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PAPER

Synthesis of isoxazoles *en route* to semi-aromatized polyketides: dehydrogenation of benzonitrile oxide–*para*-quinone acetal cycloadducts†‡

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A variety of highly functionalized polycyclic isoxazoles are prepared by a two-step protocol: (1) 1,3-dipolar cycloaddition of *o*,*o'*-disubstituted benzonitrile oxides to *para*-quinone mono-acetals, then (2) dehydrogenation. The cycloaddition proceeds in a regioselective manner, favouring the formation of the 4-acyl cycloadducts, which are suitable intermediates for the synthesis of *semi-aromatized* polycyclic targets derived from polyketide type-II biosynthesis.

Introduction

Complex molecular architectures commonly found in biologically active polyketide-derived natural products represent challenging synthetic targets, which demand innovative approaches to the introduction, management, and transformation of sensitive functional arrays. Polyketide derivatives, further decorated by oxygenation of the aromatic π-system, display novel chemical functionalities, structural complexities, and stereochemical elements that raise the level of difficulty for the synthetic chemist.[1] The cycloaddition–dehydrogenation strategy described herein provides access to isoxazoles as synthetic intermediates *en route* to polycyclic polyketide derivatives of the fully-aromatized and semi-aromatized variety (Fig. 1).

Seragakinone A (**1**),[2] a marine natural product having a densely functionalized pentacyclic structure with an angular carbon substituent derived from a prenyl group, provided us with the impetus for the development of a viable strategy to construct polycyclic systems with such architectural, functional and stereochemical complexity. Two reaction processes emerged as particularly valuable in this regard (Scheme 1): (1) *Cyclocondensation* of benzonitrile oxide **I** and 1,3-diketone **II** gives the key isoxazole intermediate **III**;[3] (2) NHC-catalyzed benzoin reaction converts to linear tricarbocycle **IV** with excellent enantioselectivity.[4] α-Ketol **IV**, which corresponds to the BCD ring system in **1**, is a key platform for synthesis of angularly prenylated compound **VI** *via* two steps including the stereoselective addition of a prenylbarium reagent[5] and the stereospecific pinacol-type 1,2-shift.[6] The isoxazole moiety serves not only as a 1,3-dicarbonyl equivalent,[7] but also as a directing group for the regioselective 1,2-shift with its ability of α-cation stabilization.

Although this model study showed a viable way for constructing the BCD ring system, a serious drawback to intermediates **IV–VI** was the poor functionalization at the B ring, making further elaboration tedious, if not impossible.

Intermediate **III′**, a more oxidized form of **III**, could solve this problem (Scheme 2, *cf.* Scheme 1), if *para*-quinone (**VII**) reacts with nitrile oxide **I**.[8] In addition, if mono-masked quinone **VII′** could be employed in this process, the functionalities in the resulting product **III″** would be nicely discriminated and ideally suited for further elaboration.

One could envision an indirect way for synthesizing more functionalized isoxazole intermediates by a two-step protocol; 1,3-dipolar cycloaddition of nitrile oxides **I** to *para*-quinone mono-acetals **VII′** followed by dehydrogenation; however, the reactivity of **VII′** toward the cycloaddition to **I**, and oxidation of the cycloadduct to **III″** gives one reason to pause.

Nitrile oxides tend to react with electron-deficient olefins, *e.g.* α,β-unsaturated carbonyl compounds, with the interaction between the HOMO of the dipoles and the LUMO of the dipolarophiles. When an oxygen of nitrile oxides, which has the largest HOMO coefficient, binds to a carbon β to a carbonyl of dipolarophiles, a 4-acyl cycloadduct is formed as a major regioisomer.[9] However, in the reaction of *acyclic* enones varying degrees of regioselectivity are observed[10] to produce a mixture of 4- and 5-acylisoxazolines (Scheme 3). Despite these concerns, several studies suggested that reaction of *cyclic* enones with nitrile oxides would lead to the preferential formation of the 4-acyl cycloadducts,[11] which would make *para*-quinone mono-acetal **VII′** a promising dipolarophile that undergoes regioselective 1,3-dipolar cycloadditions with nitrile oxides.[12] The remaining concern was whether the presence of substituents in the 1,3-dipoles and dipolarophiles might disturb the regiocontrol.[13]

