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Note

High yield solvent free synthesis of novel isoxazolines using novel *N*-cyclohexyl-α-amino nitrone

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Some novel isoxazolines have been synthesized from novel *N*-cyclohexyl-α-amino nitrone using 1,3 dipolar cycloaddition reaction with alkynes in solvent free conditions at room temperature.

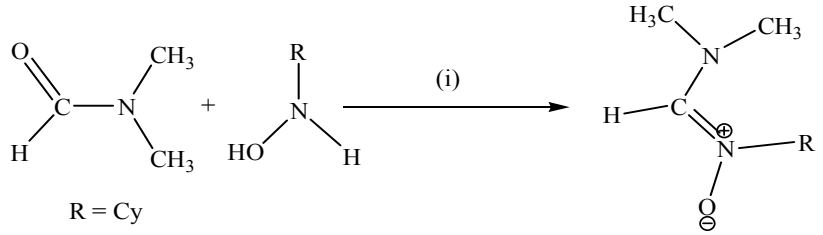
Keywords: *N*-Cyclohexyl-α-amino nitrone, 1,3 DCR, isoxazolines, stereoselectivity, solvent free conditions

In continuation of the earlier work on isoxazolidine synthesis using α-amino nitrones in solvent free conditions (synthesized from formamide and N-phenylhydroxylamine)[1,2], herein is now reported an efficient method for the stereoselective synthesis of isoxazolines from N-cyclohexyl-α-amino nitrone **1** (**Scheme I**, ref. 3) with an excellent yield under solvent free conditions[4] (**Scheme II, Table I**). The products of such cycloadditions have a variety of applications, including as potential antimicrobial agents. 1,3-Dipolar cycloadditions are powerful methods for constructing a variety of five membered heterocycles in a convergent manner from relatively simple precursors and these heterocycles have a variety of applications including as antibacterial agents[5]. Cycloadditions of alkynes even with electron deficient and unsymmetrical alkynes are often conducted at elevated temperature[6]. In this communication is reported the synthesis of isoxazolines at RT with high yield. Stereoselective synthesis of isoxazolidines at RT using nitrone **1** has been already reported[3]. This is because of the fact that N-cyclohexyl-α-amino nitrone is very reactive due to the presence of a filled up anti bonding molecular orbital which hastens cycloaddition to take place at RT (Ref. 7).

Results and Discussion

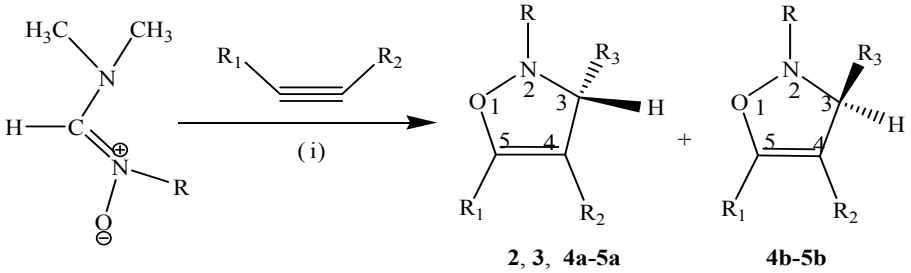
In an initial investigation, the reaction of nitrone **1** with ethyl propiolate was examined at elevated temperature having only 28% yield of isoxazoline in 14 hr while at RT 92% yield of isoxazolines are reported in 12 hr which indicates the decomposition of nitrone at elevated temperature. This could also be explained due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolarophile (LUMO), (ref. 7). The concerted nature of these cycloaddition reactions with nitrone as 1,3 dipole has been generally accepted. The regioselectivity in these reactions was rationalized by using the frontier orbital theory[8]. The ethyl propiolate and propiolic acid adducts correspond to this theory. Therefore, the 5-substituted adduct for ethyl propiolate and propiolic acid is due to LUMO (nitrone)- HOMO (dipolarophile) interaction[8]. For the present study, highly electron deficient and unsymmetrical alkynes like dimethyl acetylene dicarboxylate, phenyl methyl propiolate, propiolic acid and ethyl propiolate respectively have been chosen to study the stereoselectivity in these cycloadditions.

