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Study on the tandem synthesis of optically active 2-substituted 4 (or 5)-phenyl-1,3-oxazolines

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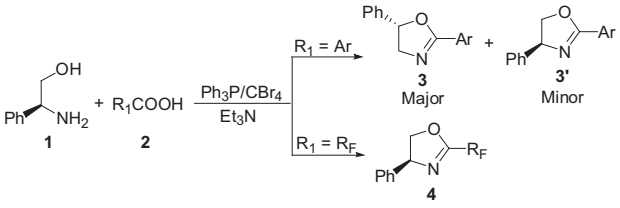
ABSTRACT

Optically active (*S*)-2-aryl-4 (or 5)-phenyl-1,3-oxazolines and (*S*)-2-fluoroalkyl-4-phenyl-1,3-oxazolines were synthesized from a tandem one-pot reaction of (*S*)-2-amino-2-phenylethanol with a corresponding carboxylic acid in toluene at 90 °C in the presence of PPh_3/CBr_4 and excess Et_3N. The use of aromatic carboxylic acids were determined to proceed through *N*-(2-bromo-1-phenyl-ethyl)-arylamides **5** and *N*-aroyl aziridine intermediates **6**, which resulted in the formation of (*S*)-2-aryl-4-phenyl-1,3-oxazolines and (*S*)-2-aryl-5-phenyl-1,3-oxazolines, respectively. Concurrently, the reaction with fluorinated aliphatic carboxylic acid substrates proceeded via *N*-(2-hydroxy-1-phenyl-ethyl)-fluoroalkyl amide intermediates **8**, which were converted into *N*-(2-bromo-1-phenyl-ethyl)-fluoroalkyl amide intermediates **9**, and then into (*S*)-2-fluoroalkyl-4-phenyl-1,3-oxazolines as final products. Reaction mechanisms that mainly passed through the formation of aziridine intermediates **6** in the reaction with aromatic carboxylic acids and the formation of fluoroalkyl amide intermediates **8** and **9** in the reaction with fluorinated aliphatic carboxylic acid were proposed. The acidities of the carboxylic acids that were employed were found to play a key role in the selective formation of various intermediates during this reaction.

1. Introduction

Optically active 1,3-oxazoline heterocycles are a fundamental motif present in many bioactive molecules, natural products, and organomaterials.[1] In addition, 1,3-oxazoline heterocycles are versatile chiral ligands.[2] Many methods have been developed for the synthesis of 1,3-oxazoline;[3] however, most of these methods suffer from having complicated procedures, being multistep reactions and using harmful solvents or result in low yields.[4] Aziridines are important organic synthetic intermediates.[5] *N*-substituted aziridines have been used extensively for ring-opening, ring-expansion and cycloaddition chemical transformations because of the presence of inherent ring-strain.[6] Recently, we reported that *N*-aroyl aziridines generated in situ from the reaction of (*S*)-2-amino-3-phenylpropanol with various aromatic carboxylic acids in the presence of PPh_3/CBr_4 could be transformed into the optically active (*S*)-4-benzyl-1,3-oxazolines or (*S*)-5-benzyl-1,3-oxazolines via ring-opening of the aziridines and subsequent cyclization.[7] This synthetic methodology was demonstrated to be an effective tandem reaction process for the synthesis of optically active 4 or 5-benzyl-1,3-oxazoline. As part of our ongoing studies, we present a tandem reaction for the synthesis of optically active 2-aryl or fluoroalkyl-4 (or 5)-phenyl-1,3-oxazolines (Scheme 1), and explore the reason for the selective formation of different products as various types of carboxylic acids were employed.



Scheme 1. Synthesis of 4 (or 5)-phenyl-1,3-oxazolines.

