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Synthesis of Oxazolidin-2-ones and Imidazolidin-2-ones Directly from 1,3-Diols or 3-Amino Alcohols using Iodobenzene Dichloride and Sodium Azide

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Abstract: A general and efficient method for the synthesis of oxazolidin-2-ones and imidazolidin-2-ones directly from 1,3-diols and 3-amino alcohols has been developed using the same reagent combination of iodobenzene dichloride ($PhICl_2$) and sodium azide (NaN_3).

Keywords: imidazolidin-2-ones; iodobenzene dichloride; oxazolidin-2-ones; sodium azide

Oxazolidin-2-one and imidazolidin-2-one motifs are common structural units in many natural products,[1] pharmaceuticals,[2] and biologically active compounds,[3] as exemplified by (−)-agelastatin A,[1a] linezolid,[2b] and KVI-020[3a] (Figure 1). Oxazolidin-2-ones and imidazolidin-2-ones can also serve as chiral auxiliaries in a number of asymmetric reactions;[4] in particular, Evans auxiliaries, bearing oxazolidin-2-one moiety, are extensively applied in asymmetric alkylation,[5] aldol reaction,[6] Diels–Alder reaction,[7] and asymmetric fluorination reaction.[8] Furthermore, oxazolidin-2-ones and imidazolidin-2-ones can be employed as synthetic intermediates for the preparation of 2-amino alcohols and 1,2-diamines.[9] Accordingly, various synthetic methods have been developed for their syntheses.[10] Conventionally, oxazolidin-2-ones and imidazolidin-2-ones are prepared respectively from 2-amino alcohols and 1,2-diamines with carbonyl source compounds such as phosgene,[11] phosgene derivatives,[12] carbon monoxide,[13] and carbon dioxide.[14] However, phosgene and carbon monoxide are highly toxic compounds and they are difficult to handle in the laboratory; using carbon dioxide as the carbonyl source always requires harsh reaction conditions, i.e., high temperature and/or high pressure. Alternative synthetic routes with aziridines,[15] epoxides,[16] and olefins[17] as the starting materials have also been developed. Although the above mentioned methods focus on the intermolecular reactions to afford oxazolidin-2-ones and imidazolidin-2-ones, the *intramolecular* cyclization approaches to synthesize these two heterocyclic compounds have also been developed, including palladium(II)-catalyzed diamination of alkenes to synthesize imidazolidin-2-ones,[18] transition metal-catalyzed amidation of saturated C–H bonds for the conversion of *O*-alkyl carbamates to oxazolidin-2-ones,[19] the Hofmann rearrangement of 3-hydroxy or 3-amino amides,[20a,b] and Curtius rearrangement of β-functionalized carboxylic acids promoted by polymer-supported diphenylphosphoryl azide (PS-DPPA).[20c] Among the metal-free strategies,[20] the methods involving Hofmann rearrangement had a narrow substrate scope and offered only one type of heterocycle; although the Curtius rearrangement of β-functionalized carboxylic acids could

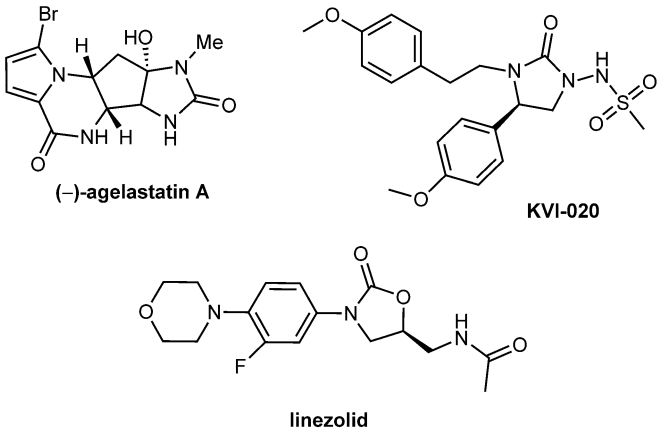


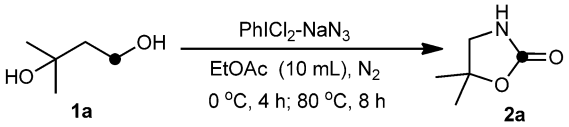
Figure 1. Selected molecules bearing oxazolidin-2-one and imidazolidin-2-one moieties.

realize the synthesis of both oxazolidin-2-ones and imidazolidin-2-ones, the multistep synthesis of PS-DPPA has limited its synthetic application.[20e] Moreover, it seems inevitable that all these intramolecular methods need the carbonyl group to be embedded in the starting materials. Therefore, it is still highly desirable to explore a general intramolecular route to synthesize oxazolidin-2-ones and imidazolidin-2-ones from the low oxidation state functionality such as a hydroxy group *via* facile oxidative manipulation using readily available oxidants.

