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Amine-promoted cyclocondensation of highly substituted aromatic nitrile oxides with diketones

Jeffrey W. Bode, Yoshifumi Hachisu, Tomoo Matsuura and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology and CREST, Japan Science and Technology Corporation O-okayama, Meguro-ku, Tokyo 152-8551, Japan

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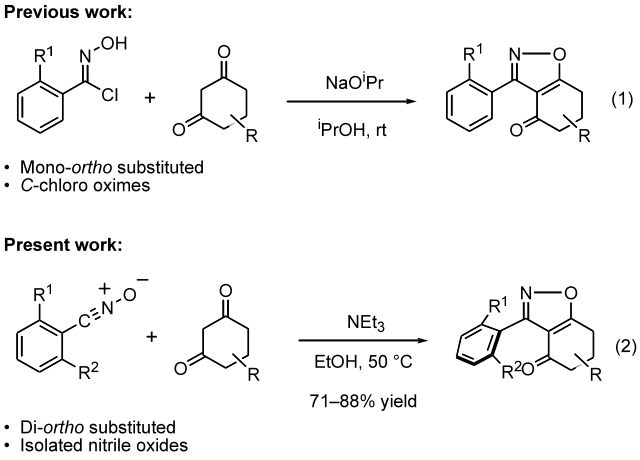
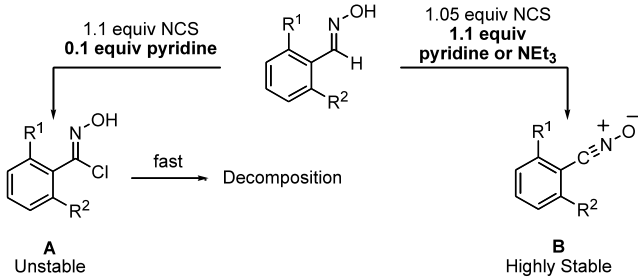
Abstract—Base-promoted cyclocondensation of hindered nitrile oxides and cyclic diketones affords highly functionalized, sterically-encumbered isoxazole products in good yield. The mild reaction conditions (NEt_3, EtOH) are tolerant to a wide variety of functionality and permit the preparation of precursors to complex polycycles typically inaccessible via direct, intermolecular carbon–carbon bond forming reactions. The ability to effect the cyclocondensation reaction with a catalytic amount of amine points to the intermediacy of an ammonium enolate as a key reactive species. A convenient, single step preparation of crystalline, stable nitrile oxides from the corresponding oximes enhances the advantages of this methodology for the preparation of functionalized polycycles.

Recently, we reported the base-promoted cyclocondensation of *C*-chloro oximes and cyclic diketones to afford various isoxazoles (Scheme 1, Eq. (1)).[1] The convenient reaction conditions and broad tolerance to sensitive functional groups prompted us to explore the potential utility of this chemistry for the construction of complex polycyclic and heterocyclic structures. Particularly, we focused our attention on the viability of more sterically demanding substrates, which, if successful, would offer the opportunity to prepare a variety of aromatic derivatives typically accessible only with difficulty.



Scheme 1.

A critical limitation in this endeavor was the *C*-chloro oxime starting materials (Scheme 2). While we have found mono-*ortho* substituted *C*-chloro oximes, including functionalized ones, to be readily prepared, tractable starting materials, the corresponding di-*ortho* substituted analogs **A** proved to be unstable and prone to decomposition. As a potential solution, we were delighted to find that the corresponding di-*ortho* substituted nitrile oxides **B** proved to be highly stable, crystalline compounds conveniently prepared from oximes in a single step (vide infra). Since at the onset of our



Scheme 2.

Keywords: nitrile oxide; cyclocondensation; benzophenone; organocatalytic; coleophomone.

