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Ethyl Imidazole-1-carboxylate (EImC) as a Carbonylating Agent: Efficient Synthesis of Oxazolidin-2-ones from Amino Alcohols

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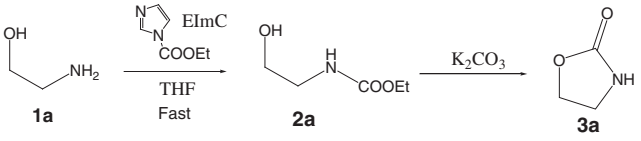
Various substituted oxazolidin-2-ones were synthesized from the corresponding amino alcohols using ethyl imidazole-1-carboxylate (EImC). Highly substituted and sterically hindered amino alcohols and amino alcohols having a free hydroxy group were cyclized to oxazolidin-2-ones efficiently. This method is simple and produces oxazolidin-2-ones in very good yield.

Oxazolidinones are a very important class of heterocycles, which has many pharmaceutical and synthetic uses. Oxazolidinones are synthetic molecules and different oxazolidinone derivatives have been exhibited as antimicrobial and antitubercular agents.[1] Linezolid, an oxazolidinone ring containing drug is approved for the treatment of Gram positive bacterial infections in humans.[2] Oxazolidinone derivatives have been studied in the areas of fine chemicals, pesticides, and herbicides and in many other applications.[3] Besides their biological importance, oxazolidinones are also very useful in synthetic organic chemistry as chiral auxiliaries[4] and in the synthesis of oxazolines,[5] and also oxazolidinones are useful synthetic intermediates in the synthesis of aminocyclitol.[6]

There are many reported methods to synthesize 2-oxazolidinones such as epoxide ring opening with cyanates,[7] reaction of β-halo alcohols with cyanates,[8] oxidation of oxazolidin-2-thiones to oxazolidin-2-ones,[9] and carbonylation of β-amino alcohols. Among these, carbonylation of β-amino alcohols using different carbonylating reagents is the most widely used method to synthesize oxazolidin-2-ones. Triphosgene,[10] phosgene,[11] and, diphosgene[12] are most commonly used for this cyclization, but these reagents are hazardous and require careful and safe handling. Carbon monoxide[13] and carbon dioxide[14] are also used as carbonylation agents, but these methods suffer by using poisonous carbon monoxide and sensitive palladium catalysts and also difficulties in removing the by-products of triphenylphosphine and azodicarboxylates. Two-step processes of synthesizing oxazolidin-2-ones from amino alcohols using chloroformates[15] and di-*t*-butyl oxycarbonate[16] have also been reported. Dimethyl carbonate[17] and dimethyl thiocarbonates[18] are also used in the synthesis of oxazolidinones, but these methods suffer by using strong base and the release of dangerous dimethyl sulfide gas during the reaction. Imidazole derivative, 1,1′-carbonyldiimidazole[19] (CDI) is also widely used for this transformation, but this reagent is moisture sensitive and decomposes quickly. By considering the above drawbacks and difficulties, there is a need to develop a new and easy method to synthesize these biologically and synthetically important oxazolidin-2-ones starting from amino alcohols.

Acylimidazoles and imidazole carboxylates are very active synthetic intermediates in organic synthesis. Carbonylimidazoles are industrially useful because of their relative stability to carbonyl compounds.[20] Recently we, as well as Sarpong, have explored the use of imidazole carboxylates in the synthesis of α-arylmalonic acid ethyl esters and esters and amides from acids.[21] Very recently Sarpong et al. reported the use of pyridinium salts of imidazole carboxylates in the synthesis of oxazolidin-2-ones.[22] Herein, we wish to report the simple and efficient synthesis of oxazolidin-2-ones from amino alcohols using ethyl imidazole-1-carboxylate (EImC). To test our hypothesis initially, we tried a reaction of ethanolamine (**1a**) with EImC at room temperature without any solvent and starting material remained as such (Scheme 1). When the above reaction mixture was heated to 80 °C, it produced intermediate **2a** as single product. But the intermediate **2a** did not result in the cyclized oxazolidin-2-one (**3a**) even after heating to 140 °C for 16 h (Entry 1, Table 1). Reactions in THF at 80 °C in the presence of triethylamine (TEA) and *N*,*N*-diisopropylethylamine (DIPEA)



