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A new and concise way to enamides by fluoroalkanosulfonyl fluoride mediated Beckmann rearrangement of α,β-unsaturated ketoximes

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ABSTRACT

The reaction of α,β-unsaturated ketoximes with fluoroalkanosulfonyl fluorides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) underwent the Beckmann rearrangement smoothly to afford the corresponding acid-sensitive enamides in moderate to excellent yields, which provides a new efficient method for the preparation of acid-sensitive enamides.

Enamide moiety exists in a number of biological active natural products (Fig. 1), such as TMC-95A,[1] crocacin A,[2] chondriamide A,[3] salicylihalamide A,[4] and lansiumamide I,[5] etc;[6] and it is a key subunit related to the biological activity.[7] Furthermore, as versatile organic intermediates, enamides have been widely applied in the synthesis of pyrrole derivatives,[8] functionalized pyridines,[9] oxazole derivatives,[10] α-bromohemiaminal, and α-fluorohemiaminal,[11] etc.[12] A variety of methods have been developed for the construction of enamide motif, including the direct acylation of imine with acyl chloride or anhydride and the thermal decomposition of alkylidenbisamides,[13] and the condensation of carbonyl compounds with amide,[14] etc.[15] In recent years, Pd-, Cu-, and Rh-catalyzed cross-coupling of amides with olefins or alkynes provided promising approach for the preparation of enamides.[16] Among the various methods mentioned above, the Beckmann rearrangement of α,β-unsaturated ketoximes represents one of the most efficient and straightforward means for the preparation of enamides.[17] However, due to the high acid-sensitive nature of enamides, this reaction is largely underdeveloped and only limited examples in cyclic systems are well known.[18]

Fluoroalkanosulfonyl fluorides including perfluoroalkanosulfonyl fluorides and polyfluoroalkanosulfonyl fluorides (R_fSO_2F, such as *n*-$C_8F_{17}SO_2F$, *n*-$C_4F_9SO_2F$, $HCF_2CF_2OCF_2CF_2SO_2F$, etc) are commercially available (in bulk quantities), and cost-effective, non-toxic, and moisture-tolerant. In the R_fSO_2F-mediated reactions, by-products are water-soluble fluoroalkanesulfonic acid anions, which make their work-up procedure very easy to handle; On the other hand, fluoroalkanesulfonic acid salt $R_fSO_3^-M^+$ is a class of highly valuable surfactants. R_fSO_2F has been used as hydroxyl group-activating reagent for the synthesis of fluorinated compounds from alcohols,[19] for the preparation of *cis*-epoxides from chiral vicinal diols resulting in the smooth total synthesis of (−)-dehydroclausenamide,[20] for the homoallylic carbocation rearrangement of 19-hydroxymethyl steroid leading to a total synthesis of (±)-Spiniferin,[21] and for cyclodehydration of β-hydroxy sulfonamides and β-hydroxy thioamides leading to smooth formation of the corresponding aziridines and thiazolines.[22] Furthermore, fluoroalkanosulfonyl fluoride has also been successfully employed to activate the hydroxyl group of carboxylic acid as a condensing agent for esterification, amidation, and anhydridization.[23] As a continuation of our previous report on the abnormal Beckmann rearrangement of steroid 17-oximes using fluoroalkanosulfonyl fluorides,[24] herein we report the Beckmann rearrangement of α,β-unsaturated ketoximes with fluoroalkanosulfonyl fluoride in basic media to afford the corresponding acid-sensitive enamides in moderate to excellent yields.

We began our studies by choosing a steroidal α,β-unsaturated ketoxime, (3β,5α)-3-acetyloxypregn-16-en-20-one oxime (**1a**), as a model substrate due to which we need its enamide in our project of the synthesis of steroidal drugs. Treatment of **1a** with *n*-$C_4F_9SO_2F$ (1.2 equiv) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 equiv) in CH_2Cl_2 at 0 °C for 1 h gave the desired enamide *N*-[(3β,5α)-3-acetyloxyandrost-16-en-17-yl]acetamide (**2a**) in 53% yield (Table 1).

