Synthesis of some new class of isoxazoline derivatives and their functionalization to 1,3-amino ketones: A new approach

Bhaskar Chakraborty* & Neelam Rai
Organic Chemistry Laboratory, Sikkim Government College (Sikkim State University), Gangtok 737 102, India
E-mail: bhaskargtk@yahoo.com

Received 24 January 2018; accepted (revised) 19 November 2018

Synthesis of few new scaffolds for isoxazolidine derivatives have been reported from amino nitrones in solvent free conditions. These new molecules are further functionalized into synthetically more important 1,3-amino ketone derivatives. Significant rate acceleration, high yield of products in solvent free conditions and atom efficiency are the salient features observed in these syntheses.

Keywords: Isoxazolines, cycloaddition reaction, solvent free reaction, atom efficiency

The use of microwaves in organic synthesis has increased dramatically within the past decade, receiving widespread acceptance and becoming an indispensable tool1-3. Microwave irradiation can be used as a facile and general method for the construction of variety of isoxazolidine and isoxazoline derivatives where considerably shortened reaction time is involved and is considered as an important approach towards ‘Green Chemistry’ because of its eco-friendly nature1-3. In continuation of our green methodological synthesis of spiro isoxazolidine, isoxazolidine, aldehyde, ketone synthesis using α-amino and α-chloro nitrones in solid phase and in hydrated media4-11, in this communication, we have reported microwave assisted solvent-less green synthesis of some new scaffolds of isoxazoline derivatives 3-6 having high synthetic potential using N-phenyl-α-amino nitrone 1 with different activated alkynes with excellent yields (Scheme I; Table I)12. The 1,3-dipolar cycloaddition reaction between a nitrore and an alkyne derivative is an efficient method for the synthesis of the isoxazoline ring system13. The wealth of literature reports on cycloaddition reactions of nitrone and for the synthesis of novel isoxazolidine, isoxazoline derivatives and their further applications has been widely illustrated14. Isoxazolines possess medicinal activities such as antibacterial, anticonvulsant, antibiotic, antitubercular and antifungal activity14. Despite their potential utility, many of these procedures require high temperature, hazardous solvents and prolonged reaction times (drastic experimental conditions). Initially, we surveyed the reactions in conventional methods but in terms of reaction rate, yield and greener approach our group was encouraged by the microwave technology. The notable feature in this synthesis is atom efficiency as the newly synthesized isoxazoline molecules can be converted into new 1,3-amino ketone derivatives by the reductive cleavage of N-O bond.

Results and Discussion

For the present study, we have chosen activated alkynes like dimethyl acetylene dicarboxylate, phenyl methyl propiolate and acetylene dicarboxylic acid (but-2-ynedioic acid), propiolic acid respectively as dipolarophiles in 1,3-dipolar cycloaddition reaction with N-phenyl-α-amino nitrone (1a)12 for the synthesis of new isoxazoline derivatives 3-6 (Scheme I; Table I). These results can be rationalized by an exo approach of the nitrone 1 in Z configuration (transition state 1, Figure 1)12,15,16 for the dipolarophiles (alkynes) in the development of new cycloadducts.

Stereochernistry of the new isoxazoline derivatives 3-6 could not be determined in detail since two most important protons are absent at C4 and C5 positions and the lone singlet signal due to C3 proton unable to predict it. Expected broad signal for amino groups at δ 3.05-2.80 and sharp singlet for ester methyl protons at δ 3.30-3.20 were obtained while carboxylic protons showed sharp singlet signals around δ 10.15 in the
The major and minor conformers of the new isoxazoline ring systems 3-6 may be represented in Figure 1.

