Synthetic Methods

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Cascade Formation of Isoxazoles: Facile Base-Mediated Rearrangement of Substituted Oxetanes**

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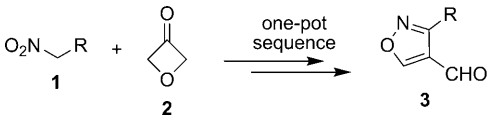
Heterocycles play an important role in pharmaceutical sciences and many other areas of organic chemistry. Among the most widely employed nitrogen-containing five-membered rings are the isoxazoles. Their preparation has been extensively discussed in the literature and typical access routes involve condensations with hydroxylamine, cyclizations of ketoxime dianions, and propargylic oximes, and in particular 1,3-dipolar cycloaddition reactions.[1–3] Surprisingly, only few of the reported methods are general and versatile, as many suffer from low functional group tolerance, and modest regioselectivities and yields. Herein, we report a novel approach to 3-substituted isoxazoles-4-carbaldehydes **3** from the condensation reaction of nitroalkanes **1** with 3-oxetanone (**2**) [Eq. (1)].[4] The process represents not only a mechanistically intriguing cascade transformation but also provides preparative access to 3,4-disubstituted isoxazoles, which are otherwise underrepresented structures as building blocks in the drug discovery process. Given the fact that oxetanone has become commercially available[5,6] and that 3,4-disubstituted isoxazoles are underrepresented in the literature, we have examined the scope of this intriguing process.



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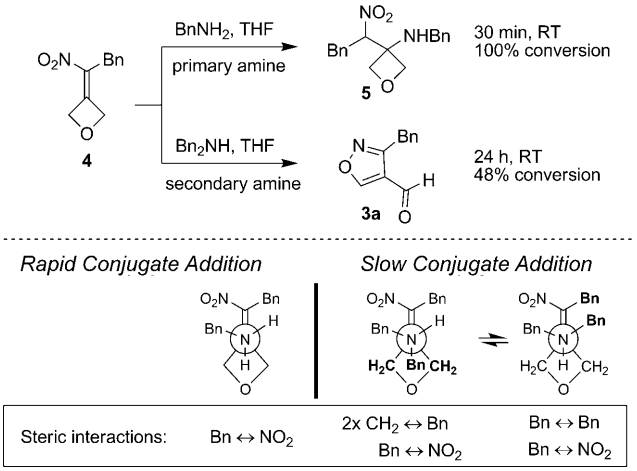
We have been engaged in a program aimed at the development and study of substituted oxetanes and azetidines as small molecule modulators of key biophysical and chemical properties of pharmaceutically relevant compound scaffolds.[7] In this context we have reported that 3-(nitromethylene)oxetane is in general a good acceptor, a property that can be employed in the preparation of compounds bearing the oxetane moiety.[7a,8] Thus, treatment of **4** with benzylamine affords the conjugate addition product **5** within 30 minutes at room temperature. Oxetane building blocks have only recently become widely available and in turn have generated considerable interest in the pharmaceutical sector (for example, Abbott, AstraZeneca, Genentech, Merck, Novartis, Roche, Sanofi Aventis, Takeda).[8,9] Consequently, it is important to define their reactivity landscape. In examining further their chemistry and reactivity profile, we have observed that treatment of **4** with dibenzylamine led to an unexpected rearrangement, producing isoxazole-4-carbaldehyde **3a** (Scheme 1). We speculate that the key difference



Scheme 1. Differential reactivity of nitromethyleneoxetanes reacting with either benzyl- or dibenzylamine.

between these two reaction processes stems from steric demands inherent to dibenzylamine that lead to significant attenuation in the rate of conjugate addition to nitromethyleneoxetane **4** versus Bn_2NH and instead favors a cascade process initiated by deprotonation.

A survey of a collection of bases and solvents revealed that in general tertiary amines (in particular *i*Pr_2NEt) were superior to other bases (e.g., Cs_2CO_3, LiHMDS, NaOMe, or pyridine) in favoring the formation of isoxazoles. When the reaction was conducted in THF clean product formation was observed; in contrast, in CH_3CN, pyridine, or MeOH significant amounts of oligomeric side products were noted.

The synthesis of the nitroalkene acceptor is effected by condensation of oxetan-3-one with nitroalkanes. Our initial findings suggested that a one-pot operation as shown in Scheme 2 would be feasible, since amine bases can be employed for all steps: the Henry addition (step A), the elimination/condensation (step B), and, as highlighted above, the rearrangement to isoxazole (step C).

