An efficient method for the synthesis of 1,2,3-triazole functionalized isoxazolidine derivatives by 1,3-dipolar cycloaddition of nitrones with terminal olefins

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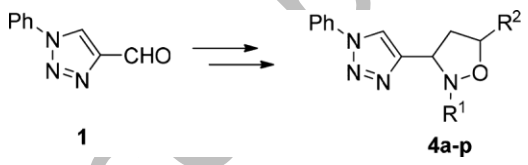
Abstract

1-Phenyl-1,2,3-triazole-4-carbaldehyde **1** was treated with different *N*-alkyl hydroxylamine hydrochlorides **2** using $NaHCO_3$ to obtain 1,2,3-triazole substituted *N*-alkyl nitrones **3a-c**. The nitrones **3a-c** were further reacted with different substituted olefins and furnished 2-alkyl-3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5-(substituted)isoxazolidine derivatives **4a-p** in high yields via 1,3-dipolar cycloaddition reaction.

GRAPHICAL ABSTRACT



KEYWORDS: 1,2,3-Triazole, Nitrones, Olefins, 1,3-Dipolar cycloaddition, Isoxazolidine

INTRODUCTION

There has been an ever increasing quest for natural products containing the isoxazolidine moiety due to their vast applications as biologically active substances, e.g., plant growth regulators,[1,2] antiviral and anticancer compounds.[3-5] The 1,3-dipolar cycloaddition reaction of an alkene with a nitrone is one of the most reliable strategies for the construction of highly substituted five membered isoxazolidine derivatives.[6] Isoxazolidines can be used as potential precursors for the synthesis of exceptionally useful natural products such as alkaloids, β-lactams, sugar derivatives, and amino acids.[7-12] Isoxazolidines are useful synthetic intermediates towards the synthesis of 1,3-amino alcohols,[13] as well as a variety of bicyclic heterocycles. Synthetic applications as well as biological activities of isoxazolidines prompted us to synthesize the title compounds. Based on our earlier work on synthesis of substituted triazoles, isoxazoles and their anticancer activity,[14-17] we have developed an efficient method for the synthesis of 1,2,3-triazole functionalized isoxazolidine derivatives.

It is known that 1,3-dipoles are of two types such as allyl anion type and the propargyl/allenyl anion type. Nitrones belongs to allyl anion type of 1,3-dipoles.[18] The most commonly used dipolarophiles are alkenes and alkynes. [19] The 1,3-dipolar cycloaddition of alkenes with nitrones produce substituted isoxazolidines as racemic mixtures[20] or with stereo induction if chirality is present either in dipole or dipolarophile.[21] More recently, Romeo and co-workers[5d-f] reported the synthesis and biological activity of 1,2,3-triazolyl functionalized isoxazolidines. Aouadi and co-workers[22] also reported a stereoselective synthesis of 1,2,3-triazolyl-functionalized isoxazo lidines via two consecutive 1,3-dipolar cycloadditions. The 1,3-dipolar

cycloaddition reaction of menthone derived chiral nitrone as a dipole with allyl bromide as a dipolarophile resulted as a single stereoisomer of substituted isoxazolidine. Cu(I)-catalyzed azide alkyne cycloaddition (CuAAC) applied to an azidomethyl intermediate afforded to a series of six heterocycles possessing a 4-substituted-(1,2,3-triazolyl) methyl moiety linked to an isoxazolidine.[22]

We have choosen triazole functionalized nitrones as 1,3-dipoles and terminal olefins as dipolarophiles for the synthesis of racemic isoxazolidines via 1,3-dipolar cycloaddition.

RESULTS AND DISCUSSION

The reaction of 1-phenyl-1,2,3-triazole-4-carbaldehyde **1** and *N*-benzylhydroxylamine hydrochloride **2** was performed in the presence of sodium bicarbonate in ethanol at reflux temperature to furnish nitrone **3a**. Subsequent treatment of nitrone **3a** with styrene in toluene at reflux temperature afforded the triazole functionalized isoxazolidine. The sequence of the reaction is mainly by condensation of 1-phenyl-1,2,3-triazole carbaldehyde **1** with *N*-benzylhydroxyl amine hydrochloride **2** to form nitrone **3a** which underwent 1,3-dipolar cycloaddition with styrene to result in 1,2,3-triazole functionalized isoxazolidine product **4a,** the reaction is outlined in Scheme 1.

