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Mild Intramolecular Ring Opening of Oxetanes

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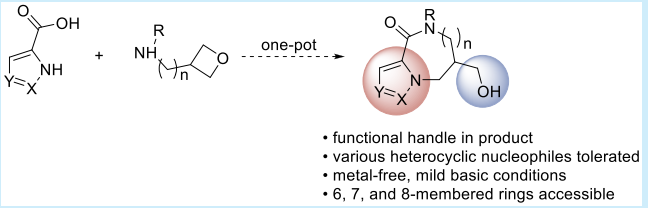
Supporting Information

ABSTRACT: Oxetanes have been increasingly used as stable motifs in medicinal chemistry as well as versatile synthetic intermediates. Herein, an intramolecular ring opening of oxetane carboxamides with mild nucleophiles, such as nitrogen heterocycles, is presented. The reaction proceeds under metal-free basic conditions which is highly unusual in ring opening reactions of oxetanes. Amide formation and oxetane ring opening/cyclization in a one-pot approach affords high levels of molecular complexity in a single step from simple, readily available substrates.



In recent years, oxetanes have received significant attention from the pharmaceutical industry as stable motifs in medicinal chemistry that can be employed to modulate the physicochemical properties of a drug candidate (Figure 1).[1]

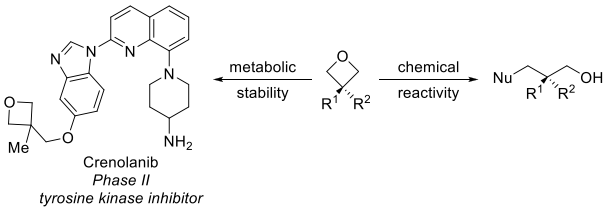


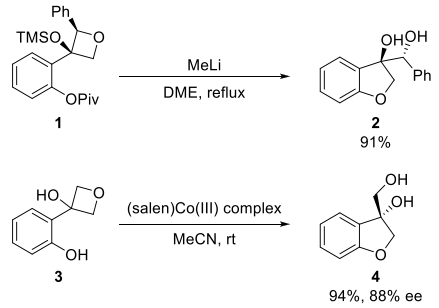
Figure 1. Oxetane use by medicinal and synthetic communities.

In seeming contradiction with the stability required of the oxetane ring in medicinal chemistry applications, the reactivity of oxetanes and their propensity to undergo a variety of synthetic transformations via ring opening have led to their use by the synthetic community in generating complex scaffolds.[2]

The susceptibility of oxetanes to ring opening can be traced back to the inherent ring strain of the four-membered ring. Oxetane has similar ring strain (106 kJ/mol) as compared to oxirane (112 kJ/mol),[3] and both undergo acid-catalyzed hydrolysis by sulfuric or perchloric acid in aqueous dioxane at similar rates.[4] However, the rates of hydrolysis under alkaline conditions differ greatly between the two with oxetane being hydrolyzed 3 orders of magnitude slower than oxirane. A few theoretical studies have been carried out in an attempt to explain this reactivity difference resulting in several possible explanations.[5] Consequently, the ring opening of oxetanes typically require activation with Lewis or Brönsted acids or elevated temperatures (Scheme 2).[1a,2]

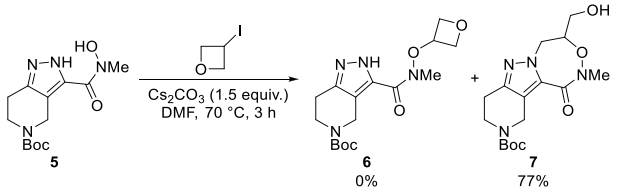
Though readily accessible via commercial reagents, oxetanes were largely neglected by the synthetic community. However, over the past decade new methodologies have emerged utilizing oxetanes to furnish valuable compounds via ring opening reactions.[1a,2] Furthermore, Jacobsen[6] and Sun[7] have reported asymmetric ring opening of oxetanes using chiral cobalt complexes or phosphoric acids, respectively, as the catalyst (Scheme 1).

