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Advanced Synthesis & Catalysis

Synthesis of Oxazolidinones by a Hypervalent Iodine Mediated Cyclization of *N*-Allylcarbamates

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Abstract: The preparation of oxazolidinones by the hypervalent iodine mediated cyclization of allylcarbamates is described. A versatile range of substrates can be converted into substituted oxazolidinones primed for further transformations. Derivatization of the products at both ends is demonstrated. A preliminary attempt at the enantioselective formation of an oxazolidinone using a chiral iodane is also presented.

Keywords: Iodine; Addition to alkenes; Cyclization; Hypervalent compounds; Allylic compounds; C–O bond formation

Oxazolidinone antibiotics are useful in the treatment of drug-resistant bacterial infections, especially tuberculosis which is still one of the top 10 causes of death worldwide.[1] Linezolid **1** was the first such drug to receive clinical approval and has a unique mode of action which leads to bacterial protein synthesis inhibition (Figure 1).[2] Numerous structurally related compounds are clinically approved or in clinical trials e. g. tedizolid **2**,[3] delpazolid **3**,[4] and AZD5847 **4**.[5]

A reported synthesis of linezolid **1**, and related compounds, involves formation of the oxazolidone through reaction of an aniline with an epoxide to form an aminoalcohol followed by carbonylative ring closure (Scheme 1a).[6] Such carbonylation of amino alcohols to generate oxazolidinone rings is a popular strategy with many examples and variations in the literature.[7] A closely related strategy is the cyclization of carbonylated aminoalcohols.[8] Ring expansion of epoxides or aziridines into oxazolidinones is also a common approach. For example, Toda and co-workers reported the phosphonium salt catalyzed coupling of epoxides and aryl isocyanates (Scheme 1b).[9] Aggarwal and co-workers described the Pd-catalyzed ring-opening carbonylation of 2-vinylaziridines with carbon dioxide (Scheme 1c).[10] Metal-catalyzed cyclization of allylcarbamates is also a widely utilized tactic, such as Liu and co-workers Pd-catalyzed aminohydroxylation protocol (Scheme 1d).[11]

Our experience with developing hypervalent iodine mediated cyclizations prompted us to develop a new approach to oxazolidinones that complements existing methods.[12] Cyclization of *N*-allylcarbamates, mediated by a hypervalent iodine reagent, was envisaged as a useful addition to the synthetic canon (Scheme 1e).

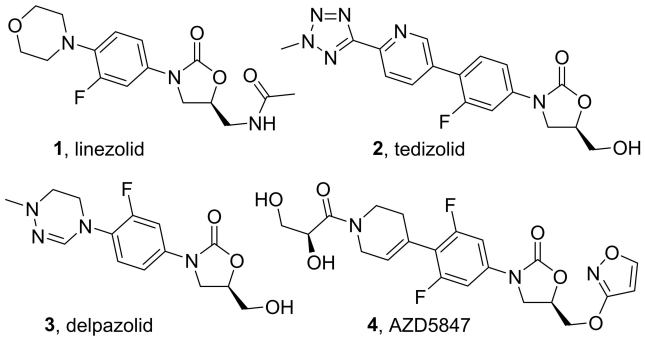
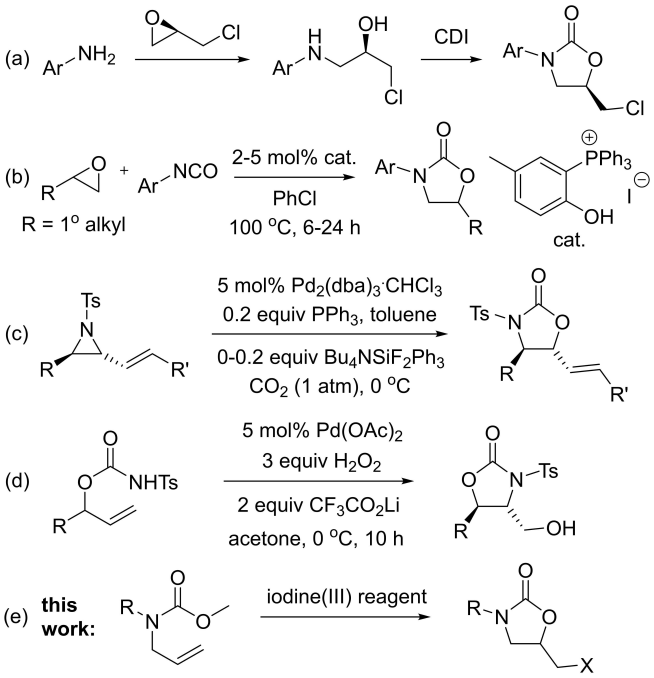


Figure 1. Examples of oxazolidinone derivatives displaying antibiotic and antimicrobial activities.