As already reported, nitrone **1** is highly unstable and hence for 1,3-dipolar cycloaddition reaction, the nitrone was trapped *in situ* by different alkynes to afford isoxazolines with high yield. Dimerization of nitrone could also be controlled under this condition. Like most of the nitrones reported from this group[9-11], nitrone **1** also exists exclusively in the *Z* configuration and hence the cycloadducts were formed from *Z* nitrone through an *exo* transition state geometry. Excellent diastereofacial selectivity is observed in case of reaction of nitrone **1** with ethyl propiolate and propiolic acid and results in a mixture of diastereomer **4a, 4b** and **5a, 5b** (**Scheme II,** almost 70:30 ratio). These results can be rationalized by an *exo* approach of the nitrone for the major cycloadducts **4a, 5a** which have the *Z* configuration (transition state **I**)[12]. The minor cycloadducts **4b, 5b** may be formed by the *endo* approach of *Z* nitrone (transition state **II**)[12]. Most relevant are the coupling constants ($J_{H3,\ H4}$ for **4** and **5**) of the diastereomer. For **4a** and **5a**, the coupling constants are 9.3 and 9.4 Hz, implying a *cis* relationship between H_3 and H_4 whereas **4b** and **5b**



(i) anhydrous $MgSO_4$, RT, 8 hr, N_2 atmosphere **1**

Scheme I



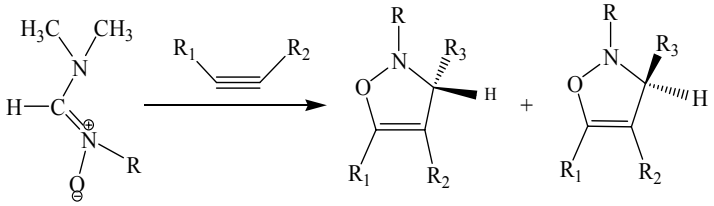
2, **3**, **4a-5a** **4b-5b**

(i) RT, 6-8 hr, N_2 atmosphere

2 : R_1 = Ph; R_2 = $COOCH_3$
3 : R_1 = R_2 = $COOCH_3$
4 : R_1 = $COOC_2H_5$; R_2 = H
5 : R_1 = COOH ; R_2 = H
R_3 = -NMe_2
R = Cy

Scheme II

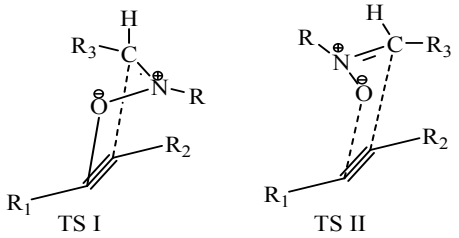
Table I — Physicochemical data of synthesized compounds



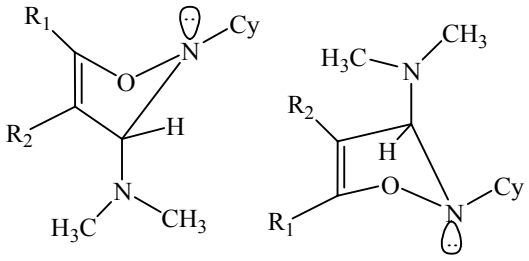
Entry	Nitrone	Dipolarophile	Time (hr)	Cycloadducts[a] (**2-5**)	R_f	Yield[b] (%)
1	N-cyclohexyl-α-amino nitrone	Phenyl methyl propiolate	6	Pale yellow gummy liquid	0.62	96
2	N-cyclohexyl-α-amino nitrone	Dimethyl acetylene dicarboxylate	7	Red liquid	0.58	92
3	N-cyclohexyl-α-amino nitrone	Ethyl propiolate	6	White viscous liquids	0.44, 0.50	92
4	N-cyclohexyl-α-amino nitrone	Propiolic acid	8	Yellow liquids	0.38, 0.54	89

[a]All the reactions were carried out at RT
[b]Isolated yields after purification

have coupling constants of 2.58 and 2.64 Hz respectively which implies a *trans* relationship between H_3 and H_4[13-15]. Comparing the ^{1}H NMR spectrum of **4a-5a** and **4b-5b** we suggest the major and minor conformers of isoxazoline ring systems[13] for **4a-5a** and **4b-5b** (**Figure 1**). In the cycloadducts **2** and **3**, since C-4 and C-5 protons were absent, so the coupling constant values could not be calculated.



