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Highly efficient synthesis of β-nitrate ester carboxamides through the ring-opening of 2-oxazolines

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Kai Qiao,[a] Xin Yuan,[a] Li Wan,[a,b] Ming-Wei Zheng,[a] Dong Zhang,[a] Bing-Bing Fan,[a] Zhe Chen Di,[a] Zheng Fang[a] and Kai Guo*[a,b,c]

A novel method for the synthesis of β-nitrate ester carboxamides using non-corrosive *tert*-butyl nitrite (TBN) as the nitro source and easily available oxygen as the oxidant has been developed. Variously substituted 2-oxazolines were efficiently ring-opened to deliver the corresponding products in excellent yields. Notably, this reaction provides fast access to pharmaceuticals such as nicorandil.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used as antipyretic and anti-inflammatory agents for many years. However, the long-term use of these pharmaceuticals increases the risk of gastrointestinal disorders.[1,2] To overcome these problems, drugs with a fragment that produces NO attached to the NSAID core, i.e., NO-donating non-steroidal anti-inflammatory drugs (NO-NSAIDs), have been developed. These have a much lower negative impact on the gastrointestinal tract (Fig. 1a).[3,4] Organic nitrate and nitrite esters, which are NO-donors, have been used to treat cardiovascular diseases since the 19th century. For many years, nitroglycerin, nicorandil, and other organic nitrates have been the mainstays of cardiovascular therapy (Fig. 1b),[5] and are especially beneficial in the treatment of diangina pectoris, unstable angina, and the early stages of acute myocardial infarction.[6-8] However, there are only two general methods for preparing nitrate esters: direct esterification of the appropriate alcohol using nitrosonitric acid, dinitrogen tetroxide, and nitric acid/acetic anhydride;[9-12] or substitution reactions of the corresponding halides with silver or mercury nitrate.[13-15] These established methods require acidic conditions, expensive reagents, toxic chemicals, and elaborate

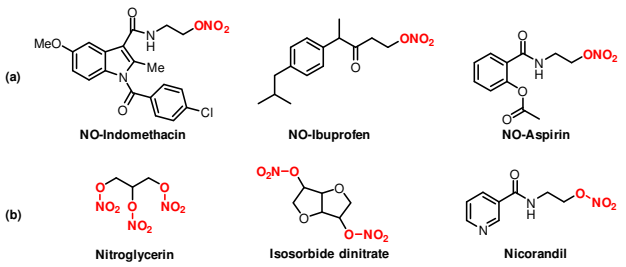

Fig. 1 Representative pharmaceuticals that contain nitrate ester motif.

safety precautions, and some of them are not suitable for large-scale preparations. Novel efficient, more economic, and environmentally benign procedures for the preparation of nitrate esters are therefore needed.

2-Oxazolines are the fundamental structural motifs in numerous bioactive compounds of relevance to crop protection and medicinal chemistry.[16,17] 2-Oxazolines are easily generated from amino alcohols and carboxylic acids, or through alternative synthetic procedures starting from alkenes or epoxides as substrates.[18,19] The oxazoline moiety is resistant to a range of reagents such as nucleophiles, bases, or radicals, and is therefore widely used as a protecting or directing group.[20,21] However, oxazolines are susceptible to SN_2 attack by nucleophilic ring-opening at the C5 position of the ring, leading to the production of β-substituted carboxamides.[22-24] This reaction is extensively employed in glycoside synthesis, in which an anomeric oxazoline is used as a glycopyranosyl donor.[25] Recently, numerous multi-target drugs have been designed and synthesized with the goal of achieving enhanced efficacy and improved safety compared with those of existing drugs. Among these, NO-releasing ability has been identified as a useful additional property of pharmaceuticals, and this has led to the development of important multi-target drugs.[26-28] On the basis of the properties and uses of 2-oxazolines and nitrate esters, we have developed a metal-free method for preparing β-nitrate ester carboxamides from 2-substituted oxazolines. To our delight, *tert*-Butyl nitrite (TBN) has been used as a precursor for the generation of NO_2 to avoid the

[a] *College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, P. R. China*
Fax: (+86)-25-5813-9926; phone: (+86)-25-5813-9926; e-mail: guok@njtech.edu.cn
[b] *Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), Nanjing 211816, P. R. China*
[c] *State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, Nanjing 210009, P. R. China*
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utilization of highly corrosive H_2SO_4/HNO_3 or N_2O_5 in many nitration protocols.[29,30] It is also easy to produce the ONOO· radical with oxygen under mild conditions.[31-33] Here, we report a novel procedure for preparing β-nitrate ester carboxamides through the ring-opening of 2-substituted oxazolines under environmentally friendly conditions.

