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Regiospecific β-lactam ring-opening/recyclization reactions of *N*-aryl-3-spirocyclic-β-lactams catalyzed by a Lewis–Brønsted acids combined superacid catalyst system: a new entry to 3-spirocyclicquinolin-4(1*H*)-ones†

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The regiospecific β-lactam ring-opening/recyclization reaction of *N*-aryl-3-spirocyclic-β-lactams, made by the one-pot cyclization reaction of acetoacetanilides, has been achieved for the first time using a Lewis–Brønsted acids combined superacid catalyst system, thus providing an efficient entry to 3-spirocyclicquinolin-4(1*H*)-ones. A mechanism involving superacid-catalysis was proposed.

Although most of the current attention is paid to their renewed biological and medicinal significance as antibiotics and enzyme inhibitors, β-lactams,[1] due to the ring strain (25 kcal mol^{-1}) associated with 2-azetidinones and their selectivity in bond cleavage (ring-opening), have been recognized as versatile intermediates in the synthesis of a variety of valuable organic molecules, such as α- and β-amino acids, alkaloids, other heterocycles, and complex natural products.[2] The regioselective N_1–C_2 ring-opening/recyclization (intramolecular acyl migration) reaction of *N*-aryl-β-lactams, promoted by Brønsted acids or Lewis acids, remains attractive since it represents an atom economic approach for the synthesis of quinolin-4(1*H*)-ones, an important heterocyclic scaffold.[3] Kano and coworkers have done the pioneering work and firstly surveyed the intramolecular acyl migration of *N*-aryl-β-lactams using a Brønsted acid or a Lewis acid.[4] Further, Tepe and coworkers developed this reaction and realized the synthesis of quinolin-4(1*H*)-ones under significantly milder conditions by using equivalent amount of trifluoromethanesulfonic acid.[5a,b] Until now, this transformation has been exploited to some extent, including the preparation of bioactive compounds.[5c–e] On the other hand, the exploration of the synthetic and medicinal utility of 3-spirocyclicquinolines, an interesting class of quinoline derivatives, was restrained by the lack of efficient synthetic methods.[6] Herein, we wish to report the first superacid-catalyzed chemoselelctive β-lactam ring-opening/recyclization of *N*-aryl-3-spirocyclic-β-lactams,[7] which were prepared by a one-pot cyclization reaction of readily available acetoacetanilide derivatives, thus providing a new atom economic approach to 3-spirocyclicquinolin-4(1*H*)-ones. The key point in this research is the discovery of a superacid catalyst system constituting a Lewis acid and Brønsted acid conjugate, like $FeCl_3$ and HOTf, that can promote the regiospecific β-lactam ring-opening reaction of 3-spirocyclic β-lactams, even in the presence of much more strained cyclopropyl unit (27.5 kcal mol^{-1}).

In the past few years, the study of iron-catalyzed reactions has received great attention,[8] because, compared with precious metal catalysts such as Pt, Rh, Ru, Pd, Au, and Ag, iron is cheaper, nontoxic, and above all abundant on earth. As part of our continuing interest in exploiting iron salts as catalyst in organic reactions, particular in the synthesis of heterocycles,[9] we became interested in investigating iron-catalyzed ring-opening/recyclization reaction of *N*-aryl-3-spirocyclic-β-lactams. In this paper, we disclosed that the combination of an iron salt and a protonic acid regiospecifically induced β-lactam ring-opening of *N*-aryl-3-spirocyclic-β-lactams, featuring well with high reaction efficiency as well as good regioselectivity for unsymmetrical substrates.

