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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 887–890

Reaction of allenylmagnesium and allenylindium bromides with nitrile oxides: synthesis of novel 5-butynyl- and 5-methylisoxazoles☆

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Received 16 May 2006; revised 16 November 2006; accepted 22 November 2006
Available online 19 December 2006

Abstract—5-Butynylisoxazoles were obtained in high yields through a domino addition, C–O heterocyclization involving allenylmagnesium bromide and benzonitrile oxide in dry THF, in which the corresponding 5-methylisoxazoles were isolated in trace amounts. However, when the reactions were attempted in aqueous media using allenylindium bromide, 5-methylisoxazoles were formed as the sole products in high yields.

Nucleophilic additions of organometallic reagents to various C=N compounds such as imines, hydrazones, and oxime-ethers are well established.[1] Nitrones have been successfully employed as substrates for such additions;[1b,c] however, nitrile oxides have not been studied in depth despite the fact that they are known to add to a number of nucleophiles to generate substituted oximes. Of particular interest would be the addition of nitrile oxides to acetylenic compounds to give synthetically and pharmacologically valuable isoxazoles.[1,2] Isoxazoles and their derivatives have found several applications[3] as antibiotics, analgesics, anesthetics, anabolics, anthelmenthics, diuretics, GABA-agonists, anticonvulsants, muscle relaxants, and herbicides; some isoxazole derivatives display antileprous, antitumour, mutagenic behavior, and plant growth regulatory activity. Furthermore, isoxazoles are masked synthetic equivalents of 1,3-dicarbonyl functions via the lability associated with the N–O bond. Isoxazoles can be functionalized, readily unmasked[4,5] and elaborated for further synthetic applications. As part of our continued interest in exploring organometallic addition reactions to various C=N compounds,[6] we herein present the nucleophilic addition of allenylmagnesium bromide to nitrile oxides, the resulting intermediate from which undergoes C–O heterocyclization followed by the addition to another mol of allenylmagnesium bromide to generate 5-butynylisoxazoles in good yields. Several benzonitrile oxides[7] generated in situ, were reacted with excess (>2 mol equiv) propargylmagnesium bromide in THF together with a catalytic quantity (3% w/w) of mercuric(II) chloride[8] under an inert atmosphere (mercuric chloride on interaction with propargylmagnesium bromide generates allenylmagnesium bromide in situ). In most cases, 5-butynylisoxazoles were isolated in good yields (67–84%, Table 1) after 5–6 h reaction at an ambient temperature[9] with only a trace amount of the corresponding 5-methylisoxazoles (5–8%). The reaction was found to be general with regard to various substituted nitrile oxides bearing electron-donating or electron-withdrawing groups on the aromatic ring. However, hindered nitrile oxides such as 2,6-dichlorobenzonitrile oxide gave trace amounts of 5-methylisoxazole without any butynylated product.

When this reaction was attempted in the absence of mercuric chloride, no product was namely observed even after a prolonged reaction. The formation of 5-butynylisoxazoles could occur in a domino fashion, nucleophilic addition of allenylmagnesium bromide to the nitrile oxide followed by C–O-heterocyclization to

Keywords: Allenyl organometallic compounds; Nitrile oxide; 5-Butynylisoxazoles; 5-Methylisoxazoles.
☆ RRL Communication No. 2445.
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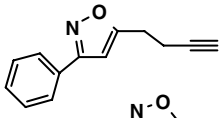
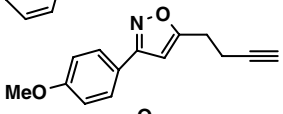
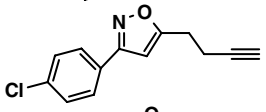
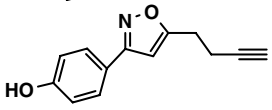
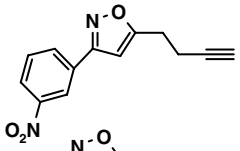
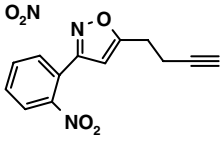
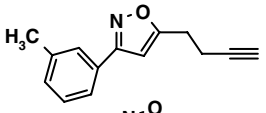
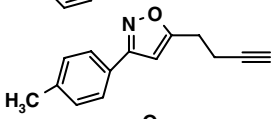
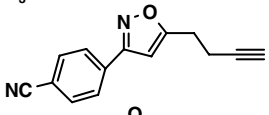
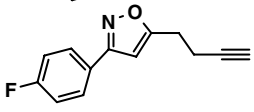
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.140