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‡ Electronic supplementary information (ESI) available. CCDC 859931 (**4**), 859932 (**5**), 859933 (**9a**), 859934 (**8c**), 859935 (**8b**), 859936 (**8i**), 874424 (**8g**), 874422 (**2a**), and 874423 (**2c**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25423a

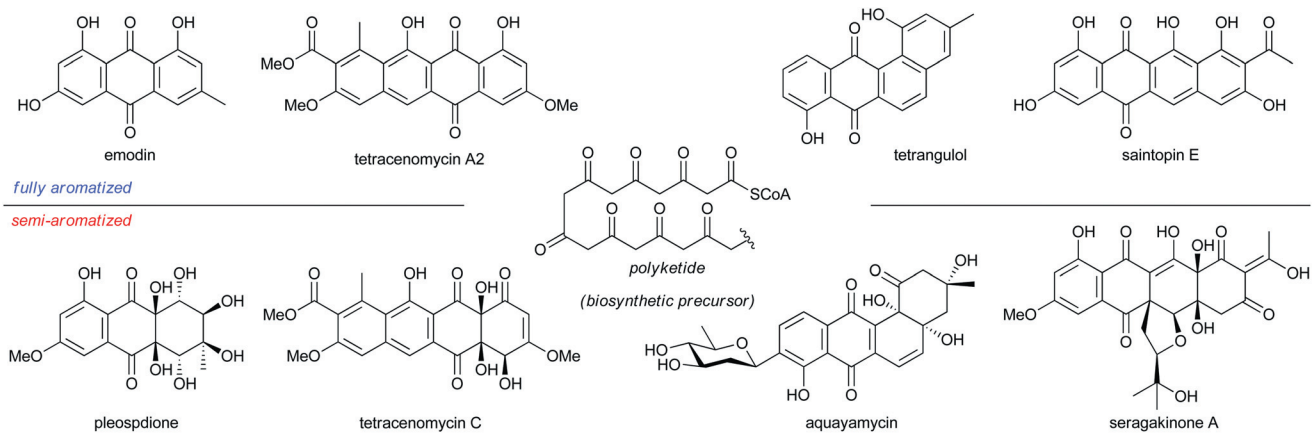
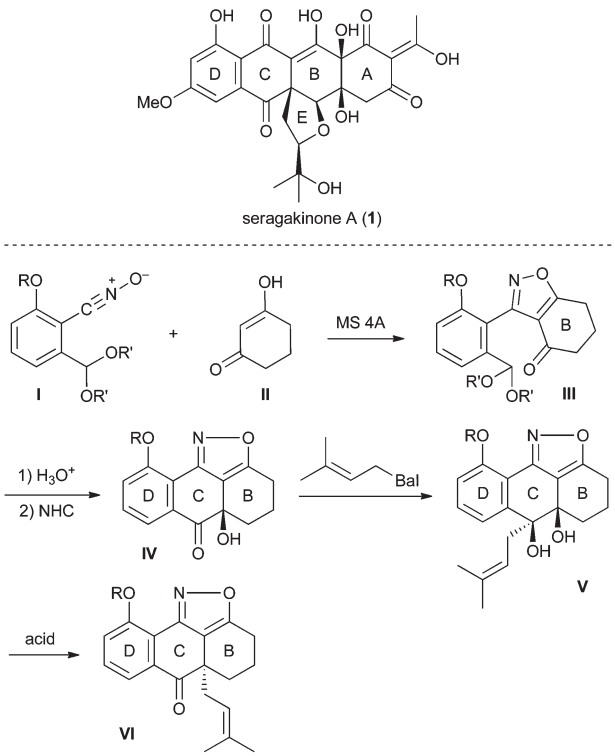
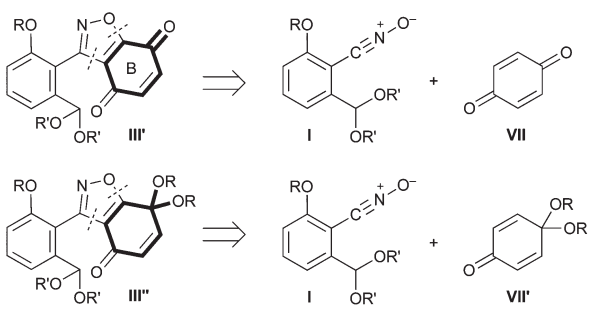


