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Facile Construction and Divergent Transformation of Polycyclic Isoxazoles: Direct Access to Polyketide Architectures

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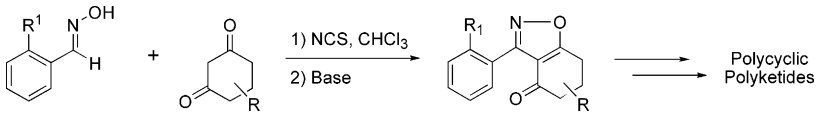
ABSTRACT

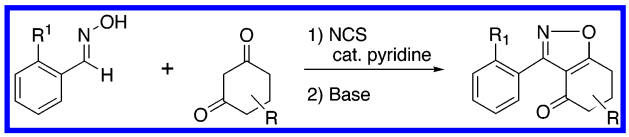


Base-promoted cyclocondensation of *C*-chloro oximes with cyclic 1,3-diketones affords functionalized isoxazoles in good yield and under convenient reaction conditions. This process enables the synthesis of highly substituted products with notable functional group tolerance. The products obtained are directly converted to a variety of polyketide-derived polycyclic structures including xanthenes, anthracenes, and benzophenones.

Considerable attention is currently centered on the synthesis and properties of a variety of structurally complex polycyclic natural products of polyketide origin.[1] In addition to subtle functional group modifications, diversity in their molecular architecture stems from enzymatically controlled folding, oxidation and reduction, and skeletal rearrangement of common polyketide precursors. In light of the significant biological activities inherent to this class of compounds, flexible and efficient approaches to such polycyclic frameworks are in great demand.

We now report the facile synthesis of compounds ideally suited to achieving this goal by serving as a common precursor to a variety of structurally diverse polyketide-derived, polycyclic compounds. Our novel approach relies on base-promoted cyclocondensations of 1,3-diketones and nitrile oxides (Scheme 1), affording highly functionalized isoxazoles.[2] The promise and versatility of these products as key intermediates have led to our development of new methodologies for their synthesis and transformation.

Scheme 1



Although there is an isolated precedent for a reaction providing related compounds, the value of this approach has been largely neglected, possibly as a result of limitations of the reported protocol.[3,4] We believed that careful choice of reaction conditions would permit the direct coupling of

(1) For reviews, see: (a) Rix, U.; Fischer, C.; Remsing, L. L.; Rohr, J. *Nat. Prod. Rep.* **2002**, *19*, 542−580. (b) Stauton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380−416.

(2) For a review of isoxazole chemistry, see: Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147−204.

(3) (a) Ahkrem, A. A.; Lahkvich, A. L.; Khripach, V. A.; Pozdeyev, A. G. *Synthesis* **1978**, 43. (b) This process requires the prior preparation and isolation of the corresponding enamino-ketone, utilizes a great excess of the nitrile oxide precursors, and fails for more functionalized reaction partners. (c) A cyclocondensation of hydroxy quinones has been reported: Selvaraj, S.; Dhanabalan, A.; Arumugam, N. *Indian J. Chem.* **1995**, *34B*, 141−142.

(4) An alternative, three-step approach via the corresponding triketone has been reported. This chemistry, however, suffers from considerable limitations due to the regioselectivity of the key isoxazole formation. For a discussion, see: Rubinov, D. B.; Rubinova, I. L.; Akhrem, A. A. *Chem. Rev.* **1999**, *99*, 1047−1066.

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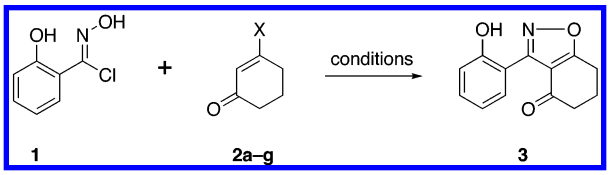
readily available cyclic diketones and activated oximes to afford isoxazoles. Utilizing hydroximinoyl chloride **1**, derived from commercially available salicylaldoxime,[5] we undertook an investigation on the reaction protocol (Table 1). Critical

Table 1. Optimization of Isoxazole Formation from Phenolic Hydroximinoyl Chloride **1**