It is commonly accepted that, the 1,3-dipolar cycloaddition reaction of nitrones represent a one-step concerted mechanism in which two new σ bonds are formed as shown in Scheme 2.

The regiochemistry was determined based on ^{1}H and ^{13}C NMR for compounds **4a-p**. The stereochemistry of our synthesized compounds **4a-p** has been determined based on 2D NOESY spectrum of one of our synthesized compound **4h.**

The reaction of nitrones (1,3-dipole) with monosubstituted alkenes (unsymmetrical dipolarophiles) resulted 3,5-disubstituted isoxazolidine derivatives **4a-p** and the reaction is considered to be regioselective. More specifically, the 1,3-dipolar cycloaddition of nitrone **3a** with styrene furnished only one regioisomer 3,5-disubstituted isoxazolidine **4a** as shown in Scheme 1. NMR data supports the presence of only one proton on C-5 carbon in down field at δ 4.62 ppm. In general, the 1,3-dipolar cycloaddition reactions with alkenes are cis stereoselective. In this case, 1,3-dipolar cycloaddition of nitrones with mono substituted alkenes resulted **4a-p** as 1:1 ratio of cis stereoisomers. It is also confirmed by measuring the optical rotation as zero and found to be racemic. The NOESY spectrum of representative compound **4h** shows that there is NOE between C-3 and C-5 protons as shown in Figure 1 and enclosed in supporting information.

1-Phenyl-1,2,3-triazole-4-carbaldehyde **1** was reacted with different *N*-alkyl hydroxylamine hydrochlorides **2a-c** in presence of sodium bicarbonate as a base in ethanol at reflux temperature and obtained 1,2,3-triazole substituted *N*-alkyl nitrone derivatives **3a-c**[16] in a single step. These nitrone derivatives **3a-c** were further underwent 1,3-dipolar cycloaddition with various terminal olefins and furnished 2-alkyl-3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5-(substituted)isoxazolidine derivatives **4a-p** in high yields.

The products formed in each case, are described in Scheme 3 and the results are tabulated in Table 1.

CONCLUSIONS

In conclusion, we have developed an efficient method for the synthesis of 1,2,3-triazole functionalized isoxazolidine derivatives by 1,3 dipolar cycloaddition of nitrones with various terminal olefins.

EXPERIMENTAL

General Procedure For The Synthesis Of (1,2,3)-Triazole Substituted-N-Alkylnitrone Derivatives (3a-C)[16]

A mixture of the corresponding 1-substituted-1H-1,2,3-triazole-4-carbaldehyde (1 equiv), *N*-alkylhydroxylamine hydrochloride (1.5 equiv) and sodium bicarbonate (1.5 equiv) in absolute ethanol (6mL/mmol) as solvent was heated to reflux until the aldehyde consumed (after 2-3 hours checked by TLC). The reaction mixture was brought to room temperature and ethanol was removed under reduced pressure. The residue was diluted with water and the product was extracted with ethyl acetate. The organic layers were combined and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluted in petroleum ether/EtOAc).

N-((1-Phenyl-1H-1,2,3-Triazol-4-Yl)Methylene)Cyclohexanamine Oxide (3c)

White solid, m.p.102-104 ^{o}C, Yield: 82%, I.R. (KBr, cm^{-1}): 2992 (HC=C), 1606 (-C=N), 1459 (N-O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30-1.48 (m, 6H, -$(CH_2)_3$), 1.99-2.18 (m,

4H, -$(CH_2)_2$), 3.95 (m, 1H, CHN), 7.46 (t, J=7.6 Hz, 1H, Ar-H), 7.54 (t, J=8.1 Hz 2H, Ar-H), 7.80 (d, J=8.1 Hz, 2H, Ar-H), 7.92 (s, 1H, Triazole-H), 9.32 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.3, 136.6, 129.7, 128.8, 125.2, 123.2, 120.3, 74.1, 31.1, 24.8; MS (ESI, 70eV): m/z: 293 (M+Na); HRMS m/z calcd. for $C_{15}H_{18}N_4ONa$ ($[M+Na]^+$): 293.1372. Found 293.1369.