Scheme 1. Intramolecular Ring Opening of Oxetanes



As part of a recent medicinal chemistry program, efforts were pursued to access a route toward target scaffold **6**.[8] Surprisingly, when mild basic conditions were employed to alkylate the *N*-hydroxyamide **5** with 3-iodooxetane, facile cyclization to afford the oxadiazepanone **7** was observed (Scheme 2). This result was quite intriguing when compared

Scheme 2. Preliminary Ring Opening of Oxetane Result



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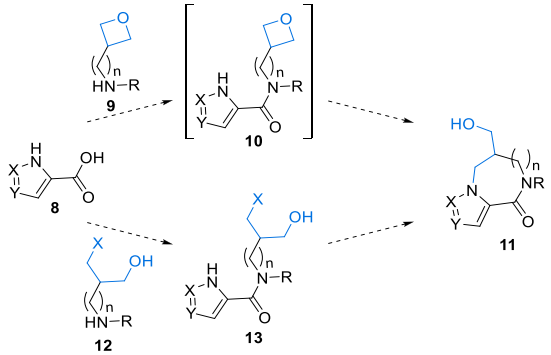
to commonly reported conditions to open the oxetane ring. As noted previously, most methods use harsh conditions with metal additives[9] or proceed under acidic conditions.[10] Interestingly, to the best of our knowledge, there has not been a report of intramolecular ring opening of oxetanes under basic conditions with mild heterocyclic nucleophiles such as pyrazoles. Inspired by this result and attracted to the molecular complexity generated from simple starting materials, we sought to further develop and expand this reaction. The results of this work are presented herein.

Attracted by the resemblance of these building blocks to motifs commonly found in medicinal chemistry, evaluation of this oxetane ring opening reaction was of high interest. Thus, it was envisioned that a system such as **10** would maintain enough geometrical constraint to enable a facile ring opening and furnish biologically relevant scaffolds[11] with a resultant hydroxymethyl group as a synthetic handle for further functionalization (Scheme 3). Based on the preliminary

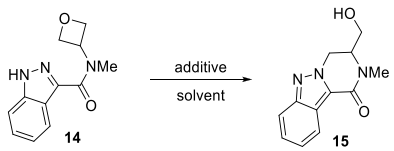
Scheme 3. General Proposed Reaction



result above, this reaction could avoid the use of metals and harsh conditions with an array of heterocyclic nucleophiles being tolerated. Overall, it would constitute an efficient method, with the advantage of using readily available oxetanyl amines **9**, to form the lactam **11** as compared to preparation of the requisite amino alcohol **12** and proceeding through a stepwise approach via manipulation of protecting and leaving groups. In effect, the oxetane serves as both the leaving and protecting group to provide the unprotected primary hydroxyl after cyclization.

To study this type of oxetane ring opening and ensure it could be extended beyond the oxadiazepanone, the indazole substrate **14** was prepared in a single step and subjected to a number of conditions to promote cyclization (Table 1).

Table 1. Optimization of Oxetane Ring Opening Conditions

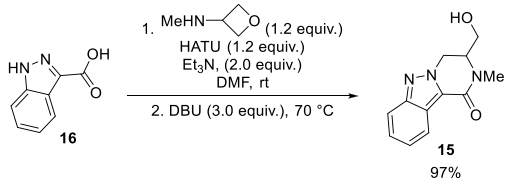


entry	T (°C)	additive	solvent	conversion to **15**
1	70	Cs_2CO_3	DMF	>99%
2	70	DBU	DMF	>99%
3	50	DBU	DMF	>99%
4	0	$BF_3{\cdot}OEt_2$	THF	trace