In our previous work, it has been reported that the combined reagent system of $PhICl_2$-NaN_3 could be used for the efficient transformation of primary alcohols to the corresponding carbamoyl azides in CH_3CN;[21] subsequently, the same reagent combination has also been applied to the synthesis of substituted ureas directly from primary alcohols and amines *via* the key intermediate carbamoyl azides in EtOAc.[22] Herein, as part of our continuing research on new synthetic applications of the $PhICl_2$-NaN_3 system, we disclose a novel and *general* intramolecular method for the synthesis of oxazolidin-2-ones and imidazolidin-2-ones *via* oxidation of 1,3-diols and 3-amino alcohols, respectively. To the best of our knowledge, as an intramolecular cyclzation protocol, this is the first example to synthesize oxazolidin-2-ones and imidazolidin-2-ones from the low oxidation state substrates without embedded carbonyl groups.

The initial study was carried out with 3-methylbutane-1,3-diol (**1a**) as the model substrate under the standard conditions (5 equiv. $PhICl_2$/10 equiv. NaN_3) for the effective transformation of primary alcohols to carbamoyl azides in ethyl acetate, which were the key intermediates for the synthesis of substituted ureas in our previous work.[22] Pleasingly, 5,5-dimethyloxazolidin-2-one (**2a**) was obtained in 86% yield (Table 1, entry 1). Reducing the amount of NaN_3 alone resulted in a dramatically decreased yield of **2a** (entry 2). When the amounts of $PhICl_2$ and NaN_3 were reduced proportionally, the yield of **2a** was however slightly increased to 89% (entry 3). Further reducing the amount of $PhICl_2$ and NaN_3 resulted in a decreased yield of **2a** (entry 4). Consequently, the optimized reaction system for the efficient synthesis of oxazolidin-2-one **2a** from 1,3-diol **1a** was composed of 4.0 equivalents of $PhICl_2$, 8.0 equivalents of NaN_3, and ethyl acetate as the solvent, with stage-wise reaction temperature modulation.

Table 1. Optimization of reagent amount in the synthesis of oxazolidin-2-one **2a**.[a]



1a 2a

Entry	$PhICl_2$ (equiv.)	NaN_3 (equiv.)	Yield [%][b]
1	5.0	10.0	86
2	5.0	5.0	51
3	4.0	8.0	89
4	3.0	6.0	78

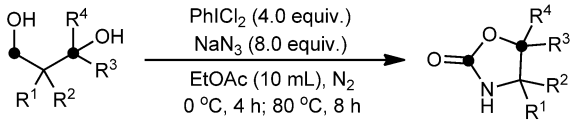
[a] The reactions were carried out using 1 mmol of **1a**.
[b] Isolated yield.

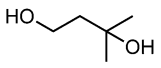
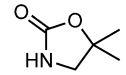
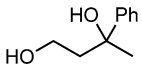
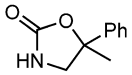
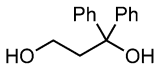
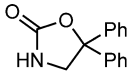
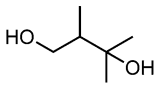
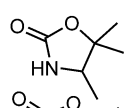
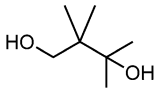
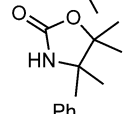
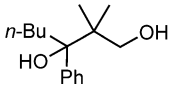
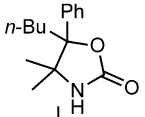
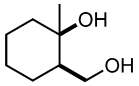
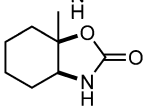
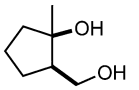
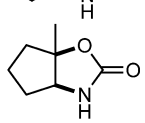
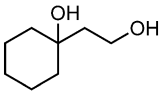
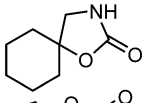
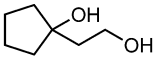
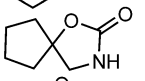
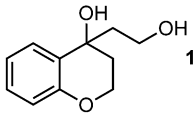
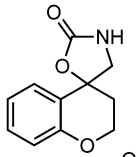
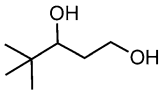
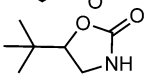
To test the generality and scope of this method, a series of 1,3-diols was subjected to the optimal reaction conditions and the results are summarized in Table 2. 3-Phenylbutane-1,3-diol (**1b**) and 1,1-diphenylpropane-1,3-diol (**1c**), both bearing the phenyl ring, were smoothly converted into **2b** and **2c** in 83% and 74% yields, respectively (Table 2, entries 2 and 3). It was worth noting that **2a** and **2c** have been used for the preparation of *N*-phosphoryloxazolidin-2-ones, which were effective phosphorylating agents for a variety of alcohols.[23]