General Procedure For The Synthesis Of 2-Alkyl-3-(1-Phenyl-1H-1,2,3-Triazol-4-Yl)-5-(Substituted)Isoxazolidine (4a-P)

A mixture of (1,2,3)-triazole substituted-*N*-alkyl nitrone (1 equiv) and 1-substituted ethylene (1.5 equiv) in toulene (5mL) as solvent was refluxed until the nitrone was consumed (after 3-4 hours checked by TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, eluted with petroleum ether/EtOAc).

2-Benzyl-5-Phenyl-3-(1-Phenyl-1H-1,2,3-Triazol-4-Yl)Isoxazolidine (4a)

White solid, m.p. 124-126 ^oC, Yield: 81%, I.R. (KBr, cm^{-1}): 2957 (HC=C), 1598 (-N=N), 1495(N-O), 1295(C-N), 1282(C-O); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.65-2.75 (m, 1H, -CH), 3.26-3.36 (m, 1H, -CH), 4.21 (s, 2H, CH_2N), 4.62 (t, J=6.6 Hz, 1H, -CH), 5.40 (t, J=7.9 Hz, 1H, -CH), 7.24-7.37 (m, 7H, Ar-H), 7.38-7.47 (m, 3H, Ar-H), 7.49-7.58 (m, 3H, Ar-H), 7.69 (d, J=7.6 Hz, 2H, Ar-H), 7.89 (s, 1H, Triazole-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.3, 136.2, 135.7, 129.4, 129.0, 128.6, 128.0, 127.1, 126.2, 122.1, 119.1, 76.6, 61.2, 40.2, 28.4, 21.6; MS (ESI, 70eV): m/z: 383 (M+H); Anal. Calcd. for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65%. Found: C, 75.35; H, 5.81; N, 14.68 %.

2-(Tert-Butyl)-5-Phenyl-3-(1-Phenyl-1H-1,2,3-Triazol-4-Yl)Isoxazolidine (4g)

White solid, m.p. 142-144 ^{o}C, Yield: 84%, I.R. (KBr, cm^{-1}): 2986 (HC=C), 1539 (-N=N), 1421(N-O), 1245(C-N), 1212(C-O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (s, 9H, $(CH_3)_3$), 2.46-2.57 (m, 1H, -CH), 3.09-3.20 (m, 1H, -CH), 4.88 (t, J=7.9 Hz, 1H, -CH), 5.24 (t, J=8.6 Hz, 1H, -CH), 7.28-7.36 (m, 3H, Ar-H), 7.39-7.46 (m, 3H, Ar-H), 7.50 (t, J=7.2 Hz, 2H, Ar-H), 7.68 (t, J=7.9 Hz, 2H, Ar-H), 7.89 (s, 1H, Triazole-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.6, 139.9, 137.1, 128.2, 129.6, 126.3, 119.4, 120.2, 80.3, 60.4, 56.7, 47.8, 26.2; MS (ESI, 70eV): m/z: 349 (M+H); HRMS m/z calcd. for $C_{21}H_{25}N_4O$ ($[M+H]^+$): 349.2022. Found 349.2016.

2-Cyclohexyl-5-Phenyl-3-(1-Phenyl-1H-1,2,3-Triazol-4-Yl)Isoxazolidine (4k)

White solid, m.p. 144-146 ^{o}C, Yield: 82%, I.R. (KBr, cm^{-1}): 2988 (HC=C), 1556 (-N=N), 1387(N-O), 1245(C-N), 1198(C-O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18-1.35 (m, 6H, $(CH_2)_3$), 1.61-1.87 (m, 4H, $(CH_2)_2$), 2.22 (m, 1H, NCH), 2.49-2.62 (m, 1H, -CH), 3.18-3.30 (m, 1H, -CH), 4.83 (t, J=6.1 Hz, 1H, -CH), 5.21 (t, J=7.5 Hz, 1H, -CH), 7.24-7.36 (m, 5H, Ar-H), 7.41 (t, J=8.3 Hz, 1H, Ar-H), 7.50 (t, J=7.5 Hz, 2H, Ar-H), 7.72 (d, J=8.3 Hz, 2H, Ar-H), 8.01 (s, 1H, Triazole-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.3, 137.1, 129.6, 128.5, 127.8, 126.7, 120.2, 119.5, 78.8, 44.8, 31.2, 29.7, 25.8, 24.7, 24.5; MS (ESI, 70eV): m/z: 375 (M+H); HRMS m/z calcd. for $C_{23}H_{27}N_4O$ ($[M+H]^+$): 375.2179. Found 375.2178.