2 R_1 = Ph; R_2 = $COOCH_3$ **3** R_1 = R_2 = $COOCH_3$
4 R_1 = $COOC_2H_5$; R_2 = H; **5** R_1 = COOH; R_2 = H
R_3 = - NMe_2



2 R_1 = Ph; R_2 = $COOCH_3$ **3** R_1 = R_2 = $COOCH_3$
4 R_1 = $COOC_2H_5$; R_2 = H **5** R_1 = COOH; R_2 = H
R_3 = - NMe_2

Figure 1

Hence, nothing could be inferred about their conformational structures. All the cycloadducts are stable and detailed study of the mass spectrum (**Scheme III**) reveals that prominent molecular ion peak and base peaks are obtained as expected. Like other isoxazoline derivatives reported in the literature[4,6], expected fragmentation peaks have also been obtained due to the development of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate, COOH for propiolic acid and $COOC_2H_5$ for ethyl propiolate respectively. Hence, it is confirmed that during mass fragmentation, the adducts undergo rearrangement to aziridine derivatives. The detailed mass fragmentation pattern is shown in **Scheme III**.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX1 881 machine as film or as KBr pellets for all the products. Mass spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q–Tof micro instrument (YA-105). Elemental analyses (CHN) were perfomed with a Perkin-Elmer 2400 series CHN analyzer. TLC were run on Fluka precoated silica gel TLC plates. N-cyclohexylhydroxylamine was prepared according to the published procedures[10]. All other reagents and solvents were used as received from commercial suppliers.

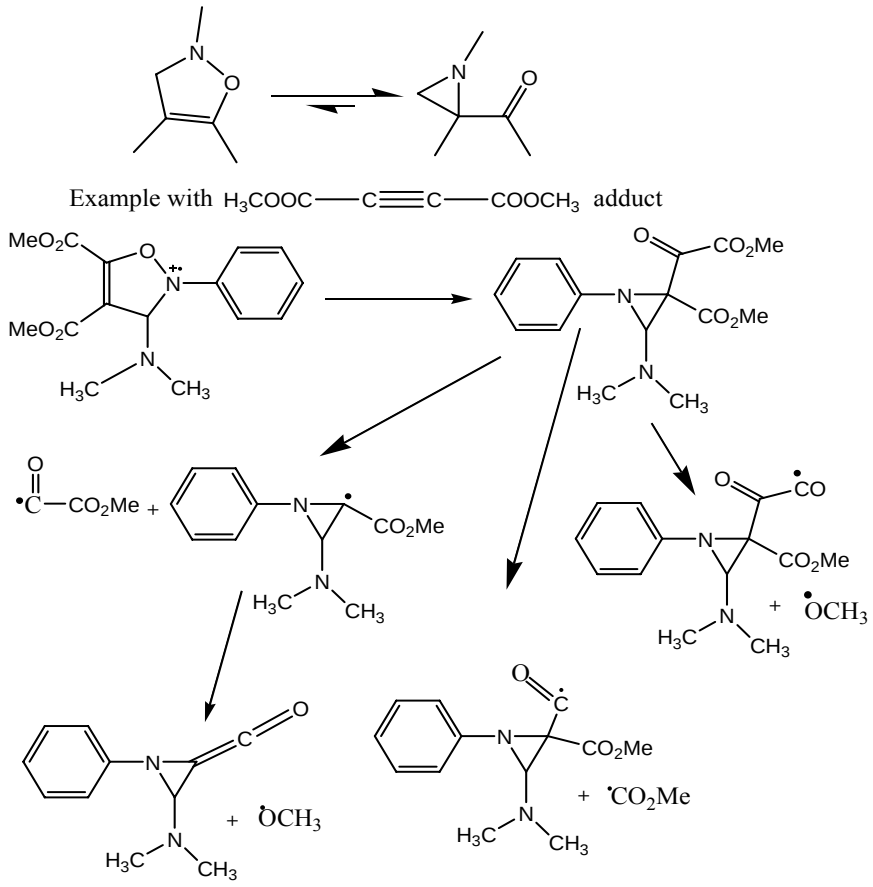
General procedure for one pot cycloaddition at elevated temperature

Initially, the cycloaddition reaction was performed at elevated temperature in case of ethyl propiolate following the methodology of cycloaddition reactions as already reported[6]. A mixture of N-cyclohexylhydroxylamine[10] (2.17 mmoles) and N,N-dimethyl formamide (9 mL) was heated in presence of anhydrous $MgSO_4$ with stirring with a magnetic stirrer for 6 hr. The formation of nitrone **1** was monitored by TLC (R_f = 0.38) and ethyl propiolate (1 equivalent) was added *in situ* at this stage and heating continued with stirring for another 6 hr (monitored by TLC). The crude products were isolated by extraction with ether and washed with saturated brine. Finally, gummy products were obtained by concentration of the organic layer under reduced pressure after column chromatography using ethyl acetate and hexane. But this methodology was abandoned because of poor yield (28%) which may be due to decomposition of nitrone at elevated temperature.