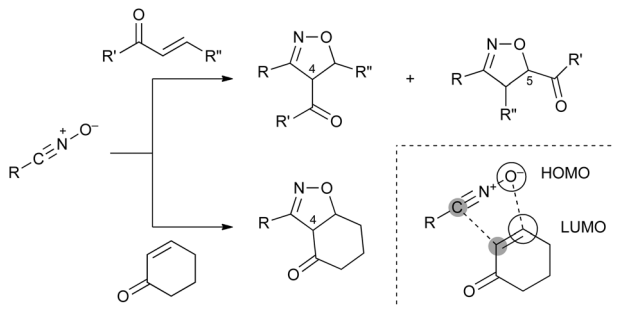
Fig. 1 Naturally-occurring aromatic polyketides.



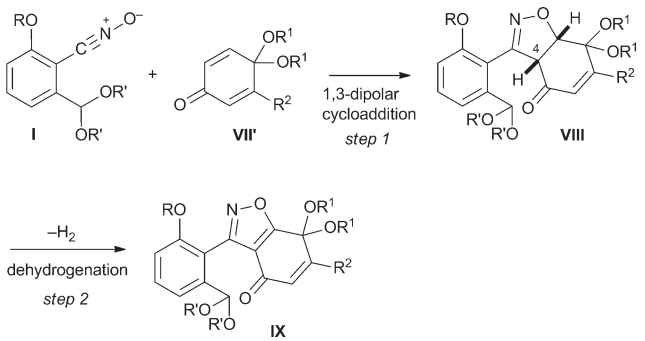
Scheme 1 Previous work: cyclocondensation approach to isoxazole intermediates **III–VI**.



Scheme 2 Quinones and masked quinones as dipolarophiles.



Scheme 3 Regioselectivity for nitrile oxides reacting with acyclic and cyclic enones.



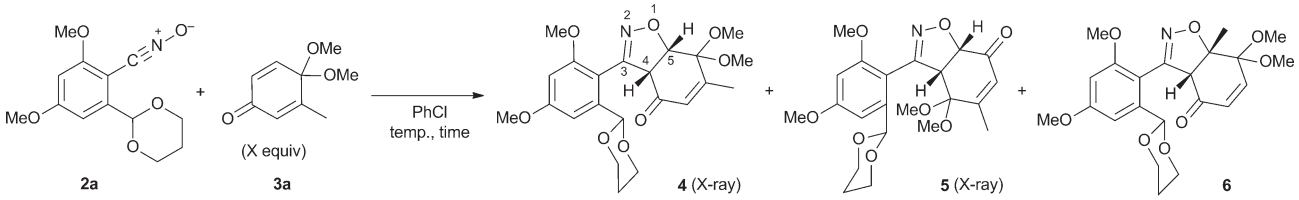
Scheme 4 1,3-Dipolar cycloaddition–dehydrogenation approach toward functionalized isoxazoles **IX**.

Herein, we report two-step synthesis of highly functionalized isoxazoles **IX** by 1,3-dipolar cycloaddition of nitrile oxide **I** to *para*-quinone mono-acetal **VII′** (step 1) followed by dehydrogenation (step 2) (Scheme 4). This two-step operation has already been employed in our recent synthesis of seragakinone A,[14] but we describe here its optimization, establishing a practical one-pot protocol for carrying out these two steps. Particular emphasis is placed on its scope and limitations using various nitrile oxides and *para*-quinone mono-acetals.

Results and discussion

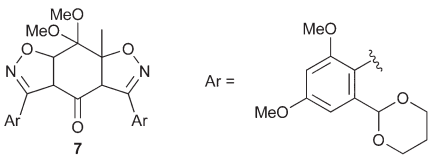
Quinone mono-acetal **3a**[15] was used for the initial model study, examining in detail the reaction with nitrile oxide **2a**[14] (Table 1).