The 2-aryl oxazoline bearing benzamide **1a** was chosen as a model substrate for optimization of reaction parameters because of its wide use in C–H functionalization reactions (Table 1). The desired product **3a** was obtained in 36% yield with $Co_2(CO)_8$ as the catalyst [22,34] and 1,4-dioxane as the solvent at 80 °C for 24 h under an air atmosphere (Table 1, entry 1). The molecular structure of **3a** was unambiguously identified using single-crystal X-ray diffraction (Fig. 2). This result is interesting because this method enables the synthesis of β-nitrate ester carboxamides through the ring-opening of 2-oxazoline, which is inaccessible by using conventional methods. To improve the reaction efficiency, various transition-metal catalysts were also tested. $Ni(acac)_2$ had the highest catalytic activity among the tested catalysts, giving product **3a** in 65% yield (Table 1, entries 2–6). Surprisingly, the reaction proceeded smoothly in the absence of a transition metal catalyst, and a slightly higher yield (70%) of **3a** was obtained (Table 1, entry 7). A number of solvents were screened. The results showed that DMSO, AcOH, DMF, THF, and MeOH were inappropriate for this reaction, and none of them matched the efficacy of 1,4-dioxane (Table 1, entries 8–17). Moreover, different temperatures were also screened and the results showed that 80 °C was the most suitable reaction temperature (Table 1, entries 18 and 19). The effect of the TBN loading was also investigated. Unsatisfactory results were obtained when the loading of TBN was changed (Table 1, entries 20 and 21). Finally, the best yield was achieved by performing the reaction under O_2 atmosphere (Table 1, entry 22).

With the optimized reaction conditions in hand, we explored the versatility of the esterification with regards to a series of diversely substituted carboxamides. As shown in Table 2, aromatic amides bearing a variety of substituted

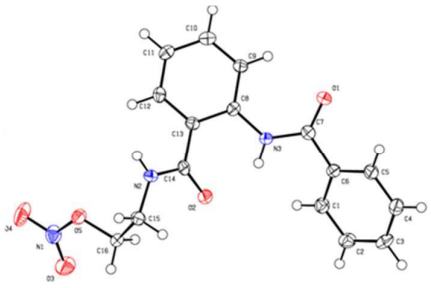
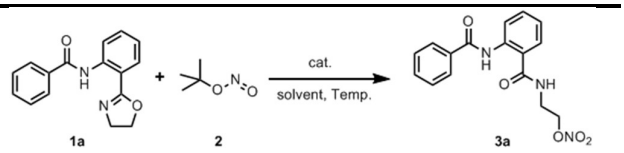


Fig. 2 X-ray structure of **3a**.

