EurJOC
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A Journal of
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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900844

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900844

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SO_2F_2-Activated Efficient Beckmann Rearrangement of Ketoximes for Accessing Amides and Lactams

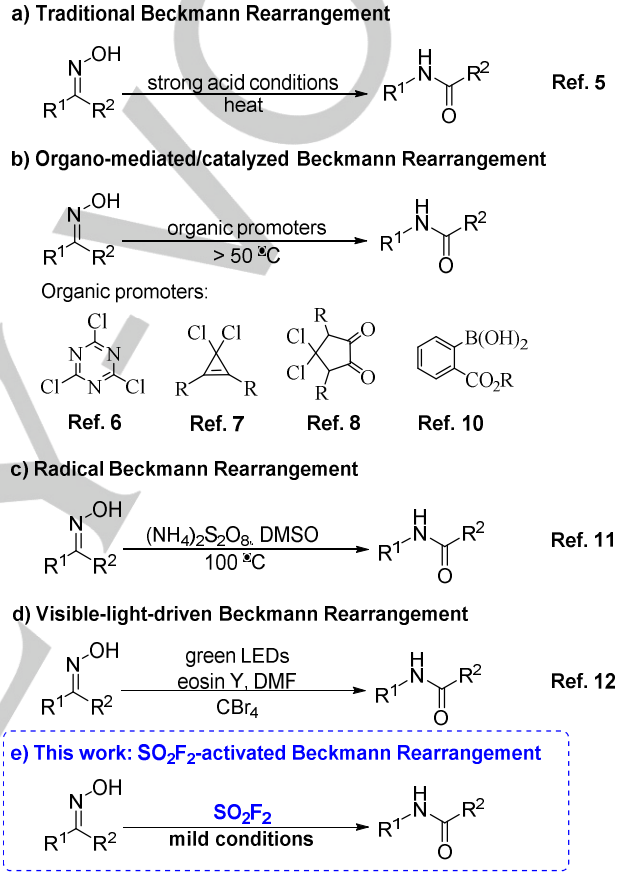
Guofu Zhang,[a] Yiyong Zhao,[a] Lidi Xuan,[a] and Chengrong Ding*[a]

Dedication ((optional))

Abstract: A novel, mild and practical protocol for the efficient activation of the Beckmann rearrangement utilizing the readily available and economical sulfuryl fluoride (SO_2F_2 gas) has been developed. The substrate scope of the operationally simple methodology has been demonstrated by 37 examples with good to nearly quantitative isolated yields (over 90% yield in most cases) in a short time, including $B(OH)_2$, COOH, NH_2, and OH substituted substrates. A tentative mechanism was proposed involving formation and elimination of key intermediate, sulfonyl ester.

Introduction

The Beckmann rearrangement, discovered in 1886,[1] is undoubtedly a powerful and atom-economic tool to construct amides and lactams from their corresponding oximes.[2] The Mona Lisa of molecular rearrangement, rightly termed by Jones,[3] is generally used in manufacturing monomers for polymerization of polyamides nylon-6 and nylon-12 on a large scale in industrial chemistry and in the synthesis of several bioactive natural products.[4] This reaction, however, traditionally requires high reaction temperature, a large amount of a strong Bronsted or Lewis acids and dehydrating media, which generates considerable amounts of byproducts and precludes its compatibility with sensitive substrates (Scheme 1**a**).[5] In response to these deficiencies, several interesting variants via the activation of the oxime hydroxy group have been developed in recent years (Scheme 1**b**). Most notably, the self-propagation mode of "organocatalytic" Beckmann rearrangements,[6-9] as elegant studies, is activated by organic promoters, such as cyanuric chloride,[6] chlorocyclopropenium,[7] and dichloroimidazolidinediones.[8] Intriguingly, a boronic acid were identified as an efficient catalyst for the activation of oximes.[10] Other amusing variants, such as a facile radical (Scheme 1**c**) and visible-light-driven (Scheme 1**d**) Beckmann rearrangements,[11,12] also provides alternative strategies. Although those above related organic compounds could be employing as promoters or catalysts to achieve effective activation of oxime N−OH bonds in the Beckmann rearrangement, pre-synthesis of those structurally specific organic compounds is oftentimes required and mild catalytic manifolds are rare. Accordingly, developing a novel, efficient and practical activation method for the Beckmann rearrangement using green, readily available and economical substrates without unnecessary steps or energy waste still maintain challenging in modern sustainable chemistry.[13]



Scheme 1. Strategies for Beckmann rearrangement.