1 **2a–g** **3**

entry	X	solvent	equiv **2**	time (h)	yield (%)
1	OH (**2a**)	$CHCl_3$	2.0	18	–
2	OEt (**2b**)	$CHCl_3$	1.0[a]	18	<10
3	$O^-N^+HEt_3$ (**2c**)	EtOH	1.2[b]	1	60
4	O^-Na^+ (**2d**)	EtOH	2.0[b]	2	63
5	O^-Na^+ (**2d**)	^{i}PrOH	2.0[b]	0.5	77
6	O^-K^+ (**2e**)	toluene	2.0[b]	2	34
7	O^-Cs^+ (**2f**)	EtOH	2.0[c]	4.5	35
8	O^-Li^+ (**2g**)	EtOH	2.0	5.5	52
9	O^-Na^+ (**2d**)	toluene	2.0[d]	0.25	83
10	O^-Na^+ (**2d**)	toluene	1.2[d]	3.5	82

[a] 5 equiv of **1** and 5 equiv of NEt_3 were used; reaction temperature was 60 °C. [b] Salt of **2** generated in situ from **2a** (X = OH). [c] Cs_2CO_3 (2 equiv) was used as base. [d] Preformed, isolated **2d** ($X = O^-Na^+$) was used.

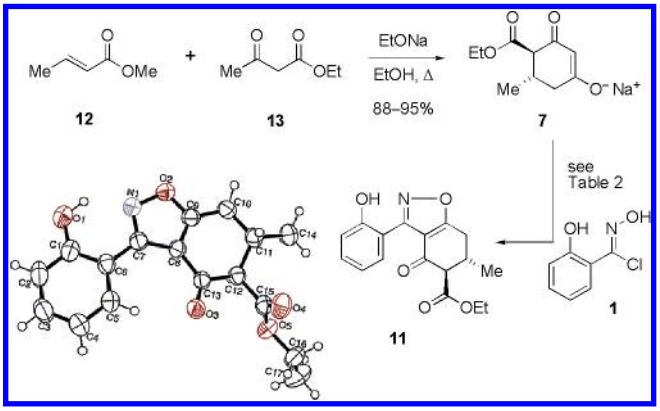
to the successful development of this methodology was the discovery that use of a slight excess of the 1,3-diketone salts, relative to the nitrile oxide precursor **1**, resulted in the rapid and high-yielding formation of the desired product **3** (entry 3).[6] In contrast, typical reaction protocols for thermal cycloadditions with **2a** or **2b** were unsuccessful, even when high temperatures or slow addition techniques were employed.[7]

Further studies identified the use of readily prepared sodium salt **2d** as advantageous (entries 4 and 5). From these studies, two useful reaction protocols emerged. In the first, addition of the free diketone **2a** to a solution of NaO^iPr in ^{i}PrOH followed by addition of the hydroximinoyl chloride **1** afforded the desired isoxazole **3** in 77% yield (entry 5). Alternatively, utilization of isolated **2d** as a suspension in toluene slightly improved the yield (entry 9).[8] Reducing the amount of **2d** employed diminished the rate of the reaction but not the chemical yield (entry 10).

The reaction conditions, thus identified, were amenable to the synthesis of a wide variety of functionalized isoxazoles (Table 2). Yields, reaction protocol, and conversion times were largely unaffected by variation of the reaction partners. Notably, no apparent complications were experienced with substrates containing sensitive functional groups. Thus, aryl bromides (entry 3), phenols (entries 1, 5, and 6), and ester groups (entries 5 and 6) were readily tolerated.

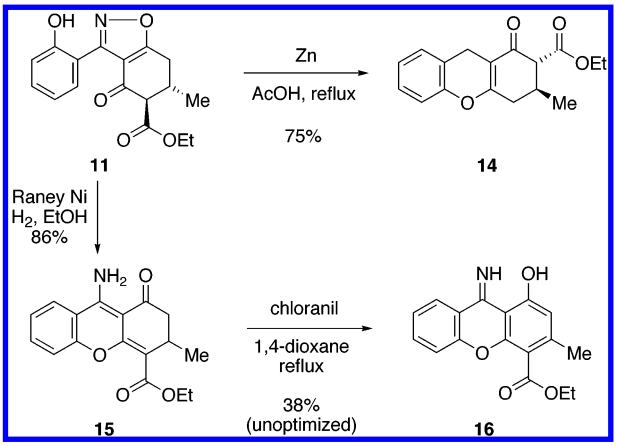
Scheme 2 highlights the salient features of this methodology in the regioselective formation of **11** from highly