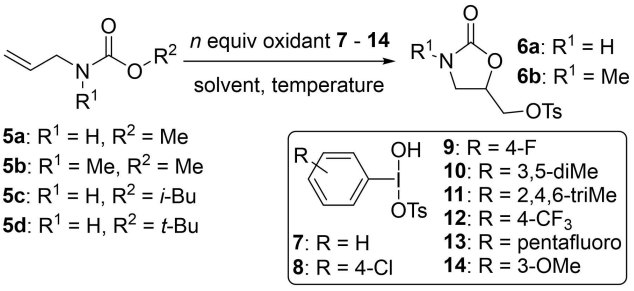


Scheme 1. Strategies for oxazolidinone formation. CDI is carbonyl diimidazole.

Notably, Minakata and co-workers reported a related cyclization employing *t*-butyl hypoiodite with allyl amines and CO_2.[13] The popularity of using hypervalent iodine in synthesis has soared in recent years because of the ease of use, the low cost and toxicity as well as the plethora of useful reactivity that has been uncovered.[14] Cariou and co-workers have reported the cyclization of *N*-allylguanidines using Koser's reagent **7**,[15] and the cyclization of unsaturated *N*-alkoxyureas with iodine(III) reagents.[16] Lovick and Michael demonstrated the cyclization of unsaturated sulfonamides employing iodine(III) reagents.[17] Wang and co-workers reported the cyclization of unsaturated oximes with Koser's reagent **7** but an iron(II) catalyst was required for efficient conversion.[18]

We initiated our investigation by attempting to cyclize methyl allylcarbamates **5a** by treatment with 3 equiv. of Koser's reagent **7** in MeCN at 80 °C (Table 1, entry 1). Pleasingly, the desired transformation took place, but in modest yield. Methylation of the carbamate nitrogen provided a new substrate **5b** which was subjected to the same conditions for cyclization and a superior yield of oxazolidinone was observed (entry 2). Lowering the temperature for the cyclization to 50 °C led to a slight decrease in yield (entry 3). Changing solvent to DCE led to a similar result (entry 4) whereas MeOH provided a complex mixture of compounds (entry 5). Using trifluoroethanol as solvent, led to a jump in yield to 48% (entry 6) and hexafluoroisopropanol (HFIP) resulted in a yield of 59% (entry 7). Increasing the number of equivalents of

Table 1. Optimization of carbamate cyclization.



Entry	5	[O]	*n*	Solvent	T/°C	Yield/%[a]
1	**5a**	**7**	3	MeCN	80	15 (**6a**)
2	**5b**	**7**	3	MeCN	80	36 (**6b**)
3	**5b**	**7**	3	MeCN	50	33 (**6b**)
4	**5b**	**7**	3	DCE	50	31 (**6b**)
5	**5b**	**7**	3	MeOH	50	Mixture
6	**5b**	**7**	3	TFE	50	48 (**6b**)
7	**5b**	**7**	3	HFIP	50	59 (**6b**)
8	**5b**	**7**	5	HFIP	50	67 (**6b**)
9	**5b**	**7**	2	HFIP	50	41 (**6b**)
10	**5a**	**7**	5	HFIP	50	22 (**6a**)
11	**5c**	**7**	5	HFIP	50	33 (**6a**)
12	**5d**	**7**	3	HFIP	50	76 (**6a**)
13	**5d**	**8**	3	HFIP	50	69 (**6a**)
14	**5d**	**9**	3	HFIP	50	66 (**6a**)
15	**5d**	**10**	3	HFIP	50	95 (**6a**)
16	**5d**	**10**	2	HFIP	50	90 (**6a**)
17	**5d**	**10**	1.2	HFIP	50	65 (**6a**)
18	**5d**	**11**	3	HFIP	50	Trace
19	**5d**	**12**	3	HFIP	50	67 (**6a**)
20	**5d**	**13**	3	HFIP	50	50 (**6a**)
21	**5d**	**14**	3	HFIP	50	53 (**6a**)

[a] Isolated yields are reported using ~0.5 mmol of **5**.

Koser's reagent to 5, led to an increased yield of 68% (entry 8) whereas using just 2 equiv. gave an inferior 41% (entry 9). We then turned our attention back to the original substrate (where $R^1 = H$), and subjected it to the modified reaction conditions, but only a low yield was returned (entry 10). Modifying the carbamate oxygen group led to a striking change in yield, with *i*-butyl **5c** performing somewhat better (entry 11) than the methyl **5b** but the *t*-butyl version **5d** was significantly better with 76% yield being obtained with 3 equiv. of Koser's reagent (entry 12). We also modified the Koser's reagent structure and investigated the impact on the yield of oxazolidinone formation. Studying the best performing *t*-butyl substrate variant **5d**, installing a chloro or fluoro substituent at the 4-position of the Koser's reagent aromatic ring led to a slight drop in cyclization yield in both cases (entries 13 and 14). Using the Koser's reagent **10** prepared from 5-iodo-*m*-xylene led to a jump in yield of cyclization to 95% (entry 15). Reducing the amount of modified Koser's reagent to 2 equiv. led to a slight drop in yield

