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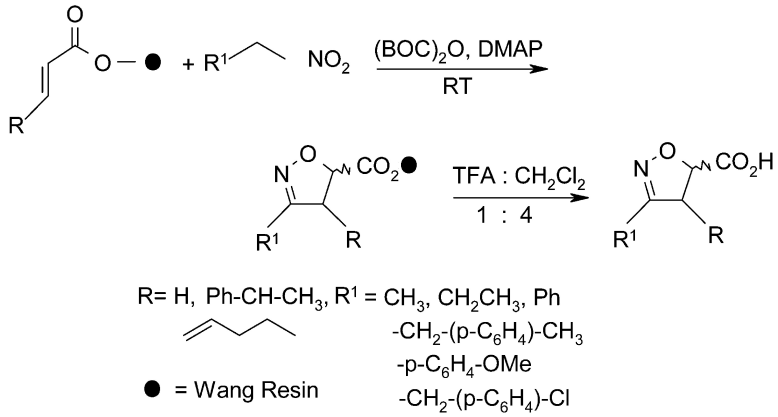

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Solid-Phase Synthesis of Isoxazolines

S. Chandrasekhar,* Abbas Raza, M. Venkat Reddy, and J. S. Yadav

Organic Division−I, Indian Institute of Chemical Technology, Hyderabad-7, India

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The polymer-supported synthesis of isoxazolines is described via nitrile oxide intermediates, starting from primary nitroalkanes in a one-pot process.

Introduction

The synthesis of chemical libraries is of great importance in the pharmaceutical and agrochemical industries. These libraries of small molecules are normally prepared either in solution or on a solid support. The greater flexibility of solution chemistry is outweighed by the need for purification of the library.[1] As a consequence, solid-phase organic synthesis (SPOS)[2] has been developed that allows the synthesis of chemical libraries in solid phase using an excess of reagents, which can be removed by simple filtration and washings without the need for a chromatographic workup.

Isoxazoline moieties represent a class of unique pharmacophores, which are observed in many therapeutic agents and are versatile intermediates for the synthesis of complex natural products and are found in GPII/IIIa inhibitors and human leukocyte elastase (HLE) inhibitors.[3] As part of a project aimed at developing new methodologies on solid support, we report herein the solid-phase synthesis of an isoxazoline[4] library starting from polymer-bound acrylic acid and its derivatives. This method allows the clean conversion of primary nitroalkanes into isoxazolines via dipolar cycloadditions of nitrile oxide intermediates in a one-pot process that gives good yields and improved purities.[5]

Nitrile oxides are important intermediates in organic synthesis,[6] but because of their marked instability and high reactivity, the study of their utility has been seriously impaired. The importance of isoxazolines is well documented for the use in 1,3-dipolar cycloadditions by both *intra* and intermolecular pathways.[7] Dipolar cycloadditions of nitrile oxides with olefinic compounds are of synthetic interest because the product isoxazolines are versatile intermediates for the synthesis of bifunctional compounds.

Results and Discussion

Even though this reaction is well studied in solution phase, there are very limited procedures available for the synthesis of this class of compounds on solid supports.[8] To address this issue, herein we disclose our findings pertaining to (3 + 2) cycloaddition of in situ generated nitrile oxide and polymer-supported electron-deficient olefin (Scheme 1).

Accordingly the polymer-supported acrylic acid resin was taken in a clean round-bottomed flask (two necked) and soaked in dry acetonitrile and hexane (1:4) mixture. A stoichiometric (excess) amount of $(Boc)_2O$ was added in the presence of a catalytic amount of DMAP, and the contents were shaken at room temperature under a nitrogen atmosphere for 1 h. Excess nitroethane in acetonitrile was then added, and the entire contents were shaken at room temperature for another 6 h. The total reaction mass was filtered and washed with excess diethyl ether and dried under vacuum. The IR spectrum of polymer-bound isoxazoline carboxylic acid (**1a**, Table 1) gave the frequencies at 1734 and 1656 cm^{-1}. The resin was cleaved using 20% TFA in CH_2Cl_2 to release the isoxazoline carboxylic acid **1a** as the end product.[9] Compound **1a** in its ^1H NMR spectrun resonated at 2.05 and 3.25 ppm as a singlet and a triplet for C3−CH_3 and C4−2H, respectively. A triplet at 5.01 ppm due to C5−H was observed. In the second instance, nitropropane was added to the polymer-bound acrylic acid and the above procedure was repeated to give the corresponding isoxazoline derivative (**1b**, Table 1). This result has prompted us to make a library of isoxazoline derivatives in a combinatorial fashion to give the respective products (Table 1) in good yields. All the products were characterized by ^1H NMR, mass, and HRMS analyses.

