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Reaction between isocyanides and nitrostyrenes in water: a novel and efficient synthesis of 5-(alkylamino)-4-aryl-3-isoxazolecarboxamides

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ABSTRACT

A novel synthesis of 5-(alkylamino)-4-aryl-3-isoxazolecarboxamides is described. Heating a mixture of an isocyanide and a nitrostyrene in water afforded the title compounds in excellent yields.

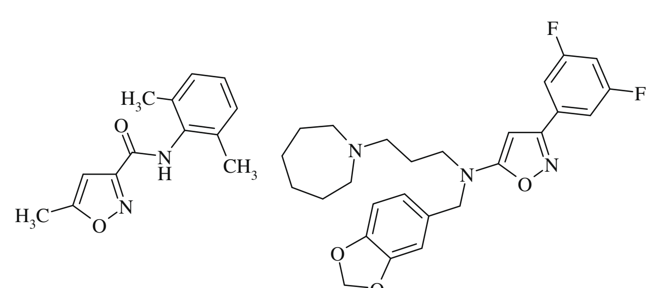
Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. Isocyanide-based MCRs are especially important in this area.[1]

Isoxazoles are five-membered aromatic ring systems containing adjacent oxygen and nitrogen atoms, and have found diverse medicinal, agricultural, and other industrial applications. Some isoxazoles are used as organic electrolytes in non-aqueous batteries, in photographic emulsions, and in fiber dyes.[2,3]

Isoxazoles containing a 3-carboxamide or 5-amino substituent have been shown to possess antiepileptic,[4] anticonvulsant (e.g., D2624, Fig. 1),[5] antifungal,[6] and insecticidal[7] properties. Other examples possess monoamine oxidase inhibitory activity and are useful for the treatment of depression and cognitive disorders.[8] 3-Isoxazolecarboxamides have also been used for the treatment of pain and/or fever.[9] 5-Aminoisoxazole **1** (Fig. 1) has been reported as an antagonist of the human platelet thrombin receptor (PAR-1),[10] and other examples function as selective endothelin ET_B receptor antagonists.[11]

The most common synthetic approach for the construction of the isoxazole ring system involves the cycloaddition of alkynes to nitrile oxides.[2,3]

A number of synthetic routes have been reported for the preparation of 5-aminoisoxazoles; these include condensation of esters with nitrile anions and then cyclization of the resulting β-ketonitriles with hydroxylamine,[12] addition of nitrile anions to α-chlorooximes,[13] condensation of α-bromo ketoximines with cyanide,[14] and rearrangement of 5-alkyl-4-cyanoisoxazoles on treatment with $LiAlH_4$.[15]



D2624 **1**

Figure 1. Examples of biologically active 3-isoxazolecarboxamides and 5-aminoisoxazoles.

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The most common synthetic methods reported for the preparation of 3-isoxazolecarboxamides involve amidation of the corresponding carboxylic acids[16] and cyclization of 2,4-dioxopentanamides with hydroxylamine.[9]

Water is a desirable solvent for chemical reactions because it is safe, non-toxic, environmentally friendly, readily available, and cheap compared to organic solvents.[17] Although enzymatic processes in Nature occur in aqueous environment by necessity, water has been avoided as a solvent for common organic reactions due to poor solubility of substrates and, in some cases, the instability of organic reagents or reaction intermediates in aqueous solutions. Since the pioneering studies on Diels–Alder reactions by Breslow,[18] there has been increasing recognition that organic reactions can proceed well in aqueous solution offering advantages over those occurring in organic solvents, such as rate enhancement and insolubility of the final products which facilitates their isolation.[17]

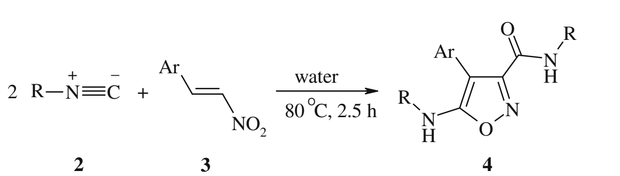
There are several reports in the literature concerning the reaction of the activated methylene isocyanides and nitroalkenes. The base-catalyzed reaction of nitroalkenes (or arenes) with isocyanoacetate is known as the Barton–Zard pyrrole synthesis,[19] which proceeds with elimination of nitrous acid in the final pyrrole ring-formation step.