Sulfuryl fluoride (SO_2F_2), as an inexpensive, abundant and relatively inert electrophile (stable up to 400 ℃ when dry),[14] has attracted significant attention to be used for Sulfur (VI) fluoride exchange (SuFEx) click chemistry and other versatile manipulations.[15-17] Especially in 2014,[15] Sharpless group initiatively reported a simple and reliable method for the synthesis of aryl fluorosulfates from phenols and SO_2F_2 in the presence of triethylamine, verifying that the proton of phenolic hydroxyl can activate the exchange of S-F bonds for S-O bonds to make functional products, and fluorosulfate functional group (-OSO_2F) could be applied in a controllable and targeted manner for varied transformations due to the sulfate connector is surprisingly stable toward hydrolysis. Most recently, prof Qin and our groups almost simultaneously reported a mild and robust method for efficiently converting aldehydes or aldoximes into corresponding nitriles mediated by SO_2F_2/base in an economical and green manner.[18] Mechanistic studies demonstrated the

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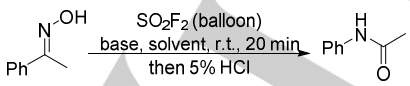
desired nitrile was formed from a base promoted β-elimination of key intermediate sulfonyl ester, which is generated from the reaction of aldoxime intermediate with SO_2F_2 under the promotion of Na_2CO_3. We hypothesized, similarly to aldoxime, that the proton of ketoxime might activate the exchange of S-F bond of SO_2F_2 for S-O bond to generate the corresponding intermediate sulfonyl ester under alkalinous conditions, which will subsequently undergo fluorosulfonic ester elimination to promote Beckmann rearrangement. Herein, we report a SO_2F_2-activated efficient Beckmann rearrangement of ketoximes to amides and lactams under mild conditions without any capricious organic promoters or catalysts (Scheme 1**e**).

Results and Discussion

We started our investigation by examining the representative substrate acetophenone oxime **1a** to test the feasibility of the proposed Beckmann rearrangement (Table 1). To our delight, the desired Beckmann product, acetanilide **2a**, was isolated in nearly quantitative yield of 98% under SO_2F_2 atmosphere at room temperature when 2.0 equiv of triethylamine (Et_3N) was employed in CH_3CN (Table 1, entry 1). Encouraged by this initial result, further screening of reaction conditions was performed with respect to bases and solvents (see supporting information for a more detailed account of optimization conditions). Although inorganic bases has significant advantages over their organic counterparts,[19] we were depressed to find that the yields of **2a** were obviously decreased when using inorganic bases, such as Cs_2CO_3, Na_2CO_3, K_2CO_3 (Table 1, entries 2-4), even though increasing the reaction time. Gratifyingly, reducing the loading of Et_3N to 1.5 equiv still maintain the excellent effective and pleasingly provided the desired product **2a** in quantitative yield (Table 1, entry 5). However, when the Et_3N loading was further reduced to 1.0 equivalent, the reaction became more sluggish to generate **2a** in 76% yield with the remaining **1a** unconverted (Table 1, entry 6). Furthermore, The usage of other common solvents, such as dichloromethane (DCM), ethyl acetate (EtOAc), dimethyl sulfoxide (DMSO) and 1,4-dioxane, did not improve the yield of this transformation (Table 1, entries 7-10). And meanwhile, it's undoubtedly that shortening reaction time caused an inferior isolated yield of **2a** in 92% (Table 1, entry 11).

