

Addition of Allylindium Bromide to Nitrile Oxides in Aqueous Media: Convenient Synthesis of 5-Methylisoxazolines

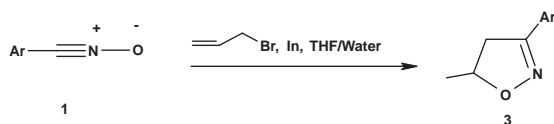
Sanghapal D. Sawant, Parvinder P. Singh, Naveed A. Qazi, and H. M. Sampath Kumar*
Regional Research Laboratory, Jammu-Tawi, 180 001, India

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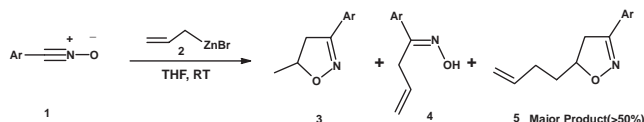
5-Methylisoxazolines were obtained in good yields through a highly selective nucleophilic addition of allylindium reagent to benzonitrile oxides with concomitant C–O heterocyclization.

The addition of organometallic reagents to C=N compounds is a well-known C–C bond-forming reaction.¹ However, the development of these addition reactions has been severely limited due to poor electrophilicity of the azomethine carbon and also by the tendency of imine and imino derivatives to undergo deprotonation in preference to additions. However, subsequent development of a variety of organometallic reactions greatly improved the scope of such addition reactions involving imines or imine derivatives. Electrophilicity of imine carbon can be enhanced through N-acylation, N-alkylation, or N-oxide formation. Use of resonance stabilized allyl organometallics that are comparatively more reactive can be alternative strategy for establishing C–C bond through the addition to C=N compounds. Thus, nucleophilic additions of organometallic reagents to various C=N compounds such as imines, hydrazones, oxime-ethers are well established.² Nitrones have been successfully employed as substrates for such additions, even though the same has not been studied in depth with regard to nitrile oxides despite the fact that nitrile oxides are known to add to a number of nucleophiles to generate hydroxamic acid derivatives.³ Among all the metals used for such purpose, indium occupies unique position due to its superior reactivity and stability under aqueous conditions, which makes it an eco-friendly metal. In the recent past, we have reported a number of addition reactions to C=N compounds like azides, nitrones, and hydrazones.⁴ Because of our continued interest in the application of indium in environmental friendly organic transformations, we report in this communication, a selective addition of allylindium bromide to various nitrile oxides under aqueous conditions.

Several in situ generated as well as stable benzonitrile oxides⁵ were reacted with allylindium bromide in THF–Water (1:1) medium. The addition reaction proceeds to completion smoothly within 24 h at ambient temperature⁶ as indicated by intermittent TLC examination. 5-Methyl isoxazolines **3** were isolated in high yields after workup and chromatographic purification (Scheme 1). The structure of the product could be unequivocally assigned based on spectroscopic data and the presence of 5-methyl group could be confirmed by DEPT experiments. It is



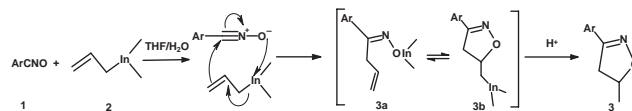
Scheme 1. Selective addition of allylindium bromide to nitrile oxides.



Scheme 2. Addition of allylzinc bromide to nitrile oxides.

important to note that, when zinc was employed instead of indium, corresponding 5-butenylisoxazolines **5**⁷ were isolated as major products (>50%) generated through domino addition, together with 10–15% of aryl oxime **4**⁸ derived from the nucleophilic allylation of nitrile oxides along with trace amounts (<4%) of 5-methylisoxazolines (Scheme 2). However, in case of indium-promoted reaction, crude product did not contain any trace of either 5-butenylisoxazolines or hydroxamic acids even when excess of allylindium bromide was used, which clearly shows the superiority of indium and aqueous conditions for achieving the high product selectivity. However, when the reaction was carried out in anhydrous THF or DMF, corresponding 5-butenylisoxazoline⁷ was isolated in 32–55% yield together with minor quantities of 5-methylisoxazolines (6–18%).