Experimental Section

General. All chemicals obtained commercially were used without further purification. Dichloromethane and dimethylformamide were distilled from CaH_2. Diethyl ether and tetrahydrofuran were distilled over sodium and benzophenone. Wang resin (capacity 1.7 mmol /g), bead size of 150−300 μm, was obtained from Polymer Laboratories, U.K. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. All ^1H NMR spectra were recorded on a Varian instrument at 200 MHz. The following abbreviations are used: DCM = dichloromethane; THF = tetrahydrofuran; MeOH = methanol; TFA = trifluoroacetic acid; DMF = dimethylformamide; DCC = dicyclohexylcarbodiimide; $(Boc)_2O$ = di-*tert*-butyl dicarbonate; DMAP = 4-(dimethylamino)pyridine.

Preparation of Resin-Bound Acrylic Acid Ester I. Wang resin (2 g, 1.7 mmol/g, loading of 3.4 mmol) was placed in a 100 mL two-neck round-bottomed flask and swelled with 20 mL of DCM for 15 min. An overhead stirrer was attached to provide gentle stirring. Triethylamine (0.729 g, 4.25 mmol) and acryloyl chloride (0.225 g, 2.21 mmol) were added in

* To whom correspondence should be addressed. E-mail: srivaric@iict.ap.nic.in.

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Scheme 1

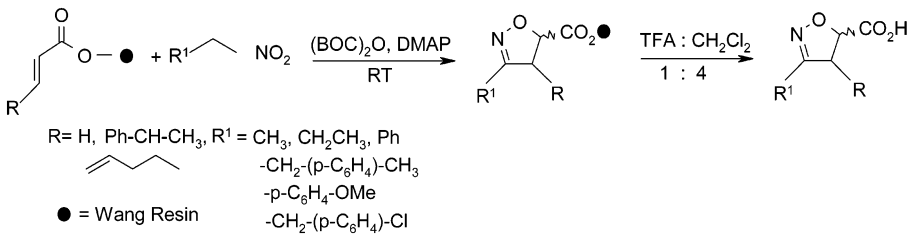

Table 1. Synthesis of Isoxazolines on Solid Support[a]

	I	II	III
$CH_3CH_2NO_2$	* 1a ** 80%	2a 78%	3a 85%
$CH_3(CH_2)_2NO_2$	1b 75%	2b 81%	3b 75%
MeO-$(CH_2)_2NO_2$	1c 73%	2c 68%	3c 65%
H_3C-$(CH_2)_2NO_2$	1d 78%	2d 75%	3d 77%
Cl-$(CH_2)_2NO_2$	1e 82%	2e 63%	3e 69%

[a] (∗) The isoxazolines are obtained after cleavage from polymer using TFA (see Experimental Section). (∗∗) The yields are based on isolation of the corresponding acid after cleavage by TFA. (●) Wang resin: 4-(hydroxymethyl)phenoxymethylpolystyrene (1.7 mmol/g).

succession, and the mixture was stirred for 4 h. The resin was then filtered and washed three times with DMF (10 mL), THF (10 mL), DCM (10 mL), MeOH (10 mL), and diethyl ether (20 mL). The resin was then dried in vacuo overnight at 25 °C. IR (KBr): 1736 cm^{-1}.

Preparation of Resin-Bound 4-Phenyl-2-butenoic Acid Ester II. Wang resin (2 g, 1.7 mmol/g) was placed in a 100 mL two-neck round-bottom flask and swelled with 20 mL of DCM for 15 min. An overhead stirrer was attached to provide gentle stirring. Added in succession were DCC (1.4 g, 6.8 mmol) and 4-phenyl-2-butenoic acid (1.25 g, 8.25 mmol) in DCM (20 mL), and the mixture was stirred for 12 h**.** The resin was then filtered and washed three times with DMF (10 mL), THF (10 mL), DCM (10 mL), MeOH (10 mL), and diethyl ether (20 mL). The resin was then dried in vacuo overnight at 25 °C. IR (KBr): 1725 cm^{-1}.