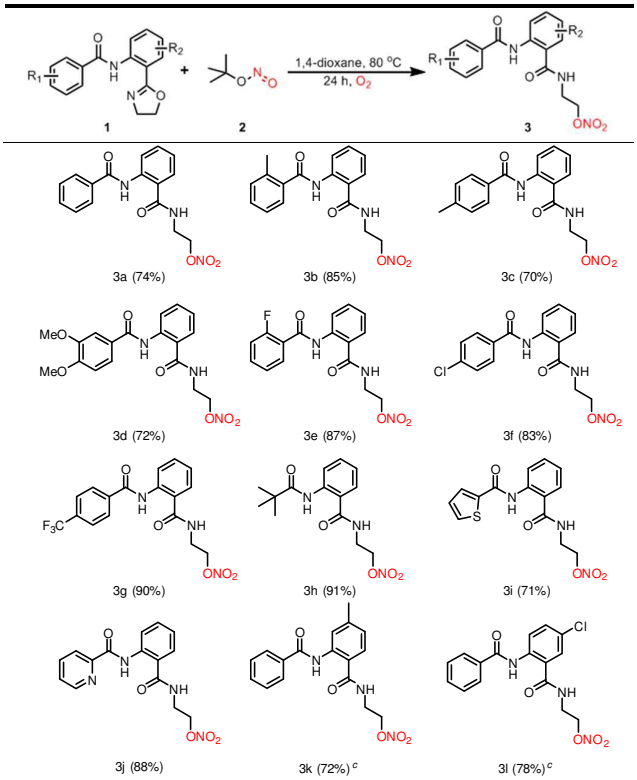
Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	TBN (equiv)	Temp (°C)	Solvent	Yield (%)[b]
1	$Co_2(CO)_8$	3	80	1,4-dioxane	36
2	$Ru_2(CO)_9$	3	80	1,4-dioxane	34
3	$Ni(acac)_2$	3	80	1,4-dioxane	65
4	$Pd(OAc)_2$	3	80	1,4-dioxane	47
5	$Cu(OAc)_2$	3	80	1,4-dioxane	51
6	$FeCl_3$	3	80	1,4-dioxane	21
7	—	3	80	1,4-dioxane	70
8	—	3	80	EtOAc	43
9	—	3	80	DMSO	8
10	—	3	80	AcOH	trace
11	—	3	80	DMF	5
12	—	3	80	ACN	54
13	—	3	80	THF	10
14	—	3	80	MeOH	6
15	—	3	80	DCE	63
16	—	3	80	toluene	38
17	—	3	80	PhCl	46
18	—	3	60	1,4-dioxane	41
19	—	3	100	1,4-dioxane	23
20	—	2	80	1,4-dioxane	59
21	—	6	80	1,4-dioxane	46
22[c]	—	3	80	1,4-dioxane	83(74)[d]

[a] Reaction conditions: **1a** (0.2 mmol), TBN, catalyst (10 mol%), solvent (2.0 mL), stirred under air for 24 h in a Schlenk tube. [b] Determined by analysis of HPLC results. [c] Under O_2 atmosphere. [d] Isolated yield.

Table 2. Substrate scope of carboxamides[a,b]



[a] Reaction conditions: **1** (0.2 mmol), TBN (3.0 equiv), 1,4-dioxane (2.0 mL), stirred under O_2 at 80 °C for 24 h in a Schlenk tube. [b] Isolated yield. [c] TBN (4.0 equiv) was used.

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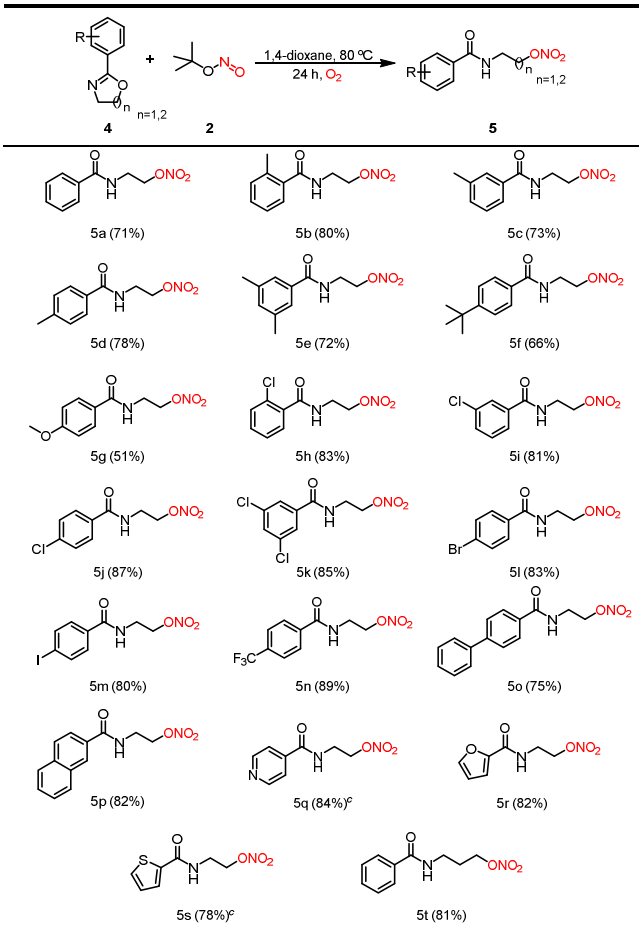
groups, including electron-donating groups (Me, MeO) and electron-withdrawing groups (F, Cl, CF_3, NO_2), on the benzene ring, showed high reactivity with TBN under the optimal reaction conditions. The desired products (**3b**–**3g**) were obtained in good to excellent yields. It is worth noting that substrates **1d** and **1e** have antifungal activities,[35] and their corresponding esterification products **3d** and **3e** could be converted to molecules with higher bioactivities. An alkyl-substituted carboxamide performed well and furnished the corresponding product in satisfactory yield (**3h**). The substrate was compatible with heterocyclic amides such as 2-thiofuran and 2-pyridine, which tolerated the reaction conditions and gave the corresponding esterification products in high yields (**3i** and **3j**). The effects of substituents on the phenyl ring of the 2-aryl oxazolines were also explored. Notably, the presence of electron-donating or electron-withdrawing halogen substituents on the phenyl ring did not significantly affect the esterification reaction, and products **3k** and **3l** were obtained in good yields.

