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Synthesis of triazole-oxazolidinones via a one-pot reaction and evaluation of their antimicrobial activity

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ABSTRACT

C-5-substituted triazole-oxazolidinones were synthesized using a bromide catalyzed cycloaddition between aryl isocyanates and epibromohydrin followed by a three-component Huisgen cycloaddition. The library of compounds was screened for antibacterial activity against *Mycobacterium smegmatis* ATCC 14468, *Bacillus subtilis* ATCC 6633, and *Enterococcus faecalis* ATCC 29212. Notably, the 3-(4-acetyl-phenyl)-5-(1*H*-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one (**18**) showed an MIC of 1 μg/mL against *M. smegmatis* ATCC 14468, fourfold lower than the MIC measured for isoniazid.

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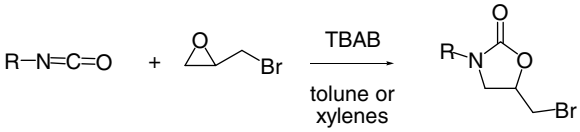
The *N*-aryloxazolidin-2-one moiety is present in a number of compounds which show diverse biological activities. Some of these activities include monoamine oxidase (MAO) inhibition,[1] GP IIb/IIIa antagonism,[2] neuroleptic activity,[3] and antibacterial activity.[4] Due to this medicinal importance, methods for generating libraries of these compounds have received significant interest.[5]

The compound class is particularly well recognized for its activity against clinically important susceptible and resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and penicillin-resistant *Streptococcus pneumouniae*.[6] *N*-aryloxazolidin-2-ones are also being rediscovered for their activity against *Mycobacterium* sp.[7] In the latter case, the increased prevalence of drug resistant *Mycobacterium tuberculosis* combined with the rise of *Mycobacterium avium* complex (MAC) infections in immuno-compromised populations has placed renewed attention on the potential use of oxazolidines for the treatment of mycobacterial infections.[8]

Recently, a new class (1*H*-1,2,3)-triazole C-5 substituted oxazolidin-2-ones was described.[9] These oxazolidinones showed impressive antibacterial activity and were less prone to inhibit MAOs. In this letter we describe an expedient method for the introduction of 1,4-disubstituted-(1*H*-1,2,3)-triazoles at the C-5 position of oxazolidinones. The resulting library of compounds were then screened against a small panel Gram-positive reference strains which included the strain *Mycobacterium smegmatis*, which has been explored as a surrogate for pathogenic *Mycobacterium*.

Chemistry. One of the earliest methods for *N*-alkyloxazolidin-2-ones preparation is the quaternary ammonium halide catalyzed cycloaddition of alkyl isocyanates with monosubstituted oxiranes reported by Speranza and Peppel.[10] In that chemistry the halide is proposed to open the oxirane to form a 1,2-alkoxy halide[11] which subsequently adds to an isocyanate. The intermediate cyclizes to form predominately 3,5-disubstituted oxazolidin-2-ones. A variety of halides; for example, LiBr–$OPPh_3$,[4b,12] *n*-Bu_3S-nI–Lewis base complexes,[13] and lanthanide chlorides,[14] also catalyze the reaction. Since alkyl isocyanates are abundant the method allows for considerable variation of the *N*-aryl moiety and was therefore chosen to prepare various *N*-aryl-substituted C-5 (bromomethyl)-oxazolidinones, Scheme 1. Tetrabutylammonium bromide (TBAB) was chosen as a catalyst as it is inexpensive, commercially available, soluble in most solvents, and can be removed by aqueous extraction. Phenyl isocyanate **1a**, tolyl isocyanate **1b**, or 4-acetylphenyl isocyanate **1c** were then condensed



1a: R = Ph
1b: R = *p*-CH_3-Ph
1c: R = *p*-$COCH_3$-Ph

2a: R = Ph
2b: R = *p*-CH_3-Ph
2c: R = *p*-$COCH_3$-Ph

Scheme 1. Preparation of C-5 (bromomethyl)-oxazolidinones from 1,2-epoxides and isocyanates.

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with epibromohydrin in the presence of TBAB to form oxazolidinones **2a–c**.