* Corresponding author. Tel./fax: +81-3-5734-2228; e-mail: ksuzuki@chem.titech.ac.jp

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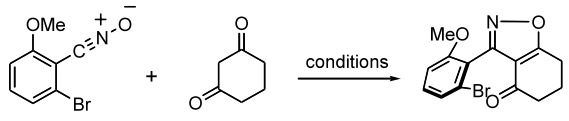
studies it was not known if nitrile oxides were actively involved in the cyclocondensation reaction, it was unclear if isolated nitrile oxides were mechanistically viable surrogates. Furthermore, we had no precedent for the use of more sterically demanding substrates.

Faced with these challenges, we have developed a straightforward and mechanistically revealing solution. We now report that tertiary-amine bases promote the condensation of sterically-demanding aromatic nitrile oxides with cyclic diketones to afford fused isoxazoles in excellent yield (Scheme 1, Eq. (2)).

Using stable nitrile oxide **1** as a model substrate, we surveyed conditions for its cyclocondensation with diketone **2**. In the absence of base, attempted coupling provided only trace amounts of desired product **3** after prolonged reaction times (Table 1, entry 1), indicating

Table 1. Cyclocondensation of sterically hindered nitrile oxide **1** with diketone **2**[a]



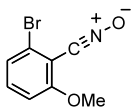
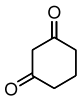
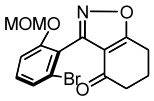
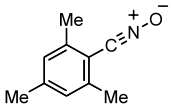
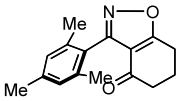
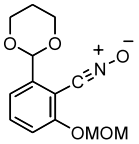
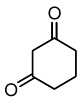
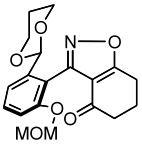
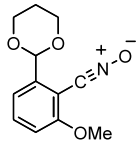
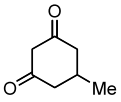
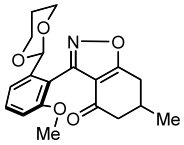
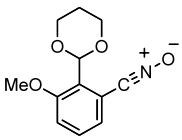
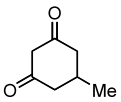
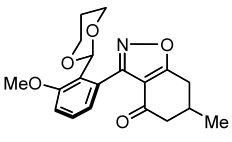
(1)

1 **2** **3**

Entry	Base	Equiv.	Solvent	Time (h)	Yield[b] (%)
1	–	–	^{i}PrOH	180	19
2	Na^{i}OPr	1.4	^{i}PrOH	2[c]	35
3	NEt_3	1.4	^{i}PrOH	19	76
4	NEt_3	1.4	EtOH	16	87
5	NEt_3	0.1	EtOH	110	86

[a] All reactions were performed at ambient temperature at 0.1 M using 1.0 equiv. of **1** and 1.5 equiv. of **2**.
[b] Isolated yields of pure material based on **1**.
[c] Nitrile oxide **1** was consumed in non-productive pathways.

Table 2. Synthesis of functionalized, highly substituted fused isoxazoles by amine-promoted cyclocondensation reactions[a]

entry	nitrile oxide	cmpd.	ketone	cmpd.	product	cmpd.	time / h	yield[b] / %
1		**1**		**2**		**3**	16	87[c]
2		**4**		**2**		**5**	36	71
3		**6**		**2**		**7**	24	76
4		**8**		**9**		**10**	24	88
5		**11**		**9**		**12**	24	81[d]