Table 1. Optimization of the reaction conditions. [a]



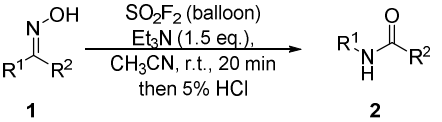
1a **2a**

Entry	Base (equiv)	Solvent	Isolated yield (%)
1	Et_3N (2.0)	CH_3CN	98
2	Cs_2CO_3 (2.0)	CH_3CN	87
3	K_2CO_3 (2.0)	CH_3CN	50
4	Na_2CO_3 (2.0)	CH_3CN	9
5	Et_3N (1.5)	CH_3CN	98
6	Et_3N (1.0)	CH_3CN	76
7	Et_3N (1.5)	DCM	85
8	Et_3N (1.5)	EtOAc	67
9	Et_3N (1.5)	DMSO	34
10	Et_3N (1.5)	1,4-dioxane	18
11[b]	Et_3N (1.5)	CH_3CN	92

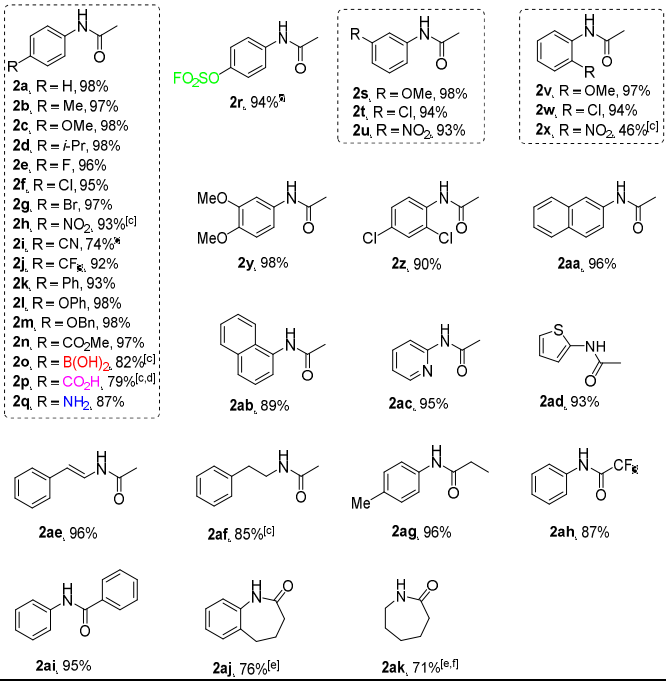
[a] Reaction conditons: acetophenone oxime **1a** (1.0 mmol), base, solvent (5.0 mL), and SO_2F_2 balloon, rt, 20 min; then 5% HCl (1.0 mL, 1.35 mmol, 1.35 eq.) was introduced into the reaction mixture for an additional 10 min. [b] Stirring for 10 min.

With the optimized conditions being established, the scope and generality of this SO_2F_2-activation protocol were subsequently tested (Table 2). Gratifyingly, a broad range of aromatic and alkyl substituted oximes was found to be rearranged smoothly under this protocol to afford the corresponding amides/lactams in good to excellent yields and a functional group-tolerant fashion. The acetophenone oximes bearing either electron-donating (Me, OMe, *i*-Pr, Ph, OPh, OBn) or electron-withdrawing (F, Cl, Br, CN, CF_3) substituents, mostly in a short time, delivered the corresponding acetanilides in high yields (**2b**-**2n** and **2y**, **2z**). Surprisingly, the transformative, base-sensitive or acid labile moieties, such as boronate (**2o**), carboxyl (**2p**) and amino (**2q**), were well tolerated when the reaction conditions were fine adjusted. It is noteworthy that the 4'-hydroxyacetophenone derived oxime **1r** containing both SuFEx-sensitive aromatic hydroxy group and Beckmann-active oxime hydroxy group was smoothly achieved to form 4-acetamidophenyl fluorosulfate **2r** in 94% yields.[20] Although the satisfactory results showed the position of substituents on the aryl rings exhibited insignificant influence on the efficiency (**2c**, **2s**, **2v**, and **2f**, **2t**, **2w**, and **2aa**, **2ab**), the yield of *ortho*-nitroacetanilide (**2x**) was exactly poorer than that of *para*- or *meta*-nitroacetanilide (**2b**, **2u**). Moreover, ketoximes featuring an aromatic fused ring (**2aa**, **2ab**) and a heterocyclic aromatic ring (**2ac**, **2ad**) which furnished their corresponding rearranged products in gratifying yields. Besides, other variations in the R^1 moiety of the ketoximes **1**, such as cinnamenyl (**2ae**) and phenylethyl (**2af**), were studied and found to be efficiently engaged in the Beckmann rearrangement. In the case of diverse R^2 moieties, representative ketoximes (**2ag**-**2aj**) were also successfully transformed into their corresponding rearrangement products in good to excellent yields. Excitingly, cyclohexanone oxime, a notoriously challenging substrate,[21] gave a 71% isolated yield of caprolactam **2ak** under more forcing conditions.