The esterification reaction was not restricted to carboxamides as the substrate. As illustrated in Table 3, 2-aryl oxazolines also produced the corresponding products in high yields. Electron-rich arenes and electron-deficient arenes furnished the desired products **5b–5p** in 51–89% yields. When the arenes were substituted with electron-withdrawing groups such as Cl–, Br–, I–, CF_3–, and Ph–, the reactions proceeded efficiently to provide esterification products **5h–5p** in high yields. In contrast, when electron-donating groups such as Me–, *t*Bu– and MeO– were present on the benzene ring, the reaction was suppressed slightly (**5b–5g**). Compounds with the aryl group replaced by pyridyl, furan, and thiofuran were also suitable for the transformation, furnishing the corresponding products in good yields (**5q**–**5s**). It is important to note that the product **5q** (*p*-nicorandil) has antinociceptive activity similar to that of nicorandil.[37] Notably, the esterification reaction was not limited to oxazoline substrates. The aryl 1,3-oxazine **4t** reacted smoothly to deliver the desired product **5t** in 81% yield.

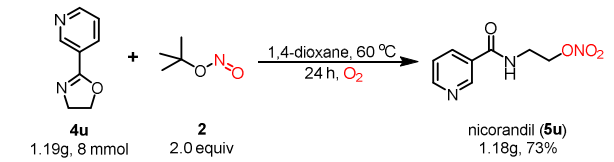
As a further demonstration of the synthetic usefulness of this methodology, a gram-scale reaction was conducted with **4u** (1.19g, 8.0 mmol) and TBN (2.0 equiv) at 60 °C under the standard reaction conditions (Scheme 1). The product **5u** was obtained in 73% isolated yield. Our approach has several advantages compared with the traditional method,[36] including higher yields and avoidance of the use of highly corrosive HNO_3. It is worth noting that nicorandil is an effective drug for the treatment of angina. Moreover, it has both nitric oxide (NO) donor and direct opening effects on sarcolemmal and mitochondrial ATP-sensitive potassium (K-ATP) channels. It is suitable for treatment of various types of angina, including effort angina and spastic angina. It can also improve the prognosis of patients with ischemic heart disease.[37] The development of a new methodology for the synthesis of nicorandil is a potentially important development in pharmaceutical chemistry.