Table 1. Magnesium-mediated synthesis of 5-butynylisoxazoles

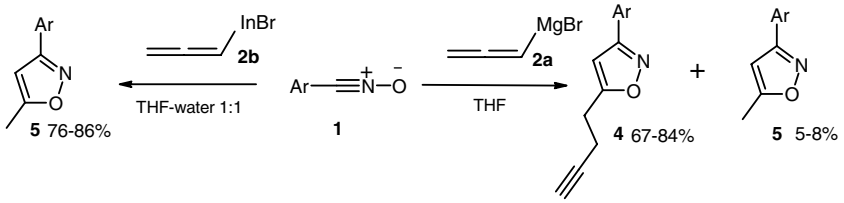
Entry	Isoxazole **4**[a]	Reaction time (h) (yield, %)[b,c]
a		5 (78)
b		6 (70)
c		5 (82)
d		5 (78)
e		6 (84)
f		6 (80)
g		5 (72)
h		6 (70)
i		5 (67)
j		5 (73)

[a] All products were characterized by IR, $^{1}H/^{13}C$ NMR and mass spectral analysis.
[b] Isolated yields after column chromatography.
[c] The corresponding 5-methylisoxazoles were isolated in 5–8% yields.

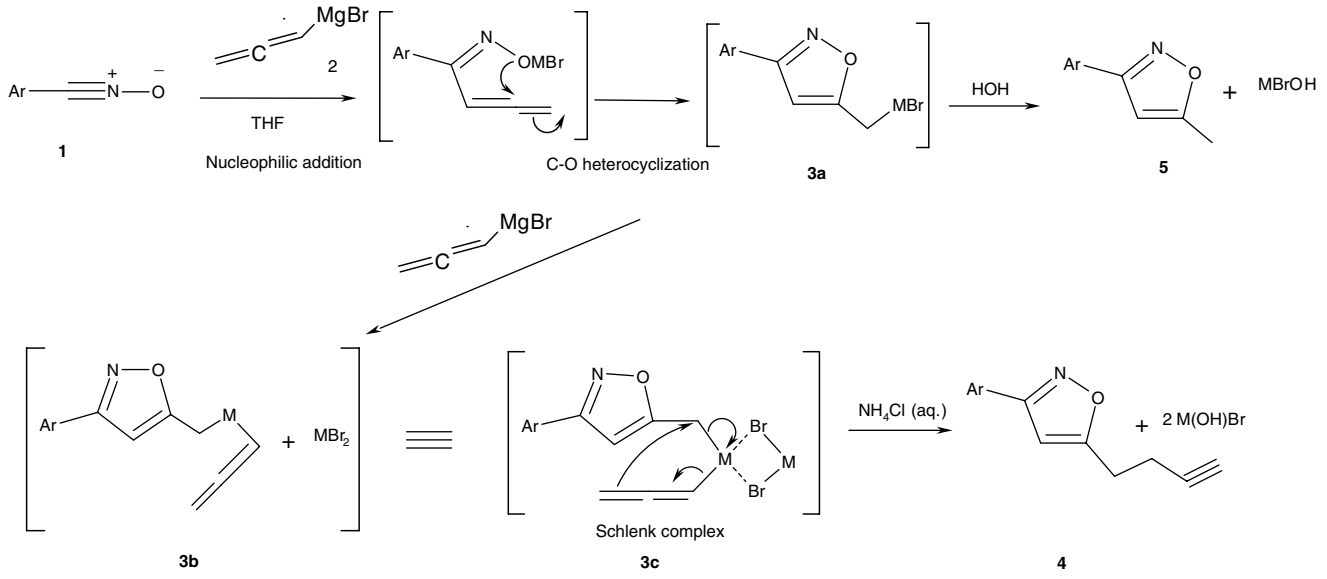
generate an organometallic isoxazole intermediate **3a** (see Scheme 2), which undergoes reaction with an additional mol of allenylmagnesium bromide **2a** (Scheme 1) to generate **4**. A plausible mechanism for the generation of 5-butynylisoxazole **4** from intermediate **3a** can be visualized either through, (i) Wurtz-type of coupling of organometallic intermediate **3b** with an additional mol of free propargyl bromide if present in the medium or, (ii) S_Ni type reaction via intermediate **3c** generated through Schlenk equilibrium[10] (Scheme 2). Since the propargyl bromide was treated with an excess of metal to completely convert it into allenylmagnesium bromide, the possibility of a Wurtz-type coupling can be ruled out. This was further confirmed by the fact that no trace of the cycloaddition product arising from the dipolar addition of nitrile oxide to propargyl bromide (unreacted, if any) could be detected in the crude product mixture. It is pertinent to mention here that propargyl bromide readily undergoes dipolar cycloaddition with nitrile oxides to generate 5-bromomethylisoxazole under the given experimental conditions. Hence, product formation can be attributed to an S_Ni reaction as shown in Scheme 2 involving a Schlenk equilibrium (similar coupling between two Grignard species has already been explained mechanistically by Schlenk[10]). 5-Methylisoxazole is likely to be formed through proton capture by intermediate **3a** during quenching. The possibility of a 1,3-dipolar cycloaddition of nitrile oxide to allenylmagnesium bromide to generate the isoxazole nucleus can be ruled out since allenylmagnesium halides do not form Diels Alder adducts with any dienes under the given experimental conditions, which shows the poor dipolarophilic nature of these resonance stabilized species.

