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Domino addition of allylzinc bromide to nitrile oxides: synthesis of 5-butenylisoxazolines

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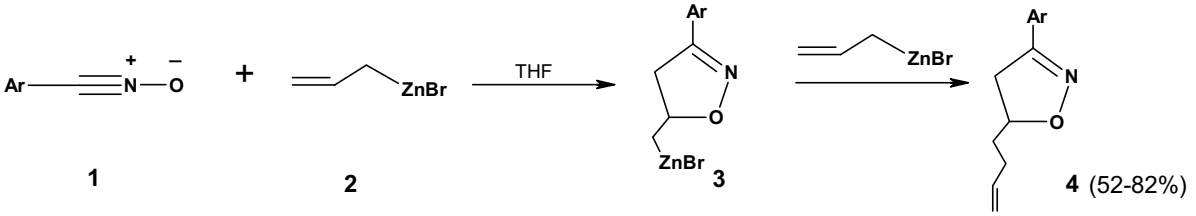
Abstract—Nitrile oxides undergo addition to allylzinc bromide to generate 5-butenylisoxazolines in good yields.

1,3-Dipolar cycloaddition reactions are important tools for the synthesis of a variety of five-membered heterocyclic compounds that are difficult to access through other routes. In the past two decades, much work has been carried out to examine and optimize these reactions with various dipoles viz., nitrile oxides, nitrones, azides, silyl nitronates, etc., and a host of dipolarophiles.[1] Of particular interest is the dipolar cycloaddition of nitrile oxides to various alkenes and alkynes, which give synthetically and pharmacologically valuable isoxazolines and isoxazoles.[1,2] The importance of nitrile oxide and nitrone cycloadditions in synthetic organic chemistry is ascribed mainly to the utility of the cycloaddition products as latent synthetic equivalents. Thus, one can cleave isoxazolines and isoxazolidines to produce β-hydroxyl ketones and β-amino alcohols,[2] which occur in a large number of important natural products. Our continued interest in organometallic additions to various C=N compounds,[3] prompted us to present in this communication, 1,3-dipolar cycloadditions of nitrile oxides to allylzinc bromide, the intermediate products undergoing addition in a domino fashion to generate 5-butenylisoxazolines in good yields. Several stable benzonitrile oxides and some generated in situ, were reacted withexcess (>2 mol equiv) allylzinc bromide in THF under an inert atmosphere (Scheme 1). In most cases, 5-butenylisoxazolines were isolated in moderate to good yields (52–82%) after 12–14 h reaction at ambient temperature.[4] The reaction was found to be general with regard to various substituted nitrile oxides[5] bearing electron-donating or electron-withdrawing groups on the aromatic ring (Table 1).

In some cases, the crude product mixture also contained minor quantities (10–15%) of oximes **5**[6] derived from adduct **7**, as well as 5-methylisoxazolines (**6**, Scheme 2).[7]



Ar= C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2,3-$(MeO)_2C_6H_3$
3-HOC_6H_4, 3,4-$(MeO)_2C_6H_3$, 4-NMe_2-C_6H_4

Scheme 1. Domino addition of allylzinc bromide to nitrile oxides.

Keywords: Nitrile oxide; Allylzinc bromide; 1,3-Dipolar cycloaddition; 5-Butenylisoxazolines.
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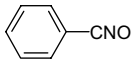
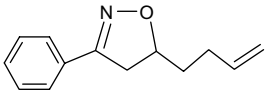
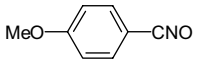
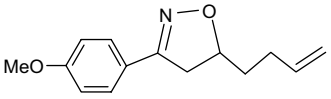
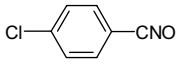
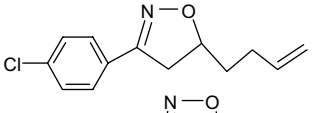
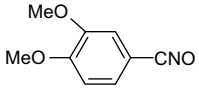
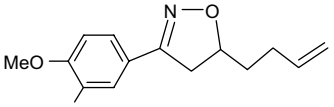
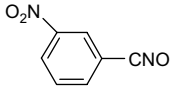
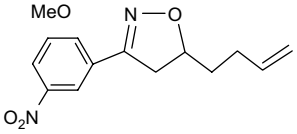
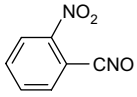
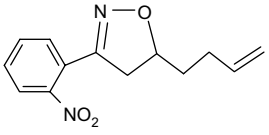
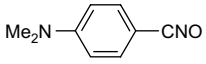
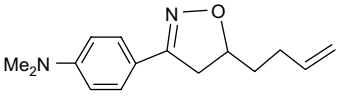
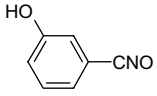
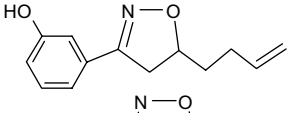
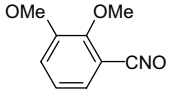
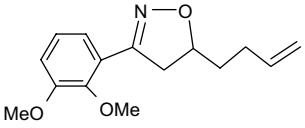
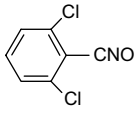
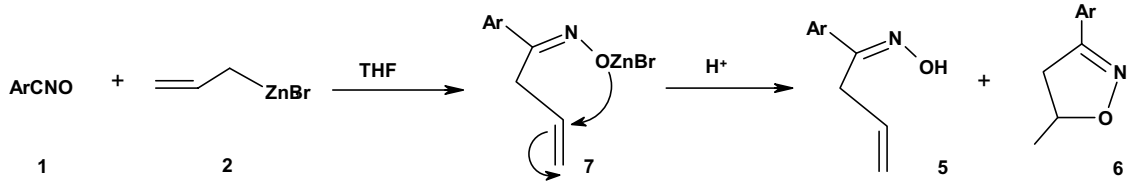
Table 1. Synthesis of 5-butenylisoxazolines