In all the nitrile oxides studied, 5-methylisoxazoline was the sole product at the end of 24-h reaction. The preparation of 5-methylisoxazolines can be otherwise visualized only through 1,3-dipolar nitrile oxide cycloaddition to propylene gas which might be relatively inconvenient as the reaction has to be carried out under adiabatic conditions^{3h} or via a tandem rearrangement–cyclization reaction of *O*-propargylic hydroxylamines.³ⁱ Thus, it may not be presumptuous to anticipate that the methodology displayed in this paper may find utility as attractive alternative to existing preparative protocols for 5-methylisoxazolines required for any possible biological and synthetic application. The formation of 5-methylisoxazolines can be visualized through nucleophilic addition of allylindium bromide with nitrile oxide followed by concomitant C–O heterocyclization (Scheme 3). However, the high product selectivity may be attributed to relatively low stability of the intermediate **3b** as compared to the stabilized allylindium bromide which readily undergo proton capture to generate 5-methylisoxazolines. Even though the possibility of allylindium species under going dipolar cycloaddition can not be ruled out, the same could not be supported either through any literature precedent or establish empirically. However, as discussed before, nucleophilic addition of various organometallic species to nitrile oxides has been well established and hence we propose the plausible mechanism to explain the product



Scheme 3. Plausible mechanism for the formation of 5-methylisoxazolines.

Table 1. Indium-mediated synthesis of 5-methylisoxazolines

Entry	Nitrile oxide	Isoxazoline ^a	Reaction Time/h	Yield/% ^b
a			24	81
b			24	83
c			22	75
d			20	84
e			24	64
f			20	73
g			24	65
h			24	79
i			24	81

^aAll products were characterized by IR, ¹H and ¹³CNMR, DEPT, and mass spectroscopy. ^bYields obtained after column chromatography, based on allylindium species (allyl)₃InBr₂ generated.

formation via nucleophilic addition pathway as depicted above.

In conclusion, we presented in this paper unprecedented synthesis of 5-methylisoxazolines in high yields through the addition of allylindium bromide to nitrile oxides (Table 1).

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References and Notes

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- In a typical procedure, a suspension of indium powder (1.15 g, 10 mmol) and allyl bromide (1.2 g, 10 mmol) taken in 15 mL of THF/water (1:1) was stirred at ambient temperature for 3 h until the metal dissolved completely to form allylindium 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*-chlorobenzonitrile oxide generated in situ (equiv. 1.53 g, 10 mmol) in THF (15 mL), while maintaining the temperature between 0–5 °C. The reaction mass was allowed to attain room temperature and stirring was continued at ambient temperature for 20 h followed by quenching with aqueous ammonium chloride solution (10 mL). Reaction mass was diluted with dichloromethane (50 mL) and extracted (2 × 20 mL). Combined organic layers were dried (anhydrous Na₂SO₄) and evaporated under reduced pressure to afford crude product that was subjected to column chromatography (silica gel, finer than 200 mesh, elution; *n*-hexane/EtOAc gradient) to afford pure 3-(4-chlorophenyl)-5-methyl-4,5-dihydroisoxazole (3 d, 1.63 g, 84%) as pale yellow amorphous solid; m.p. 53–54 °C; IR (KBr, cm⁻¹): 1379, 1459, 1596, 2852, 2924, 2956, 3443. ¹H NMR (CDCl₃, 200 MHz): δ 1.43 (d, 3H, *J* = 6.2 Hz), 2.85–2.95 (q, 1H, *J* = 8.0 Hz), 3.33–3.46 (dd, 1H, *J* = 10.1 and 6.3 Hz), 4.88 (m, 1H), 7.36 (d, 2H, *J* = 9.0 Hz), 7.59 (d, 2H, *J* = 9.0 Hz). ¹³C NMR (50 MHz, CDCl₃): δ 20.9, 41.4, 77.8, 127.8, 128.4, 128.9, 135.8, 155.5; MS (EI, 70 eV): *m/z* (rel. int.) 195 (M⁺, 100), 180 (28), 152 (51), 135 (18), 111 (35), 91 (16), 75 (24), 56 (34). Elemental analysis calcd. for C₁₀H₁₀NOCl: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.49; H, 5.07; N, 7.30; Cl, 18.27.
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- (1*E*)-1-(2,6-Dichlorophenyl)but-3-en-1-one oxime (**4**, Scheme 2); m.p. 94–96 °C; IR (KBr, cm⁻¹): 732, 778, 940, 1427, 3241. ¹H NMR (CDCl₃, 200 MHz): δ 1.65 (br s, 1H), 3.53 (d, 2H, *J* = 7.3 Hz), 4.98–5.16 (m, 2H), 5.63–5.83 (m, 1H), 7.14–7.36 (m, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 33.6, 118.7, 128.0, 130.2, 130.9, 134.1, 135.0, 155.9; MS (EI, 70 eV): *m/z* (rel. int.) 229 (M, 23), 187 (100), 170 (47), 136 (27), 124 (34), 74 (32).