For 1,3-diols having alkyl and phenyl substituents, such as **1d**, **1e**, and **1f**, the reaction also worked well, affording **2d**, **2e**, and **2f** in good to excellent yield (entries 4–6). For the substrates like **1g** and **1h**, whose tertiary hydroxy group and the hydroxymethyl group were joined to the vicinal carbon on the cyclic ring, the desired fused-oxazolidin-2-one **2g** and **2h** were obtained in good yield (entries 7 and 8). As for the substrates whose tertiary hydroxy group and hydroxyethyl group were attached at the same ring carbon, such as **1i**, **1j**, and **1k**, the corresponding spiro-oxazolidin-2-ones **2i–k** were produced in 83%, 78%, and 72% yields, respectively (entries 9–11). After the successful construction of oxazolidin-2-ones from 1,3-diols with a tertiary hydroxy group, 4,4-dimethylpentane-1,3-diol (**1l**) containing a secondary hydroxy group adjacent to a bulky *t*-Bu group was tested under the optimal reaction conditions, however, the desired 5-*tert*-butyloxazolidin-2-one (**2l**) was produced only in 10% yield, and the major product was 1-hydroxy-4,4-dimethylpentan-3-one due to the preferential oxidation of secondary alcohols over primary ones using the reagent combination of $PhICl_2$-NaN_3 (entry 12).[21]

After the successful construction of oxazolidin-2-ones from 1,3-diols, we surmised that imidazolidin-2-ones could also be obtained following the same strategy if we changed the nucleophilic functionality embedded in the substrate from a hydroxy group to an amino group. Therefore, we tested this hypothesis using $PhICl_2$ (4.0 equiv.) and NaN_3 (8.0 equiv.) with *N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (**3a**) as the model substrate, as expected, 1-tosylimidazolidin-2-one (**4a**) was formed in 63% yield (Table 3, entry 1). Results of the screening study of the amount of employed reagents indicated that 5.0 equivalents of $PhICl_2$ and 10.0 equivalents of NaN_3 were best for this transformation (entries 2 and 3). Next, several other commonly used *N*-protecting groups, such as 4-

Table 2. Intramolecular cyclization of 1,3-diols to oxazolidin-2-ones with the $PhICl_2$-NaN_3 system.[a]

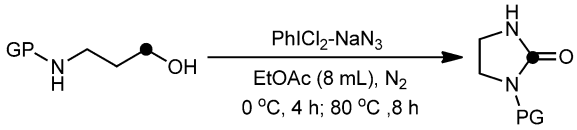


Entry	Substrate		Product		Yield [%][b]
1		**1a**		**2a**	89
2[c]		**1b**		**2b**	83 (93)[d]
3[c]		**1c**		**2c**	74 (87)[d]
4		**1d**		**2d**	86
5		**1e**		**2e**	81
6[c]		**1f**		**2f**	70 (79)[d]
7		**1g**		**2g**	82
8		**1h**		**2h**	78
9		**1i**		**2i**	83
10		**1j**		**2j**	78
11[c]		**1k**		**2k**	72 (77)[d]
12[e]		**1l**		**2l**	10

[a] The reaction was run with 1 mmol of 1,3-diol compounds.
[b] Isolated yield.
[c] 5.0 equivalents of $PhICl_2$ and 10.0 equivalents of NaN_3 were used.
[d] The data in the parentheses are the chemical yields based on the recovered 1,3-diol.
[e] 45% of 1-hydroxy-4,4-dimethylpentan-3-one was obtained.

nitrobenzenesulfonyl (*p*-Ns), methanesulfonyl (Ms), acetyl (Ac), *tert*-butoxycarbonyl (Boc), and trifluoroacetyl (CF_3CO) were also checked, however, none of them showed a superior result compared with the *para*-toluenesulfonyl (Ts) group (entries 4–8 *vs.* entry 2). When the *N*-protecting group was an acetyl group, a complex reaction mixture was obtained and no hetero-annulation product was detected. As for *N*-Boc and *N*-CF_3CO protected 3-amino alcohols, no desired imidazolidin-2-ones were detected, and the main products were *tert*-butyl 2-(azidocarbonylamino)ethylcarbamate and [2-(2,2,2-trifluoroacetamido)ethyl]carbamoyl azide, respectively, which were produced *via* the addition of hydrazoic acid generated *in situ* to the corresponding isocyanates formed from the conversion of the primary alcohol functionality of 3-amino alcohols.[22]