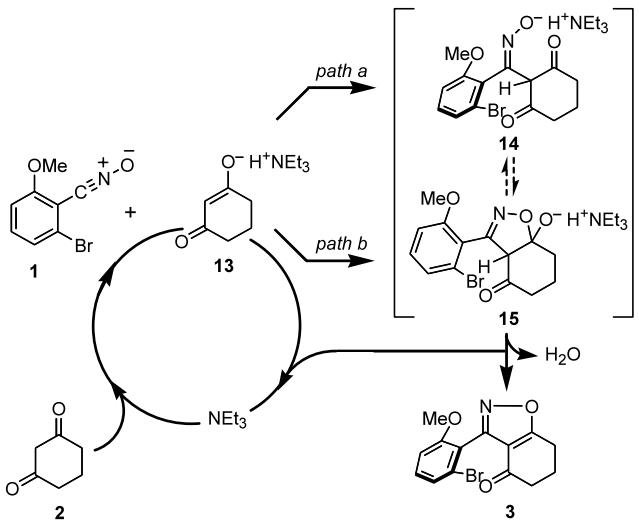
[a] All reaction were performed using 1.0 equiv of nitrile oxide, 1.5 equiv of diketone, and 1.4 equiv of NEt_3 in EtOH at 50 °C unless otherwise noted.
[b] Yield refers to isolated yield of pure cyclocondensation product.
[c] This reaction was performed at ambient temperature.
[d] This reaction was achieved using 1.4 equiv of NaO^{i}Pr in ^{i}PrOH. Using 1.4 equiv of NEt_3, the desired compound was formed in 69% yield after 21 h.

that strictly thermal cycloaddition processes were not effective. Progress was achieved by utilizing our conditions for the cyclocondensation of *C*-chloro oximes and diketones (NaO^{i}Pr, ^{i}PrOH),[1] which significantly accelerated the product formation (entry 2). This result, however, was far from satisfactory as it was accompanied by rapid decomposition of the nitrile oxide starting material. Fortunately, however, a screen of alternative reaction conditions revealed tertiary amine bases as effective promoters of the cyclocondensation of nitrile oxide **1** with diketone **2** (entry 3). Further studies identified EtOH as superior to ^{i}PrOH as the reaction solvent (entry 4). Significantly, the reaction also proceeded smoothly using only a catalytic amount of amine base (entry 5), albeit at a diminished reaction rate.

The conditions thus identified were amenable to the synthesis of a wide variety of highly functionalized, sterically-encumbered isoxazoles (Table 2).[2,3] Interestingly, in most cases the products were obtained as mixtures of atropisomers about the aryl–isoxazole bond, attesting to the hindered nature of the products achieved by this coupling process.

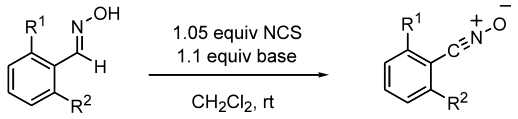
The amine-promoted reaction conditions appear to be particularly suited for highly hindered substrates rather than simply for isolated nitrile oxides. Thus, although the mono-*ortho* substituted nitrile oxide **11** was highly stable and amenable to silica-gel chromatography and long-term storage, its condensation with cyclic diketones proceeds more smoothly using sodium isopropoxide in isopropyl alcohol (Table 2, entry 5, footnote d). In general, we have found the amine-promoted conditions to be preferable only for *ortho*,*ortho′*-disubstituted nitrile oxides.

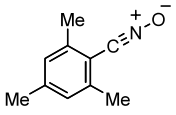
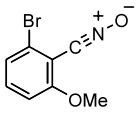
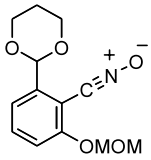
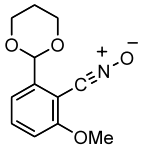
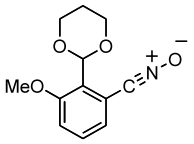
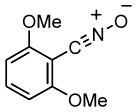
The ability to effect the cyclocondensation reaction with only catalytic amounts of amine offers implications both for further methodological development as well as mechanistic considerations (Scheme 3). The necessity of base catalysis suggests a key role for ammonium enolate **13** in the carbon–carbon bond forming step, either via



Scheme 3. Possible mechanistic pathways for the catalytic generation of fused isoxazoles.