In 2008, a new organocatalytic asymmetric formal [3+2] cycloaddition reaction of isocyanoesters to nitroolefins leading to the corresponding dihydropyrroles was reported.[20] Another reported pyrrole synthesis involved cycloaddition of nitro-substituted ketene *S*,*S*- and *N*,*S*-acetals with the activated methylene isocyanides.[21] In both these cycloadditions the nitro group is retained in the dihydropyrrole and pyrrole products.

Due to the pharmacological properties of isoxazoles containing 3-carboxamide or 5-amino substituent, the development of synthetic methods, enabling easy access to these compounds, are desirable. As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[22] herein, we describe a novel synthesis of functionalized isoxazoles using various nitrostyrenes and isocyanides. Thus, a mixture of an isocyanide **2** and a nitrostyrene **3** was heated at 80 °C in water to produce the corresponding 5-aminoisoxazole-3-carboxamide **4** in 80–93% yields (Scheme 1, Table 1).

All the reactions reached completion within 2.5 h. ^{1}H NMR analysis of the reaction products clearly indicated the formation of the corresponding 5-(alkylamino)-4-aryl-3-isoxazolecarboxamides **4a**–**l** in good to excellent yields.[23]

The isolated products **4** were characterized on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **4a** displayed a molecular ion (M^+) peak at *m/z* 367, which is consistent with the 2:1 adduct of cyclohexyl isocyanide and 1-nitro-2-phenylethylene. The ^{1}H NMR spectrum of **4a** exhibited characteristic signals with appropriate chemical shifts and coupling constants for the 22 protons of the two cyclohexyl rings (δ 1.18–2.08 and 3.52–3.92) and the five phenyl H atoms (δ 7.27–7.42) along with two fairly sharp doublets (δ 4.59, J = 7.5 Hz and δ 6.51, J = 7.9 Hz) for the amine and amide NH protons. In the ^{13}C NMR spectrum of **4a**, the cyclohexyl and phenyl carbon atoms resonated at appropriate chemical shifts. A shielded carbon (δ 93.44 for ONC=*C*) and three deshielded carbons



Scheme 1.

Table 1
Synthesis of 5-aminoisoxazole-3-carboxamides **4a**–**l**

4	Ar	R	Mp[a] (°C)	% Yield[b]
a	C_6H_5	Cyclohexyl	74–76	87
b	C_6H_5	^{t}Bu	120–121	91
c	4-$CH_3C_6H_4$	Cyclohexyl	125	90
d	4-$CH_3C_6H_4$	^{t}Bu	117	92
e	4-$CH_3C_6H_4$	1,1,3,3-Tetramethylbutyl	101–102	80
f	4-BrC_6H_4	^{t}Bu	156	90
g	4-BrC_6H_4	Cyclohexyl	155–156	88
h	2-Thienyl	^{t}Bu	106	83
i	2-Thienyl	Cyclohexyl	96–97	85
j	3-$CH_3C_6H_4$	Cyclohexyl	67	89
k	4-FC_6H_4	^{t}Bu	135	93
l	4-ClC_6H_4	Cyclohexyl	187–188	92

[a] Recrystallized from *n*-hexane/EtOAc (1:1).
[b] Isolated yield.