(entry 16) whereas using 1.2 equiv. resulted in 65% yield (entry 17). The Koser's reagent **11** derived from 2-iodomesitylene proved ineffective at mediating cyclization (entry 18). Koser's reagents **12**, **13** and **14** derived from 1-iodo-4-(trifluoromethyl)benzene, iodopentafluorobenzene and 3-iodoanisole led to moderate yields of oxazolidinone (entries 19–21).

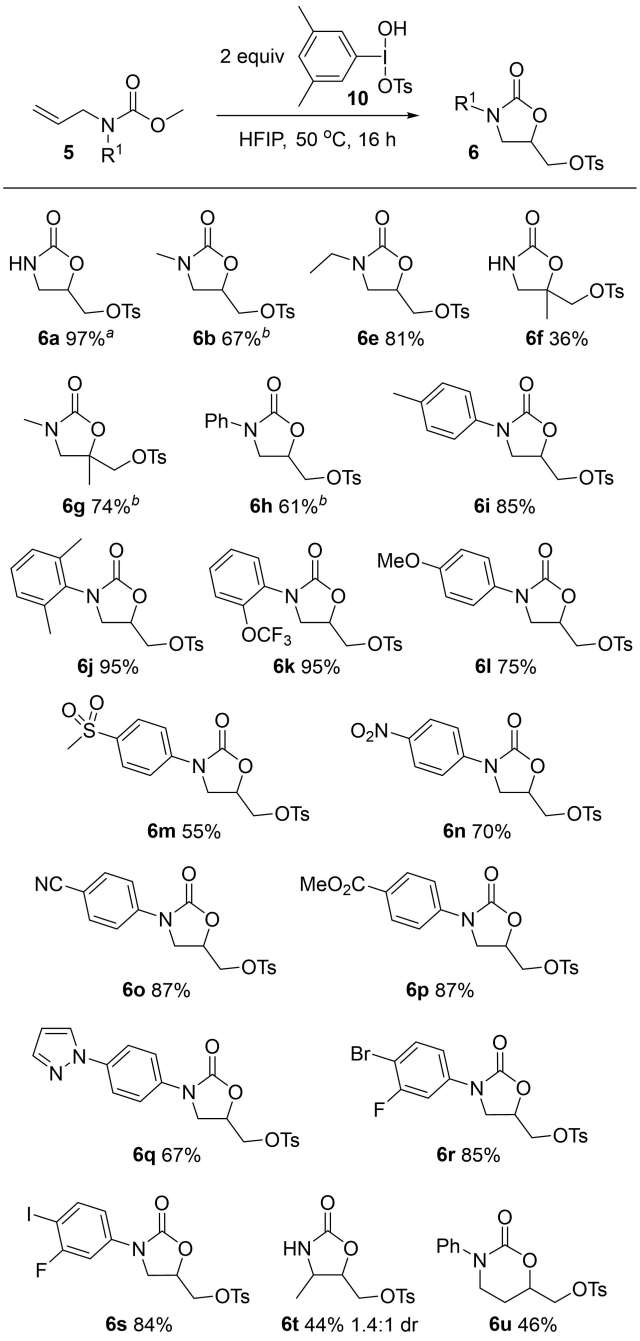
It was decided that using three equivalents of oxidant was undesirable for the modest increase in yield obtained over using two equivalents, therefore the optimized reaction conditions were taken to be 2 equivalents of 5-iodo-*m*-xylene derived Koser's reagent **10** in HFIP at 50 °C. Subsequently, the scope of the cyclization reaction was explored (Scheme 2). The nitrogen substituent was changed from hydrogen to alkyl and to aryl and all examples were successfully cyclized. The methyl carbamate, rather than the *t*-butyl carbamate in **5d**, was used in all cases with little to no drop in yields being observed. Aryl substrates containing electron-withdrawing or electron-donating groups such as a nitro, an ester, a nitrile, a methoxy, a trifluoromethoxy and alkyls were investigated. Potentially oxidizable substrates such as **5q** and **5s** containing a pyrazole and an iodoaryl group respectively were successfully cyclized. Further substitution on the oxazolidinone ring was also found to be possible with **6t** formed in moderate yield, but with low selectivity. Six-membered ring **6u** was prepared in a similar manner from the homoallyl carbamate.

In order to demonstrate the utility of these compounds, a couple of derivatizations were effected (Scheme 3). Treatment of **6r** with morpholine led to smooth S_N2 displacement of the tosylate to give **15** in 94% yield. Suzuki coupling of **6s** with a pyridine derivative, under unoptimized conditions,[8a] generated the tosylated analog of tedizolid **16** in moderate yield.