Hoping to avoid the high temperatures and prolonged reactions times reported for isocyanate–epoxide cycloadditions,[10] we briefly investigated the dependence of oxazolidinone yield with respect to reaction time, temperature, and stoichiometry using phenyl isocyanate **1a–c**, Table 1. Overall higher yields corresponded with longer reaction times and temperatures. Lower yields were accompanied by the formation of putative isocyanurate side products. The results are consistent with rapid isocyanurate formation followed by a relatively slow reaction of the isocyanurate with epoxide leading to oxazolidinone, a conclusion supported both experimentally and computationally.[15] We noted isocyanates with electron-withdrawing groups required higher temperatures and longer reaction times compared with less electrophilic isocyanates also consistent with earlier studies.[13]

In order to familiarize ourselves with the properties of the triazole-oxazolidin-2-ones we first investigated the yield of a stepwise displacement of bromide **2b** with NaN_3 to provide C-5 (azidomethyl)-oxazolidinone **3b**.[4b] Azide **3b** was subsequently converted to 1,4-disubstituted-triazoles **4–6** in the presence of either 1-decyne, 3-butyn-1-ol, or phenyl acetylene using a Cu(I) catalyzed 1,3-dipolar Huisgen cycloaddition to afford triazoles in high yield and regioselectivity, Scheme 2.[16] For these initial studies Cu(I) was generated in situ by the reduction of Cu(II)SO_4 10 mol % to Cu(I) with 10 mol % ascorbic acid in 1:1 *tert*-butanol water.

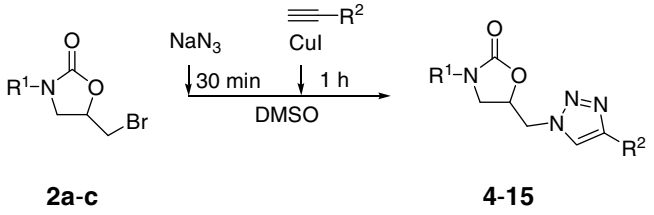
Having produced the targets in high yield by the stepwise approach we proceeded to developed a convenient multi-component variant of this chemistry that could potentially be employed to produce larger libraries of 1,4-disubstituted-triazole-oxazolin-2-ones without the need to isolate (azidomethyl)-oxazolidinones (**2a–c**).[17] During the investigation we noted that trimethylsilyl acetylene failed to react in the Huisgen cycloaddition using the Cu(II)SO_4 10 mol %–10 mol % ascorbic acid–1:1 *tert*-butanol water conditions; however, the reaction proceeded when run in DMSO using 10 mol % CuI as catalyst (data not shown). It has been recently reported that the copper catalyzed Huisgen cycloaddition proceeds faster in aqueous media when the alkyne is electron poor while electron rich alkynes are more reactive in non-aqueous media.[18] In our case, trimethylsilyl acetylene was the most electron rich alkyne employed. Since DMSO was compatible with both the azide displacement and all the Huisgen cycloadditions, this solvent was chosen to explore a one-pot three-component variant of the reaction. Thus, bromomethyl-oxazolidinones **2a–c** and NaN_3 were dissolved in DMSO and heated to at 80–90 °C. Azide formation was followed by TLC and was generally complete within 30 min. At that time 1-decyne, 3-butyn-1-ol, phenyl acetylene, or trimethylsilyl acetylene were added directly to the reaction followed by addition of 10 mol % CuI as shown in Scheme 3. Reactions were maintained at 80–90 °C and were generally complete within 1 h. The conditions are essentially the same as those reported by Molander.[17c] The structures and isolated yields of the various triazole 1,4-disubstituted-(1*H*-1,2,3)-triazole-oxazolidinones **4–15** are reported in Table 2.

Overall the isolated yields for the one-pot reactions were modest, 39–61%. However, it should be noted that the reactions were clean when monitored by TLC. The yields were negatively impacted as result of using impure starting materials **2a–c**. While the starting materials could be purified from the closely migrating isocyanurate by silica gel chromatography, the process was arduous. Surprisingly, recrystallization was also ineffective at removing the contaminant. Therefore, partially purified starting materials (ca. 70% pure) **2a–c** were used. After the trizole formation step of