SUPPORTING INFORMATION

Full experimental details, copies of ^{1}H and ^{13}C NMR spectra, can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGEMENTS

B.N, KCA, PVSS, BVT are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for providing funding through XII five year plan project DITSF code: CSC-0204. The other authors are also thankful to the CSIR, New Delhi, India for providing financial assistance in the form of senior research fellowships.

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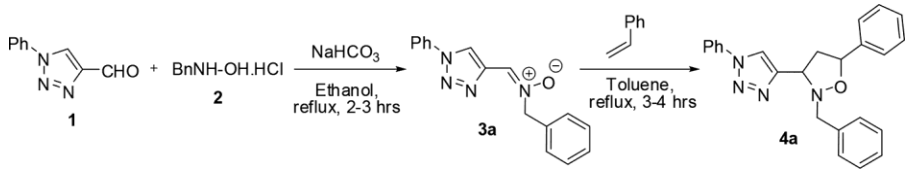
Table 1. Preparation of compounds **3c** and **4a-p**

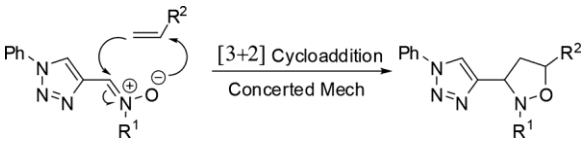
S. No	Compound No	R^1	R^2	Yield (%)[a]
1	**3c**	Cyclohexyl	–	82
2	**4a**	Benzyl	C_6H_5	81
3	**4b**	Benzyl	4-$CH_3C_6H_4$	84
4	**4c**	Benzyl	4-$CH_3OC_6H_4$	86
5	**4d**	Benzyl	Naphthalene-2-yl	82
6	**4e**	Benzyl	CN	84
7	**4f**	Benzyl	COOEt	78
8	**4g**	*t*-Butyl	C_6H_5	84
9	**4h**	*t*-Butyl	4-$CH_3C_6H_4$	82
10	**4i**	*t*-Butyl	4-$CH_3OC_6H_4$	78
11	**4j**	*t*-Butyl	Naphthalene-2-yl	79
12	**4k**	Cyclohexyl	C_6H_5	82
13	**4l**	Cyclohexyl	4-$CH_3C_6H_4$	84
14	**4m**	Cyclohexyl	4-$CH_3OC_6H_4$	80
15	**4n**	Cyclohexyl	Naphthalene-2-yl	78
16	**4o**	Cyclohexyl	CN	74
17	**4p**	Cyclohexyl	COOEt	72

[a]Isolated yields.

Scheme 1. Synthesis of 2-benzyl-5-Phenyl-3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)isoxazolidine **4a**



Scheme 2. Plausible mechanism for conversion of **3a-c** to **4a-p**



Scheme 3. Synthesis of 2-alkyl-3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5-(substituted)isoxazolidine derivatives **4a-p**

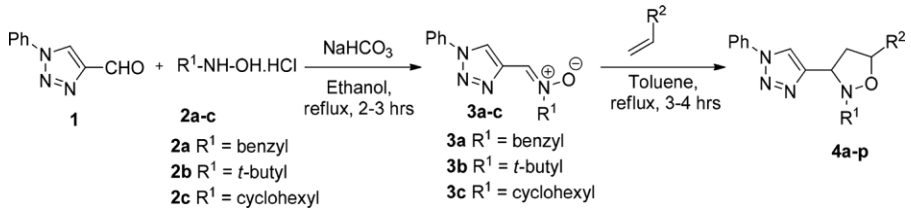


Figure 1. Characterestic NOE of compound 4h