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A novel and convenient synthesis of 5-aryl-4-bromo-3-carboxyisoxazoles: useful intermediates for the solid-phase synthesis of 4,5-diarylisoxazoles

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Abstract—A novel synthesis of 5-aryl-4-bromo-3-carboxyisoxazoles employing a [3+2] cycloaddition of a nitrile N-oxide with 2-aryl-1-bromoalkynes as the key step is described. The utility of these 5-aryl-4-bromo-3-carboxyisoxazoles in the solid-phase synthesis of 4,5-diarylisoxazoles is demonstrated.
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The isoxazole moiety represents an interesting pharmacophoric element which is found in a variety of potentially useful therapeutic agents.[1] More specifically, isoxazoles possessing two neighboring aryl substituents have recently been shown to exhibit biological activity as COX-2 inhibitors.[1e–h] Therefore, a diverse collection of diarylisoxazoles is a potentially useful source of new drug leads.

A solid-phase route to an encoded[2] combinatorial collection of 4,5-diarylisoxazole derivatives was envisaged which would utilize custom-made 5-aryl-4-bromo-3-carboxyisoxazole scaffolds **2** as one of three diversity elements[3] (Scheme 1). Herein, we report our recent findings on the [3+2] cycloaddition reaction of 2-aryl-1-bromoalkynes with the nitrile N-oxide derived from THP-protected 2-nitroethanol for the synthesis of the requisite 5-aryl-4-bromoisoxazole scaffolds **2**, and their utility in the solid-phase synthesis of 4,5-diarylisoxazoles **5** via Suzuki coupling[4] with boronic acids.

The [3+2] cycloaddition reaction of nitrile oxides with 2-aryl-1-haloalkynes has received little attention in the literature to date.[5,6] To further demonstrate the utility of arylhaloalkynes as precursors to arylhaloisoxazoles, and because a diverse collection of 2-aryl-1-bromoalkynes are readily accessible from functionalized benzaldehydes via a two-step protocol involving Corey–Fuchs reaction[7] followed by DBU-mediated HBr elimination,[8] we undertook a study of the scope of the cycloaddition reaction of arylbromoalkynes as shown in Table 1.

In an attempt to directly access the requisite carboxy functionality at C(3) of isoxazoles **2** we initiated our studies on the scope of arylbromoalkyne cycloaddition reactions with nitrile N-oxide **6** ($R^1 = C(O)OEt$) derived from base-induced dehydrohalogenation of commercially available ethylchlorooximidoacetate (Table 1, entry 1).[9] This reaction was unsuccessful and gave no desired isoxazole containing products. The 2-phenyl-1-bromoalkyne **7** ($R^2 = Ph$) was recovered unchanged after the attempted reaction. Failure of the reaction is attributed to a rapid and competing dimerization of the nitrile N-oxide derived from the chlorooximidoacetate.[10]

Next, we examined the use of the nitrile N-oxide generated in situ from the dehydration of nitroethane ($R^1 = Me$) using the Mukaiyama method.[11] As shown in entry 2, the methyl substituted isoxazole **8b** was formed in 23% yield as a single regioisomer. Given the success of this method, we reasoned that the carboxy functionality ultimately needed for attachment of resin-bound amines at C-3 of the isoxazole scaffolds could be indirectly accessed from the use of commercially available THP-protected 2-nitroethanol[12] as the nitrile N-oxide precursor (vide infra). We were pleased to find that reaction of **6** ($R^1 = CH_2OTHP$) with 1-phenyl-2-bromoethyne gave **8c** in 28% yield as a single regioisomer (entry 3).