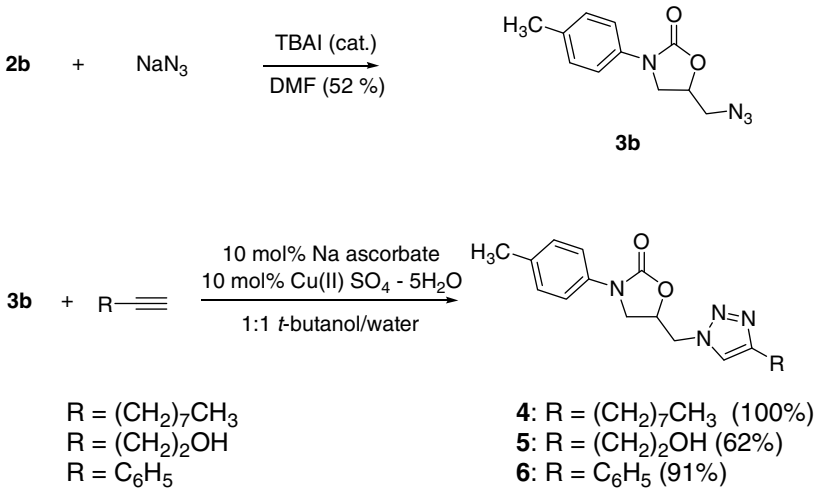
Table 1
Yield of C-5 (bromomethyl)-oxazolidinones for the TBAB catalyzed condensation of 1,2-epoxides with isocyanates[a]

Isocyanate	Solvent	Time (h)	Yield **2a–c** (%)
1a	Toluene[b]	1.5	3
1a	Xylenes[b]	1.5	38
1a	Xylenes[c]	1.5	33
1a	Xylenes[c]	3.0	60
1b	Toluene[b]	1.0	53
1c	Xylenes[b]	3.0	65

[a] 1.3–1.9 mol % TBAB, reactions in toluene run at 85–90 °C, reactions in xylenes run at 140 °C.
[b] Isocyanate–oxirane (1:1–1.1).
[c] Isocyanate–oxirane (1:1.5).

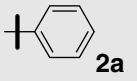
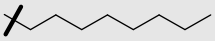
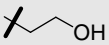
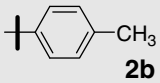
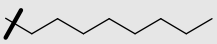
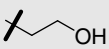
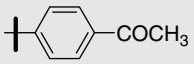
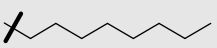
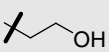


Scheme 3. Three-component reaction to form 1,4-disubstituted-(1*H*-1,2,3)-triazole-oxazolidinones.



Scheme 2. Stepwise reaction to form 1,4-disubstituted-(1*H*-1,2,3)-triazole-oxazolidinones.

Table 2
Structures and isolated yields for 1,4-disubstituted-(1*H*-1,2,3)-triazole-oxazolidinones prepared using the three-component reaction between 5-(bromomethyl)-oxazolidinones, sodium azide, and alkynes

Entry	R^1	R^2	Yield (%)
4	 **2a**		40
5	**2a**		57
6	**2a**		58
7	**2a**		59
8	 **2b**		40
9	**2b**		40
10	**2b**		40
11	**2b**		40
12	 **2c**		52
13	**2c**		61
14	**2c**		48
15	**2c**		39

the one-pot reaction the compound polarity showed a marked increase and flash chromatography became straightforward.

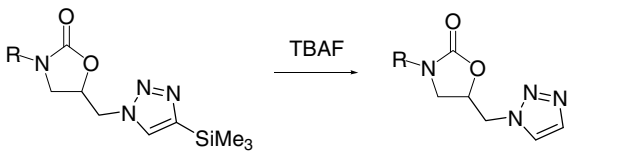
Small or sp^2 hybridized groups at the 4-position of the triazole in triazole-oxazolidinones have been reported to posses higher antimicrobial activities.[9] Therefore, we replaced 4-TMS moiety of triazoles **7**, **10**, and **15** with hydrogen by treatment with TBAF to afford the mono-substituted triazoles **16**–**18**, respectively, Scheme 4.

Biology. The compound library was screened using a disk diffusion assay on the Gram-positive bacterial reference strains,[19] *M. smegmatis* ATCC 14468, *Bacillus subtilis* ATCC 6633, and *Enterococcus faecalis* ATCC. *Mycobacterium smegmatis* was inoculated into Middlebrook 7H9 containing 0.2% glycerol and ADC enrichment while the other strains were inoculated into Mueller–Hinton broth. The inocula of all strains were allowed to incubate for approximately 24 h at 37 °C and 180 rpm. *Mycobacterium smegmatis* was plated on Middlebrook 7H10 agar containing 0.5% glycerol and OADC enrichment. While the other strains were plated on nutrient agar. Aliquots (10 μL) of oxazolidinone derivatives dissolved in DMSO (1 mg/mL) were applied to 6 mm diameter sterile paper disks. INH and vancomyocin (1 mg/mL) were used as positive controls for *M. smegmatis* and other Gram-positive bacteria, respectively. The *M. smegmatis* and other Gram-positive bacteria plates were incubated for 48 and 24 h, respectively, at 37 °C and then analyzed. DMSO was used as a negative control. The diameters of the zones of inhibition (DZIs) are summarized in Table 3A for compound **13** and compound **18**, both of which showed significant antibacterial activity.