Based on our previous studies on the synthetic utility of acetoacetanilide derivatives,[10] the preparation of *N*-aryl-3-spirocyclic-β-lactams was started from the stepwise cyclization reaction of cyclopropane-containing acetoacetanilide **1a** by sequential reduction of carbonyl with $NaBH_4$, esterification of hydroxyl reacting with *p*-toluenesulfonyl chloride, and finally intramolecular nucleophilic substitution (Scheme 1). Further, the stepwise reaction was optimized into an operation economic one-pot procedure, which afforded 3-spirocyclic-β-lactam **2a** in 75% yield. The structure of **2a** was unambiguously confirmed by X-ray crystallography (CCDC 816903). Under the one-pot conditions, we next investigated the scope for the preparation of 3-spirocyclic-β-lactams **2**. As shown in Table 1, substituted 3-spirocyclic-β-lactams **2b–2m** were prepared in good to high yields, even with a size variation of the 3-spirocyclic unit from 3-spirocyclopropyl (entries 1–10) to 3-spirocyclopentyl (entries 11–12). Even though many methods are presently available for the synthesis of

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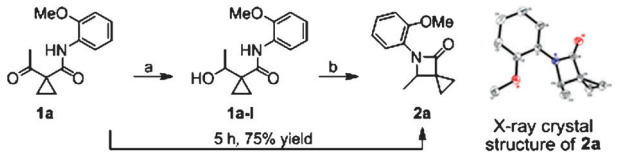
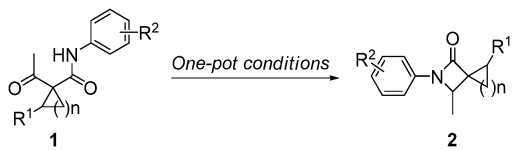


Scheme 1 *Reagents and Conditions*: (a) **1a** (5 mmol), $NaBH_4$ (6 mmol), EtOH (25 mL), at room temperature, 1 h, 95% yield. (b) KOH (25 mmol), TsCl (7.5 mmol), CH_2Cl_2 (25 mL), 40 °C, 4 h, 87% yield.

Table 1 One-pot synthesis of 3-spirocyclic *N*-aryl-*β*-lactams **2**[a]



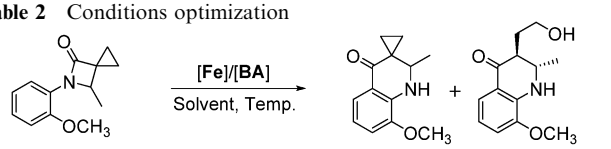
Entry	R^1	R^2	*n*	Time (h)	**2**	Yield (%)[b]
1	H	4-MeO	1	5	**2b**	65
2	H	H	1	5	**2c**	75
3	H	2-Me	1	3	**2d**	73
4	H	4-Me	1	3	**2e**	71
5	H	2,4-diMe	1	5	**2f**	66
6	H	2-Cl	1	3	**2g**	68
7	H	3-Cl	1	4	**2h**	87
8	H	4-Cl	1	3	**2i**	70
9	H	1-Naphthyl	1	3	**2j**	75
10[c]	COOEt	H	1	2.5	**2k**	82
11	H	4-Me	3	4	**2l**	77
12	H	4-Cl	3	7	**2m**	66

[a] Reactions were performed with **1** (5.0 mmol) under one-pot operation of (a) $NaBH_4$ (6.0 mmol), THF (25 mL), at room temperature, 1.0–1.5 h, and (b) KOH (25 mmol), TsCl (10 mmol), 40 °C, 4.0–6.0 h. [b] Isolated yields. [c] The configuration of **2k** was determined with NOE experiment.

3-spirocyclic-*β*-lactams,[11] yet specific procedures for the synthesis of 3-spirocyclopropyl *β*-lactams are still limited.[12] The one-pot procedure described here represents a highly efficient approach to this kind of transformations.