Using Cs_2CO_3 as base in DMF at 70 °C, **14** fully converted to the cyclized product **15** within 1 h (entry 1).[12] For a homogeneous reaction, DBU was also a suitable base for this transformation providing quantitative conversion to the cyclized product (entry 2). The temperature could be reduced to 50 °C and the reactivity maintained, although slightly longer reaction times were required (entry 3). *Interestingly, when* **14** *was treated under Lewis acid conditions, an entirely different ring opened product was obtained and trace desired product* **15** *was observed* (entry 4).[13]

With the cyclization reaction proceeding exceptionally well under basic conditions, a one-pot transformation was explored to achieve amide bond formation and cyclization in a single flask. Toward this end, conditions were optimized[12] to furnish **15** in 97% yield in the one-pot reaction starting from indazole carboxylic acid **16** (Scheme 4).

Scheme 4. Development of One-Pot Approach



With the one-pot conditions established, the scope of the nucleophile in the ring opening was studied (Table 2). Imidazole nucleophiles (entries 1–2) afforded the cyclized product in moderate yields, primarily due to an incomplete amide coupling. However, the benzimidazole (entry 3) was an effective substrate in this transformation affording the product in 73% yield. Additionally, pyrazoles (entries 4–5) and indazoles (entries 6–8) formed the corresponding piperazinone rings in high yields (76–97%). Triazole was also a competent nucleophile in the reaction, forming product **24** in 74% yield (entry 9). Furthermore, the pyridone reacted smoothly under the standard reaction conditions providing **25** in 77% yield (entry 10). Notably, indoles **26** and **27** were formed in remarkably high yields, 98% and 91%, respectively, despite the low nucleophilicity of indoles. The indole substrate was also chosen to study the substituent effect on the reaction. Adding an electron-donating group did not affect the yield of the reaction. However, the reaction rate was lowered, requiring longer reaction times to fully convert to the cyclized product (entry 13). Incorporation of an electron-withdrawing group resulted in a facile reaction with high yields (entry 14).

Seeking to expand the nucleophile component beyond heterocyclic nitrogens, other heteroatom nucleophiles were investigated in the one-pot amidation/cyclization sequence (Table 3). For the formation of larger ring systems, sulfonamide, phenol, and thiophenol were all suitable nucleophiles to open the oxetane ring, furnishing diazepanones, oxazepanones, and thiazepanones, respectively, in high yields (entries 1–3). Other seven-membered ring systems could be obtained using the 7-substituted carboxylic acid as the substrate (entries 4–5). An additional methylene could be incorporated between the nitrogen and the oxetane, affording product **35** in 87% yield (entry 6). The eight-membered ring **36** was generated in 72% yield as shown in entry 7, albeit elevated temperatures were required to cyclize

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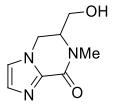
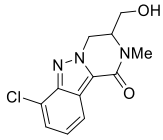
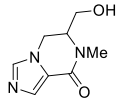
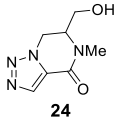
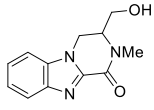
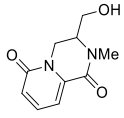
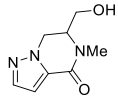
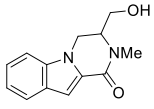
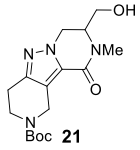
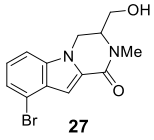
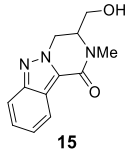
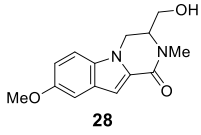
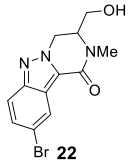
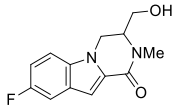
Table 2. One-Pot Formation of Six-Membered Rings[a]

entry	product	yield	entry	product	yield
1[b]	 **17**	56%	8	 **23**	76%
2[b]	 **18**	52%	9	 **24**	74%
3	 **19**	73%	10	 **25**	77%
4	 **20**	98%	11	 **26**	98%
5	 **21**	94%	12	 **27**	91%
6	 **15**	97%	13	 **28**	92%
7	 **22**	81%	14	 **29**	98%