Table 3. Optimization of reagent amount and the screening of *N*-protecting groups in the synthesis of imidazolidin-2-ones.[a]

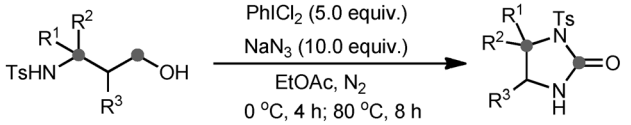


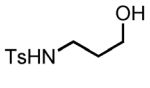
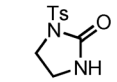
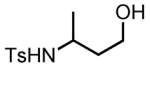
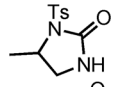
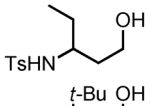
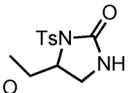
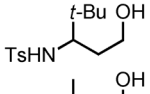
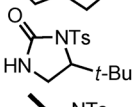
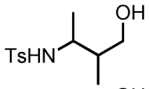
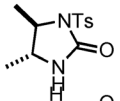
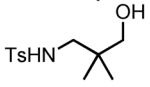
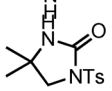
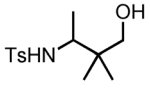
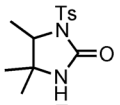
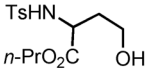
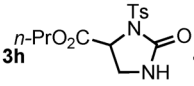
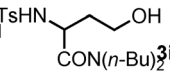
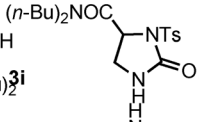
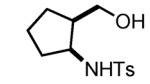
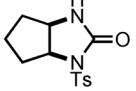
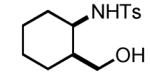
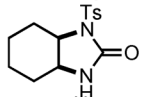
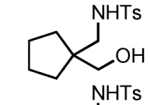
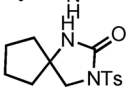
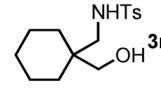
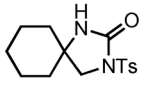
Entry	PG	$PhICl_2$ (equiv.)	NaN_3 (equiv.)	Yield [%][b]
1	Ts	4.0	8.0	63
2	Ts	5.0	10.0	76
3	Ts	6.0	12.0	75
4	*p*-Ns	5.0	10.0	73
5	Ms	5.0	10.0	31
6	Ac	5.0	10.0	0
7[c]	Boc	5.0	10.0	0
8[d]	CF_3CO	5.0	10.0	0

[a] The reactions were run with 0.5 mmol of substrates.
[b] Isolated yield.
[c] *tert*-Butyl 2-(azidocarbonylamino)ethylcarbamate was obtained in 42% yield.
[d] [2-(2,2,2-Trifluoroacetamido)ethyl]carbamoyl azide was obtained in 79% yield.

With the optimized reaction conditions in hand, a series of *N*-Ts protected 3-amino alcohols was tested and the results are summarized in Table 4. For substrates bearing alkyl substituents such as methyl, ethyl, and *tert*-butyl groups, the reaction also worked as well as with **3a**, affording the desired imidazolidin-2-ones especially for multi-substituted ones in good to excellent yields (Table 4, entries 1–7). It should be noticed that there was no deleterious influence on the imidazolidin-2-one yield even though a bulky group like *tert*-butyl group was close to the tosylamido group (entry 4 *vs.* entry 1). Two substrates bearing ester and amide functional groups were well tolerated under the present reaction conditions as indicated by the successful transformation of **3h** and **3i** to the products **4h** and **4i** (entries 8 and 9). As for the substrates whose tosylamido group and the hydroxymethyl group were joined to the vicinal carbon on the ring,

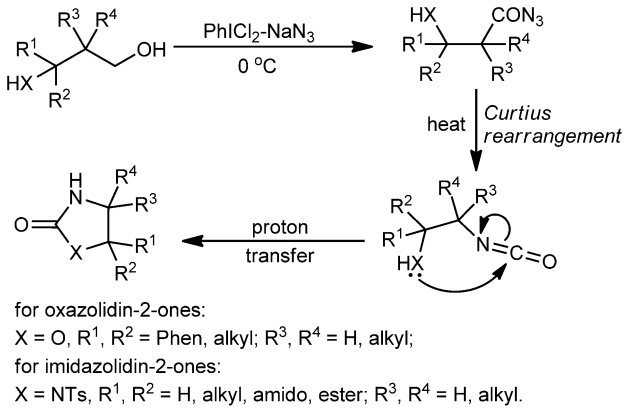
Table 4. Intramolecular cyclization of 3-amino alcohols to imidazolidin-2-ones with the $PhICl_2$-NaN_3 system.[a]