In all the new isoxazoline derivatives 3-6, we have obtained expected fragmentation peaks due to the development of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, COOCH₃ for dimethyl acetylene dicarboxylate and COOH for acetylene dicarboxylic acid cycloadducts respectively. Hence it is confirmed that during mass fragmentation, the isoxazoline cycloadducts underwent rearrangement to aziridine derivatives. Structures of all the new isoxazoline derivatives have been confirmed on the basis of expected signals obtained in ¹H and ¹³C NMR, MS and FT-IR spectra. Satisfactory elemental analysis values were also obtained for all the new cycloadducts. Furthermore, good synthetic
potentiality of the new isoxazoline derivatives 3-6 have been observed as they could be easily converted into new 1,3 bifunctional amino ketones (7-10, Scheme II, Table II) by the reductive cleavage of the N-O bond. These conversions have been achieved by simply treating the substrates with zinc powder in dil. acetic acid under microwave irradiation. Spectral characterization of compound 10 is going on at present and its basic characteristics only are reported.

The relative configurations of H-2 and H-3 protons of the newly developed 1,3-amino ketones 7-10 are syn as evidenced from their coupling constant values ($J_{H1,H2} \sim 6.70$ Hz; $J_{H2,H3} \sim 6.10$ Hz). Expected broad signals for N-H proton around $\delta$ 3.40 and alcoholic OH groups around $\delta$ 5.20 are also obtained. Significant IR and $^{13}$C NMR absorption bands have been observed for carbonyl groups in all the new amino keto molecules and thus confirms in favour of their synthesis.

**Experimental Section**

Melting points were determined in open capillary tubes and are uncorrected. $^1$H NMR spectra were recorded with a Bruker Avance DRX-300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. $^{13}$C NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants ($J$) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. Elemental analyses (CHN) were performed with a Perkin-Elmer 2400 series CHN Analyzer. TLC was carried out on Fluka silica gel TLC cards while column chromatography was performed with silica gel (E. Merck India) 60–200 mesh. Phenylmethyl propiolate, dimethylacetylene dicarboxylate, acetylene dicarboxylic acid and propiolic acid were purchased from Sigma-Aldrich Chemical Company and used as received. All other reagents and solvents were purified after receiving from commercial suppliers. $N$-Phenylhydroxylamine was prepared following standard methods available in literature and has been used in various reported synthesis. Microwave studies were carried out in Discover Bench Mate system (Make: CEM-USA) producing continuous irradiation at 2445 MHz and infrared control system. Microwave experiments were carried out in open vessels with effective magnetic stirring and reflux (which avoids all problems of non homogeneity in temperature).

**General procedure for the synthesis of new isoxazoline derivatives 3-6 using $N$-phenyl-$\alpha$-amino nitrone under microwave irradiation (MWI)**

A mixture of nitrone 1 (250 mg, 2.29 mmol) and activated alkyne (1 equivalent) was taken in a 25 mL Erlenmeyer flask and made into a paste. It was subjected to microwave irradiation at medium power (50%) for 5-10 min. The completion of reaction was monitored by TLC. The reaction mixture was cooled to RT and

![Scheme II — Synthesis of new 1,3-amino ketones](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoxazoline</th>
<th>Reagent</th>
<th>Time (min)</th>
<th>1,3 amino ketones (7-10)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Zn &amp; dil acetic acid</td>
<td>5</td>
<td>7: Brown liquid</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Zn &amp; dil acetic acid</td>
<td>6</td>
<td>8: Red liquid</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Zn &amp; dil acetic acid</td>
<td>8</td>
<td>9: Colourless liquid</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>Zn &amp; dil acetic acid</td>
<td>8</td>
<td>10: Pale yellow liquid</td>
<td>77</td>
</tr>
</tbody>
</table>

*a Reaction condition: Isoxazolidine (50 mg), Zn (5 mg), glacial acetic acid (3 mL), MWI
b Isolated yields after purification
extracted with diethyl ether. The product was concentrated in a rotary vacuum evaporator and finally purified by recrystallization from ethanol to afford pure cycloadducts (isoxazoline derivatives). This procedure was followed for the substrates listed in Table I.