Table 3. One-pot preparation of sterically hindered, stable nitrile oxides[a]

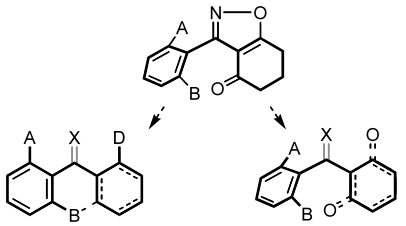


entry	nitrile oxide	base	yield[b] / %
1	 **4**	NEt_3	99
2	 **1**	NEt_3	99
3	 **6**	NEt_3	95
4	 **8**	NEt_3 pyridine	99 95
5	 **11**	pyridine	99
6	 **16**	NEt_3	99

[a] Unless otherwise indicated, all reactions were performed in CH_2Cl_2 at 0.1 M and at ambient temperature.

[b] Yield refers to the isolated yield of pure product. In practice, the unpurified nitrile oxides were often used directly in the subsequent cyclocondensation reaction.

nucleophilic addition to the nitrile oxide (path a) or [2+3] cycloaddition (path b). Discrimination between the involvement of either **14** or **15** is obscured by the fact that these structures may readily interconvert under the reaction conditions before undergoing a dehydration step affording the isoxazole functionality and regenerating the amine base. The diminished reaction rates observed using catalytic amounts of tertiary amine suggest the coupling of the nitrile oxide **1** and the ammonium enolate **13** to afford either **14** or **15** to be the rate-limiting step.



Scheme 4. Structural motifs accessible from isoxazoles.

Further investigations and kinetic studies on catalytic couplings are underway.

Finally, a key feature of this methodology is the advantages of the stable nitrile oxides themselves. In addition to their inherent stability and ease of handling, they are also easily synthesized from the corresponding oxime. Although stable nitrile oxides have been prepared by a two-step chlorination–base-induced elimination procedure, we have found this process to be incompatible with acid labile substrates.[4] However, the nitrile oxides are readily prepared in excellent yield from the oximes in a single reaction step (Table 3), simply by portionwise addition of *N*-chlorosuccinimide to a mixture of the oxime and a slight excess of amine base. Acid labile substrates present no complications, and nitrile oxides such as **6**, **8**, and **11** are readily prepared (entries 3–5). The base effects rapid elimination of HCl from the initially formed *C*-chloro oxime and, notably, does not interfere with the oxime chlorination nor react with the nitrile oxide itself. These nitrile oxides are easily purified by silica-gel chromatography, but are typically obtained in analytically pure form and can be used directly in the cyclocondensation reactions.

The highly functionalized isoxazole products represent a novel entry to substituted polycyclic structures (Scheme 4) and provide access compounds including xanthones, benzophenones and related structures.[5] Coupled with the unique chemistry of the isoxazole products, this process offers a novel and promising route to the synthesis of biologically active natural products including balanol[6] and the coleophomones.[7,8]

In conclusion, we have described the efficient, amine-promoted coupling of readily prepared, stable nitrile oxides with cyclic diketones to afford functionalized isoxazole products. These studies have established 1) the utility and intermediacy of nitrile oxides in the cyclocondensation process; 2) the viability of highly hindered substrates, which give isoxazoles in high yield; and 3) a critical role for the base in promoting the coupling reaction. Further studies will lead to novel processes and applications based on this technology.

Acknowledgements

J.W.B. thanks the Japan Society for the Promotion of Science for a postdoctoral fellowship. This research was partially supported by the 21st Century COE Program.