The mechanism of this cyclization process is proposed to proceed through activation of the alkene by the modified Koser's reagent, which induces cyclization by attack of the carbonyl oxygen (Scheme 4).[19] Removal of the methyl by the solvent, or an adventitious tosylate, generates iodonium **17** which undergoes S_N2 displacement by tosylate to furnish the final product. It is envisaged that the acidic solvent HFIP aids this process.

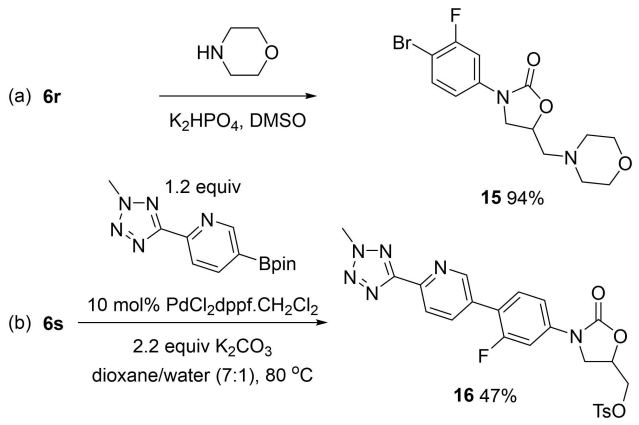
Next, we turned our attention to the use of chiral λ^3-iodanes in order to effect this transformation in an enantioselective fashion. We needed to prepare chiral derivatives of Koser's reagent; however, most chiral iodanes reported are diacetates.[13] After some experimentation, we were able to prepare the iodane **18** from the known diacetoxyiodoarene and we added it to a solution of carbamate **5b** (Scheme 5). Pleasingly, the oxazolidinone **6b** was isolated in an encouraging 62% ee.

In conclusion, a hypervalent iodine mediated approach to oxazolidinone formation has been presented. It was discovered that a modified version of Koser's reagent was necessary in order to obtain high yields in most cyclisation reactions and that the products can be readily derivatized. Preliminary work

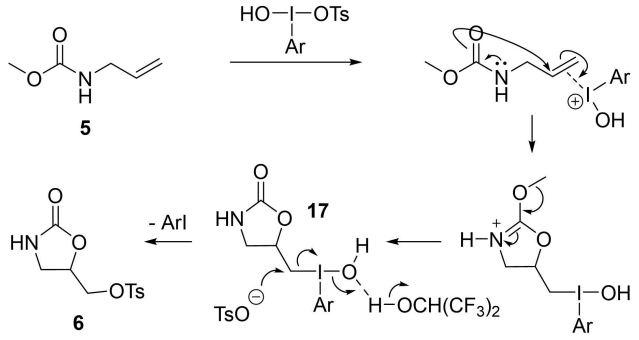


[a] Reaction performed on 1.0 mmol scale using *t*-Bu carbamate starting material **5d**.
[b] Using 5 equiv. **7** rather than **10**.

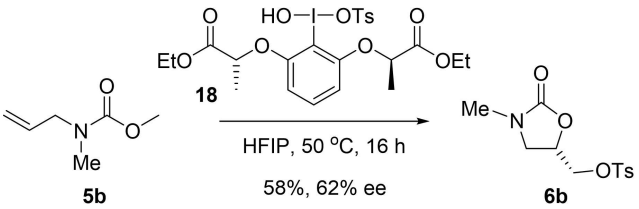
Scheme 2. Scope of cyclization. Isolated yields are reported typically using between 0.2 and 0.6 mmol of **6**.



Scheme 3. Derivatization of oxazolidinones. dppf is 1,1′-bis (diphenylphosphino)ferrocene.



Scheme 4. Postulated cyclization mechanism.



Scheme 5. Asymmetric cyclization with chiral iodane **18**.

has revealed that enantioselective cyclization is possible with a chiral iodane.

Experimental Section

Representative procedure for cyclization: *tert*-butyl allyl carbamate **5d** (0.16 g, 1.0 mmol, 1 equiv) and (3,5-dimethylphenyl)(hydroxy)-λ^3-iodaneyl 4-methylbenzenesulfonate **10** (1.26 g, 3.0 mmol, 3 equiv) were dissolved in HFIP (10 mL). The mixture was heated at 50 °C for 16 hours, then cooled and concentrated under vacuum. The residue was diluted with ethyl acetate (10 mL) and passed through a 2 cm plug of silica gel. The crude product was purified by flash chromatography (silica gel; 3:7 petroleum ether/EtOAc) and **6a** was isolated as a white solid (0.26 g, 97%). HFIP is 1,1,1,3,3,3-hexafluoroisopropanol.

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