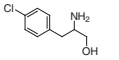
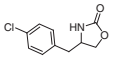
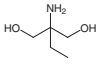
Scheme 1. Synthesis of oxazolidin-2-one (**3a**).[24]

Table 1. Optimization of reaction using different bases and solvents (synthesis **3a**)

Entry	Base	Temp/°C	Time/h	**2a**[a]	**3a**[a]
1	—	40	24	0	0
2	TEA	80	24	90[b]	0
3	DIPEA	75	24	82[b]	0
4	K_2CO_3	RT	48	0	0
5	K_2CO_3	80	15	0	92[b]
6	Cs_2CO_3	80	18	0	71[b]
7	NaH	RT	24	87[b]	0
8	NaH	70	15	0	55[b]
9	2 M NaOH	70	12	0	0
10	K_2CO_3	80	24	0	87[c]
11	K_2CO_3	80	24	0	69[d]
12	K_2CO_3	75	24	—	64[e]

[a]Isolated yield. [b]THF was used as a solvent. [c]DMF was used as solvent. [d]Acetonitrile was used as solvent. [e]Toluene was used as solvent.

Table 2. Synthesis of oxazolidin-2-ones from amino alcohols[23,24]

Entry	Substrate		Product		Yield[a]/%
1		**1a**		**3a**	89
2		**1b**		**3b**	89
3		**1c**		**3c**	89
4		**1d**		**3d**	88
5		**1e**		**3e**	98
6		**1f**		**3f**	95
7		**1g**		**3g**	89
8		**1h**		**3h**	96
9		**1i**		**3i**	78[b]
10		**1j**		**3j**	88
11		**1k**		**3k**	90
12		**1l**		**3l**	90
13		**1m**		**3m**	87
14		**1n**		**3n**	92[b]
15		**1o**		**3o**	78

[a]Isolated yield. [b]Corresponding intermediates (ethyl carbamates) yield.

produced similar results. Reaction of **1a** with EImC in THF at 80 °C, in the presence of K_2CO_3 gave the required oxazolidin-2-one in very good yield (Entry 5).

We carried out a number of reactions to optimize the reaction conditions using different solvents and bases, the results are summarized in Table 1. Among the bases screened K_2CO_3 and Cs_2CO_3 both gave very good results. Organic bases such as TEA and DIPEA produced only the intermediate **2a** and did not go for further cyclization even after refluxing in THF for longer time. Reaction with NaH at RT gave only the intermediate and produced 55% desired compound after heating the reaction mixture to 70 °C for 15 h. Reaction of **1a** with EImC even using aq. 2 M NaOH in THF, did not produce the intermediate **2a**. **1a** was completely unreacted and EImC disappeared by TLC (maybe EImC was hydrolyzed in this condition). After fixing a suitable base, the reaction was repeated using different solvents (Entries 10–12, Table 1). Among the solvents, acetonitrile and toluene gave moderate to good yields. Both DMF and THF were found to be equally good for this transformation.

To test the generality of this method, we carried out a number of reactions with different amino alcohols and the results are summarized in Table 2. Almost all the substrates reacted smoothly and produced oxazolidin-2-ones in good yield. Sterically hindered substrate (Table 2, Entry 9) and sterically fixed substrate (Table 2, Entry 14) did not undergo the reaction completely and stopped in the intermediate stage only. Substrates having two hydroxy groups were also well tolerated without producing any by-product. In many cases, crude compounds were pure enough and the by-product imidazole was easily removed by simple aqueous workup.

In summary, we have developed an efficient and simple method for the synthesis of oxazolidin-2-ones from amino alcohols. This method produces different and highly substituted oxazolidin-2-ones in very good yield.

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23 General procedure for the oxazolidin-2-ones synthesis: The mixture of amino alcohol (16.3 mmol), ethyl imidazole-1-carboxylate (24.5 mmol), K_2CO_3 (48.9 mmol) in THF (15 mL) was refluxed for 15 h. Reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4. Purification of the crude by column chromatography on silica gel (30% of ethyl acetate in pet ether) afforded the pure product.

24 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

