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Solution-phase combinatorial synthesis of isoxazolines and isoxazoles using [2+3] cycloaddition reaction of nitrile oxides

Kyung Ho Kang,[a] Ae Nim Pae,[a] Kyung Il Choi,[a] Yong Seo Cho,[a] Bong Young Chung,[b] Jee Eun Lee,[c] Sun Ho Jung,[c] Hun Yeong Koh[a,*] and Hee-Yoon Lee[d,*]

[a]*Biochemical Research Center, KIST, Box 131, Cheongyang, Seoul, South Korea*
[b]*Department of Chemistry, Korea University, Seoul 136-701, South Korea*
[c]*Department of Chemistry, Sungshin Women's University, Seoul 136-742, South Korea*
[d]*CMDS, Department of Chemistry & School of Molecular Science (BK21), KAIST, Taejon 305-701, South Korea*

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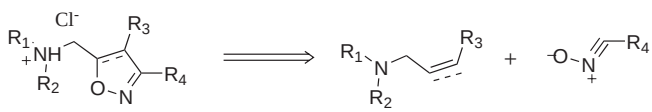
Abstract—An efficient way to construct a library of isoxazoles and isoxazolines was developed by solution-phase 1,3-dipolar cycloaddition reaction of nitrile oxides with olefins and alkynes followed by precipitation of the products as HCl salts.

Since combinatorial chemistry introduced a new paradigm in drug discovery,[1] combinatorial technology was expected to take a major role in post-genome projects[2] as well as in research for drug discovery,[3] new materials[4] and catalyst[5] development. Solid-phase synthesis has been the major tool for combinatorial chemistry with apparent advantages over solution-phase chemistry.[6] However, solution-phase combinatorial chemistry is emerging as a viable alternative to solid-phase synthesis due to the homogeneous nature and generality of solution phase chemistry.[7]

Herein, we wish to report an efficient solution-phase combinatorial strategy for the construction of a library of isoxazol(in)es. Since isoxazol(in)es were utilized as scaffolds for peptidomimetics[8] and core structures in medicinal chemistry,[9] several combinatorial synthesis of isoxazol(in)e libraries were reported. In most cases, however, most substitution possibilities of the isoxazol(in)e rings could not be realized since isoxazol(in)es were incorporated as building blocks instead of being constructed in combinatorial chemistry. To fully utilize the diversity feature of isoxazol(in)e ring, [2+3] cycloaddition reaction of nitrile oxides is most suitable. Unfortunately, solid-phase synthesis of isoxazol(in)es via nitrile oxides has not been successful due to low yields and low purities of the products.[7a] We envisioned that the solution-phase 1,3-dipolar cycloaddition[7c] would be a good alternative to the solid-phase synthesis if the solid-solution biphasic nature of products and reagents of solid-phase synthesis could be implicated into the solution-phase synthesis for ready isolation of products from the reaction mixture. We added amine functionality to the isoxazol(in)e scaffold since amines could serve two purposes. One is to provide a facile means of purification and the other is to serve as a pharmacophoric group required for certain G-Protein Coupled Receptors (GPCR).[10] Therefore every compound in the libraries contains an amine functionality in addition to the isoxazol(in)e ring. This feature allows four sites of attachment for pharmacophoric groups. The library was constructed through 1,3-dipolar cycloaddition reactions of nitrile oxides with dipolarophiles[11] (Scheme 1). The amine functionality in the scaffold is the key to solution-phase combinatorial chemistry as it provides an expeditious way of purification and isolation of the products from the reaction through precipitation of the products as HCl salts.

The library was constructed from cyclic amines attached to dipolarophiles and oximes (precursors of nitrile oxides) as listed in Fig. 1. The dipolarophiles



Scheme 1.

* Corresponding authors.