Scheme 2



functionalized diketone salt **7**. Although several possible reaction products were possible, the optimized conditions afforded predominantly **11**. Simple precipitation of the product from Et_2O provided isoxazole **11** as a single diastereomer in good yield, and the structure was confirmed by X-ray crystallographic analysis. While the diketone corresponding to **7** is commercially available, it was more convenient to directly prepare the sodium salt via the single-

Scheme 3

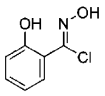
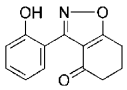
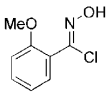
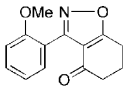
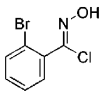
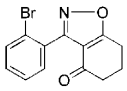
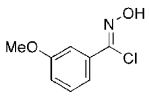
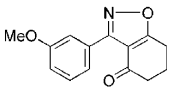
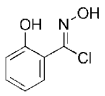
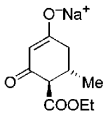
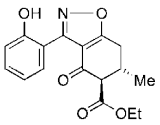
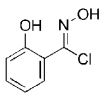
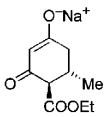
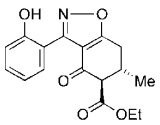


(5) (a) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1988**, *B42*, 303−308. (b) This compound was obtained as an analytically pure solid by oxime chlorination with 1.1 equiv of NCS in the presence of 10 mol % pyridine as a catalyst and used without further purification. It could be stored for several weeks without decomposition. See Supporting Information for an experimental procedure.

(6) (a) A few examples of base-promoted isoxazole formations have appeared. To the best of our knowledge, no comprehensive study of the isoxazole formation from diketone enolates has been undertaken. For a related reaction with α-nitroketones, see: Dal Piaz, V.; Pinzauti, S.; Lacrimini, P. *Synthesis* **1975**, 664−665. (b) For an isolated example employing a cyclic diketone and trifluoroacetonitrile oxide in modest yield, see: Tanaka, K.; Kishida, M.; Maeno, S.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2631−2632.

(7) We have identified nitrile oxides as the key reactive intermediates in the isoxazole-forming reaction. The role of the base, however, is not solely to effect elimination of chloride from the hydroximinoyl chloride. The reaction of isolated nitrile oxides and diketones in the absence of base does not proceed on a useful time scale. Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. Unpublished results.

Table 2. Direct Synthesis of Highly Functionalized Isoxazoles[a]

entry	nitrile oxide precursor	dione	base	solvent	time (h)	product	yield (%)[b]
1	 **1**	 **2a**	NaO^iPr	^{i}PrOH	0.5	 **3**	77
2	 **4**	 **2a**	NaO^iPr	^{i}PrOH	0.5	 **8**	70
3	 **5**	 **2a**	NaO^iPr	^{i}PrOH	0.5	 **9**	62
4	 **6**	 **2a**	NaO^iPr	^{i}PrOH	0.5	 **10**	64
5	 **1**	 **7**	—	EtOH–H_2O (2:1)	6	 **11**	65[c]
6	 **1**	 **7**	—	toluene	0.5	 **11**	70[c]

[a] Unless otherwise indicated, all reactions were run at 0.1 M using 2.0 equiv of diketone and 1.9 equiv of base; hydroximinoyl chlorides **1** and **4**−**6** were prepared by chlorination of the corresponding oxime (NCS, cat. pyridine) and used without further purification. [b] Overall yield for the chlorination and isoxazole formation. [c] Minor stereoisomers could be detected prior to trituration from Et_2O.

step condensation of methyl crotonate (**12**) and ethyl acetoacetate (**13**) in the presence of sodium ethoxide.[9] Simple heating of these precursors in equal parts resulted in precipitation of the pure salt **7** in excellent yield. Preliminary studies on the development of a versatile three-component coupling approach to **11** and related structures are promising.