Table 2. Substrate scope of the SO_2F_2-promoted Beckmann rearrangement. [a,b]

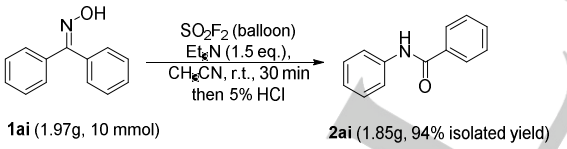


1 **2**



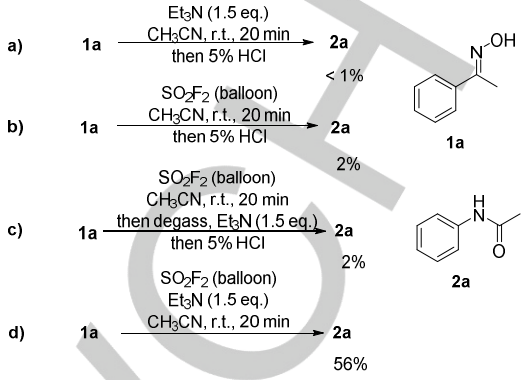
[a] Reaction conditons: ketoxime substrate **1** (1.0 mmol), Et_3N (209 uL, 1.5 mmol, 1.5 eq.), 5.0 mL of CH_3CN as the solvent, and SO_2F_2 gas (balloon), rt, 20 min; then 5% HCl (1.0 mL, 1.35 mmol, 1.35 eq.) was introduced into the reaction mixture for an additional 10 min. [b] Isolated yields based on **1**. [c] 60 min. [d] 3.0 equiv of Et_3N was used. [e] 3.0 h. [f] 1.5 equiv of DBU was used.

To explore the synthetic utility of this SO_2F_2-promoted Beckmann rearrangement in the presence of Et_3N, the gram-scale preparation of N-phenyl benzamide **2ai**, which is an important organic intermediates with a broader range of uses in medicine, pesticides and dyes,[22] was carried out (Scheme 2). Under the standard conditions, the reaction of diphenylmethanone oxime **1ai** proceeded smoothly, delivering the desired product **2ai** in 94% isolated yield.



Scheme 2. Gram-scale synthesis of N-phenyl benzamide.

As illustrated in Scheme 3, a series of control experiments were performed to gain further insight into the mechanism of this transformation. Mixing the acetophenone oxime **1a** just with Et_3N without the presence of SO_2F_2, the desired acetanilide **2a** was not generated (Scheme 3**a**). Meanwhile, mixing 1a just with SO_2F_2 without 1.5 equivalent of Et_3N, only a trace of **2a** was observed (Scheme 3**b**). Pre-mixing the **1a** with SO_2F_2, then removing SO_2F_2 and adding 1.5 equivalent of Et_3N, the acetanilide was formed in negligible yield (Scheme 3**c**). In addition, without the additional 1.0 mL of 5% muriatic acid for terminal treatment, the Beckmann product **2a** was only in 56% isolated yield (Scheme 3**d**). All above experiment results demonstrate that the generation and elimination of sulfonyl ester were crucial for this Beckmann rearrangement process.