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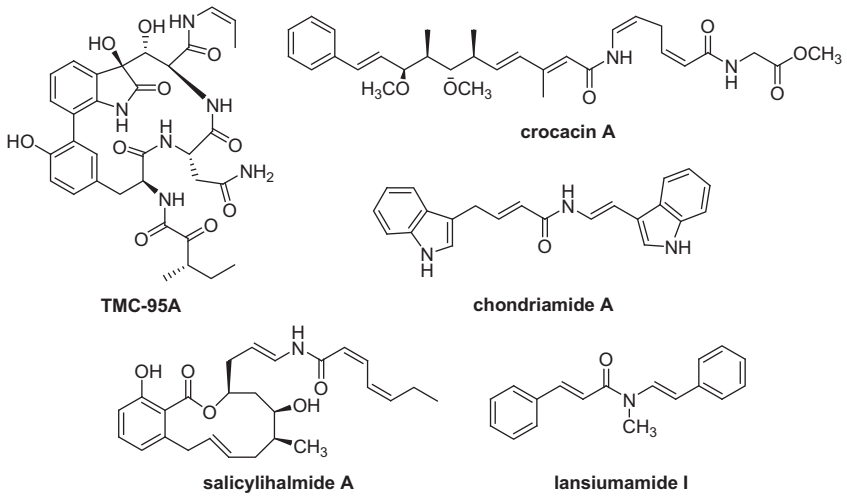
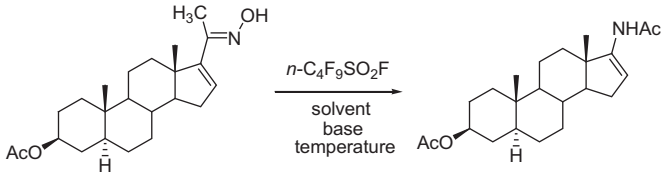


Figure 1. Some natural products with enamide moiety.

In order to further improve the reaction efficiency, the reaction conditions were optimized. When the molar ratio of **1a**/*n*-$C_4F_9SO_2F$/DBU was increased to 1:1.5:3.0, a higher yield of 73% was obtained. However, addition of more amounts of *n*-$C_4F_9SO_2F$ and DBU and prolonged reaction time did not lead to a higher yield. Next, solvent effects on the transformation were also investigated (Table 1). Among solvents screened for the Beckmann rearrangement, chloroform was found to be the best choice providing **2a** in 87% yield (Table 1, entry 7), and the use of other solvents proved to be less effective providing **2a** in 62–78% yields (Table 1, entries 1–6). When pyridine was used as solvent, no reaction occurred (Table 1, entry 8). Further optimization of reaction temperature revealed that 0–15 °C was the best choice (Table 1, entries 7 and 13). Lower reaction temperature than 0 °C resulted in the incomplete conversion of **1a** (Table 1, entries 9–12), and higher temperature than 15 °C caused the formation of more amounts of by-products (Table 1, entry 14). When Et_3N was used as the base instead of DBU, **2a** was afforded in 73% yield (Table 1, entry 15). Finally, we screened other fluoroalkanosulfonyl fluoride reagents and found that both *n*-$C_8F_{17}SO_2F$ and $HCF_2CF_2OCF_2CF_2SO_2F$ possessed similar activity to that of *n*-$C_4F_9SO_2F$. It is noteworthy that the by-products formed in the Beckmann rearrangement of **1a** were mainly (3β,5α)-3-acetyloxy-androstan-17-one (the decomposition product of **2a** and its structure was confirmed by comparing with the authentic sample) and unreacted starting material **1a**.

Table 1
Effects of solvent, temperature, and base on Beckmann rearrangement of **1a**[a]



1a **2a**

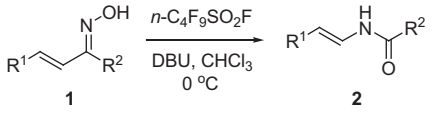
Entry	Solvents	Room temperature (°C)	Base	Yield of **2a**[b] (%)
1	Toluene	0	DBU	69
2	Ethyl ether	0	DBU	77
3	Dichloromethane	0	DBU	73
4	Tetrahydrofuran	0	DBU	73
5	Acetonitrile	0	DBU	62
6	Acetone	0	DBU	78
7	Chloroform	0	DBU	87
8	Pyridine	0	DBU	0
9	Chloroform	−40	DBU	63
10	Chloroform	−20	DBU	73
11	Chloroform	−10	DBU	74
12	Chloroform	−5	DBU	76
13	Chloroform	15	DBU	86
14	Chloroform	25	DBU	62
15	Chloroform	0	Et_3N	73