2. Results and discussion

As previously reported,[7] the tandem reaction of (*S*)-2-amino-3-phenylpropanol with various aromatic acids in the presence of PPh_3/CBr_4 provided (*S*)-4-benzyl-1,3-oxazolines as the major products and unexpectedly produced (*S*)-5-benzyl-1,3-oxazoline as minor products. However, the use of (*S*)-2-amino-2-phenylethanol

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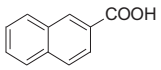
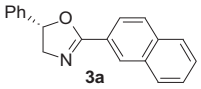
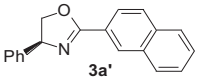
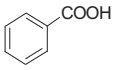
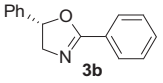
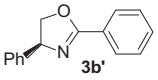
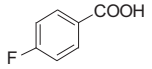
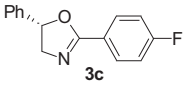
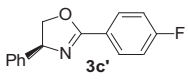
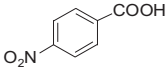
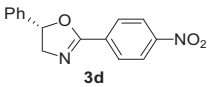
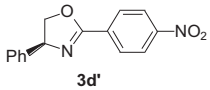
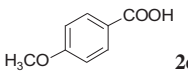
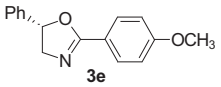
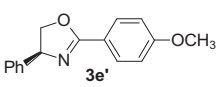
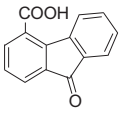
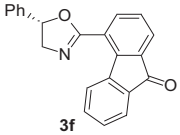
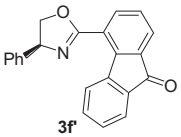
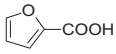
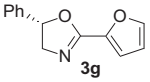
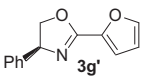
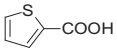
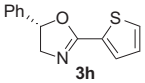
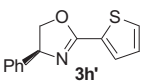
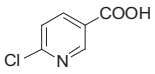
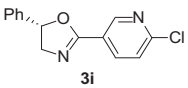
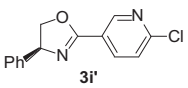
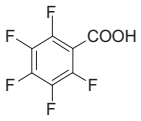
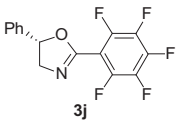
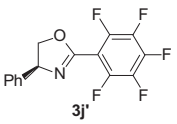
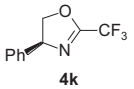
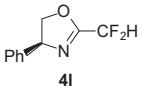
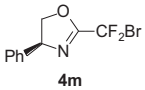
and naphthalene-2-carboxylic acid resulted in the opposite distribution of products: (*S*)-5-phenyl-1,3-oxazoline (**3a**) was the major product, while (*S*)-4-phenyl-1,3-oxazoline (**3a′**) was the minor product (entry 1, Table 1). In addition, the reaction of (*S*)-2-amino-2-phenylethanol with trifluoroacetic acid resulted in the formation of (*S*)-2-trifluoromethyl-4-phenyl-1,3-oxazoline (**4k**) (entry 11, Table 1) as the only product. The interesting experimental results prompted us to further investigate the tandem reaction and explore the transformation process.

The reaction was performed in the presence of 3 equiv of PPh_3/CBr_4 in toluene at 90 °C via a one-pot process. The reaction of the-various aromatic carboxylic acids with (*S*)-2-amino-2-phenylethanol

Table 1
The reaction of (*S*)-2-amino-2-phenylethanol with aromatic (or fluorinated) carboxylic acids

Entry	R_1COOH (**2**)	pK_a	Product (**3**, **3′**, or **4**)	Time (h)	Yield[a] (%) (**3**, **3′**, or **4**)
1	 **2a**	4.17	 **3a**  **3a'**	2	62, 28
2	 **2b**	4.19	 **3b**  **3b'**	6	48, 29
3	 **2c**	4.14	 **3c**  **3c'**	8	62, 31
4	 **2d**	3.42	 **3d**  **3d'**	8	62, 31
5	 **2e**	4.47	 **3e**  **3e'**	10	45, 31
6	 **2f**	3.51	 **3f**  **3f'**	14	53, 24
7	 **2g**	3.16	 **3g**  **3g'**	14	49, 21
8	 **2h**	3.51	 **3h**  **3h'**	8	42, 23
9	 **2i**	3.24	 **3i**  **3i'**	13	19, 34
10	 **2j**	1.6	 **3j**  **3j'**	20	43, 20
11	CF_3COOH **2k**	0.5	 **4k**	42	61
12	HCF_2COOH **2l**	1.3	 **4l**	55	42
13	$BrCF_2COOH$ **2m**	0.2	 **4m**	18	65
14	CH_3COOH **2n**	4.75	/	42	/[b]

[a] Isolated yields.
[b] No desired product was observed.