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Synthesis and characterization of isoxazole derivatives from strained bicyclic hydrazines

K. Rameshbabu, K. Venu Gopal, A. Jayaraju, G. Nageswara Reddy and J. Sreeramulu*

Department of Chemistry, Sri Krishnadevaraya University, Anantapuramu, Andhra Pradesh, India

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ABSTRACT

A novel method for the synthesis of isoxazoles derivatives with bicyclic hydrazines has been proposed. This methodology involves the cycloadducts, which can be easily elaborated to various functionalized structures with significant bio-activity those are not directly accessible by 1,3-dipolarcycloadditions.

Key words: 1, 3-dipolar cycloadditions, isoxazoles, bicyclic hydrazines, Heterocyclics.

INTRODUCTION

2,3-diazabicyclo[2.2.1]hept-5-ene derived from Diels-Alder reaction between alkyl azodicarboxylate and cyclopentadiene[1], which holds tremendous synthetic potential as intermediates in the construction of a variety of biologically active molecules[2-4].Cyclo addition of bicyclic olefins with various dipoles are limited[5]. Prior works cyclo addition reactions [2+2],[6-8] [3+2],[9-11] or [4+2][12] have been reported on bicyclic hydrazines diastereo selectively. Investigation of the dipolar cycloaddition reactions of 2,3-diazabicyclo[2.2.1]hept-5-ene with aryl nitrile oxides is one of the important areas of modern drug discovery It. Since the cycloadducts forming in these reactions are isoxazoles.[13], with potent bio-activity, they carry a higher importance in synthetic organic chemistry. Among them, 1, 3-dipolar cycloaddition reactions offer a convenient route to multi-functionalized five member heterocyclic compounds in a highly regiospecific and stereo specific fashion[14]. One of the major structurally diverse groups of heterocyclic compounds synthesized by 1, 3-dipolar cyclo-additions with Nitrile N-oxides which can undergo [3+2] cycloaddition with a variety of alkenes to form isoxazoles[15,16].Nitrile-N-oxides fall under propargyl-allenyl type of 1, 3-dipoles and they can be considered as resonance hybrid of the mesomeric structures.[17,18]Present study is aimed to synthesize series of isoxazoles through 1,3-dipolar reactions on sterically hindered bicyclic olefins.

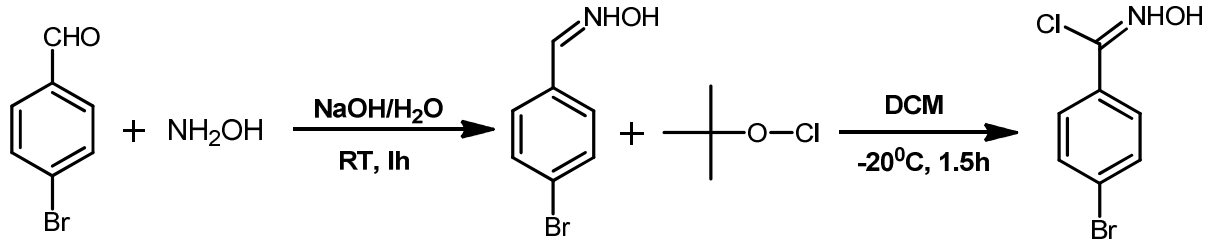
EXPERIMENTAL SECTION

All reactions were conducted in oven-dried glassware. Solvents used for all experiments were distilled or dried and specified melting points were recorded on a Buchi-530 melting point apparatus. High resolution mass spectra were recorded under EI/HRMS (5000 resolution, Auto spec Mass spectrometer). The IR spectra were recorded on Bruker Alpha FT-IR spectrophotometer. NMR spectra were recorded on Bruker 500 MHz NMR spectrometers. NMR spectra were obtained using chloroform-d as solvent TMS as internal standard. Chemical shifts are given in δ scale with tetramethylsilane as the internal standard. All reactions were monitored by TLC (Silica gel $F_{254,}$ 0.25 mm, Merck) and visualization was done with UV or by staining in McGill or Enholm Yellow solution.