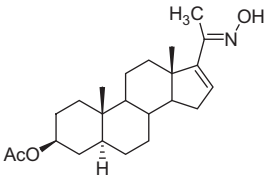
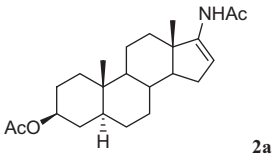
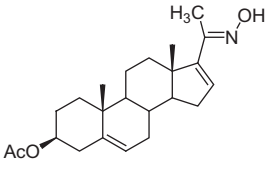
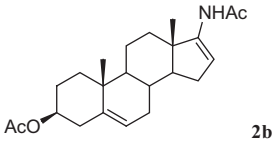
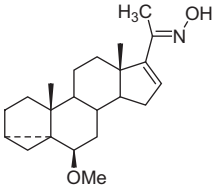
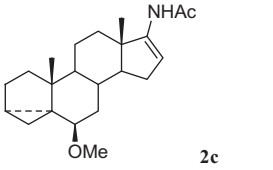
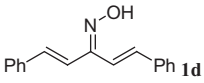
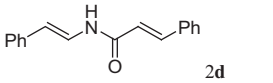
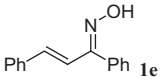
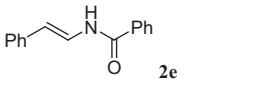
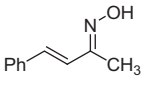
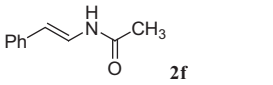
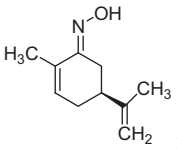
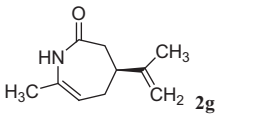
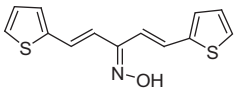
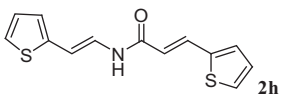
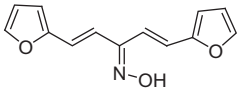
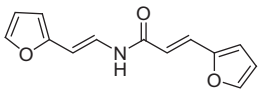
[a] Reaction conditions: **1a** (1.0 mmol), *n*-$C_4F_9SO_2F$ (1.5 mmol), and DBU (3.0 mmol) in solvent at different temperatures for 1 h.
[b] Isolated yields.

With the optimized conditions in hand, we went on to explore the scope and limitation of the reaction, and the results are summarized in Table 2. A range of α,β-unsaturated ketoximes were tested for conversion to enamides. All the substrates in Table 2 proceeded the Beckmann rearrangement on treatment with *n*-$C_4F_9SO_2F$ in the presence of DBU affording the corresponding enamides in moderate to excellent yields. The Beckmann rearrangement of 3β-acetyloxy-prega-5,16-dien-20-one oxime (**1b**) gave the corresponding enamide product **2b** in an excellent yield of 93% (Table 2, entry 2). Boruah and co-workers[25] reported the Beckmann rearrangement of **1b** with $POCl_3$ in Pyridine to give **2b** in 81% yield. However, when we repeated this reaction under the same condition of $POCl_3$/Pyridine, **2b** was only obtained in 61% yield. The reaction of **1c** with *n*-$C_4F_9SO_2F$ provided **2c** in 59% yield along with 33% of unreacted **1c** (Table 2, entry 3). Acyclic ketoxime substrates **1d** and **1e** worked well to afford enamides **2d** and **2e** in 81% and 71% yields, respectively (Table 2, entries 4 and 5). However acyclic ketoxime **1f** furnished enamide **2f** only in poor yield of 33%, accompanied by the formation of more polar byproduct (Table 2, entry 6), which might result from the concurrent competitive Neber rearrangement of **1f** under the same reaction conditions due to the presence of the active CH_3 group. Cyclic α,β-unsaturated ketoxime **1g** was also tested for the Beckmann rearrangement to form the ring-enlargement product, and indeed, seven-membered enamide **2g** was obtained as expected, albeit in poor yield (Table 2, entry 7). Likewise, the reason for low yield of **2g** probably resulted from the Neber rearrangement due to the presence of the active methylene group. The Beckmann rearrangement of two heteroarene substrates **1h** and **1i** also worked well and the corresponding enamide products **2h** and **2i** were formed in 75% and 65% yields, respectively (Table 2, entries 8 and 9).

To further evaluate the application of the above mentioned method, **2d** was treated with iodomethane in the presence of NaH in THF at room temperature, affording the naturally occurring enamide Lansiumamide-I[5] **3** in 90% yield (Scheme 1).