To shed some light on the mechanism, several control experiments were performed (Scheme 2). When the reaction was performed under Ar atmosphere, the yield of **5a** was only 8%. This shows that oxygen is crucial for the high-yielding synthesis of **5a**. The addition of 3 equiv of TEMPO completely suppressed the formation of **5a** under the standard conditions, suggesting the involvement of a radical pathway in this reaction. In addition, a strong molecular ion peak (*m/z* = 244.1913) was detected using Electrospray Ionization-Time-of-Flight-Mass Spectrometry (ESI-TOF-MS) and attributed to $[\mathbf{7}+H]^+$ (exact mass: 244.1907). This result indicates that 1,4-dioxane might be involved in this process. To gain further insights into the reaction mechanism, the probable intermediate *N*-(2-hydroxyethyl)benzamide **6** was synthesized. We then used **6** under our optimized reaction conditions.

Table 3. Substrate scope of 2-aryl oxazolines[a,b]



[a] Reaction conditions: **1** (0.2 mmol), TBN (3.0 equiv), 1,4-dioxane (2.0 mL), stirred under O_2 at 80 °C for 24 h in a Schlenk tube. [b] Isolated yield. [c] TBN (2.0 equiv) was used at 60 °C.



Scheme 1 Gram-scale synthesis of **5u**.

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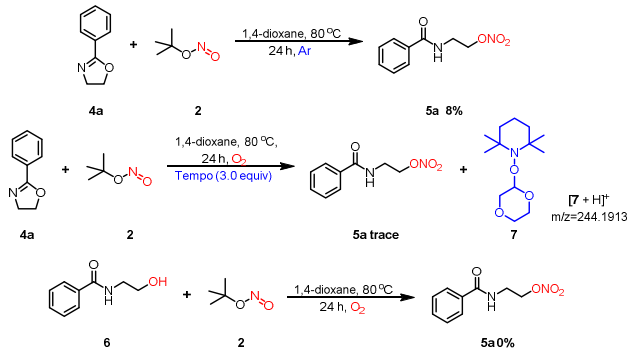
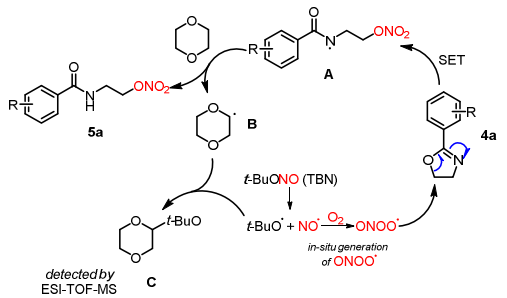


Scheme 2 Control experiments.



Scheme 3 Plausible mechanism.

However, the desired product was not detected. This result implies that the esterification process did not involve this intermediate.

On the basis of the above results and previous literature reports[31-33,38] a plausible mechanistic pathway for the formation of **3a** is proposed (Scheme 3). Initially, $ONOO^{\cdot}$ is generated in situ from TBN with O_2 under thermal conditions. Then 2-aryl oxazoline **4a** is ring-opened by the nucleophile $ONOO^{\cdot}$. Next, intermediate **A** is generated *via* intermolecular single-electron transfer (SET) between the 2-aryl oxazoline moiety and $ONOO^{\cdot}$. Finally, the desired product **5a** is obtained through hydrogen abstraction of the sp^3 C–H bond in 1,4-dioxane, and radical intermediate **B** is generated. Radical transmission is terminated when radical intermediate **B** reacts with the *tert*-butoxy radical to form byproduct **C**.

Conclusions

In conclusion, we have developed a novel and efficient method for the synthesis of β-nitrate ester carboxamides through the ring-opening of 2-oxazolines. The esterification reaction with 2-substituted oxazolines tolerates a wide range of functional groups, and the reaction proceeds smoothly to provide the corresponding products in excellent yields. The utilization of non-corrosive TBN and easily available oxygen gives this method several advantages over traditional procedures because it avoids the use of highly corrosive H_2SO_4/HNO_3 or N_2O_5 as reagents. This reaction system is environmentally friendly, shows high functional group tolerance, gives fast access to pharmaceuticals such as nicorandil, and can be easily scaled up.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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[a] College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, P. R. China
Fax: (+86)-25-5813-9926; phone: (+86)-25-5813-9926; e-mail: guok@njtech.edu.cn

[b] Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), Nanjing 211816, P. R. China

[c] State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, Nanjing 210009, P. R. China