(R)-Methyl 3-amino-2,3-dihydro-2,5-diphenylisoaxazole-4-carboxylate, 3: Red viscous liquid. Yield 93%. Rf = 0.48; IR (KBr): 3379 (br), 3050 (s), 2935 (m), 1780 (s), 1707 (s), 1445 (m), 1295 (m), 900 (s) cm−1; 1H NMR (CDCl3): δH 7.77–7.04 (m, 5H, C6H5 hydrogens), 4.68 (br, 2H, -NH2), 3.32 (s, 3H, - COOCH3), 2.68 (s, 1H, C3H); 13C NMR (CDCl3): δc 172.66 (ester carbonyl carbon), 170.69, 169.72 (ester carbonyl carbons), 134.12, 136.47, 136.30, 136.21, 135.95, 130.78, 130.66, 129.86 (aromatic carbons), 80.58 (C3), 69.52 (C2), 21.47 (-COOCH3), 18.10 (-COOCH3); MS: m/z 278 (M+), 265, 253, 247, 219, 203, 191, 178, 175, 160, 147, 105, 87, 77, 59. Anal. Found: C, 56.09; H, 5.44; N, 9.12. C17H18N2O3 requires: C, 68.88; H, 5.30; N, 9.23.

(R)-Dimethyl 3-amino-2,3-dihydro-2-phenylisoaxazole-4,5-dicarboxylate, 4: Dark yellow liquid. Yield 91%. Rf = 0.50; IR (KBr): 3447 (br), 2962 (m), 2852 (M+), 278 (M+), 265, 253, 247, 219, 203, 191, 178, 175, 160, 147, 105, 87, 77, 59. Anal. Found: C, 68.23; H, 5.88; N, 9.12. C17H18N2O3 requires: C, 68.42; H, 6.07; N, 9.39%.

(R)-3-Amino-2,3-dihydro-2-phenylisoaxazole-4,5-dicarboxylic acid, 5: Colourless gummy liquid. Yield 90%. Rf = 0.46; IR (KBr): 3516–3428 (br), 3035 (s), 1725 (s), 1665 (m), 1345 (m), 766 (s) cm−1; 1H NMR (CDCl3): δH 10.02 (s, 2×1H, COOH), 7.66–7.44 (m, 5H, C6H5 hydrogens), 3.38 (s, 2×3H, -COOCH3), 2.68 (s, 1H, C3H), 1.25 (br, 2H, -NH2); 13C NMR (CDCl3): δc 170.23, 169.70 (ester carbonyl carbons), 134.39, 131.40, 129.33, 128.15 (aromatic carbons), 94.84 (C3), 77.65 (C2), 63.12 (C4), 30.88, 25.63 (-COOCH3); MS: m/z 278 (M+), 265, 253, 247, 219, 203, 191, 178, 175, 160, 147, 105, 87, 77, 59. Anal. Found: C, 55.92; H, 4.86; N, 9.90. C13H14N2O5 requires: C, 56.09; H, 5.30; N, 10.07%.

General procedure for synthesis of 1,3 amino ketones (MWI)

A mixture of isoxazoline 3 (50 mg) and Zn dust (5 mg) in dil acetic acid (3 mL) was taken in a 25 mL Erlenmeyer flask and made into a paste. The reaction mixture was subjected to microwave irradiation for 5 min at 60°C (entry 1; Table II). The completion of reaction was monitored by TLC (Rf = 0.66). The reaction mixture was cooled to RT, extracted with diethyl ether and filtered. Excess acetic acid in the filtrate was removed through basic work-up and finally column chromatographic purification resulted in the isolation of desired 1,3 amino ketone 7 in 84% yield (entry 1; Scheme II; Table II). This procedure was followed for other substrates listed in Table II.