Column chromatography was performed by using 100-200 mesh silica gel and appropriate mixture of hexane and ethyl acetate for elution. The solvents were removed using Heidolph rotary evaporator**.**

RESULTS AND DISCUSSION

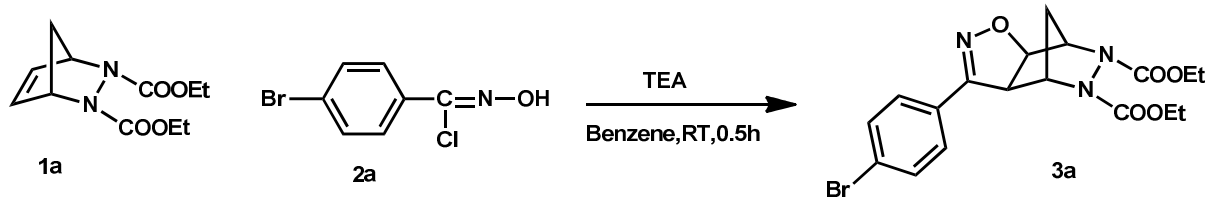
4-Bromobenzaldeydewas added to sodium hydroxide solution in water in addition to hydroxylamine hydrochloride and stirred at room temperature for 1h. This reaction afforded oxime in 84% yield. 4-Bromobenzaldeydeoxime on treatment with tert-butylhypochlorite at room temperature for 1.5h gave N-hydroxy-4-bromobenzimidoyl chloride in 96% yield. Similarly, hydroximoyl chlorides of corresponding aryl halides were synthesized.



Scheme 1

Aryl hydroximoyl chloride (1.02 mmol) in benzene (5 mL) was added to a solution of azabicyclic olefin (0.68 mmol) and triethylamine (1.02 mmol) in benzene (5 mL) at room temperature. Reaction mixture was filtered to remove triethyl amine hydrochloride and the solvent was evaporated through rotary evaporator. The residue was chromatographed on silica gel column with ethyl acetate in hexane which afforded the product in higher yields (Scheme1).

In this study, our main objective was to perform cyclo addition reactions of azabicyclic olefin with nitrile oxide, which lead to the formation of isoxazoles. So, firstly we added 3-diazabicyclo [2.2.1]hept-5-ene-2,3-dicarboxylate **(1a)** with 4-bromo benzohydroximoy chloride (**2a)** and triethylamine in benzene at room temperature for 5 hour afforded isoxazole derived product (**3a)** in 95% yield(Scheme 2).