(δ 156.85, 158.97, and 166.85; for N=C, ONC=C, and C=O, respectively) were in agreement with the proposed structure.[23] Single-crystal X-ray analysis of one example, **4b**, conclusively confirmed the structures of these compounds. An ORTEP diagram of **4b** is shown in Figure 2.[24]

A mechanistic rationalization for this reaction is provided in Scheme 2. On the basis of the chemistry of isocyanides,[25–28] it is reasonable to assume that the first step could involve Michael addition of isocyanide **2** to the nitrostyrene **3** leading to the nitronate intermediate **5**, which may undergo cyclization via nucleophilic addition of the nitronate oxygen to the adjacent nitrilium to form 4,5-dihydroisoxazolium N-oxide intermediate **6**. A 1,3-H

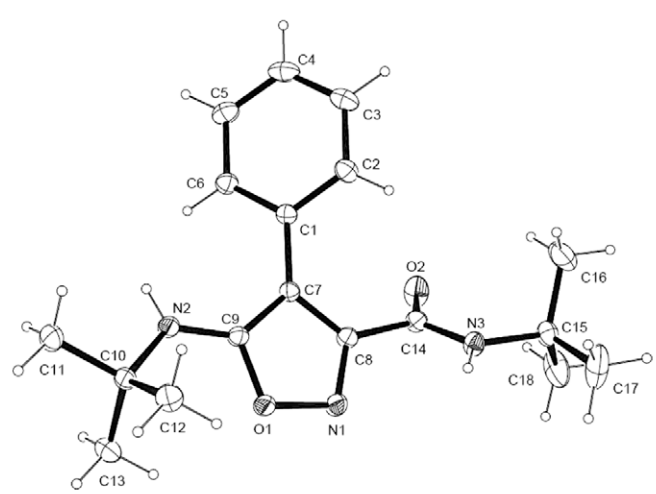
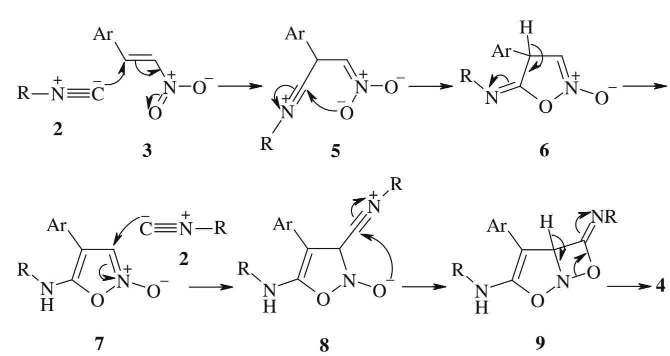


Figure 2. ORTEP representation of the molecular structure of **4b**.



Scheme 2.

shift may then result in isoxazolium N-oxide intermediate **7**. Nucleophilic addition of a second isocyanide to **7** would yield the 2:1 adduct **8**, which can undergo cyclization to form bicyclic intermediate **9**. This bicyclic intermediate would then rearrange to afford 5-(alkylamino)-4-aryl-3-isoxazolecarboxamide **4**.

In conclusion, we have reported a convenient, simple, and efficient synthesis of 5-(alkylamino)-4-aryl-3-isoxazolecarboxamides of potential synthetic and pharmacological interest. The use of water as a green medium, simple and readily available starting materials, and good to excellent yields of the products are the main advantages of this method. The simplicity of this method makes it an interesting alternative to other isoxazole syntheses.[29] To the best of our knowledge, this is the first synthesis of 5-amino-3-isoxazolecarboxamides. In this reaction, the nitrogen and oxygen atoms in the isoxazole ring are unusually derived from the nitro group of the activated styrene. In the previously reported condensation of methylene isocyanides and nitroolefins, the nitro group is eliminated or appears in the obtained pyrrole product.