Next, we decided to screen reaction conditions for the selective lactam ring-opening of 3-spirocyclic-*β*-lactams **2**, that lead to 3-spirocyclicquinolin-4(1*H*)-ones. The ring-opening reaction of compound **2a** was used as a model, and representative data are summarized in Table 2. The use of $FeCl_3$ alone as catalyst in toluene at 100 °C only resulted in a slight conversion of **2a** into the desired product **3a** (entry 1). Interestingly, an increase in the $FeCl_3$ catalyst to one equivalent amount dramatically influenced the transformation by offering 61% of **3a**, along with a 13% of cyclopropane ring-opening/oxidized product **4a** and 26% of unreacted substrate **2a**, in which the ratio of **3a**, **4a** and **2a** was determined by ^{1}H-NMR spectra analysis of crude product (entry 2). Further, when three equivalents of trifluoroacetic acid (TFA) was employed as an additive, the desired 3-spirocyclicquinoline **3a** was obtained in 82% yield within 2 h, with notably no by-product of **4a** detected (entry 3). Other iron sources swapped with $FeCl_3$ by varying anion and oxidation state were also examined, and results revealed that all the trivalent iron salts, irrespective of the anions attached, offered a single transformation product of **3a** with high yields (entries 4 and 5), while $FeCl_2$ and metallic iron (Fe) either produced a mixture of **3a** and **2a** or proved

Table 2 Conditions optimization



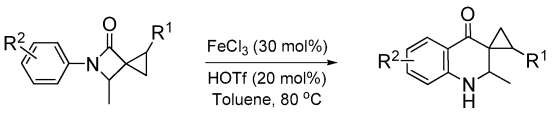
Entry	[Fe] (30 mol%)	BA[a] (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$FeCl_3$	—	toluene	100	3	9 : 91 : 0[c]
2	$FeCl_3$ (1 eq)	—	toluene	100	1	61 : 26 : 13[c]
3	$FeCl_3$	TFA (300)	toluene	100	2	82
4	Fe $(OTf)_3$	TFA (300)	toluene	100	2	83
5	$FeBr_3$	TFA (300)	toluene	100	2	86
6	$FeCl_2$	TFA (300)	toluene	100	2	75 : 25 : 0[c]
7	Fe	TFA (300)	toluene	100	2	0
8	$FeCl_3$	HOTf (100)	toluene	100	0.2	87
9	$FeCl_3$	HOTf (20)	toluene	100	0.5	92
10	**$FeCl_3$**	**HOTf (20)**	**toluene**	**80**	**1**	**91**
11	$FeCl_3$	HOTf (20)	toluene	60	3	46 : 38 : 16[c,d]
12	—	HOTf (20)	toluene	80	1	48 : 28 : 24[c]
13	$FeCl_3$	HOTf (20)	DCE	80	1	68 : 23 : 9[c]
14	$FeCl_3$	HOTf (20)	DMF	80	2	0
15	$FeCl_3$	HOTf (20)	MeOH	80	2	trace

[a] Brønsted acid. [b] Isolated yield. [c] The ratio of **3a** : **2a** : **4a** was determined by the ^{1}H-NMR spectra analysis of crude product. [d] The *trans*- configuration of **4a** was determined by NOE experiment.

ineffective (entries 6 and 7). Following these observations, we unambiguously inferred that the combination of a trivalent iron salt with a Brønsted acid was the key factor for the chemoselective lactam ring-opening of 3-spirocyclic-*β*-lactam **2a**, and thereafter envisioned that use of a much stronger Brønsted acid (BA) such as trifluoromethanesulfonic acid (HOTf) instead of TFA could reduce the loading amount of BA and lower the reaction temperature. The results shown in entries 8–11 confirmed this hypothesis, and so the combined utility of 30 mol% $FeCl_3$ and 20 mol% HOTf as catalyst, offered a single and smooth transformation from **2a** to **3a** in high yield within 1 h at a little lower temperature (80 °C) (entry 10). The necessity of an iron salt in the combined catalyst system was verified by the fact that a mixture of **3a**, **2a** and **4a** was produced when only using 20 mol% HOTf (entry 12). Under otherwise the same conditions in entry 10, the solvent was varied and the products obtained were mixtures (entry 13), trace (entry 15) or absolutely no conversion (entry 14). In comparison, the solvent types significantly influenced the reaction. For example, aprotic solvents such as DCE and DMF as well as protic solvent such as EtOH all proved inapplicable in this reaction (entries 13–15). Consequently, the conditions in entry 10 proved optimal, and were then chosen for further investigations.