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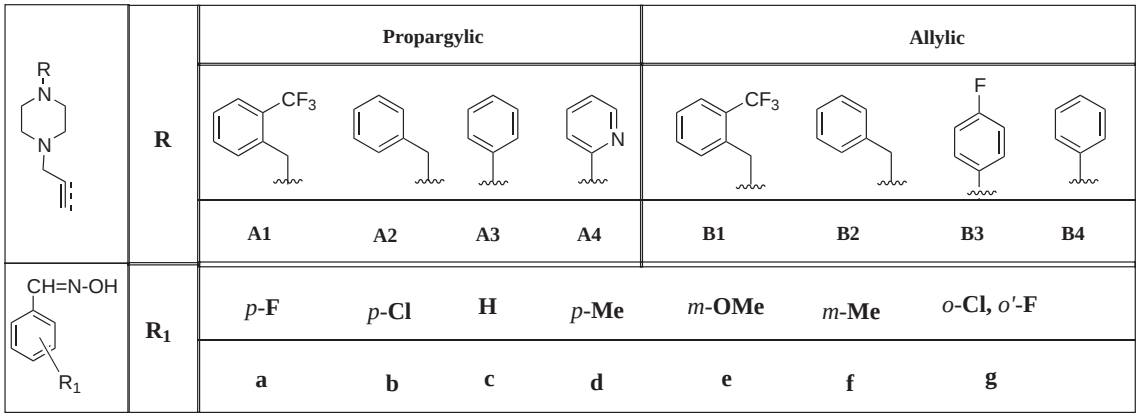
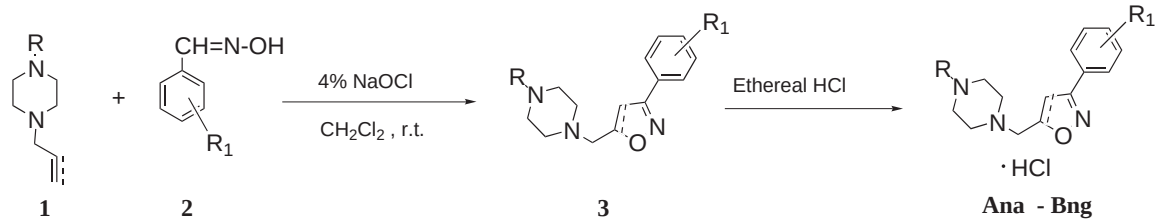


Figure 1.



Scheme 2.

were prepared from commercially available arylpiperazines with propargyl bromide or allyl bromide[12] and the oximes were prepared from aldehydes with hydroxylamine in presence of sodium hydrogen carbonate in $EtOH/H_2O$ at 60°C.

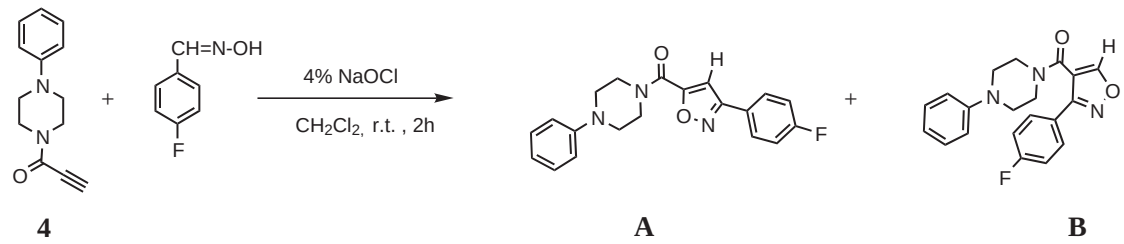
With two scaffolds in hand, the library was constructed in a single operation via successive cycloaddition reaction followed by salt formation (Scheme 2).

A solution of oxime(**2**, 5 equiv.) in dichloromethane was added to a solution of propargylic (or allylic) amine(**1**), sodium hypochlorite (4% aqueous solution (Aldrich), 5 equiv.) and Et_3N (1 equiv.). After the solvent was replaced to diethyl ether, the reaction mixture was treated with 1 M solution of HCl in diethyl ether. White solid was obtained, and was washed with diethyl ether several times. All the compounds were obtained in good yield (65% to 100%) with purities

Table 1. Isolated yields and purities[a] of isoxazolines (**A1**–**E5**)