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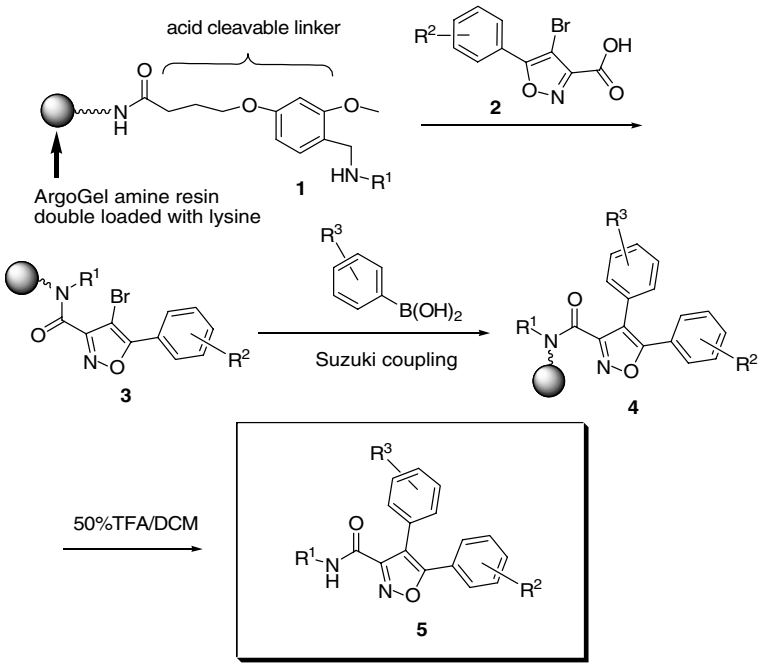
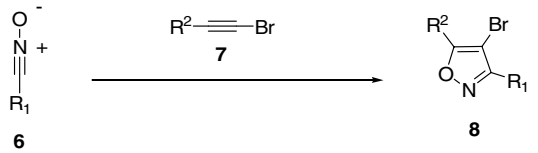


Scheme 1.

Table 1. 1,3-Dipolar cycloadditions[a]



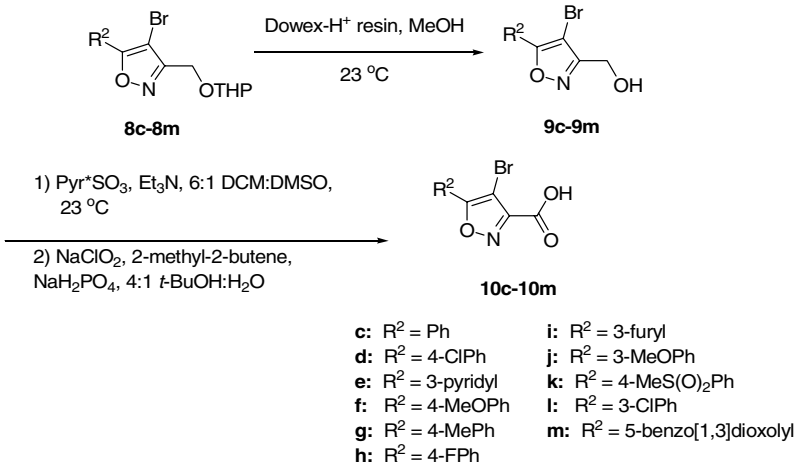
Entry[b]	R^1	R^2	Product	Yield[c] (%)
1	C(O)OMe	Ph	**8a**	No reaction
2	Me	Ph	**8b**	23
3	CH_2OTHP	Ph	**8c**	28
4	CH_2OTHP	4-ClPh	**8d**	24
5	CH_2OTHP	3-Pyridyl	**8e**	25
6	CH_2OTHP	4-MeOPh	**8f**	25
7	CH_2OTHP	4-MePh	**8g**	26
8	CH_2OTHP	4-FPh	**8h**	44
9	CH_2OTHP	3-Furyl	**8i**	32
10	CH_2OTHP	3-MeOPh	**8j**	22
11	CH_2OTHP	4-MeSPh	**8k**	31
12	CH_2OTHP	3-ClPh	**8l**	31
13	CH_2OTHP	5-Benzo[1,3]dioxolyl	**8m**	35

[a] All new compounds **8b–m** were obtained as single regioisomers; regiochemical assignment is made on the basis of diagnostic ^{13}C resonances using data for compound **8g**.
[b] For general experimental conditions see Ref. 11.
[c] Yields are unoptimized and are based upon the weight of purified material isolated after standard silica gel chromatography.