Preparation of Resin-Bound (2*E*,4*Z*)-2,4-Octadienoic Acid Ester III. Wang resin (2 g, 1.7 mmol/g, loading of 3.4 mmol) was placed in a 100 mL two-neck round-bottom flask and swelled with 20 mL of DCM for 15 min. An overhead stirrer was attached to provide gentle stirring. Added in succession were DCC (1.4 g, 6.8 mmol) and the corresponding acid (1.25 g, 8.25 mmol) in DCM (20 mL), and the mixture was stirred for 12 h. The resin was then filtered and washed three times with DMF (10 mL), THF (10 mL), DCM (10 mL), MeOH (10 mL), and diethyl ether (20 mL). The resin was then dried in vacuo overnight at 25 °C. IR (KBr): 1732 cm^{-1}.

3-Methyl-4,5-dihydro-5-isoxazolecarboxylic Acid 1a. To acrylic acid bound Wang resin **I** (1.0 g, 1.7 mmol) was added $(Boc)_2O$ (0.74 g, 3.4 mmol) and DMAP (catalytic) in hexane/acetonitrile (10 mL, 4:1) under a N_2 atmosphere. The reaction mixture was stirred gently at room temperature for 15 min. Nitroethane (0.25 g, 3.4 mmol) was added, and the contents were stirred for a further 10 h at the same temperature. The reaction mass was filtered and washed with acetonitrile (2 × 20 mL), THF (20 mL), MeOH (20 mL), DCM (20 mL), and diethyl ether (20 mL). The residue was then dried in vacuo. Several resin beads were used for IR analysis. IR (KBr): 1734, 1656 cm^{-1}.

Cleavage. To 0.5 g of the above resin vessel was added 20% TFA in DCM (10 mL), and the contents were stirred for 45 min at room temperature, after which the reaction mass was filtered. The solvent was evaporated by nitrogen blow-down to yield **1a** (0.051 g, 80%). ^{1}H NMR ($CDCl_3$): ***δ*** 2.05 (s, 3H), 3.25 (d, 2H, J = 2.2 Hz), 5.01 (t, 1H, J = 3.0 Hz). MS: m/z = 129. HRMS: calcd, 129.1143; found, 129.1139. The following compounds were synthesized using the above protocol.

Compound 1b. ^{1}H NMR ($CDCl_3$): δ 1.2 (t, 3H, J = 4.7 Hz), 2.4 (d, 2H, J = 7.0 Hz), 3.25 (q, 2H, J = 4.7 Hz), 5.0 (t, 1H, J = 5.5 Hz). MS: m/z = 143. HRMS: calcd, 143.1411; found 143.1401.

Compound 1c. ^{1}H NMR ($CDCl_3$): δ 3.15 (bs, 2H), 3.6 (d, 2H, J = 6.8 Hz), 3.85 (s, 3H), 4.8−4.95 (m, 1H), 6.85 (d, 2H, J = 5.4 Hz), 7.05 (d, 2H, J = 5.4 Hz). MS: m/z = 235. HRMS: calcd, 235.2377; found, 235.2370.

Compound 1d. ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H), 3.15 (bs, 2H), 3.65 (d, 2H, J = 2.3 Hz), 4.8 (t, 1H, J = 2.3 Hz), 7.05−7.25 (m, 5H). MS: m/z = 219. HRMS: calcd, 219.2387; found, 219.2385.

Compound 1e. ^{1}H NMR ($CDCl_3$): δ 3.1 (bs, 2H), 3.65 (m, 2H), 5.0 (m, 1H), 6.9−7.2 (m, 4H). MS: m/z = 239. HRMS: calcd, 239.6571; found, 239.6568.

Compound 2a. ^{1}H NMR ($CDCl_3$): δ 2.1 (s, 3H), 2.35−2.45 (m, 1H), 2.80−2.95 (m, 3H), 4.85−5.0 (m, 2H), 7.15−7.35 (m, 5H). MS: m/z = 233. HRMS: calcd, 233.2655; found, 233.2649.