Bearing in mind the importance of indium-mediated reactions,[11] when attempted this reaction in aqueous medium using allenylindium bromide, when the corresponding 5-methyl isoxazoles were formed as the sole products[12] without any traces of 5-butynylisoxazoles even when using excess allenylindium bromide. This clearly confirms the mechanism of formation of this product through proton capture by intermediate **3a** under aqueous conditions.

This reaction was found to be high yielding and general with regard to various nitrile oxides. With all the nitrile oxides studied, 5-methylisoxazoles were formed as the sole products after reaction using allenylindium bromide (Table 2). The preparation of 5-methylisoxazoles can be otherwise visualized only through 1,3-dipolar nitrile oxide cycloaddition to propyne gas under adiabatic conditions, which is obviously inconvenient. Thus, allenylindium bromide can be a better substitute for the synthesis of 5-methyl isoxazoles. In conclusion, we have presented the synthesis of 5-butynylisoxazoles and 5-methylisoxazoles in high yields with a high product selectivity. Thus, it may be anticipated that the method described in this work may find utility as an alternative to existing protocols for the synthesis of 5-butynyl- and 5-methylisoxazoles.

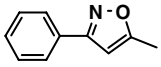
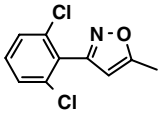
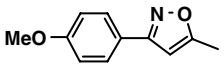
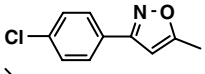
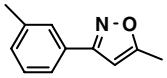
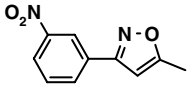
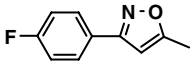
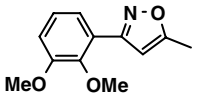
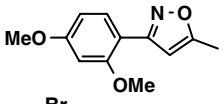
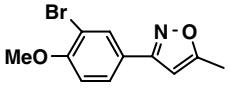


Scheme 1. Reaction of allenyl organometallic compounds with nitrile oxides.



Scheme 2. A plausible mechanism for the formation of 5-butynyl- and 5-methylisoxazoles.

Table 2. Indium-mediated synthesis of 5-methylisoxazoles in the aqueous medium

Entry	Isoxazole **4**[a]	Reaction time (h) (yield, %)[b]
a		24 (78)
b		24 (83)
c		22 (85)
d		20 (84)
e		24 (82)
f		20 (73)
g		24 (75)
h		24 (80)
i		24 (81)
j		24 (79)

[a] All products were characterized by IR, $^{1}H/^{13}C$ NMR and mass spectral analysis.

[b] Isolated yields after column chromatography.

Acknowledgements

The authors thank Dr. G. N. Qazi, Director-RRL for his interest and encouragement. P.P.S., K.S.K., S.S., D.M.R., and P.B.R. thank the CSIR, New Delhi, for the award of fellowships.