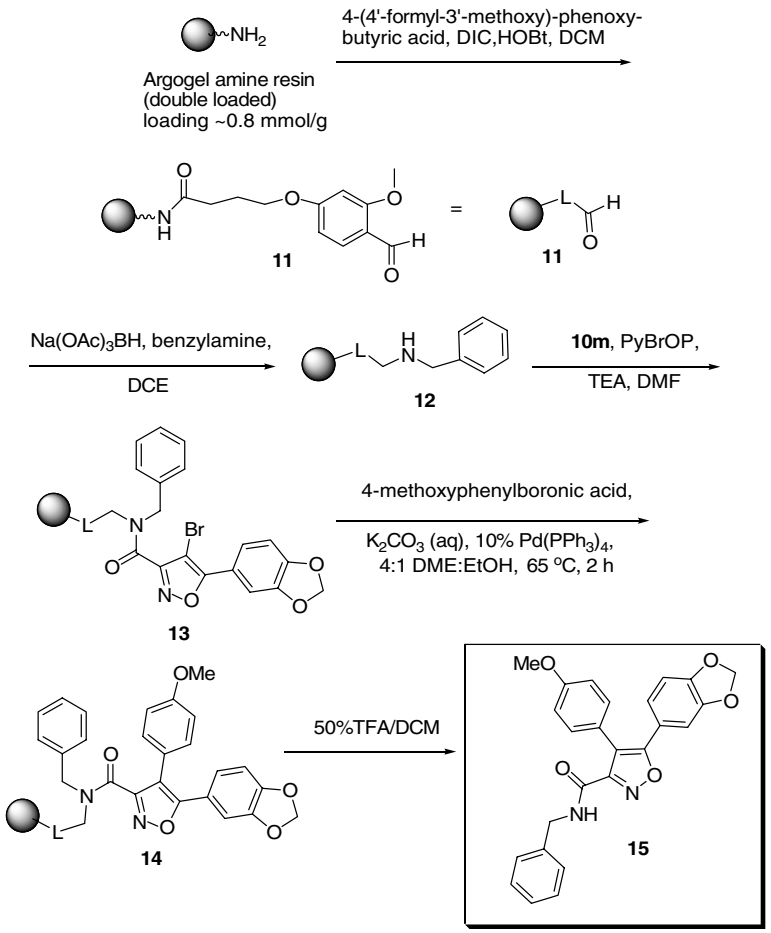
Finally, the use of substituted aryl and heteroarylbromo alkynes were investigated in the [3+2] cycloaddition with the nitrile N-oxide generated in situ via dehydration of THP-protected 2-nitroethanol (entries 4–13). All of the isoxazole products were formed as a single regioisomer[13] in yields ranging from 22% to 44%. The cycloaddition tolerates a variety of substituted phenyl groups as well as aromatic heterocycles. The reaction is currently unoptimized and it is possible that a higher dilution and a slower syringe pump addition of the 2-(2-nitroethoxy)tetrahydropyran would lead to increased yields by helping to minimize the undesired, competing dimerization of the in situ generated nitrile N-oxide.[10,14] The reactions are easily purified by flash chromatography and several grams of product, sufficient for incorporation into an encoded split synthesis,[2] are obtained in a single run.[15] The elaboration of 5-aryl-4-bromoisoxazoles **8c–m** to carboxylic acids **10c–m**, containing the requisite C-3 carboxy functionality for attachment to resin bound amines, is detailed in Scheme 2.

First, the THP ethers in **8c–m** were cleanly cleaved in a quantitative yield with Dowex-H^+ resin in MeOH[16] to unmask the hydroxymethyl group at C(3) of the 5-aryl-4-bromoisoxazoles. Alcohols **9c–m** were cleanly and efficiently oxidized to the carboxylic acids utilizing a two-step process which first involved an oxidation to the aldehyde intermediates using Pyr^*SO_3 complex[17,18] followed by sodium chlorite mediated oxidation of the crude aldehydes to give carboxylic acids **10c–n**.[19] This two step procedure was high yielding and further purification was not required beyond a simple aqueous work-up after each of the two steps.

The utility of these 5-aryl-4-bromoisoxazole scaffolds for the solid-phase organic synthesis of 4,5-diarylisoxazoles is outlined in Scheme 3. First, the acid-cleavable linker 4-(4′-formyl-3′-methoxy)phenoxybutyric acid, was attached (DIC, HOBt, DCM) to double-loaded Argogel®[20] giving resin bound aldehyde **11**. Attachment of the primary R^1 amine component, benzyl amine, was achieved using standard reductive amination conditions ($NaB(OAc)_3H$, DCE) to give resin bound amine **12**.[3] Coupling of carboxylic acid **10m** (R^2 diversity element) using PyBrOP in DMF gave the resin bound 5-aryl-4-bromoisoxazole intermediate **13**. Clean and quantitative



Scheme 2.