Table 1 1,3-Dipolar cycloaddition of benzonitrile oxide **2a** to *p*-quinone mono-acetal **3a**[a]



Run	**3a**/equiv	Temp/°C	Time/h	Yield[b]/%	**4** : **5** : **6**[e]
1	1.2	90	2	65	87 : 8 : 5
2	1.2	60	10	70	88 : 7 : 5
3	1.2	rt	8 days	74[c,d]	89 : 6 : 5
4	2.0	rt	4 days	80[c,d]	90 : 5 : 5
5	3.0	rt	2 days	84[c,d]	90 : 5 : 5

[a] 200 mg scale, 1.0 M. The structure of each of **4** and **5** was confirmed by X-ray crystallographic analysis.‡ [b] Isolated yield. [c] Yield of recovered **3a**; run 3: 31%, run 4: 56%, run 5: 67%. [d] Yield of bisisoxazoline **7**; run 3: 13%, run 4: 7%, run 5: 5%. [e] By ^{1}H NMR. rt: room temperature.



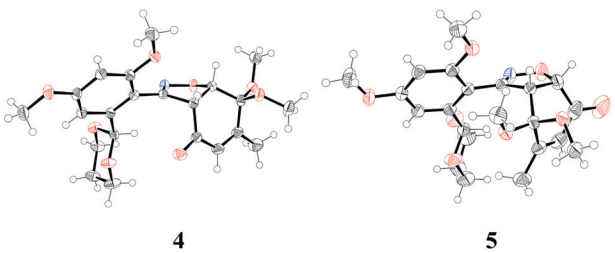
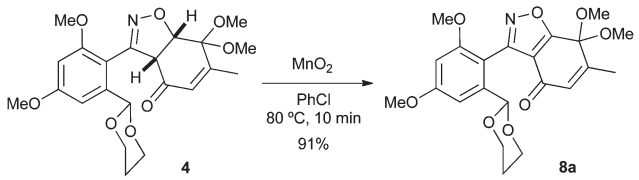


Fig. 2 ORTEP-Drawings of isoxazolines **4** and **5** (thermal ellipsoids are drawn at 50% probability level).



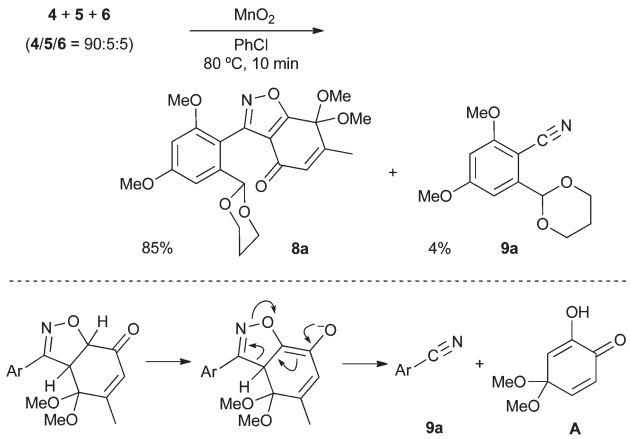
Scheme 5 Dehydrogenation of isoxazoline **4** by MnO_2.

It turned out that the cycloaddition reaction proceeded in a highly regioselective manner, providing 4-acyl isomer **4** as the major product; upon heating of **2a** and **3a** in chlorobenzene at 90 °C, a mixture of three isoxazolines **4**, **5**, and **6** (**4** : **5** : **6** = 87 : 8 : 5) was obtained in 65% yield after purification by column chromatography (SiO_2, EtOAc–hexane = 1 : 2 → 2 : 3). The major product **4** was isolated in pure form by recrystallization (EtOAc–hexane, colorless grains, mp 180.5–181.0 °C) or preparative TLC [THF : toluene : hexane = 1 : 2 : 2 (3×)]. Preparative TLC (Et_2O) allowed isolation of small amounts of the two regioisomers: 5-acyl isomer **5** resulted from the reversed cycloaddition mode to that of **4**, and 5-methylisoxazoline **6** was produced by the reaction at the trisubstituted double bond in **3a**. Each structure was confirmed by extensive NMR study and/or X-ray crystallography‡ (Fig. 2).[16]

