synthesis due to the atom-efficient creation of molecular complexity in a single-step.[1] During the course of our study on the synthetic potential of double EWGs activated cyclopropanes[2] toward various carbo- and heterocycles,[3] we have developed an intramolecular Michael addition-initiated cascade cyclization of readily available 1-alkenoylcyclopropane carboxamides **1** *via* aza-oxy-carbanion relay under basic conditions.[3c] In connection with this work and our recent interest in cationic cascades, we start to exploit the feasibility of electrophilic cyclization relying upon utilization of **1** in the presence of a halonium-producing reagent under acidic conditions (Scheme 1).[4] Consequently, we discovered a strategically novel access to structurally interesting and biologically important dihydrofuro[3,2-*c*]pyridinones **2** and/or 3(2*H*)-furanones **3**, respectively. It was found that the formation of products **2** and/or **3** depended on the nature of the β-substituent on the enone moiety. With electron-donating aromatic R^1 substituents like 4-methylphenyl, N/O heterocycles **2** were achieved exclusively *via* tandem halo-aza-cyclization, *unexpected 1,2-aryl migration*, cyclopropane ring-opening and oxa-cyclization process. While with electron-withdrawing R^1 groups, such as 4-nitrophenyl, *O*-heterocycles **3** were obtained as the sole product by sequential halo-oxa-cyclization, cyclopropane ring-opening, alkyl bromide hydrolysis and retro-aldol cascade. Both 2,3-dihydrofuro[3,2-*c*]pyridinones and 3(2*H*)-furanones constitute the core structures of many naturally occurring compounds and display important antitumor, antifungal and antibacterial activities.[5]



Scheme 1 Halonium initiated electrophilic cascades of 1-alkenoylcyclopropane carboxamides **1**.

Initially, the model reaction of 1-alkenoyl-*N*-benzylcyclopropane carboxamide (**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 $Cu(OAc)_2$, $CuBr_2$ and CuBr (10% loading amount) at 80 °C gave unsatisfactory results (entries 2–4). Then the reaction was performed in the presence of Brønsted acid (entries 5–12). To our delight, when formic acid was used both as the catalyst and solvent at 80 °C, 2,3-dihydrofuro[3,2-*c*]-pyridinone **2a** (*via* 1,2-aryl migration) was formed in 81%

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	E	Solvent	*T*/°C	**2a** Yield (%)[b]
1	—	NBS	DCE	80	n.r.
2	$Cu(OAc)_2$	NBS	DCE	80	0
3	$CuBr_2$	NBS	DCE	80	0
4	CuBr	NBS	DCE	80	0
5	HCO_2H	NBS	HCO_2H	80	81
6	HCO_2H	NBS	DCE	80	80
7	HCO_2H	NBS	DMF	80	56
8	**HCO_2H**	**NBS**	**MeCN**	**reflux**	**81**
9	$MeCO_2H$	NBS	MeCN	reflux	79
10	$PhCO_2H$	NBS	MeCN	reflux	79
11	TsOH	NBS	MeCN	reflux	80
12	TFA	NBS	MeCN	reflux	78
13	HCO_2H	NIS	MeCN	reflux	78
14	HCO_2H	NCS	MeCN	reflux	0

[a] Reactions were carried out with 1a (1.0 mmol), E (1.2 equiv.) and catalyst (10% loading amount for Lewis acid; 1.2 equiv. for Brønsted acid) in solvent (2.0 mL). [b] Isolated yield. E = electrophile.

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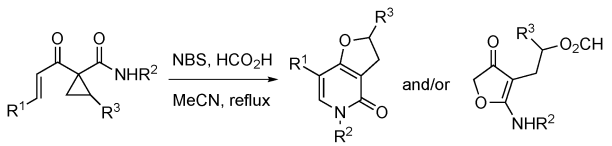
† Electronic supplementary information (ESI) available: Experimental details and characterization of all new compounds and crystal structure data. CCDC 826841 (**2a**), 829460 (**2i**) and 839385 (**3b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15319f

yield, whereas the expected halo-aza-cyclization/oxa-cyclization product **4** was not observed (entry 5). The structure of **2a** was confirmed unambiguously by X-ray single crystal diffraction.[6] The amount of formic acid could be reduced to 1.2 equiv. in DCE (entry 6). Among the solvents tested, MeCN was more efficient and was selected for the following investigation (entries 7 and 8). Besides HCO_2H, both aliphatic acids like $MeCO_2H$ and aromatic acids like $PhCO_2H$ proved to be suitable, giving **2a** in high yields (entries 9 and 10). Strong acids such as TsOH and TFA also work well (entries 11 and 12). NIS showed comparable reactivity to NBS, but NCS was inefficient (entries 13 and 14).