Scheme 2

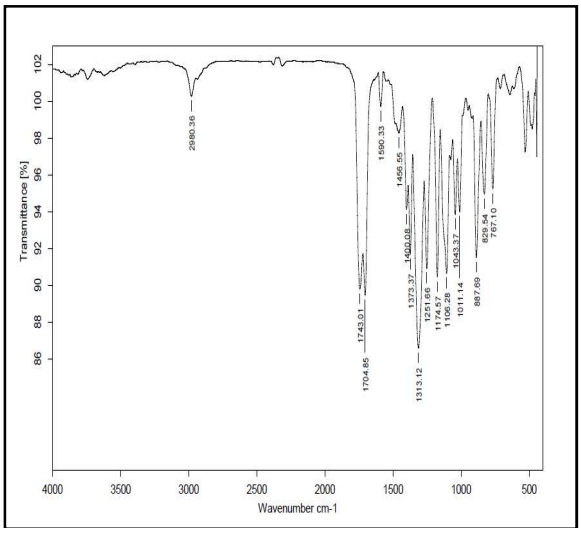


Fig. (1).IR spectrum of 3a

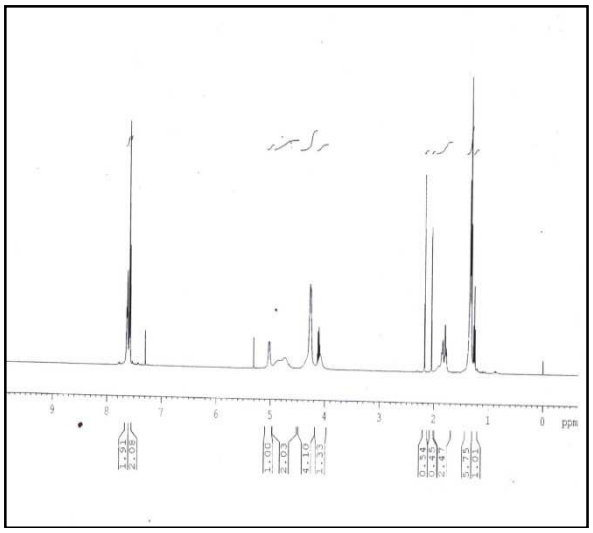


Fig. (2).^{1}H NMR spectrum of 3a

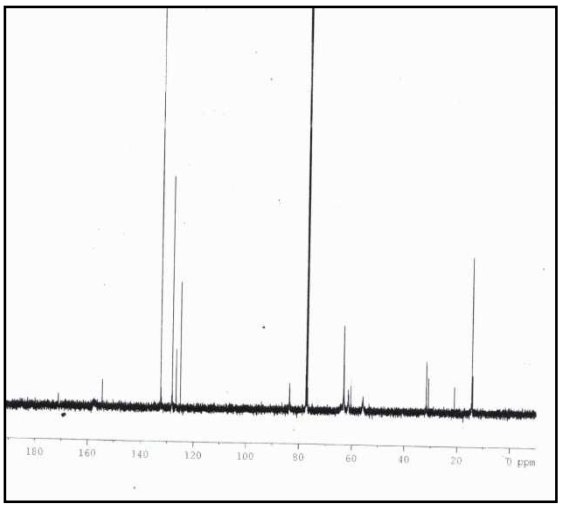


Fig. (3).^{13}C NMR spectrum of 3a

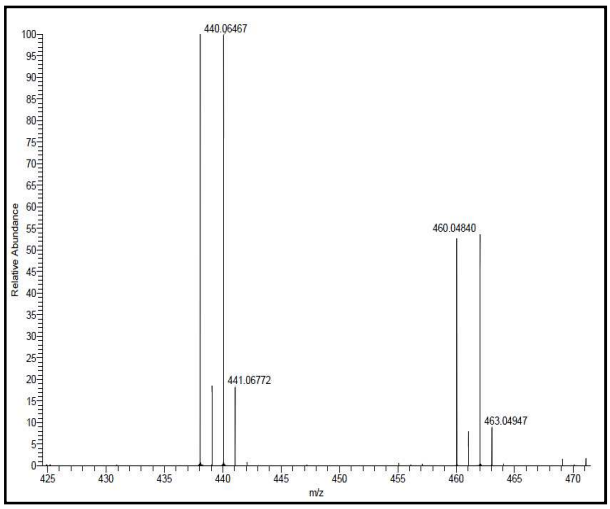


Fig. (4). Mass spectrum of 3a

The IR spectrum of the compound **3a** showed the characteristic ester carbonyl absorption at 1743 and 1704 cm^{-1} (Fig. (1)). similarly, in the ^{1}HNMR spectrum, peaks in the region δ 7.63-7.56 ppm were assigned to the aromatic protons. The proton on the carbon attached to the oxygen resonated at δ 5.30ppm. The bridge head protons of bicyclic ring appeared at δ 5.02-4.72, the proton on the carbon which is attached benzylic carbon appeared at δ 4.14-4.08 ppm. The methylene protons of the bicyclic ring appeared at δ 1.85 to 1.77 ppm (Fig. (2)). In the ^{13}C NMR spectrum ester carbonyl carbons resonated at δ 154.50 and 153.82 ppm. The carbon attached to oxygen resonated at δ 83.55 ppm. All other signals in ^{13}C NMR spectra were in agreement with the proposed structure (Fig (3)). The structure assigned was further supported by low resolution mass spectral analysis which showed a molecular ion peak at m/z 437.04 (Fig. (4)). From, the above all analysis the structure of the compound (3a) is confirmed. Similarly the structures of the corresponding synthesized compounds are also assigned by the spectral analysis.

Generality of the methodology was proved by carrying out the reactions of different bicyclic alkenes with different Nitrile oxides the results are summarized in Table 1.The chemistry of the related formal diene adducts has been extensively investigated and utilized in many synthetic applications.[19]

(3aS,4S,7R,7aR)-diethyl-3-(4-chlorophenyl)-3a,4,7,7a-tetrahydro-4,7-methanoisoxazolo[4,5-d]pyridazine-5,6-dicarboxylate(3a)
Physical appearance of the compound is light yellow color which melting point of 114^{o}C

IR (KBr): 2980, 1743, 1704, 1590, 1456, 1400, 1373, 1313, 1251, 1174, 1106, 1043, 1011, 887, 829, 767 cm^{-1}.; **^{1}H NMR (500MHz, CDCl3):** δ = 7.63 – 7.62 (m, 2H), 7.60 -7.56 (m, 2H), 5.02 – 5.01 (m, 1H), 4.83 (S, 1H), 4.72 (S, 1H), 4.27 – 4.26 (m, 4H), 4.14-4.26 (m, 4H). 1.91-1.83 (m, 1H), 1.79 – 1.77 (m, 1H), 1.38-1.27 (m, 1H).; **^{13}C NMR (125 MHz, CDCl3):** δ = 156.26, 154.50, 132.38, 128.15, 126.67, 125.67, 125.08, 83.55, 63.09, 61.30, 60.38, 55.80, 31.68, 30.92, 14.48, 14.44.; **MS (FAB**): m/z [M]$^{+}$calc for $C_{18}H_{20}BrN_3O_5$: 437.06.; found 437.04.