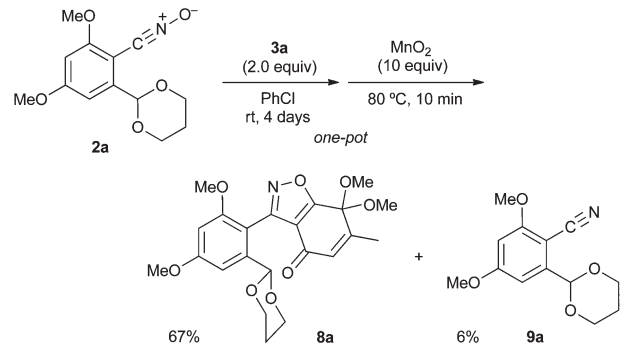
For improving the yield and regioselectivity, several reaction parameters were screened, including the solvent, the reaction temperature, and the amount of dipolarophile **3a**. While choice of the solvent (THF, DMF, 1,4-dioxane, and toluene) gave no improvement (not shown), higher yields were realized by lowering the reaction temperature (Table 1, runs 1–3); at 60 °C, the yield increased to 70% (run 2), and the reaction at room temperature gave the cycloadducts in 74% yield, although 8 days were necessary for the full conversion (run 3). In this case, a small amount of a polar byproduct was noted, which was identified as bisisoxazoline **7**.[17] We envisioned that this unfavorable double cycloaddition would be suppressed by an increased molar ratio of **3a** to nitrile oxide **2a**, leading to higher yield. Indeed, when the molar ratio of **3a** : **2a** was made 2.0 and 3.0, the reactions completed in shorter times (4 and 2 days, respectively), affording the cycloadducts in 80% and 84% combined yield of **4**–**6**, respectively (runs 4 and 5).

Having isoxazoline **4** in hand, we examined step 2, *i.e.*, the dehydrogenation of isoxazoline into the corresponding isoxazole **8a** (Scheme 5). To our delight, the projected reaction proceeded smoothly by exposure of **4** to activated MnO_2 (PhCl, 80 °C, 10 min),[18] giving isoxazole **8a** in 91% yield as the sole product.

When a mixture of **4** containing small amounts of **5** and **6** (**4** : **5** : **6** = 90 : 5 : 5) was exposed to MnO_2 under the same conditions, the desired product **8a** was obtained in 85% yield, where a small amount of nitrile **9a** was co-produced (4% yield) (Scheme 6). To our pleasant surprise, none of the isomeric product expectable from **5** was identified, enabling facile isolation of **8a**; these products **8a** and **9a** could be easily separated by column chromatography (SiO_2, EtOAc–hexane = 1 : 2 →



Scheme 6 Dehydrogenation of a mixture of isoxazolines **4**–**6** and possible mechanism for the formation of **9a**.



Scheme 7 One-pot synthesis of isoxazole **8a**, rt: room temperature.

2 : 3). Formation of nitrile **9a** could be ascribed to isomer **5**, *via* a known fragmentation reaction of 5-acylisoxazolines (Scheme 6, below), although the quinone **A** was not identified.[11a,19] This process turned out to be promoted by MnO_2, although the precise role remains unclear.[20]

Having these results, we envisaged that the above two steps may be carried out in one pot, which proved indeed the case; after completion of the cycloaddition of **2a** to **3a** (PhCl, room temperature, 4 days), activated MnO_2 (10 equiv) was added to the reaction mixture, and subsequent heating (80 °C, 10 min) afforded isoxazole **8a** and nitrile **9a** in 67% and 6% yield, respectively (Scheme 7). The yield of **8a** was comparable to that by the stepwise protocol (*vide supra*, 64% yield, 2 steps).

This one-pot protocol proved practical, working well for nitrile oxides **2a–c** and *p*-quinone mono-acetals **3a–c** (Table 2). The unreacted quinone mono-acetal was recovered after purification by column chromatography. Several trends became apparent: (1) the reactivity of quinone mono-acetals became slightly lower by the presence of an electron-donating substituent at the position β to the carbonyl, due to steric and electronic factors, and (2) the reaction of nitrile oxides having a C-5 substituent required higher temperatures.

Nitrile oxide **2a** smoothly reacted with quinone mono-acetal **3b**,[21] although a higher temperature (40 °C) was needed. The subsequent addition of MnO_2 (80 °C, 10 min) gave isoxazole **8b** in 77% overall yield (run 2). Quinone mono-acetal **3c** proved much more reactive, leading to a faster reaction with **2a** (run 3, room temperature, 30 h). In this case, however, the overreaction, that is the double cycloaddition, became serious. Pleasingly, use of an excess amount of **3c** (10 equiv) suppressed formation of the bisisoxazoline, providing **8c** in 75% yield after dehydrogenation (run 4).