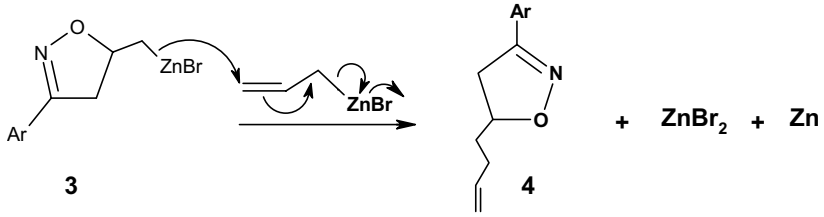
Entry	Nitrile oxide **1**	Isoxazoline **4**[a]	Reaction time (h)	Yield (%)[b]
a			12	78
b			12	71
c			13	82
d			14	58
e			12	75
f			12	80
g			14	60
h			14	52
i			14	70
j		—	24[c]	—

[a] All products were characterized by IR, ^{1}H and ^{13}C NMR, DEPT, and mass spectroscopy.
[b] Yields obtained after column chromatography.
[c] The corresponding oxime **5j** was isolated in 64% yield.



Scheme 2. Nucleophilic addition of allylzinc bromide to nitrile oxides.

The 5-methylisoxazolines **6** presumably arise by protonation of intermediate **3** on quenching with water. In the case of a sterically hindered dipole viz., 2,6-dichlorobenzonitrile oxide, only the oxime **5j** could be isolated (64%) with traces of cyclized product (<3%) and no 5-butenylisoxazoline. No products derived from nucleophilic addition of allylzinc bromide to the C=N of 5-butenylisoxazolines **4** or 5-methylisoxazolines **6** could be detected. This is in contrast to our observation[3e] that certain types of isoxazolines do undergo such addition reactions with organometallic reagents. The formation of 5-butenylisoxazolines **4** can be visualized as involving two reactions happening in a domino fashion: 1,3-dipolar cycloaddition of the nitrile oxide to allylzinc bromide generating intermediate **3** then reaction with a second mol equivalent of allylzinc bromide to generate the final product **4**, Wurtz type of coupling of **3** with unreacted allyl bromide or via an S_N2' process,



Scheme 3. A plausible mechanism for the formation of 5-butenylisoxazolines.

Scheme 3. We exclude the former possibility on the grounds that no product from reaction of (unchanged) allyl bromide and the nitrile oxide was observed and so no allyl bromide was available to participate in the Wurtz-type coupling.

In conclusion, we have presented in this paper, an unprecedented and direct synthesis of 5-butenylisoxazolines through a domino 1,3-dipolar cycloaddition of allylzinc bromide to nitrile oxides.

Acknowledgements

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References and notes

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4. In a typical procedure, a suspension of freshly activated zinc dust (0.65 g, 10 mmol) and allyl bromide (0.6 g, 5 mmol) in dry THF (20 ml) was stirred under nitrogen until the metal dissolved completely to form a clear solution. The allylzinc bromide solution generated as above was cooled to 0–5 °C and added dropwise to a solution of *p*-chlorobenzonitrile oxide[5] (equivalent to 0.15 g, 1 mmol) in THF (15 ml) over a period of 10 min while maintaining the temperature between 0 and 5 °C. The reaction mixture was then allowed to attain rt and stirring was continued at ambient temperature for 13 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, 100–200 mesh, elution; *n*-hexane/EtOAc gradient) to afford pure allyl 5-butenylisoxazoline **4c** (0.18 g, 75%) as a colorless solid (mp 60.2 °C). IR (KBr, cm^{-1}): 473, 511, 538, 825, 908, 1092, 1349, 1402, 1439, 1492, 1596, 1603, 2983, 3083, 3446. ^{1}H NMR ($CDCl_3$): δ 1.63–1.99 (m, 2H), 2.18–2.25 (m, 2H), 2.89–3.01 (q, 1H, $J = 8.1$ Hz), 3.32–3.45 (dd, 1H, $J = 10.0$ Hz, 6.2 Hz), 4.69–4.85 (m, 1H), 4.98–5.12 (m, 2H), 5.85–5.95 (m, 1H), 7.37 (d, 2H, J=8.6 Hz), 7.60 (2H, d, $J = 8.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.3, 34.5, 39.8, 81.0, 115.4, 127.8, 128.3, 128.9, 135.9, 137.4, 155.5; MS (EI, 70 eV): *m/z* (rel. int.) 237 (18), 235 (M^+, 66), 206 (17), 192 (51), 180 (100), 152 (100), 138 (70), 125 (49), 111 (97), 102 (25), 84 (34.8), 75 (62).
5. All nitrile oxides were prepared as per the literature procedures and unstable nitrile oxides were used immediately without further purification Grundmann, C.; Dean, J. M. *Angew. Chem.* **1964**, *76*, 682–695.
6. Oxime **5j**: Mp 94–96 °C; IR (KBr): λV_{max} 732, 778, 940, 1427, 3241. ^{1}H NMR ($CDCl_3$): 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), 5.74–7.36 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 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).
7. 5-Methylisoxazoline **6c**: IR (KBr): λV_{max} 1379, 1459, 1596, 2852, 2924, 2956, 3443 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, d, $J = 6.2$ Hz), 2.85–2.95 (q, 1H, $J = 8.0$ Hz), 3.33–3.46 (1H, dd, $J = 10.1$ Hz., 6.3 Hz), 4.88 (1H, m), 7.36 (2H, d, $J = 9.0$ Hz), 7.59 (2H, d, $J = 9.0$ Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$): 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).