Minimum inhibitory concentrations (MICs) of **13** and compound **18** were also determined against the same strains using a broth macrodilution assay using either Middlebrook 7H9 containing 0.2% glycerol and ADC enrichment or Mueller–Hinton broth.[20] The highest concentration for each compound tested was 32 μg/mL, and each subsequent tube was a twofold dilution of the previous. The *M. smegmatis* tubes were incubated for 48 h at 37 °C while the other strains were incubated for 24 h and then analyzed. Thiazolyl blue tetrazolium bromide (MTT) was dissolved in MeOH (10 mg/mL) and added to the solution (20 μL) to aid in bacteria visualization.[21] The MICs are summarized in Table 3B for **13** and compound **18**.

Discussion. In summary, we have successfully prepared a series of C-5 substituted (bromomethyl)-oxazolidinones from a bromide catalyzed cycloaddition of aryl isocyanates with epibromohydrin in moderate yields. The C-5 bromomethyl moiety could be displaced with azide via an S_N2 reaction with NaN_3. These 3-*N*-aryl C-5 azido substituted oxazolidin-2-ones could be transformed in situ using a 'one-pot' protocol to afford 1,4-disubstituted C-5 substituted-(1*H*-1,2,3)-triazole-oxazolidin-2-ones in moderate yields. The choice of solvent was critical for accessing the 4-trimethylsilyl substituted derivatives and the overall sequence is highly amenable to the combinatorial generation of oxazolidinone libraries by varying either the isocyanate component or the alkyne component.

The compound library resulting from the one-pot method was screened for activity against a small panel of Gram-positive



7: R = Ph
11: R = *p*-CH_3-Ph
15: R = *p*-$COCH_3$-Ph

16: R = Ph
17: R = *p*-CH_3-Ph
18: R = *p*-$COCH_3$-Ph

Scheme 4. Deprotection of 4-TMS-substituted triazole-oxazolidinones.

Table 3
Antibacterial activity of triazole-oxazolidinones

Antibiotic	*Ms*	*Bs*	*Ef*
A. Diameters of zones of inhibition (DZI), mm[a]			
13	15	17	N.A.
18	25	26	N.A.
INH	17	N.T.	N.T.
Van	N.T.	15	14
DMSO	N.A.	N.A.	N.A.
B. Minimal inhibitory concentrations (MICs), μg/mL[b]			
13	16	>32	>32
18	1	4	16
INH	4	N.T.	N.T.
Van	N.T	0.5	1

Abbreviations: Ms, *Mycobacterium smegmatis* ATCC 14468; *Bs*, *Bacillus subtilis* ATCC 6633; *Ef*, *Enterococcus faecalis* ATCC 29212.

[a] The DZIs were determined by the Kirby–Bauer disk method. Solutions of 1 mg/mL for **13**, compound **18**, and INH were prepared in DMSO. Vancomycin was prepared to the same concentration in water. Ten microliters of each solution was then applied to a susceptibility disk. N.T. indicates no data was collected, N.A. indicates no activity.

[b] MICs are given in μg/mL.

bacterial reference strains. Notably, racemic 3-(4-acetyl-phenyl)-5-(1*H*-1,2,3-triazol-1-yl)methyl)-oxazolidin-2-one (**18**) was a potent inhibitor of the growth of *M. smegmatis* ATCC 14468 and possessed an MIC fourfold higher that the INH. The trends in activity were predictable based on known structure–activity relationships for the oxazolidine compound class. The 3-(4-acetylphenyl) substituent, derived from the isocyanate reagent, is same 3-substituent found in DuP-721,[4] while the higher activity of the mono-substituted (1*H*-1,2,3)-triazol fulfills the requirement for a small substituent in the 4-position of triazole-oxazolidinones.[9] More significant is the observation that the 5-(1*H*-1,2,3-triazol-1-yl)-methyl moiety was a particularly good C-5 substituent for achieving activity in a mycobacterial strain.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.07.087.

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