References

1. Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, *5*, 391–394.
2. The preparation of isoxazole **10** is representative: To 1,3-diketone **9** (2.32 mmol, 1.50 equiv.) in 10 ml EtOH at rt was added NEt_3 (2.17 mmol, 1.40 equiv.) followed by nitrile oxide **8** (1.55 mmol, 1.00 equiv.). The resulting solution was warmed to 50°C and stirred 24 h at this temperature. Concentration under reduced pressure followed by column chromatography on silica gel (1:1 hexanes/EtOAc) afforded **10** (1.36 mmol, 88% yield) as a white foam.
3. *Physical properties of selected, key compounds*:
Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, 1H, $J=7.4$ Hz), 7.38 (dd, 1H, $J=7.4$, 4.8 Hz), 6.97 (dd, 1H, $J=7.4$, 4.8 Hz), 5.46 (s, 1H), 4.22–4.14 (m, 1H), 4.05–3.97 (m, 1H), 3.89–3.82 (m, 1H), {3.71 (s), 3.73 (s), (3H)}; 3.69–3.61 (m, 1H), 3.24–3.15 (m, 1H), 2.77–2.68 (m, 1H), 2.50–2.32 (m, 2H), 2.31–2.21 (m, 1H), 2.18–2.07 (m, 1H), 1.35–1.28 (m, 1H), {1.21 (d, $J=6.4$ Hz), 1.23 (d, $J=6.4$ Hz), 3H}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5*, 190.3, 179.9*, 179.7, 157.8*, 157.6, 155.7*, 155.6, 138.7, 130.9*, 130.9, 127.2, 118.4, 118.3*, 118.2, 116.1*, 116.0, 115.1, 112.2, 111.2*, 111.1, 99.4, 99.1, 67.4*, 67.1, 67.1*, 67.0, 61.2*, 60.3, 55.9*, 55.8, 46.6*, 46.4, 31.0*, 30.9, 30.7*, 30.2, 25.7*, 25.5, 20.7*, 20.5, 15.5*, 14.1 (the compound exists as a 1:1 mixture of atropisomers; * denotes peak doubled due to atropisomerism); IR (thin film) ν 2964, 2884, 1694, 1599, 1479, 1446, 1272, 1075, 995 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found, C, 66.16; H, 6.27; N, 4.03.
Compound **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (t, 1H, $J=8.2$ Hz), 7.00 (dd, 1H, $J=8.2$, 0.7 Hz), 6.87 (dd, 1H, $J=7.6$, 0.7 Hz), 5.97 (s, 1H), 4.02–3.94 (m, 2H), 3.87 (s, 3H), 3.77 (dt, 2H, $J=7.9$, 2.2 Hz), 3.18 (dd, 1H, $J=17.4$, 5.1 Hz), 2.74–2.67 (m, 1H), 2.58–2.46 (m, 2H), 2.29–2.25 (m, 1H), 1.83–1.70 (m, 1H), 1.25–1.18 (m, 1H), 1.22 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 178.9, 159.8, 157.0, 129.4, 128.2, 125.8, 122.9, 116.3, 112.4, 97.0, 67.1, 67.2, 56.0, 46.6, 31.0, 30.7, 25.7, 20.7; IR (thin film) ν 2959, 2931, 2855, 1694, 1600, 1446, 1383, 1236, 1152, 1105, 1002 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.24; H, 6.43; N, 4.09.
4. (a) For a typical procedure for the preparation of stable nitrile oxides via this two-step protocol see: Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410–6424 and references cited therein; (b) For example, although the *C*-chloro oxime corresponding to **8** could be prepared, it rapidly decomposed upon standing or concentration due to spontaneous elimination of HCl and subsequent destruction of the acetal moiety.
5. For the conversion of structurally related isoxazoles to benzophenones, xanthones and other polycyclic compounds, see: (a) Ref. 1; (b) Bode, J. W.; Uekusa, H.; Suzuki, K. *Org. Lett.* **2003**, *5*, 395–398.
6. For a leading reference to the challenges associated with the synthesis of balanol and related compounds, see: Skrydstrup, T.; Hazell, R.; Laursen, B.; Denieul, M.-P. *J. Org. Chem.* **2000**, *65*, 6052–6060.
7. This methodology has been applied to the synthesis and structure confirmation of coleophomone natural products: Bode, J. W.; Suzuki, K. *Tetrahedron Lett.* **2003**, *44*, 3559–3563.
8. For the use of acyl cyanides in the total synthesis of coleophomone B and C, see: Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276–3279.