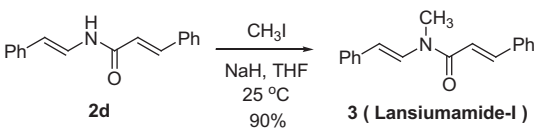
Table 2
R_fSO_2F-induced Beckmann rearrangement of α,β-unsaturated ketoximes[a]



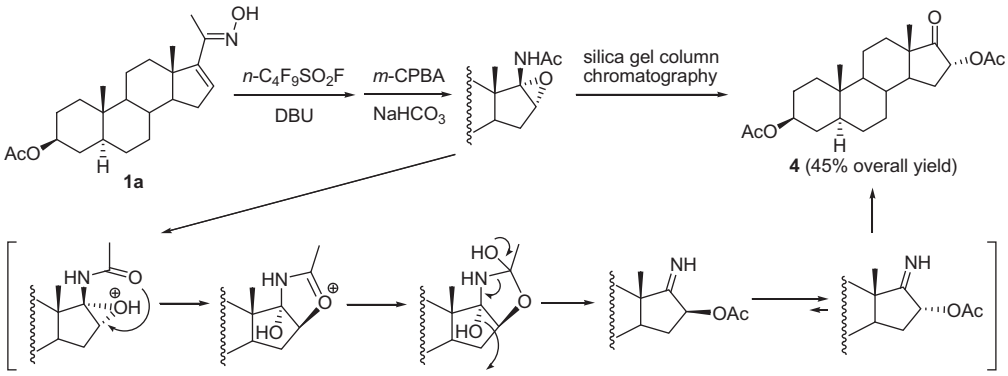
Entry	Substrates	Products	Yield of **2**[b] (%)
1	 **1a**	 **2a**	87
2	 **1b**	 **2b**	93
3	 **1c**	 **2c**	59
4	 **1d**	 **2d**	81
5	 **1e**	 **2e**	71
6	 **1f**	 **2f**	33
7[c]	 **1g**	 **2g**	31
8	 **1h**	 **2h**	75
9	 **1i**	 **2i**	65

[a] Reaction conditions: **1** (1.0 mmol), n-$C_4F_9SO_2F$ (1.5 mmol), and DBU (3.0 mmol) in $CHCl_3$ at 0 °C for 1 h.
[b] Isolated yields.
[c] Compound **1g** (1.0 mmol), n-$C_4F_9SO_2F$ (3.0 mmol), and DBU (6.0 mmol).

C-16 oxygen functionalization of steroidal D-ring is a fundamental reaction in organic synthesis. 16α-acetyloxy-17-ketones can be prepared through α-halogenation of 17-ketones and subsequent hydrolysis, or via the formation of enol acetate of 17-ketones followed by epoxidation with peracids.[26] In order to investigate the application of enamides in the synthesis of steroidal 16α-acetyloxy-17-ketones, we tentatively studied the one-pot procedure for the preparation of **4** starting from **1a** (Scheme 2). A few of epoxidation agents and systems were screened to effect the epoxidation of **2a** including m-CPBA/Na_2HPO_4, m-CPBA/K_2CO_3, m-CPBA/$NaHCO_3$, dimethyldioxirane, and n-$C_4F_9SO_2F$/H_2O_2/NaOH. Among them, m-CPBA/K_2CO_3 system led to the best result with the formation of **4** in 45% overall yield for two steps from **1a** after purification via silica gel column chromatography. It was presumed that the



Scheme 1. The preparation of Lansiumamide-I (**3**) from **2d**.



Scheme 2. The ring D functionalization of **1a**.

formation of **4** may result from the opening of the epoxide ring and the migration of the 17-acetyl group in the course of silica gel column chromatography induced by the weak acidity of silica gel[26] (Scheme 2). Therefore our method can also be efficiently applied in the C-16 oxygen functionalization of steroidal D-ring.

In summary, we have developed a system of fluoroalkanosulfonyl fluorides and base media mediated Beckmann rearrangement of α,β-unsaturated ketoximes leading to the smooth formation of the corresponding acid-sensitive enamides in moderate to excellent yields.[27] This protocol is mild and operationally simple, thus providing an efficient method for the preparation of enamides. Our results further extend the application of fluoroalkanosulfonyl fluorides in organic synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.154.

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27. *General procedure for the Beckmann rearrangement of α,β-unsaturated ketoximes mediated by fluoroalkanosulfonyl fluorides R_fSO_2F in basic media*: Under nitrogen atmosphere, a solution of **1** (3.0 mmol) and *n*-$C_4F_9SO_2F$ (4.5 mmol) in chloroform (20 mL) was stirred for 10 min at 0 °C. Then DBU (9.0 mmol) was slowly added dropwise. The resulting mixture was continued to stir at 0 °C for 10–30 min. Evaporation of the reaction mixture under reduced pressure to remove volatile components generated residue which was purified through basic Al_2O_3 column chromatography using mixture of petroleum ether and ethyl acetate as an eluent, providing the corresponding enamide products **2** in the yields of 31–93%.