General procedure for one pot cycloaddition at room temperature

A mixture of N-cyclohexylhydroxylamine[10] (2.17 mmoles) and N,N dimethyl formamide (9 mL) was stirred in presence of anhydrous $MgSO_4$ with a magnetic stirrer at RT for 8 hr. The formation of nitrone **1** was monitored by TLC (R_f = 0.40) and ethyl propiolate (1 equivalent) was added *in situ* at this stage and stirring continued at RT for another 6 hr (monitored by TLC). The crude products were isolated by extraction with ether and washed with brine water. Finally, the cycloadducts were obtained under reduced pressure after column chromatography using ethyl acetate and hexane to furnish white viscous liquid products. **4a**:172 mg, 70%; **4b**:58 mg, 22% (**Scheme II**). This procedure was followed for other substrates listed in **Table I**.

(*S*)-methyl 2-cyclohexyl-3-(dimethylamino)-5-phenyl-2,3-dihydroisoxazole-4-carboxylate, **2**: IR ($CHCl_3$): 3155(m), 1750(s), 1665(m),1658(s),



Scheme III

1430(m), 1360(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.64–7.53 (m, 5H, C_6H_5 hydrogens), 4.05 (s, 1H, C_3H), 3.63 (s, 3H, - $COOCH_3$), 2.76 (br, 6H, NMe_2), 2.34–2.22 (m, 1H, N-CH proton), 1.95 - 1.66 (m, 10H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 172.50 (carbonyl carbon), 137.22, 135.40, 134.36, 132.64 (aromatic carbons), 88.10 (C_5), 73.42 (C_3), 57.48 (C_4), 45.00 (-$COOCH_3$), 33.25, 29.55 (N - CH_3 carbons), 26.00, 24.80, 23.44, 21.85, 20.16, 18.73 (CH_2 carbons); MS: *m/z* 330 (M^+), 286, 247, 246, 225, 194, 148, 105 (base peak), 83, 77, 31; HRMS-EI: Calcd for $C_{19}H_{26}O_3N_2$ (M) *m/z* 330.1935. Found: M^+ 330.1919.

(*S*)-dimethyl-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-4,5-dicarboxylate, 3: IR ($CHCl_3$): 3145 (m), 2820 (m),1745 (s),1700 (m), 1670 (m), 1420 (s), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.75 (s, 1H, C_3H), 3.66 (s, 3H,- $COOCH_3$), 3.60 (s, 3H,- $COOCH_3$), 2.68 (br, 6H, NMe_2), 2.40–2.28 (m, 1H, N-CH proton), 2.05 - 1.64 (m, 10H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169.00, 167.40 (carbonyl carbons), 87.54 (C_5), 76.00 (C_3), 59.40 (C_4), 44.00, 43.00 ($COOCH_3$), 31.00, 29.43 (N - CH_3 carbons), 25.80, 24.33, 23.90, 22.70, 20.64, 18.56 (CH_2 carbons); MS: *m/z* 312 (M^+), 281, 268, 229, 228, 225 (base peak), 194, 185, 87, 83, 59, 44, 31; HRMS-EI: Calcd for $C_{15}H_{24}O_5N_2$ (M) *m/z* 312.1677. Found: M^+ 312.1668.

(*S*)-ethyl 2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylate, 4a: IR ($CHCl_3$): 3165(m), 2945(s), 1770(m), 1680(s), 1656(s), 1430(m), 1260 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.64 (d, 1H, *J* = 9.3 Hz, C_3H), 4.26 (dd, 2H, *J* = 6.24, 6.36 Hz, $COOCH_2CH_3$), 3.35 (d, 1H, *J* = 9. 2 Hz, C_4H), 2.76 (br, 6H, NMe_2), 2.46–2.30 (m, 1H, N-CH proton), 2.04–1.67 (m, 10H), 1.40 (t, 3H, *J* = 4.36 Hz, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 173.44 (carbonyl carbon), 86.00 (C_5), 78.00 (C_3), 55.00 (C_4), 32.00 ($COOCH_2CH_3$), 30.00 ($COOCH_2CH_3$), 28.84, 27.35 (N-CH_3 carbons), 25.00, 23.00, 22.25, 20.83, 19.00, 18.44 (CH_2 carbons); MS: *m/z* 268 (M^+), 224, 195 (base peak), 185, 184, 141, 83, 73; HRMS-EI: Calcd for $C_{14}H_{24}O_3N_2$ (M) *m/z* 268.1779. Found: M^+ 268.1763.