Scheme 3. Control exeperiments for mechanism investigation.

Based on the results of the control experiments, a plausible mechanism for this Beckmann rearrangement process was proposed (Figure 1). Initially, the ketoxime **1** was deprotonated with SO_2F_2 under the promotion of Et_3N to form the fluorosulfonate ester **A**.[18] Then the fluorosulfate functional group (-OSO_2F) of intermediate **A** was promptly eliminated with the proton of additional acid to generate a reactive nitrillium ion **B**.[21] Consequently, the water attacks this reactive intermediate, which following tautomerization, affords the requisite amide **2**.

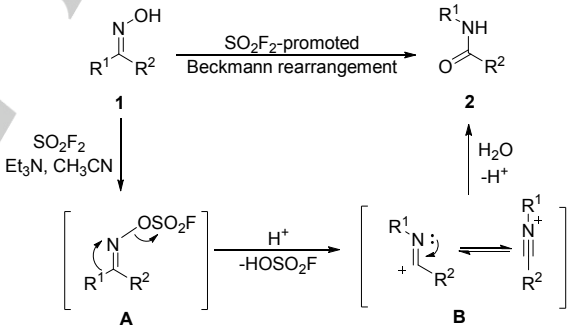


Figure 1. A plausible mechanism for the SO_2F_2-promoted Beckmann rearrangement.

Conclusions

In summary, we have developed a novel, mild, practical and robust method for the Beckmann rearrangement of ketoximes to access amides and lactams promoted by SO_2F_2 with the presence of Et_3N. More than 37 structurally diverse amides and lactams were synthesized with greater than 90% isolated yields in most cases, demonstrating that the high efficiency, broad scope and functional-group compatibility of this new protocol. In addition, a SO_2F_2-activated Beckmann rearrangement mechanism was also proposed.

Experimental Section

General procedure for the SO_2F_2-promoted Beckmann Rearrangement of ketoximes to amides/lactams. Oxime substrates **1** (1.0 mmol, 1.0 equiv), Et_3N (278 uL, 2.0 mmol, 2.0 equiv) and CH_3CN (5.0 mL, 0.2 M) were sequentially added into an oven-dried reaction tube (30 mL) equipped with a stirring bar, the reaction tube was covered with a plastic stopper before the SO_2F_2 gas was introduced into the stirring reaction mixture by slow bubbling through a SO_2F_2 balloon at the room temperature for 30 min. Then, 5% hydrochloric acid (1.0 mL, 1.35 mmol, 1.35 equiv) was added into the mixture and stirred at the room temperature for an additional 15 min. After that, the reaction diluted with water and extracted with dichloromethane (3× 20 mL). Then the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and petroleum ether as eluent to afford the desired amides or lactams **2**.

Acknowledgments

We acknowledge financial support from the National Natural Science Foundation of China (no. 20702051), the Natural Science Foundation of Zhejiang Province (LY13B020017).

Keywords: Sulfuryl fluoride • Beckmann rearrangement • Ketoximes • Amides • Sulfonyl ester

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10.1002/ejoc.201900844

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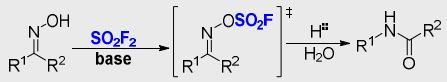

R^1 = (hetero)aryl, alkenyl, alkyl; R^2 = aryl, alkyl
Mild and robust conditions; Up to quantitative yield; Great group tolerance

A novel protocol for the efficient activation of the Beckmann rearrangement utilizing the readily available sulfuryl fluoride (SO_2F_2 gas) is reported. The substrate scope of this methodology has been demonstrated by 37 examples with good to nearly quantitative isolated yields in a short time. A tentative mechanism was proposed involving formation and elimination of sulfonyl ester.

Rearrangement

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Page No. – Page No.

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