Compound 2b. ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3H, J = 5.0 Hz), 2.1−2.3 (m, 1H), 2.31−2.40 (m, 1H), 2.80−2.95 (m, 3H), 3.50−3.75 (q, 2H, J = 5 Hz), 7.1−7.3 (m, 5H). MS: m/z = 247. HRMS: calcd, 247.2943; found, 247.2939.

Compound 2c. ^{1}H NMR ($CDCl_3$): δ 2.15−2.3 (m, 1H), 2.35−2.45 (m, 1H), 3.15 (bs, 1H), 3.8 (s, 1H), 4.8−5.0 (m, 1H), 7.0−7.25 (m, 4H). MS: m/z = 339. HRMS: calcd, 339.3889; found, 339.3881.

Compound 2d. ^{1}H NMR ($CDCl_3$): δ 2.15−2.35 (m, 1H), 2.3−2.4 (m, 1H), 2.31 (s, 3H), 3.2 (bs, 2H), 4.8−5.1 (m, 1H), 7.1−7.3 (m, 4H). MS: m/z = 323. HRMS: calcd, 323.3899; found, 323.3901.

Compound 2e. ^{1}H NMR ($CDCl_3$): δ 2.1−2.3 (m, 1H), 2.35−2.45 (m, 1H), 3.15 (bs, 2H), 3.65 (m, 2H), 5.1 (m, 1H), 7.0−7.2 (m, 4H). MS: m/z = 343. HRMS: calcd, 343.8082; found, 343.8085.

Compound 3a. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 4.15 Hz), 1.45−1.5 (m, 2H), 2.1 (s, 3H), 2.2−2.4 (m, 4H), 5.75 9 (d, 1H, J = 9.1 Hz), 6.15−6.25 (m, 2H), 7.2−7.4 (m, 4H). MS: m/z = 197. HRMS: calcd, 197.2325; found, 197.2331.

Compound 3b. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 4.15 Hz), 1.23 (t, 3H, J = 4.5 Hz), 1.4−1.5 (m, 2H), 2.2−2.4 (m, 4H), 5.71 (d, 1H, J = 9.0 Hz), 6.1−6.3 (m, 2H). MS: m/z = 211. HRMS: calcd, 211.2593; found, 211.2599.

Compound 3c. ^{1}H NMR ($CDCl_3$): δ 0.8 (t, 3H, J = 4.2 Hz), 1.4−1.55 (m, 2H), 2.2−2.45 (m, 4H), 3.2 (bs, 2H), 3.85 (s, 3H), 5.7 (d, 1H, J = 9.1 Hz), 6.15−6.35 (m, 2H), 7.2−7.4 (m, 4H). MS: m/z = 303. HRMS: calcd, 303.3599; found, 303.3585.

Compound 3d. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, J = 4.1 Hz), 1.4−1.55 (m, 2H), 2.15−2.38 (m, 4H), 3.85 (s, 3H), 5.78 (d, 1H, J = 9.3 Hz), 6.13−6.23 (m, 2H), 7.23−7.4 (m, 4H). MS: m/z = 287. HRMS: calcd, 287.3569; found, 287.3575.

Compound 3e. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 2H, J = 4.0 Hz), 1.41−1.53 (m, 2H), 2.21−2.4 (m, 4H), 3.12 (bs, 2H), 5.71 (d, 1H, J = 9.0 Hz), 6.15−6.36 (m, 2H), 7.15−7.25 (m, 4H). MS: m/z = 307. HRMS: calcd, 307.7752; found, 307.7758.

Conclusion

In conclusion, we have developed a standardized protocol for solid-phase organic synthesis of isoxazolines starting from primary nitroalkanes and resulting in good yields and improved purities.

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(9) The cleavage of the end product showed the presence of small amounts of unsaturated acid in all cases. However, after repeated cycloaddition, no traces of the unsaturated acid were found. The reaction conditions for the solid-phase synthesis of isoxazolines were optimized by varying the equivalents of $(Boc)_2O$ and nitroalkanes and also by changing the hexane/acetonitrile ratio. Apparently, the 4:1 ratio of hexane/acetonitrle and stoichiometric amounts of $(Boc)_2O$ (2 equiv) and nitroalkane (2 equiv) were found to be optimal.

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