In analogy to polyketide biosynthesis, we were pleased to find that **11** indeed undergoes a number of remarkably selective, high yielding transformations to a diverse set of polycyclic compounds (Scheme 3). Upon isoxazole reduction with Zn−AcOH, xanthene-derivative **14** was formed as a single regioisomer via cascade reductions and cyclization.[10] Interestingly, isoxazole reduction under milder conditions afforded exclusively the regioisomeric vinylogous amide **15**. This compound, in turn, was oxidized to the imino-xanthone **16**. The ability to chemo- and regioselectively transform these compounds was maintained even for more highly substituted derivatives. The isoxazole functionality represents a unique handle for the synthesis of diverse natural product-like structures.[11]

Likewise, other motifs common to polycyclic natural products are accessible from isoxazole precursors. In preliminary studies, we have found that anthracene derivatives are readily prepared from the isoxazole products, following

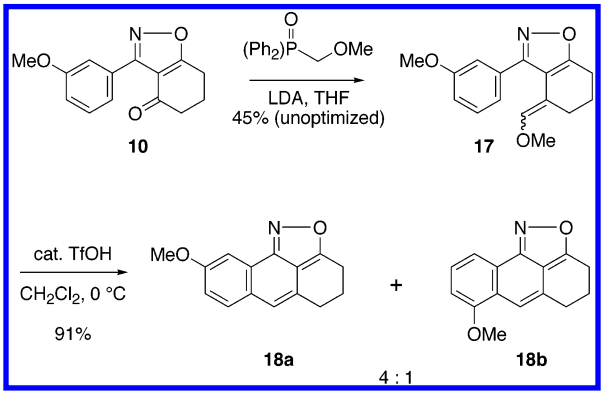
(8) In preliminary studies, we have found that aprotic solvents, such as toluene, are effective only for phenolic hydroximinoyl chlorides such as **1**. For all other cases, protic solvents are advantageous.

(9) Edafiogho, I. O.; Hinko, C. N.; Chang, H.; Moore, J. A.; Mulzac, D.; Nicholson, J. M.; Scott, K. R. *J. Med. Chem.* **1992**, *35*, 2798−2805.

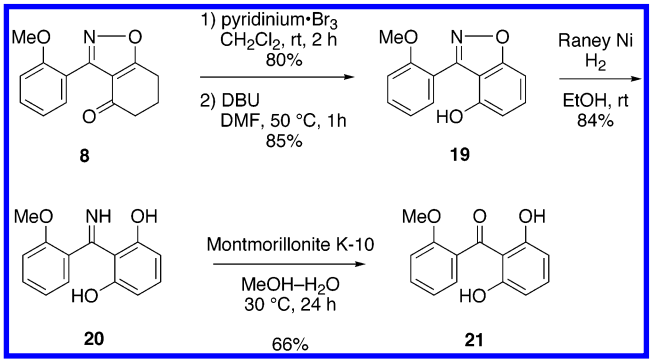
(10) The structure of this compound was determined by long-range C−H correlation (HMBC) NMR experiments.

(11) For examples of the synthesis and transformation of isoxazoles derived from **14**, see the Letter immediately following: Bode, J. W.; Uekusa, H.; Suzuki, K. *Org. Lett.* **2003**, *3*, 395−398.

Scheme 4



Scheme 5



one-carbon homologation (Scheme 4). Thus, anthracene derivative **18** is obtained, as a 4:1 mixture of positional isomers, in high yield by intramolecular cyclization of **17**.

Synthetically valuable, highly oxygenated benzophenones are also prepared via a straightforward reaction sequence (Scheme 5). Substituted isoxazoles represent a potentially general entry to this important class of compounds.

In conclusion, we have described a direct, convenient synthesis of highly substituted isoxazoles useful for the preparation of structural motifs commonly found in bioactive natural products. These products and their divergent transformations provide novel approaches to a wide variety of architecturally complex molecules with particular value for the construction of polycyclic polyketide structures. Continued efforts aimed at a mechanistic understanding of these reactions should lead to further advances and the development of novel processes.

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Supporting Information Available: Characterization data and representative experimental procedures for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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