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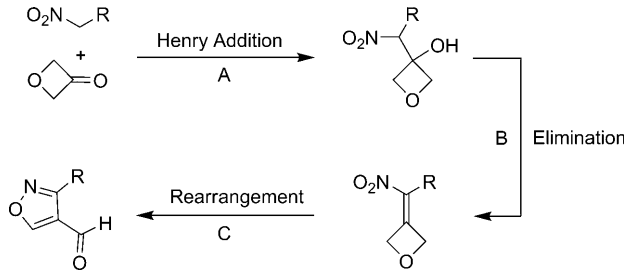


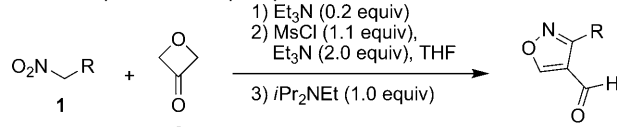
Scheme 2. Pathway toward isoxazole-4-carbaldehydes through a cascade reaction.

The Henry addition proved to be most effective when run neat or at high concentrations in CH_2Cl_2 using catalytic amounts of Et_3N (typically ca. 0.2 equiv), and the subsequent elimination step to the corresponding nitroalkene was best carried out at a 0.1 M concentration using MsCl and Et_3N at low temperature. Optimal results were observed when running the Henry addition neat, then diluting the oxetanyl alcohol in THF with subsequent cooling to −78 °C, addition of Et_3N and MsCl, and then slow warming to room temperature. Subsequent addition of iPr_2NEt and stirring the mixture at room temeprature for 12 hours led to isolation of the isoxazole **3a**, as a test substrate, in an overall yield of 70 %. Careful optimization of the individual reagent amounts allowed isolation of the targeted isoxazole **3a** in 82 % yield over the three steps (Table 1, entry 1).

With the optimized reaction conditions in hand, we were keen to define the scope of the one-pot rearrangement sequence. To our delight, replacement of the phenyl group with electron-rich and electron-deficient aromatic and heteroaromatic entities afforded the products in similarly high overall yields (Table 1, entries 2–7). In addition to aliphatic groups (entry 8), a variety of functional groups such as remotely positioned ester groups, terminal alkenes, as well as protected amines and alcohols were tolerated (entries 9–14). Furthermore, aryl nitromethanes were successfully converted into the corresponding 3-aryl isoxazole-4-carbaldehydes (entries 15 and 16). By using this procedure, 3,4-disubstituted isoxazoles, which are otherwise rather difficult to make selectively,[10] are readily available from commercially available or easily prepared nitroalkanes. The unveiled aldehyde serves as a convenient handle for further functionalization.[11]

Mechanistic studies were carried out to shed light on the final step of the cascade. The sequence originates from the nitroalkene intermediate, which can be observed when aliquots of the reaction mixture are analyzed by ^1H NMR spectroscopy at various times. Subjecting isolated nitroalkene **4** to iPr_2NEt in $[D_8]THF$ at room temperature leads smoothly to the isoxazole-4-carbaldehyde **3a** within 24 hours. Other than starting material and product, no intermediates were observed when monitored by ^1H NMR spectroscopy. Interestingly, in two separate experiments when the reaction was conducted in $[D_4]CH_3OH/[D_8]THF$ (1:1) and iPr_2NEt or in THF and a mixture of iPr_2NEt and $iPr_2NEt{\cdot}DCl$ (1:1) no deuterium incorporation was observed in the product. Therefore, we suggest that the first step of the sequence is rate limiting and involves deprotonation of oxetane **A** to give a strained oxetene intermediate **B** (Scheme 3). Subsequently, the nitronate anion may undergo in ring opening to form **C**/**C′**. Dehydration of this putative intermediate then furnishes **D**.

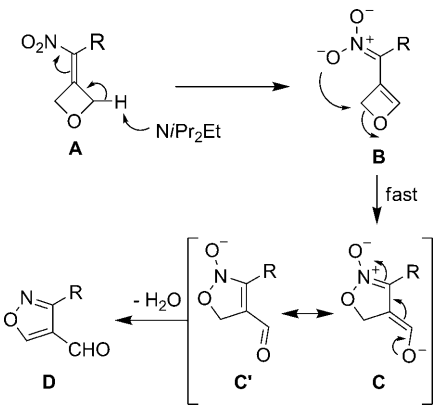
Table 1: Scope of the one-pot synthesis of isoxazoles.[a,b]