With the optimal conditions established above (Table 1, entry 8), the scope and generality of the cascade reaction were investigated. Thus, a range of reactions was carried out with various substrates **1** in the presence of NBS and HCO_2H (Table 2). The amide scope was examined first. All of the reactions based on *N*-alkylamide substrates **1a–d** proceeded efficiently to afford dihydrofuro[3,2-*c*]pyridinones **2a–d** in high yields (entries 1–4). For 1-alkenoylcyclopropaneamide **1e** bearing a methyl group on the cyclopropane ring, the reaction furnished the corresponding 2,3-dihydrofuro[3,2-*c*]pyridinone **2e** as a single regioisomer (entry 5). However, the reaction with an *N*-aryl counterpart, *i.e.*, **1f**, as the substrate, did not occur (entry 6).

Table 2 Bromonium-initiated cascade reactions leading to dihydrofuro[3,2-*c*]pyridinones **2** and 3(2*H*)-furanones **3**[a]

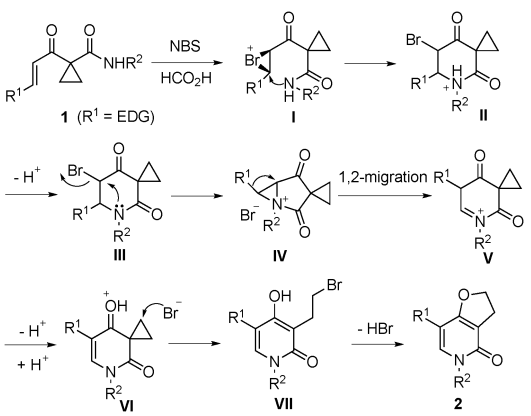


Entry	1	R^1	R^2	R^3	2/3	Yield (%)[b]
1	**1a**	4-MeC_6H_4	Bn	H	**2a**	81
2	**1b**	4-MeC_6H_4	2-Cl-$C_6H_4CH_2$	H	**2b**	80
3	**1c**	4-MeC_6H_4	4-$MeC_6H_4CH_2$	H	**2c**	85
4	**1d**	4-MeC_6H_4	$BnCH_2$	H	**2d**	83
5	**1e**	4-MeC_6H_4	Bn	Me	**2e**	81
6	**1f**	4-MeC_6H_4	Ph	H	**2f**	0
7	**1g**	4-$MeOC_6H_4$	Bn	H	**2g**	84
8	**1h**	2-$MeOC_6H_4$	Bn	H	**2h**	83
9	**1i**	3,4-$OCH_2OC_6H_3$	Bn	H	**2i**	87
10	**1j**	4-$Me_2NC_6H_4$	Bn	H	**2j**	86
11	**1k**	2-MeC_6H_4	Bn	H	**2k**	79
12	**1l**	2-thienyl	Bn	H	**2l**	80
13	**1m**	2-furyl	Bn	H	**2m**	—[c]
14	**1n**	C_6H_5	Bn	H	**2n**	50
					3a	41
15	**1o**	4-ClC_6H_4	Bn	H	**2o**	44
					3a	47
16	**1p**	4-$NO_2C_6H_4$	Bn	H	**3a**	87
17	**1q**	4-pyridyl	Bn	H	**3a**	89
18	**1r**	4-$NO_2C_6H_4$	2-Cl-$C_6H_4CH_2$	H	**3b**	86
19	**1s**	4-$NO_2C_6H_4$	4-$MeC_6H_4CH_2$	H	**3c**	89
20	**1t**	4-$NO_2C_6H_4$	$BnCH_2$	H	**3d**	88
21	**1u**	4-$NO_2C_6H_4$	Bn	Me	**3e**	85
22[d]	**1p**	4-$NO_2C_6H_4$	Bn	H	**3f**	81
23	**1v**	*t*-C_4H_9	Bn	H	**3a**	89

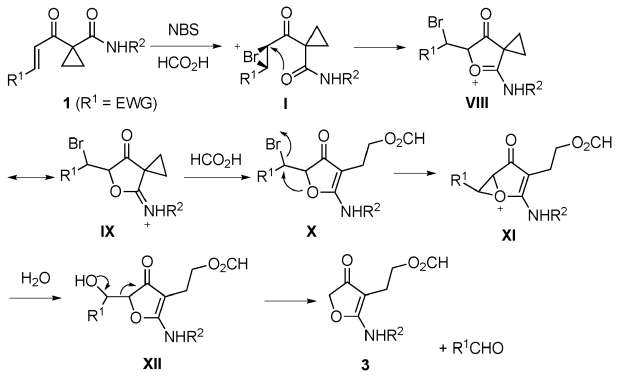
[a] Reactions were carried out with **1** (1.0 mmol), NBS (1.2 equiv.) and HCO_2H (1.2 equiv.) in MeCN (2.0 mL). [b] Isolated yield. [c] Complex mixture was obtained. [d] With HOAc as the catalyst instead of HCO_2H. The pendant ester group is $-O_2CMe$ in **3f**.