(3aS,4S,7R,7aR)-diethyl3-(5-bromo-2-methoxyphenyl)-3a.4,7,7a-tetrahydro-4,7-methanoisoxazolo[4,5-*d*]pyridazine-5,6-dicarboxylate(3b)
Physical appearance of the compound is brown color which melting point of 168^{o}C

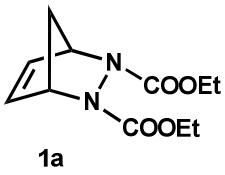
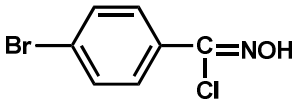
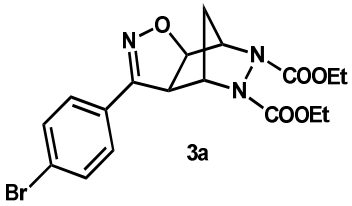
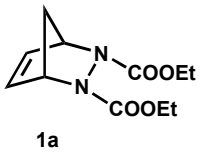
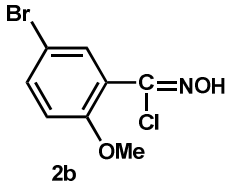
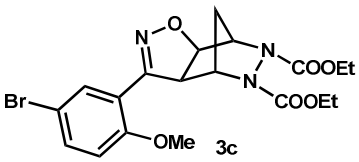
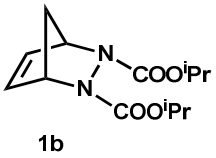
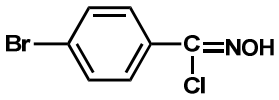
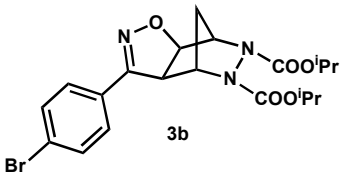
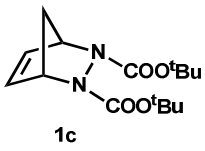
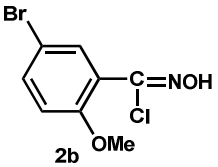
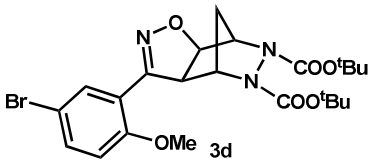
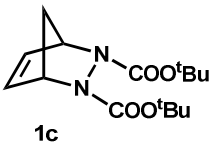
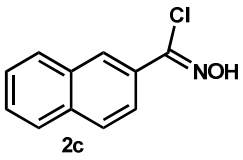
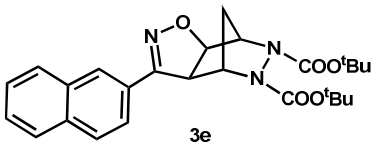
IR (KBr): 2974, 1739, 1710, 1590, 1475, 1377, 1314, 1252, 1176, 1109, 1025, 897, 808, 766, 696,623 cm^{-1}.; **^{1}H NMR (500MHz, CDCl3):** δ = 7.87(S, 1 H), 7.49-7.46 (m, 1H), 6.86-6.84 (m,1H), 4.91 (S, 1 H), 4.70 (m, 2 H), 4.23 (m, 4 H), 4.12-4.08 (m, 1 H), 3.86 (S, 3 H), 1.81-1.79 (m, 1 H), 1.73-1.70 (m, 1 H), 1.32-1.22 (m, 6 H). ; **^{13}C NMR (125MHz, CDCl3):** δ = 156.66, 155.80, 143.94, 139.02, 119.28, 117.76, 104.42, 99.09, 69.63, 48.08, 43.32, 42.35, 14.23.; **MS (FAB**): m/z [M]$^{+}$calc for . $C_{19}H_{22}BrN_3O_6$: 467.30; found 467.