1 **2** **3**

Entry	Substrate **1**, R	Product	Yield [%][b]
1	**1a**, Bn	**3a**	82
2	**1b**, piperonyl	**3b**	75
3	**1c**, $CH_2C_6F_5$	**3c**	74
4	**1d**, CH_2(3-pyridyl)	**3d**	86
5	**1e**, CH_2(*p*-$CF_3C_6H_4$)	**3e**	71
6	**1f**, CH_2(*p*-$NO_2C_6H_4$)	**3f**	60
7	**1g**, CH_2(3-indolyl)	**3g**	60
8	**1h**, CH_2Cy	**3h**	86
9	**1i**, $CH_2CH_2CO_2Me$	**3i**	91
10	**1j**, CH_2CO_2Et	**3j**	73
11	**1k**, $(CH_2)_3OAc$	**3k**	65
12	**1l**, $CH_2CH_2CHCH_2$	**3l**	85[c]
13	**1m**, CH_2CH_2NHBoc	**3m**	65
14	**1n**, CH_2OTBS	**3n**	60
15	**1o**, Ph	**3o**	62[c]
16	**1p**, *p*-$tBuC_6H_4$	**3p**	58[c,d]

[a] General procedure: nitro compound (0.75 mmol, 1.0 equiv), oxetan-3-one (0.98 mmol, 1.3 equiv), THF (0.1 M). [b] Yields of isolated products are given. [c] Rearrangement required 48 h. [d] 0.65 mmol of substrate was used. Boc = *tert*-butoxycarbonyl, Cy = *c*-C_6H_{11}, TBS = *tert*-butyldimethylsilyl.



Scheme 3. Proposed reaction mechanism.

An alternative mechanistic pathway is possible in which electrocyclic ring opening of the oxetene in **B** is followed by conjugate addition through a 5-*exo*-trig cyclization[12] that leads to the product isoxazoles. However, the fact that 2-unsubstituted oxetes at room temperature have half-lives of several hours in solution[13] would argue against the second alternative, because we did not observe the accumulation of intermediate **B** by ^{1}H NMR spectroscopy. Thus, as discussed above we favor a process in which rapid intramolecular attack on the oxetene ring in **B** occurs after deprotonation, as shown in Scheme 3. Energy calculations reveal that this process is considerably favored, since intermediate **C** resides 24.29 kcal mol^{-1} lower in energy than the strained oxete **B**.[14]

In summary, we have developed a novel access route toward isoxazoles from nitroalkanes and oxetan-3-one. The one-pot procedure is versatile and delivers the desired products in high overall yields. Moreover, the aldehyde products offer various possibilities for further manipulation, thus rendering these heterocylces versatile and enabling synthetic applications and use in medicinal chemistry. The chemistry we have described discloses unusual and unexpected reactivity of nitromethyleneoxetanes. We have previously documented the use of oxetanes to modulate pharmacokinetic properties of structures of interest in the drug discovery process. The results presented herein considerably expand the potential role of oxetanes to include their use as launching points for the generation of other building blocks. Epoxides as building blocks have had tremendous impact in chemical synthesis. Recent advances in the synthesis[15] and chemistry of oxetanes suggests that this homologue of epoxides has its own intriguing reactivity profile which can be harnessed for the synthesis of novel building blocks.[16] We thus anticipate that the impact of oxetanes will continue to grow.[17]

Experimental Section

General procedure for the one-pot reaction sequence: The nitro compound (0.75 mmol, 1.0 equiv) and oxetan-3-one (0.98 mmol, 1.3 equiv) were combined in a 10 mL flask under Ar, and the mixture was cooled to 0 °C. Et_3N (0.15 mmol, 0.2 equiv) was then added, and the reaction mixture was stirred at 0 °C for 10 min, after which time it was warmed to RT and stirred for 90 min. In most cases formation of a solid was observed. The reaction mixture was diluted with THF (7.5 mL). Et_3N (1.5 mmol, 2.0 equiv) was added and the solution was cooled to −78 °C. MsCl (0.83 mmol, 1.1 equiv) was then added dropwise and the mixture was stirred at −78 °C for 30 min, after which time it was allowed to slowly warm to RT over a 60 min period. iPr$_2$NEt (0.75 mmol, 1.0 equiv) was added and the mixture was stirred at RT for 12 h. The mixture was then diluted with CH_2Cl_2 (15 mL), quenched with H_2O (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The product was obtained after purification by flash column chromatography on silica gel.

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