	a	b	c	d	e	f	g
A1	**A1a** 78.9(77.2)[2]	**A1b** 80.7(78.8)	**A1c** 90.0(100)	**A1d** 90.0(100)	**A1e** 89.0(100)		
A2	**A2a** 46.1(100)	**A2b** 79.0(97.6)	**A2c** 93.9(72.7)	**A2d** 93.9(72.7)	**A2e** 52.5(84.5)		
A3	**A3a** 90.0(65.1)	**A3b** 40.2(100)	**A3c** 90.0(100)	**A3d** 90.0(100)	**A3e** 83.3(79.1)		
A4	**A4a** 54.8(69.2)	**A4b** 93.3(79.7)	**A4c** 90.0(70.5)	**A4d** 90.0(70.5)	**A4e** 92.2(75.1)		
B1	**B1a** 78.3(85.1)[b]	**B1b** 37.1(100)	**B1c** 87.3(85.5)			**B1f** 39.4(71.2)	**B1g** 72.9(79.8)
B2	**B2a** 37.8(72.2)	**B2b** 45.3(93.6)	**B2c** 48.7(84.6)			**B2f** 24.0(73.5)	**B2g** 78.3(89.2)
B3	**B3a** 76.3(88.6)	**B3b** 46.0(94.3)	**B3c** 75.8(81.6)			**B3f** 56.2(87.3)	**B3g** 92.3(94.1)
B4	**B4a** 39.8(86.7)	**B4b** 12.9(77.5)	**B4c** 70.9(82.0)			**B4f** 23.5(84.4)	**B4g** 77.4(100)

[a] Determined by GC–MS or HPLC.
[b] Yield (purities).



Scheme 3.

ranging from 70% to 100%. The result was quite compatible with general solid-phase synthesis as excess amount of nitrile oxides ensured complete conversion of **1** to **3** and did not pose severe contamination of the products. The purity and the identity of the products were confirmed by ^{1}H NMR and GC–MS or HPLC. All compounds were obtained as single isomeric products, though cycloaddition reaction could produce two regioisomeric products. Thus, a library of 20 isoxazoles and 20 isoxazolines was constructed (Table 1).

The main impurities were unreacted oxime derivatives and the impurities could be eliminated from the products by additional liquid–liquid extraction before the salt formation, though current protocol gave a satisfactory result.

An interesting result was observed when a conjugated alkyne, **4**[13] was subjected to the reaction with oxime **a** (Scheme 3). Though we expected a single isomeric product formation based on the literature example,[14] a mixture of regioisomeric products **(A, B** with 1.57:1 ratio)[15,16] was obtained in 64.9% yield. This unexpected result is quite noteworthy since this reaction could easily double the size of a library of isoxazol(in)es with an advantage of producing spatially well differentiated regioisomeric products that could show distinctive biological activities.

In summary, 1,3-dipolar cycloaddition reaction of nitrile oxides to alkenes or alkynes was developed into a solution-phase combinatorial chemistry for the construction of a library of 20 isoxazoles and 20 isoxazolines with good yield and purity. This methodology can readily be expanded to a bigger library construction and will serve a complimentary method to the solid-phase combinatorial synthesis. The isoxazol(in)es with biogenic amines could serve as a part of 'privileged structures'[17] for various receptors. Currently we are exploring to construct the mixture library of isomeric cycloaddition products and the application to lead a new search for GPCRs.

Acknowledgements

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12. Propargylic amines and allylic amines were prepared as follows. Propargyl (allyl) bromide (0.50 mol) was added over 20 min to a mixture of an amine (1.10 mol) in diethyl ether (500 ml). The reaction was stirred at room temperature for 18 hours. The resulting suspension was cooled to 0°C. The product was filtered and washed well with dry Et_2O and dried in vacuo.
13. 1-Phenylpiperazine (1 equiv.) and Et_3N (2 equiv.) was added to a stirred solution of propiolic acid (1.2 equiv.) and PCl_5 (1.2 equiv.) in CH_2Cl_2 at 40°C. After an hour of stirring, reaction mixture was washed with brine and water. Concentration followed by flash chromatography produced **4** in 67% yield.
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15. **Compound A**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (2H, dd, $J=7$ Hz, $J=12$ Hz), 7.33 (2H, t, $J=9$ Hz), 7.19 (2H, t, $J=12$ Hz), 7.12 (1H, s), 7.00 (3H, m), 3.99 (4H, br s), 3.32 (4H, br s). **Compound B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (1H, s), 7.77 (2H, dd, $J=6$ Hz, $J=12$

Hz), 7.29 (2H, t, $J=9$ Hz), 7.19 (2H, t, $J=12$ Hz), 6.90 (3H, m), 3.94 (2H, br s), 3.39 (2H, br s), 3.22 (2H, br s), 2.80 (2H, br s). HRMS EI^+, Anal. calcd for $C_{20}H_{18}FN_3O_2$: 351. 1383. Found: 351.1383.

16. Structural assignment of **A** and **B** are made based on the ^1H NMR of isoxazole protons and based on the assignment made in Ref. 14.
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