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7. All nitrile oxides were prepared as per the literature procedure and unstable nitrile oxides were used immedi-

ately without futher purification. Ref. Grundmann, C.; Dean, J. M. *Angew. Chem.* **1964**, *76*, 682–695.
8. Hopf, H.; Bohm, I.; Kleinschroth, J. *Org. Synth.* **1990**, *Coll. Vol. 7*, 485–490.
9. In a typical procedure, to a suspension of magnesium turnings (0.12 g, 5 mmol, 5 equiv) in anhydrous tetrahydrofuran (20 ml) and mercury(II) chloride (5 mg, 1% w/w of propargyl bromide) was added propargyl bromide (0.59 ml of an 80 wt % solution in toluene, 4 mmol, 4 equiv) in small portions while stirring the reaction mixture at room temperature. (*Note*: A small grain of iodine was generally required to promote formation of the Grignard reagent.) The mixture was stirred at room temperature for 2 h to give a cloudy light green solution. The allenylmagnesium bromide generated was cooled to 0–5 °C and added dropwise to a solution of *p*-methoxybenzonitrile oxide (1 mmol, equivalent to 0.149 g), generated in situ by the treatment of triethylamine (0.14 ml) with the corresponding chlorooxime (0.185 g, 1 mmol) in dry THF (15 ml) over a period of 10 min while maintaining the temperature between 0 and 5 °C. The reaction mass was allowed to attain rt and stirring was continued at an ambient temperature for 6 h followed by quenching with aqueous ammonium chloride solution (10 ml) and diluting with dichloromethane (50 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 ml). The combined organic layers were dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to chromatography (silica gel, 60–120 mesh, eluent; *n*-hexane/EtOAc gradient) to afford pure 3-(*p*-methoxyphenyl)-5-butynylisoxazole as a colorless solid (0.16 g, 70%, mp 71.2 °C). IR (KBr, cm^{-1}): 3281, 2966, 2937, 1608, 1527, 1459, 1431, 1256, 1176, 1064, 840, 790, 659, and 533. ^1H NMR (200 MHz, $CDCl_3$): δ 2.04 (s, 1H), 2.64 (t, 2H $J = 7.2$ Hz), 3.02 (t, 2H $J = 7.2$ Hz), 3.85 (s, 3H), 6.37 (s, 1H), 6.99 (d, 2H, $J = 8.7$ Hz), 7.51 (d, 2H, $J = 8.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.1, 26.1, 55.3, 69.7, 82.1, 99.4, 114.3, 121.7, 128.2, 160.9, 162.0, 171.4; MS (EI, 70 eV) *m*/*z* (rel. int.) 227 (75), 212 (100), 174 (43), 146 (57), 77 (21), 54 (27).
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12. In a typical procedure, a suspension of indium powder (0.126 g, 1.1 mmol), and propargyl bromide (0.13 g, 1.1 mmol, 80% solution in toluene) in 20 ml of THF/water (1:1) was stirred at an ambient temperature for 3 h until the metal had dissolved completely to form allenylindium bromide. The above reagent was cooled to 0–5 °C and added dropwise over a period of 5 min to a stirred solution of *p*-methoxybenzonitrile oxide generated in situ (equiv 0.15 g, 1 mmol) in THF (20 ml), while maintaining the temperature between 0 and 5 °C. The reaction was allowed to attain room temperature and stirring was continued at an ambient temperature for 22 h followed by quenching with aqueous ammonium chloride solution (10 ml). The reaction was diluted with dichloromethane (50 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 20 ml). The combined organic layers were dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product, which was subjected to chromatography (silica gel, 60–120 mesh, eluent; *n*-hexane/EtOAc gradient) to afford pure 3-(*p*-methoxyphenyl)-5-methylisoxazole as a colorless amorphous solid (0.16 g, 86%); mp 69.8 °C; IR (KBr, cm^{-1}): 736, 788, 838, 902, 948, 1062, 1116, 1176, 1258, 1298, 1441, 1527, 1612, 2934; ^1H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.85 (s, 3H), 6.23 (s, 1H), 6.98 (d, 2H, $J = 6.7$ Hz), 7.70 (d, 2H, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.7, 54.8, 98.9, 113.7, 123.8, 127.6, 151.4, 161.3, 165.6; MS (EI, 70 eV) *m*/*z* (rel. int.) 189 (92), 174 (100), 146 (70), 77 (18), 63 (18), 45 (53).