It should be noted that the C-3 substituent in **3a** and **3b** poses a buttressing effect on the neighboring methoxy group at the C-4 position to enhance the steric hindrance around the reaction site. In addition, a C-3 substituent in quinone mono-acetals prevents the second cycloaddition, which is ascribable to the steric repulsion with the nitrile oxide.[22]

The cycloaddition reactions of nitrile oxide **2b**,[23] lacking a methoxy group at the C4 position, proceeded smoothly to quinone mono-acetals **3a–c** (Table 2, runs 5–7). The reactions of **3a** and **3b** with **2b** gave the corresponding isoxazoles **8d** and **8e** in 67% and 73% yield, respectively, albeit with longer reaction times (runs 5 and 6). Quinone mono-acetal **3c** reacted rapidly with nitrile oxide **2b** even at room temperature; use of 10 equiv of **3c** efficiently suppressed the bisisoxazoline formation, affording isoxazole **8f** in 77% yield (run 7).

Nitrile oxide **2c**,[3d] having two methoxy substituents, proved also amenable to this reaction (runs 8–10). It turned out that **2c** was less reactive than **2a** and **2b**; the reaction of **2c** with quinone mono-acetals **3a** and **3b** proceeded at higher temperatures (60 and 80 °C, respectively) to afford the corresponding isoxazoles **8g** and **8h**, while the reaction did not finish at below 40 °C (runs 8 and 9). We rationalized that the C-5 methoxy group in **2c** posed a buttressing effect on the neighboring acetal, enhancing the steric hindrance around the nitrile oxide moiety.[24] The reaction of **2c** with **3c** (10 equiv) occurred without event, affording the corresponding isoxazole **8i** in 83% yield after dehydrogenation (run 10).

Conclusions

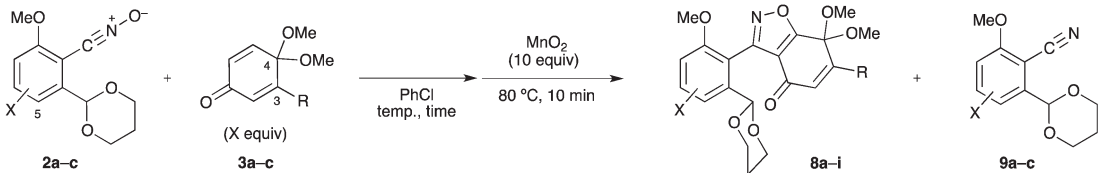
A facile access to highly functionalized polycyclic isoxazoles has been developed *via* 1,3-dipolar cycloaddition of stable benzonitrile oxides to *para*-quinone mono-acetals followed by MnO_2-mediated dehydrogenation, which has paved the way to an efficient synthesis of complex polycyclic semi-aromatized polyketides.

Experimental section

General procedure for the one-pot synthesis of isoxazole 8a

A suspension of nitrile oxide **2a** (200 mg, 0.754 mmol) and *p*-quinone mono-acetal **3a** (254 mg, 1.51 mmol) in chlorobenzene (0.75 mL) was stirred at room temperature for 4 days. To the mixture was added activated manganese(IV) oxide (656 mg, 7.55 mmol), and stirring was continued for 10 min at 80 °C. After cooling to room temperature, the reaction mixture was filtered through a Celite® pad (washed with MeOH). The collected manganese residue was suspended in MeOH, which was heated under reflux for 1 min and filtered through a Celite® pad. The combined filtrate was condensed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane–EtOAc = 2 : 1 to 3 : 2) to afford isoxazole **8a** (217 mg, 67%) as a colorless foam. Nitrile **9a**,

Table 2 One-pot synthesis of various isoxazoles *via* 1,3-dipolar cycloaddition followed by dehydrogenation[a]