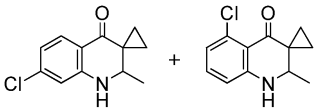
With the optimal conditions in hand, we began to study the scope for the chemoselective *β*-lactam ring-opening reactions of 3-spirocyclic-*β*-lactams **2**. As shown in Table 3, 3-spirocyclic-*β*-lactams **2** were subjected to the optimized conditions described above, and correspondingly 3-spirocyclopropyl quinolin-4(1*H*)-ones **3a–3j** were obtained in good to high yields within a short time (entries 1–9). For the unsymmetrical substrate **2h**, a good ratio of *para*- to *ortho*-selective products was produced (entry 7). Unexpectedly, when R^1 was ethoxycarbonyl (COOEt), no reaction occurred even within a longer reaction time (2.5 h), only with the recovery of starting

Table 3 Preparation of 3-spirocyclicquinolin-4(1*H*)-ones **3** through $FeCl_3$/HOTf co-catalyzed chemoselective ring-opening/recyclization of **2**



2 **3**

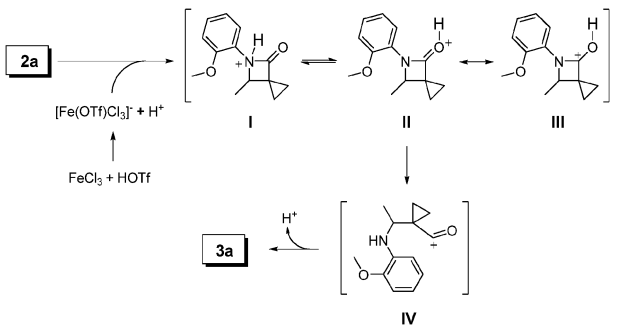
Entry	**2**	Time (h)	**3**	Yield (%)[a]
1	**2b**	1.0	**3b**	88
2	**2c**	1.0	**3c**	92
3	**2d**	0.5	**3d**	89
4	**2e**	0.5	**3e**	90
5	**2f**	1.0	**3f**	81
6	**2g**	1.5	**3g**	87
7	**2h**	1.0	**3h**	93
8	**2i**	0.5	**3i**	85
9	**2j**	0.5	**3j**	90
10	**2k**	2.5	**3k**	0



3h **3h'**

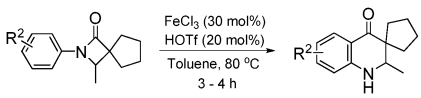
3h : **3h'** = 4 : 1

[a] Isolated yields.



Scheme 2 A plausible reaction mechanism.

material **2k** (entry 10). Similar to cyclopropyl-containing substrates, the cyclopentyl counterparts **2l** and **2m** were also subjected to the optimal reaction conditions and afforded the 3-spirocyclopentyl quinolin-4(1*H*)-ones **3l** and **3m** in 85% and 83% yields, respectively (eqn (1)).



	R^2	Yield
3l	4-Me	85%
3m	4-Cl	83%

(1)

Superacid can be prepared *in situ* by the combination of two components, a strong Lewis acid and a strong Brønsted acid.[6] The combination of $FeCl_3$ and HOTf is necessary for the chemoselective *β*-lactam ring-opening of *N*-aryl-3-spirocyclic-*β*-lactams, therefore, a possible reaction mechanism involving a superacid species like $H[Fe(OTf)Cl_3]$ is proposed (Scheme 2). The superacid $H[Fe(OTf)Cl_3]$ is first formed and then reacts with substrate **2a** to give protonated intermediates **I–III**. Following the C–N bond cleavage, which is consistent with previously reported acid-catalyzed, *N*-protonated, unimolecular (A_N1) mechanism that might be involved in the rate-limiting step,[13] an acylium ion **IV** is formed. The A_N1 mechanism is favoured due to the enhanced rate of C–N bond cleavage that occurs in 2-azetidinones, resulting from the relief in ring strain. The highly reactive acyl carbonium ion **IV** then reacts with the aromatic unit, providing the desired 3-spirocyclicquinolin-4(1*H*)-one **3a** through an intramolecular acyl migration, with the release of catalyst $H[Fe(OTf)Cl_3]$ for the next reaction.

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