(*R*)-ethyl-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylate, 4b: IR ($CHCl_3$): 3160(m), 2955(s), 1770(m), 1684(s), 1658(s), 1435(m), 1255(m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.58 (d, 1H, *J* = 2.53 Hz, C_3H), 4.32 (dd, 2H, *J* = 7.14, 6.16 Hz, $COOCH_2CH_3$), 3.26 (d, 1H, *J* = 2.58 Hz, C_4H), 2.66 (br, 6H, NMe_2), 2.24–2.12 (m, 1H, N-CH proton), 1.94–1.53 (m, 10H), 1.24(t, 3H, *J* = 4.08 Hz, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 172.00 (carbonyl carbon), 88.00 (C_5), 76.64 (C_3), 57.26 (C_4), 33.48 ($COOCH_2CH_3$), 31.70 ($COOCH_2CH_3$), 29.00, 27.85 (N - CH_3 carbons), 26.10, 24.00, 23.00, 21.42, 20.25, 18.36 (6 CH_2 carbons); MS: *m/z* 268 (M^+), 224, 223, 195 (base peak), 185, 184, 141, 83, 73, 45; HRMS-EI: Calcd for $C_{14}H_{24}O_3N_2$ (M) *m/z* 268.1779. Found: M^+ 268.1756.

(*S*)-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylic acid, 5a: IR ($CHCl_3$): 3144(m), 2942(s), 1765(m), 1684(s), 1660(s), 1440(m), 1310 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.8 (s, 1H, - COOH), 4.52 (d, 1H, *J* = 9.46 Hz, C_3H), 3.82 (d, 1H, *J* = 9. 44 Hz, C_4H), 2.58 (br, 6H, NMe_2), 2.33–2.24 (m, 1H, N-CH proton), 2.12–1.74 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 181.30 (carbonyl carbon), 87.00 (C_5), 78.54 (C_3), 56.52 (C_4), 32.27, 30.72 (N-CH_3 carbons), 27.00, 25.30, 24.24, 23.00, 21.00, 18.00 (CH_2 carbons); MS: *m/z* 240 (M^+), 196, 195 (base peak), 167, 157, 83, 73, 45; HRMS-EI: Calcd for $C_{12}H_{20}O_3N_2$ (M) *m/z* 240.1467. Found: M^+ 240.1452.

(*R*)-2-cyclohexyl-3-(dimethylamino)-2,3-dihydroisoxazole-5-carboxylic acid, 5b: IR ($CHCl_3$): 3155(m), 2950(s), 1770(m), 1680(s), 1655(s), 1444(m), 1250(m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.4 (s, 1H, - COOH), 4.63 (d, 1H, *J* = 2.56 Hz, C_3H), 3.75 (d, 1H, *J* = 2. 64 Hz, C_4H), 2.53 (br, 6H, NMe_2), 2.40–2.28 (m, 1H, N-CH proton), 1.90–1.58 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 180.00 (carbonyl carbon), 88.43 (C_5), 76.00 (C_3), 57.00 (C_4), 34.00, 32.80 (N - CH_3 carbons), 28.00, 27.40, 25.00, 23.15, 22.20, 19.00 (6 CH_2 carbons); MS: *m/z* 240 (M^+), 196, 195 (base peak), 167, 157, 156, 83, 73, 45, 44; HRMS-EI: Calcd for $C_{12}H_{20}O_3N_2$ (M) *m/z* 240.1467. Found: M^+ 240.1449.

Conclusion

In conclusion, the present procedure provides an efficient solvent free methodology for the synthesis of isoxazoline and their derivatives with stereoselectivity. The notable advantages offered by this method are simple operation, mild and environment friendly reaction conditions, much faster reactions and high yield of products. Finally, a new methodology has been developed for α-amino nitrone synthesis from N,N dimethyl formamide in solvent free conditions and literature survey reveals that synthesis of isoxazoline derivatives from N,N dimethyl formamide derived α-amino nitrone is a new approach while reports of α-amino nitrone from formamide are known[1,12,14].

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