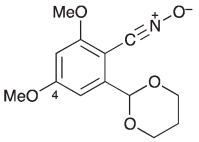
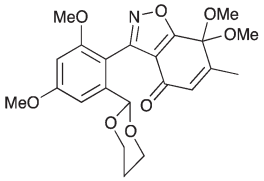
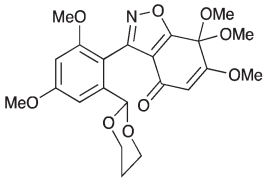
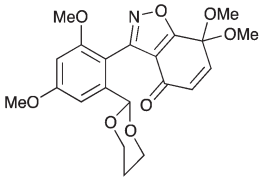
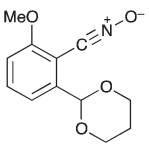
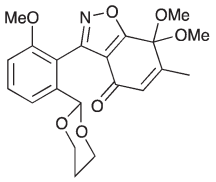
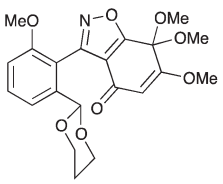
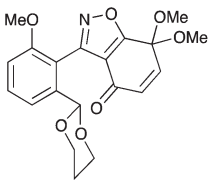
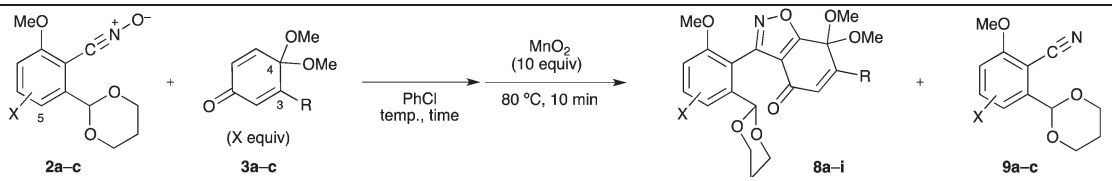
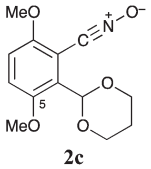
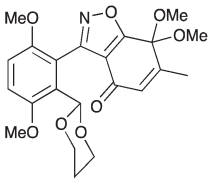
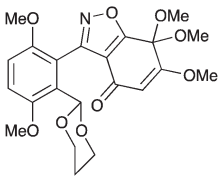
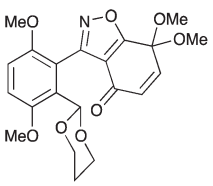
Run	Nitrile oxide	Quinone mono-acetal	X/equiv	Temp./°C[b]	Time[b]	Product	Yield of isoxazole /%	Yield of nitrile/%
1	 **2a**	R = Me (**3a**)	2.0	rt	4 days	 **8a**	67	*ca.* 6 (**9a**)
2		R = OMe (**3b**)	2.0	40	40 h	 **8b**	77	*ca.* 4 (**9a**)
3		R = H (**3c**)	2.0	rt	30 h	 **8c**	56	*ca.* 7 (**9a**)
4[c]			10.0	rt	11 h		75	*ca.* 4 (**9a**)
5	 **2b**	R = Me (**3a**)	2.0	rt	7 days	 **8d**	67	n.d.
6[d]		R = OMe (**3b**)	1.2	60	30 h	 **8e**	73	n.d.
7[e]		R = H (**3c**)	10.0	rt	24 h	 **8f**	77	n.d.

Table 2 *(Contd.)*



Run	Nitrile oxide	Quinone mono-acetal	X/equiv	Temp./°C[b]	Time[b]	Product	Yield of isoxazole /%	Yield of nitrile/%
8	 **2c**	R = Me (**3a**)	2.0	60	22 h	 **8g**	77	5 (**9c**)
9		R = OMe (**3b**)	2.0	80	8 h	 **8h**	77	Trace (**9c**)
10[e]		R = H (**3c**)	10.0	rt	24 h	 **8i**	83	*ca.* 14 (**9c**)

[a] Step 1: unless otherwise indicated, all the reactions were performed using quinone mono-acetals (2.0 equiv to nitrile oxides) in chlorobenzene (1.0 M) at room temperature for the indicated time. Step 2: MnO_2 (10 equiv) at 80 °C for 10 min. [b] For step 1. [c] In toluene (0.4 M). [d] In chlorobenzene (0.5 M) for step 2. [e] In chlorobenzene (0.4 M). n.d.: not detected. rt: room temperature.

contaminated with a trace impurity (11.7 mg, *ca.* 6%) was also obtained. Unreacted *p*-quinone mono-acetal **3a** was recovered (127 mg, 50%) as yellow oil.