Then, the scope of the substituents on the α,β-unsaturated enone moieties of substrates **1** was investigated. In particular, substrates **1g–v** bearing various R^1 groups (aryl, heteroaryl and alkyl) at the β-position of the enone moiety were subjected to the reaction sequences. It was found that the substrates containing an electron-rich R^1 group (*i.e.*, 4-methoxyphenyl, 2-methoxyphenyl, 3,4-methylenedioxyphenyl, 4-dimethylaminophenyl, 2-methylphenyl) and a heteroaryl group (*i.e.*, 2-thienyl) gave **2g–l** in high yields (79–87%, entries 7–12). The reaction of substrate **1m** with a 2-furyl group gave a complex mixture (entry 13). While the substrates containing phenyl (**1n**) and an electron-deficient group like 4-chlorophenyl (**1o**) gave **2n** and **2o**, respectively, in moderate yields (entries 14 and 15). In the reaction mixture, halo-oxa-cyclization product **3a** was separated, in respective 41% yield for **1n** and 47% yield for **1o**. When strong electron-withdrawing aromatic groups (*i.e.* 4-nitrophenyl) and heteroaromatic groups (*i.e.* 4-pyridyl) were introduced, 3(2*H*)-furanones **3a–f** could be obtained as the sole product in 81–89% yields (entries 16–22).[7] For substrate **1v** with an alkyl substituent (R^1 = *t*-C_4H_9), the corresponding 3(2*H*)-furanone **3a** was obtained in 89% yield (entry 23).[8] The structures of **2i** and **3b** were further confirmed by X-ray single crystal diffraction (Fig. S1 in the ESI†).[6] All the above results indicated the efficiency and scope of the cascade reaction reported here.

On the basis of all the results described above, a possible mechanism for the cascade transformation of highly functionalized substrates **1** (R^1 = EDG) into **2** is depicted in Scheme 2. Initially, bromonium ion intermediate **I** is formed *via* electrophilic activation of the alkene. Then, intramolecular aza-cyclization (in a 6-*endo-tet* fashion)[9] takes place, giving the β-amino-α-brominated intermediate **II**. Upon subsequent deprotonation of the ammonium ion with the release of succinimide, spirocyclic intermediate **III** is generated. Promoted by the neighbouring group participation,[10] a bromide is removed, giving the aziridinium ion **IV**.[11] 1,2-Aryl migration on **IV** furnishes iminium ion **V**,[12] followed by β-H elimination[13] with the formation of **VI**. Finally, bromide triggered ring-opening of activated cyclopropane[14] and recyclization (intramolecular oxa-cyclization) furnish the *N*,*O*-bicyclic product **2** (**VI** → **VII** → **2**). It should be noted that the dual role of NBS is critical in the cascade transformation: (i) as a bromonium-producing



Scheme 2 Possible mechanism for the formation 2,3-dihydrofuro[3,2-*c*]pyridinones **2**.



Scheme 3 Possible mechanism for the formation of 3(2*H*)-furanones **3**.

reagent to initiate the aza-cyclization, followed by the 1,2-aryl migration; and (ii) as a potential Br^- nucleophile to open the cyclopropane ring for further oxa-cyclization. Moreover, the duty of carboxylic acid is supposed to activate the carbonyl groups in both substrates **1** and NBS.[4c,4g] The 1,2-aryl migration involved in the reaction, to the best of our knowledge, represents the first example in the α,β-unsaturated enone system *via* halogen activation.

The possible mechanism for the formation of 3(2*H*)-furanones **3** from substrates **1** (R^1 = EWG) is shown in Scheme 3. Halo-oxa-cyclization takes place first (in a 5-*exo*-*tet* fashion),[9] giving oxonium intermediate **VIII** and its resonance structure, iminium **IX**. Secondly, carboxylic acid-mediated cyclopropane ring-opening affords 3(2*H*)-furanone **X**.[14] Thirdly, due to the neighbouring group participation by oxygen (**X** → **XI**),[10] the alkyl bromide **X** is readily hydrolyzed to the alcohol **XII**. The final 3(2*H*)-furanone **3** is produced *via* a retro-aldol with the release of the corresponding aldehydes.[15]

In summary, we have developed a novel strategy for the synthesis of biologically important dihydrofuro[3,2-*c*]pyridinones and 3(2*H*)-furanones *via* a carboxylic acid-catalyzed halonium-initiated cascade process. The one-pot reaction features readily available starting materials, mild conditions, high efficiency, and high chemo- and regioselectivity.

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