Entry	Substrate	Product	Conv. [%]	Yield [%][b]
1	 **3a**	 **4a**	92	76
2	 **3b**	 **4b**	87	82
3	 **3c**	 **4c**	88	80
4	 **3d**	 **4d**	95	90
5	 **3e**	 **4e**	89	82
6	 **3f**	 **4f**	84	70
7	 **3g**	 **4g**	84	79
8[c]	 **3h**	 **4h**	63	60
9[d]	 **3i**	 **4i**	69	50
10	 **3j**	 **4j**	95	79
11	 **3k**	 **4k**	76	66
12	 **3l**	 **4l**	83	78
13	 **3m**	 **4m**	79	71

[a] The reactions were run with 0.5 mmol of substrates.
[b] Isolated yield.
[c] The reaction was run on a 0.15 mmol scale.
[d] The reaction was run on a 0.1 mmol scale.

their corresponding fused imidazolidin-2-ones **4j** and **4k** were produced in good yields (entries 10 and 11). When the substrates whose tosylamido group and hydroxymethyl group were attached at the same carbon on the ring were tested, the reactions also worked well, yielding the desired spiro-imidazolidin-2-one **4l** and **4m** in, respectively, 78% and 71% yields (entries 12 and 13).



Scheme 1. Proposed mechanism.

On the basis of our previous works disclosing that primary alcohols can be converted into the corresponding carbamoyl azides *via* multiple steps including alcohols→aldehydes→acyl azides→isocyanates→carbamoyl azides,[21,22] a step-wise mechanism for the transformation of 1,3-diols and *N*-Ts protected 3-amino alcohols to oxazolidin-2-ones and imidazolidin-2-ones was proposed (Scheme 1). The primary alcohol of the starting 1,3-diols or *N*-Ts protected 3-amino alcohols was transformed into the corresponding isocyanate functionality *via* the same pathway as the above mentioned, then an intramolecular cyclization reaction occurred due to the inherent nucleophilic property of the hydroxyl- and tosyl-protected amino groups to generate the product oxazolidin-2-ones and imidazolidin-2-ones, respectively.[24]

In summary, we have presented here a general, metal-free, and efficient method for the facile access to oxazolidin-2-ones and imidazolidin-2-ones directly from 1,3-diols and 3-amino alcohols with the combined reagent $PhICl_2$-NaN_3. The ready availability of $PhICl_2$[25] which was quickly and quantitatively prepared from iodobenzene using bleach in acidic aqueous media and low-cost nitrogen source compound NaN_3, the simple work-up, and the broad substrate generality make the present protocol an attractive way to synthesize oxazolidin-2-ones and imidazolidin-2-ones.

Experimental Section

Caution! Although no explosion occurred in our laboratory during our investigation of the applications of the combined reagent system of $PhICl_2$-NaN_3, azido compounds are hazardous and may explode when heated. A safety shield, gloves, and eye protection are highly recommended.

Typical Procedure for the Synthesis of Oxazolidin-2-ones

To a solution of **1a** (104 mg, 1 mmol) in EtOAc (10 mL) were added $PhICl_2$ (1.1 g, 4 mmol) and NaN_3 (520 mg, 8 mmol) under an N_2 atmosphere at 0 °C, and the reaction mixture was stirred at 0 °C for 4 h. Subsequently, the reaction mixture was heated to 80 °C for 8 h. Then, the reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL). The resulting mixture was quenched with saturated $Na_2S_2O_3$ (15 mL) and extracted with EtOAc (2× 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product. Pure **2a** was obtained in 89% yield after the flash column chromatography.

Typical Procedure for the Synthesis of imidazolidin-2-ones

To a solution of **3a** (115 mg, 0.5 mmol) in EtOAc (8 mL) were added $PhICl_2$ (688 mg, 2.5 mmol) and NaN_3 (325 mg, 5 mmol) under an N_2 atmosphere at 0 °C, and the reaction mixture was stirred at 0 °C for 4 h. Subsequently, the reaction mixture was heated to 80 °C for 8 h. Then, the reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL). The resulting mixture was quenched with saturated $Na_2S_2O_3$ (15 mL), and extracted with EtOAc (2× 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Pure **4a** was obtained in 76% yield after the flash column chromatography.

Acknowledgements

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