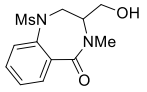
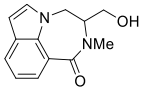
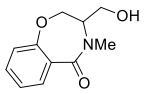
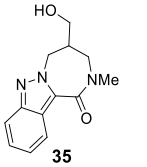
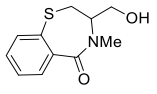
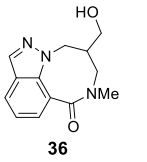
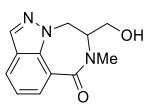
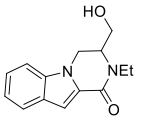
[a]Standard conditions: amine (1.2 equiv), HATU (1.2 equiv), Et_3N (2.0 equiv), DMF, rt then DBU (3.0 equiv), 70 °C. [b]CDI as coupling agent.

completely. Lastly, in addition to methyl, an ethyl substituent is tolerated on the aminooxetane (entry 8).

To gain a deeper understanding of the ring opening aspect of this reaction, additional control substrates were subjected to the reaction conditions (Figure 2). The amine **38** resulted in no reaction under the basic cyclization conditions. Additionally, incorporating a methylene spacer between the heteroaromatic and amide functionality as demonstrated with **39** led to a loss of reactivity. Lastly, minimal reaction was observed in substrate **40** that has removed the alkyl substitution on the amide nitrogen. These results suggest that the rigidity and conformation of the substrate are an important factors for increased susceptibility of the oxetane to undergo ring opening by such mild nucleophiles.

In an expansion of the amidation/cyclization sequence under basic conditions, a one-pot alkylation/cyclization could

Table 3. One-Pot Reaction To Form Larger Ring Systems and N-Substitution Effect[a]

entry	product	yield	entry	product	yield
1	 **30**	75%	5[c]	 **34**	85%
2[b]	 **31**	77%	6[c]	 **35**	87%
3	 **32**	70%	7[c,d]	 **36**	72%
4[c]	 **33**	90%	8	 **37**	80%

[a]Standard conditions: amine (1.2 equiv), HATU (1.2 equiv), Et_3N (2.0 equiv), DMF, rt and then DBU (3.0 equiv), 70 °C. [b]CDI as coupling agent. [c]Cs_2CO_3 as base. [d]100 °C.

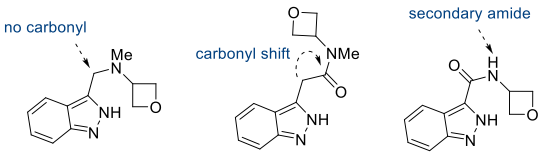
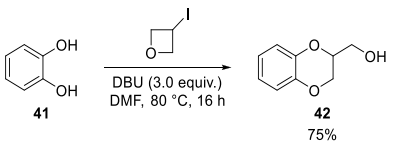


Figure 2. Control substrates for cyclization reaction.

also be envisioned to access other valuable scaffolds. Dihydrobenzodioxine **42** can be obtained using similar basic conditions with 3-iodooxetane in 75% yield (Scheme 5), highlighting the carboxamide function is not essential in promoting the cyclization.

Scheme 5. One-Pot Alkylation Followed by Ring Opening To Afford Dihydrobenzodioxines



In summary, an intramolecular ring opening of oxetanes under metal-free, basic conditions has been reported. A facile intramolecular ring opening of this type under mild basic conditions is largely unprecedented in the literature. In addition, the scope of the nucleophile for this reaction is extensive and a variety of biologically prevalent and moderately complex ring systems can be generated from readily available starting materials in a one-pot fashion in high yields. Further studies on the ring opening reaction of

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oxetanes are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03810.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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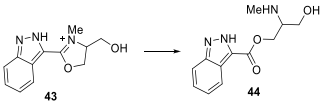

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