(3aS,4S,7R,7aR)-diisopropyl3-(4-Chloropheny)-3a.4,7,7a-tetrahydro-4,7-methanoisoxazolo[4,5-d]pyridazine-5,6-dicarboxylate(3c)
Physical appearance of the compound is light yellow color which melting point of 122^{o}C

IR (KBr): 2981, 1741, 1702, 1590, 1460, 1372, 1306, 1252, 1176, 1102, 888 cm^{-1}. **^{1}H NMR (500MHz, CDCl3):** δ = 7.62 (s, 2H), 7.58-7.56 (m, 2H), 5.01 (s, 3H), 4.87 (s, 1H), 4.70 (S, 1H), 4.13-4.05 (m, 1H), 1.81 (S, 1H), 1. 76 –

1.74 (m, 1H), 1.31-1.30(m, 12H).; **^{13}C NMR (125MHz, CDCl3):** δ =154.51, 132.33, 128.14, 126.74, 125.02, 83.57, 70.99, 61.20, 60.36, 56.42, 31.58, 30.91, 21.92.; **MS (FAB**): m/z $[M]^+$calc for. $C_{20}H_{24}BrN_3O_5$: 465.09; found 465.07.

Table 1: Dipolar reactions with azabicyclic alkenes

Entry	Alkene	Oxime	Product	Yield %
a	 1a	 2a	 3a	95
b	 1a	 2b	 3c	88
c	 1b	 2a	 3b	96
d	 1c	 2b	 3d	91
e	 1c	 2c	 3e	90

Reaction conditions: alkene(1.0 equiv.), chloro oxime (0.7 equiv.), base (1.0 equiv.), solvent (5ml), at Room temperature, time 0.5h.

(3aS,4S,7R,7aR)-di-tert-butyl-3-(5-bromo-2-methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methanoisoxazolo[4,5-*d*]pyridazine-5,6-dicarboxylate(3d)

Physical appearance of the compound is light yellow color which melting point of 196^{o}C

IR (KBr): 2977, 2935, 1737, 1701, 1592, 1482, 1365, 1329, 1247, 1145, 1045, 902, 853, 807, 767, 623 cm$^{-1;}$ **^{1}H NMR (500MHz, CDCl3):** δ =7.61 (S, 1 H), 7.22-7.21 (m, 1 H), 6.61-6.59 (m, 1 H), 4.42 (S, 1 H), 4.34 (S, 1 H), 4.05 (S, 1 H), 3.87-3.83 (m, 1 H), 3.66 (m, 3 H), 1.50-1.47 (m, 1 H), 1.43- 1.42 (m, 1 H), 1.25-1.21 (m, 18 H).; **^{13}C NMR (125MHz, CDCl3):** δ = 156.30, 153.82, 134.65, 132.13, 113.13, 113.16, 112.70, 112.67, 83.19, 82.17, 61.95, 61.23, 55.94, 31.46, 30.88, 28.05. ; **MS (FAB**): m/z $[M]^+$calc for . $C_{23}H_{30}BrN_3O_6$: 523.13; found 523.12.

(3aS,4S,7R,7aR)-di-tert-butyl,3-(naphthalene-1-yl)-3a,4,7,7a-tetrahydro-4,7-methanoisoxazolo[4,5-*d*]pyridazine-5,6-dicarboxylate(3e)

Physical appearance of the compound is light brown color which melting point of 127^{o}C

IR (KBr): 2977, 2928, 1733, 1702, 1456, 1364, 1324, 1250, 1150, 1105, 1044, 998, 964, 900, 857, 820, 756 cm$^{-1;}$ **^{1}H NMR (500MHz, CDCl3):** δ = 7.97 (S, 1 H), 7.86-7.85 (m, 1 H), 7.76-7.74 (S, 3 H), 7.45-7.43 (m, 2 H), 4.96 (S, 1 H), 4.7 (S, 1 H), 4.67 (S, 1 H), 4.10-4.01 (m, 1 H), 1.87 (S, 1 H), 1.66 (S, 1 H), 1.43 (S, 1 H).; **^{13}C NMR (125MHz, CDCl3):** δ = 156.62, 155.45, 134.13, 133.02, 128.95, 128.32, 127.88, 127.51, 126.96, 122.56, 123.48, 82.47, 62.57, 61.32, 57.00, 31.72, 30.91, 29.68. ; **MS (FAB**): m/z $[M]^+$calc for . $C_{26}H_{31}BrN_3O_5$: 465.23; found 465.21.

CONCLUSION

In this study, we demonstrated the significance of 1,3–dipolar cycloaddition reactions of bicyclic olefins with Nitrile-N-Oxides derived from various benzohydroximoyl chlorides, which provided an efficient and simple route to synthesize biologically important isoxazoles compounds. Since these compounds contain various heteroatoms, we strongly believe that they possess biological properties like anti-bacterial, anti-fungal, anti-malarial activity etc. Currently, the evaluation of biological activities of all isoxazoles is in progress.

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