8a: R_f 0.43 (hexane–EtOAc = 1 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (brd, 1H, J = 12.2 Hz), 2.01–2.19 (m, 1H), 2.04 (d, 3H, J = 1.5), 3.31 (s, 3H), 3.49 (s, 3H), 3.58 (ddd, 1H, J = 12.2, 11.3, 2.7 Hz) 3.69 (s, 3H), 3.85 (ddd, 1H, J = 11.9, 11.5, 2.4 Hz), 3.88 (s, 3H), 3.83–3.95 (m, 1H), 4.20 (dd, 1H, J = 11.5, 5.1 Hz), 5.57 (s, 1H), 6.15 (d, 1H, J = 1.5 Hz), 6.53 (d, 1H, J = 2.4 Hz), 6.94 (d, 1H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.5, 25.4, 52.0, 52.3, 55.4, 55.8, 67.0, 67.1, 95.0, 98.9, 99.2, 102.1, 106.9, 118.0, 130.4, 139.6, 152.1, 155.6, 159.1, 162.2, 172.5, 178.8; IR (ATR) 2945, 2843, 1678, 1612, 1433, 1377, 1333, 1286, 1201, 1161, 1120, 1076, 920 cm^{-1}; Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25; Found: C, 61.18; H, 5.84; N, 3.17; mp 143 °C (decomp.) (acetone–hexane, colorless prisms).

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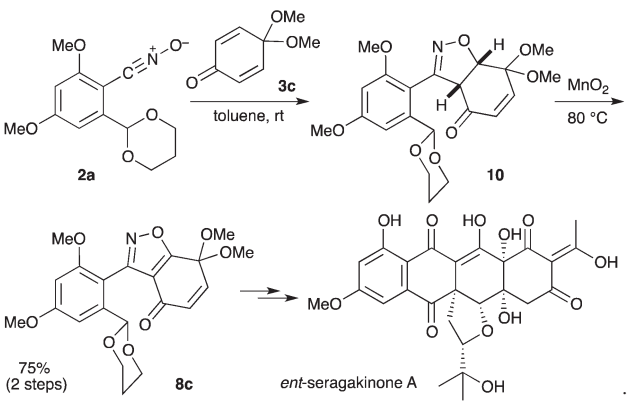

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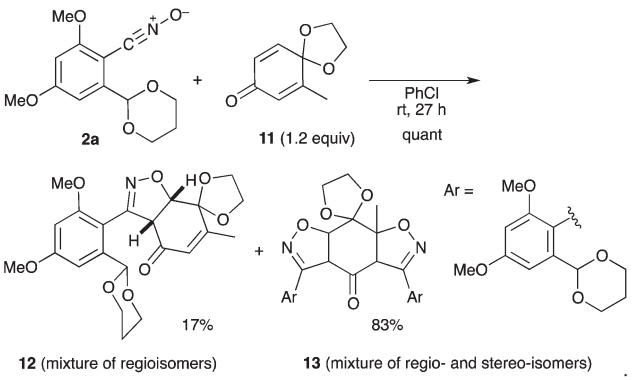

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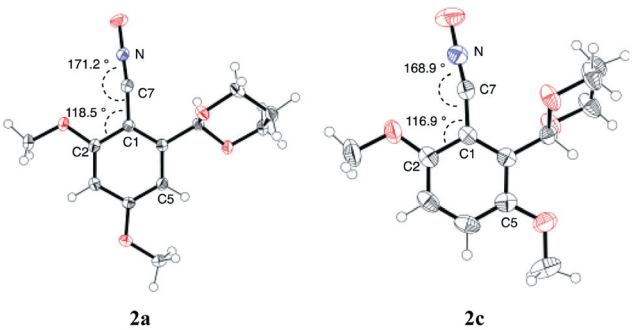
24 X-Ray crystal structures of nitrile oxides **2a** and **2c** suggested the possible buttressing interaction of the methoxy group on the C5 position by two points: (1) while the ring system of the acetal in **2c** is oriented to the CNO side, that in **2a** lies on the opposite side, and (2) judging from the narrower bond angles of C2–C1–C7 and N–C7–C1 in 2c (116.9° and 168.9°, respectively) than those in **2a** (118.5° and 171.2°, respectively), the CNO group in **2c** may be forced to lie closer to the C2 side.



ORTEP-Drawings of nitrile oxide **2a** and **2c**
(thermal ellipsoids are drawn at 50% probability level).