Spectral data of new 1,3-amino keto molecules

7: Brown liquid. Yield 84%. Rf = 0.64; IR (KBr): 3540 (br), 3485 (br), 3042 (s), 2930 (m), 1785 (s), 1680 (s), 1660 (s), 1455 (m), 880 (s) cm−1; 1H NMR (CDCl3): δH 7.38–6.90 (m, 5H, C6H5 hydrogens), 4.53 (br, 2H, -NH2), 4.34 (br, 1H, -NH), 3.37 (s, 3H, - COOCH3), 2.60 (d, 1H, J = 4.54 Hz, C2H), 2.20 (d, 1H, J = 4.30 Hz, C3H); 13C NMR (CDCl3): δc 172.30 (ester carbonyl carbon), 169.35 (C=O), 136.47, 136.30, 136.21, 135.95, 130.78, 130.66, 129.86 (aromatic carbons), 80.58 (C3), 69.52 (C2), 21.47 (-COOCH3), 18.10 (-COOCH3); MS: m/z 278 (M+), 221, 205, 193, 177, 105, 77. Anal. Found: C, 68.23; H, 5.88; N, 9.12. C13H14N2O5 requires: C, 68.42; H, 6.07; N, 9.39%.

8: Red liquid. Yield 81%. Rf = 0.56; IR (KBr): 3555 (br), 3490 (br), 3030 (s), 2936 (m), 1782 (s), 1760 (s), 1445 (m), 785 (s) cm−1; 1H NMR (CDCl3): δH 6.85–6.44 (m, 5H, C6H5 hydrogens), 5.24 (br, 2H, -NH2), 4.72 (br, 1H, -NH), 3.30 (s, 2×3H, -COOCH3), 2.33 (d, 1H, J = 3.24 Hz, C2H), 2.14 (d, 1H, J = 3.12 Hz, C3H); 13C NMR (CDCl3): δc 172.84, 171.68 (ester carbonyl carbons), 168.78 (C=O), 133.40, 133.15, 132.80, 132.66 (aromatic carbons), 81.34 (C3), 70.60
(C2), 22.58, 22.40 (2×-COOCH3), 18.77, 18.54 (2×-COOCH3); MS: m/z 280 (M'), 203, 193, 187, 177, 87, 77. Anal. Found: C, 55.46; H, 5.52; N, 9.43. C13H16N2O5 requires: C, 55.69; H, 5.75; N, 10.00%.

9: Colourless liquid. Yield 80%. Rf = 0.50; IR (KBr): 3530–3480 (br), 3465-3436 (br), 3030 (s), 1740 (s), 1660 (m), 1340 (m), 780 (s) cm−1; 1H NMR (CDCl3): δH 10.22 (s, 2×1H, COOH), 7.10-7.00 (m, 5H, C6H5 hydrogens), 3.80 (br, 2H, -NH2), 3.53 (br, 1H, -NH), 2.16 (d, 1H, J = 3.80 Hz, C2H), 1.95 (d, 1H, J = 3.16 Hz, C3H); 13C NMR (CDCl3): δC 170.34, 170.20 (carboxyl carbons), 167.66 (C=O), 128.54, 128.38, 128.24, 128.10 (aromatic carbons), 80.17 (C3), 72.15 (C2); MS: m/z 252 (M'), 179, 175, 163, 77. Anal. Found: C, 52.30; H, 4.80; N, 10.78. C11H12N2O5 requires: C, 52.36; H, 4.79; N, 11.11%.

Conclusion

In conclusion, we have reported a green chemistry protocol for the synthesis of new scaffolds of isoxazoline derivatives with good to excellent yields. These new molecules are further functionalized into synthetically more important new class of 1,3-amino ketones. The salient feature and the point of attraction in the present methodology is atom efficient green chemistry methodology, simple reaction condition and easy isolation of products which should attract synthetic chemists.

Acknowledgements

The authors are pleased to acknowledge the financial support from the Science and Engineering Research Board (SERB), Government of India, New Delhi (grant no: SR/S1/OC-34/2011). The authors are equally grateful to SAIF (Sophisticated Analytical Instrumentation Facility), CDRI (Central Drug Research Institute), Lucknow, India for providing spectral data.

References