Acknowledgment

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23. The procedure for the preparation of *N^3-cyclohexyl-5-(cyclohexylamino)-4-phenyl-3-isoxazolecarboxamide* (**4a**) is described as an example: A mixture of 1-nitro-2-phenylethylene (0.149 g, 1 mmol) and cyclohexyl isocyanide (0.240 g, 2.2 mmol) in H_2O (2 mL) was stirred at 80 °C for 2.5 h, and then the reaction mixture was cooled to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2×5 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography using *n*-hexane/EtOAc (4:1) as an eluent. The solvent was removed and the product was obtained as colorless crystals, mp 74–76 °C, yield 0.32 g, 87%. IR (KBr) (ν_{max}/cm^{-1}): 3314 (NH), 1664 (C=O), 1614, 1553, 1510, 1479, 1450, 1371, 1348, 1313, 1245, 1231, 1207, 1144, 1114, 1086, 1010, 891, 837, 758, 698. EI-MS *m/z* (%): 367 (M^+, 46), 319 (6), 242 (75), 187 (16), 160 (57), 133 (31), 117 (17), 83 (100), 55 (69). Anal. Calcd for $C_{22}H_{29}N_3O_2$ (367.49): C, 71.9; H, 8.0; N, 11.4. Found: C, 71.8; H, 8.1; N, 11.2%. ^1H NMR (300.1 MHz, $CDCl_3$): δ 1.18–2.08 [20H, m, 2CH(CH_2)$_5$], 3.52–3.67 [1H, m, NC*H*(CH_2)$_5$], 3.80–3.92 [1H, m, NC*H*(CH_2)$_5$], 4.59 (1H, d, *J* = 7.5 Hz, NH), 6.51 (1H, d, *J* = 7.9 Hz, NHC=O), 7.27–7.32 (1H, m, CH), 7.38–7.42 (4H, m, 4CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.76, 24.79, 25.39, 25.47, 32.83 and 33.84 (6CH_2), 48.18 and 52.41 (2NHCH), 93.44 (ONC=*C*), 127.10, 128.66 and 129.66 (3CH), 129.75 (C), 156.85 (N=C), 158.97 (ON*C*=C), 166.85 (C=O). *N^3-(tert-Butyl)-5-(tert-butylamino)-4-phenyl-3-isoxazolecarboxamide* (**4b**): Yield 0.29 g, 91%. Colorless crystals, mp 120–121 °C. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.40 and 1.41 [18H, 2s, 2C(CH_3)$_3$], 4.64 (1H, s, NH), 6.45 (1H, br s, NHC=O), 7.30 (1H, tt, *J* = 1.4, 7.3 Hz, CH), 7.36 (2H, d, *J* = 7.7 Hz, 2CH), 7.41 (2H, dd, *J* = 7.3, 7.7 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.71 and 29.96 [2C(CH_3)$_3$], 51.59 and 53.28 [2C(CH_3)$_3$], 95.11 (ONC=*C*), 127.16, 128.76 and 129.55 (3CH), 129.92 (C), 156.50 (N=C), 158.98 (ON*C*=C), 167.43 (C=O). *N^3-Cyclohexyl-5-(cyclohexylamino)-4-(4-methylphenyl)-3-isoxazolecarboxamide* (**4c**): Yield 0.34 g, 90%. Colorless crystals, mp 125 °C. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.15–2.05 [20H, m, 2CH(CH_2)$_5$], 2.36 (3H, s, CH_3), 3.54–3.63 [1H, m, NC*H*(CH_2)$_5$], 3.82–3.91 [1H, m, NC*H*(CH_2)$_5$], 4.51 (1H, d, *J* = 8.1 Hz, NH), 6.47 (1H, d, *J* = 7.9 Hz, NHC=O), 7.21 (2H, d, *J* = 8.1 Hz, 2CH), 7.28 (2H, d, *J* = 8.1 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.20 (CH_3), 24.73, 24.77, 25.43, 25.51, 32.84 and 33.87 (6CH_2), 48.17 and 52.43 (2NHCH), 93.53 (ONC=*C*), 126.68 (C), 129.37 and 129.61 (2CH), 136.87 (C), 156.53 (N=C), 159.03 (ON*C*=C), 166.87 (C=O). *4-(4-Bromophenyl)-N^3-cyclohexyl-5-(cyclohexylamino)-3-isoxazolecarboxamide* (**4g**): Yield 0.39 g, 88%. Colorless crystals, mp 155–156 °C. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.16–2.04 [20H, m, 2CH(CH_2)$_5$], 3.54–3.63 [1H, m, NC*H*(CH_2)$_5$], 3.81–3.90 [1H, m, NC*H*(CH_2)$_5$], 4.50 (1H, d, *J* = 8.1 Hz, NH), 6.52 (1H, d, *J* = 7.8 Hz, NHC=O), 7.27 (2H, d, *J* = 8.3 Hz, 2CH), 7.51 (2H, d, *J* = 8.3 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.71, 24.80, 25.39, 25.49, 32.86 and 33.84 (6CH_2), 48.29 and 52.48 (2NHCH), 92.58 (ONC=*C*), 121.13 and 128.81 (2C), 131.44 and 131.77 (2CH), 156.18 (N=C), 158.84 (ON*C*=C), 166.81 (C=O). *N^3-Cyclohexyl-5-(cyclohexylamino)-4-(2-thienyl)-3-isoxazolecarboxamide* (**4i**): Yield 0.31 g, 85%. Colorless crystals, mp 96–97 °C. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.16–2.05 [20H, m, 2CH(CH_2)$_5$], 3.58–3.67 [1H, m, NC*H*(CH_2)$_5$], 3.84–3.93 [1H, m, NC*H*(CH_2)$_5$], 4.82 (1H, d, *J* = 7.5 Hz, NH), 6.46 (1H, br s, NHC=O), 7.06 (1H, dd, *J* = 3.6, 5.2 Hz, CH), 7.19 (1H, d, *J* = 3.6 Hz, CH), 7.29 (1H, d, *J* = 5.2 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.64, 24.79, 25.41, 25.50, 32.83 and 33.73 (6CH_2), 48.30 and 52.45 (2NHCH), 87.19 (ONC=*C*), 125.00, 127.37 and 127.47 (3CH), 130.50 (C), 156.37 (N=C), 158.74 (ON*C*=C), 167.05 (C=O). *4-(4-Chlorophenyl)-N^3-cyclohexyl-5-(cyclohexylamino)-3-isoxazolecarboxamide* (**4l**): Yield 0.37 g, 92%. Colorless crystals, mp 187–188 °C. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.15–2.00 [20H, m, 2CH(CH_2)$_5$], 3.50–3.61 [1H, m, NC*H*(CH_2)$_5$], 3.79–3.87 [1H, m, NC*H*(CH_2)$_5$], 4.56 (1H, d, *J* = 8.0 Hz, NH), 6.56 (1H, d, *J* = 8.0 Hz, NHC=O), 7.32 (2H, d, *J* = 8.9 Hz, 2CH), 7.33 (2H, d, *J* = 8.9 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.69, 24.77, 25.34, 25.45, 32.78 and 33.77 (6CH_2), 48.25 and 52.44 (2NHCH), 92.47 (ONC=*C*), 128.26 (C), 128.74 and 131.08 (2CH), 132.92 (C), 156.17 (N=C), 158.83 (ON*C*=C), 166.81 (C=O).
24. *Selected X-ray crystallographic data for compound* **4b**: $C_{18}H_{25}N_3O_2$, monoclinic, space group = $P2_1/n$, a = 10.3226(12) Å, b = 15.1764(18) Å, c = 12.1519(14) Å, $\alpha = 90°$, β = 108.478(2)°, $\gamma = 90°$, V = 11805.6(4) Å^3, T = 295(2) K, Z = 4, D_{calcd} = 1.160 g cm^{-3}, μ = 0.077 mm^{-1}, 2306 observed reflections, final R_1 = 0.048, wR_2 = 0.139 and for all data R_1 = 0.072, wR_2 = 0.159. CCDC 716964 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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