Scheme 3.

conversion to resin bound bromoisoxazole **13** was observed as determined by bromophenol blue test and LC–MS examination of the product obtained from TFA cleavage of a small sample of resin. Compound **13** was then cleanly coupled with 4-methoxyphenyl boronic acid (R^3 diversity element) at 65 °C using 10% $Pd(PPh_3)_4$ in 4:1 DME/EtOH in the presence of K_2CO_3 (aq) for 2 h. To achieve a full conversion to **14**, the Suzuki coupling reaction was performed twice. Finally, the desired 4,5-diarylisoxazole product was cleaved from the solid support with 50% TFA in DCM for 2 h. The desired product **15** was obtained in a good purity (84% by HPLC) and in 47% yield after purification by standard silica gel chromatography.[21]

In conclusion, we have developed a concise synthesis of 5-aryl-4-bromo-3-carboxyisoxazoles which utilizes a novel [3+2] cycloaddition of a nitrile N-oxide and a

2-aryl-1-bromoalkyne as the key step. In addition, we have demonstrated the utility of these 5-aryl-4-bromo-3-carboxyisoxazoles for the solid-phase synthesis of 4,5-diarylisoxazoles.

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15. All new isoxazoles **8c**–**m** gave satisfactory ^1H NMR and mass spectroscopy data. Compound **8g** was fully characterized (see data below). A typical experimental procedure is exemplified by the synthesis of **8g**: To a solution of 1-bromoethynyl-4-methylbenzene (9.10 g; 46.65 mmol), phenylisocyanate (9.89 g; 90.97 mmol), and DIPEA (8.13 mL; 46.65 mmol) in toluene (150 mL) at 90 °C was added 2-(2-nitroethoxy)tetrahydropyran (7.15 mL; 46.65 mmol) as a solution in toluene (10 mL) via syringe pump over a period of 16 h. After complete addition of the nitro alkane, the reaction mixture was stirred for an additional 2 h. The reaction mixture was cooled, filtered through a plug of Celite to remove the diphenylurea by-product and concentrated in vacuo. The crude residue was purified by silica gel chromatography (elution with 8:1 hexanes/EtOAc) providing 3.94 g of isoxazole **8g** (24%) and 5.40 g of recovered 1-bromoethynyl-4-methylbenzene (83% b.o.r.s.m.); data for **8g**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (2H, d, 8.0 Hz, Ar–*H*), 7.30 (2H, d, 8.0 Hz, Ar–*H*), 4.85 (1H, t, 3.0 Hz) 4.72 (2H, ABq, 12.4 Hz, $\Delta\nu_{AB} = 64.5$ Hz, CH_2OTHP), 3.97 (1H, ddd, 11.5, 9.2, 3.0 Hz), 3.60 (1H, dtd, 11.3, 4.1, 1.7 Hz), 2.41 (3H, s), 1.94–1.50 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5, 160.8, 141.2, 129.6, 126.8, 123.9, 98.5, 98.4, 89.6, 62.0, 59.6, 59.5, 30.3, 25.5, 21.7, 18.9; MS (ESI): *m*/*z* (% relative intensity, assignment) 268.0 + 270.0 (100, $[M+H-THP]^+$); Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.39; H, 4.97; N, 3.99.
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18. The pyridyl containing isoxazole **9e** was oxidized to the aldehyde with the Dess-Martin periodinane instead of pyridine$^*SO_3$ complex. The methylthio substituent in **8k** was oxidized to a sulfonyl group with 2 equiv of *m*-CPBA prior to THP deprotection and subsequent oxidation to the carboxylic acid.
19. *Typical experimental procedure as exemplified by the synthesis of acid* **10g**: To a solution of THP ether **8g** (4.12 g; 11.70 mmol) in MeOH (50 mL) was added 132 mg

of Dowex-H^+ resin. The mixture was stirred at room temperature for 16 h and then filtered and concentrated in vacuo giving 2.91 g of alcohol **9g** (93%). The crude alcohol was taken up in 6:1 DCM/DMSO (56 mL) and to this was added TEA (10.60 mL; 75.95 mmol) and pyridine$^*SO_3$ complex (6.91 g; 43.42 mmol). The reaction mixture was stirred at room temperature for 2 h. The DCM was removed in vacuo and the crude residue was diluted with EtOAc (300 mL). This was washed with 2 M HCl (aq) (1×100 mL), water (1×100 mL), and brine (1×100 mL). The organic phase was then dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude aldehyde thus obtained was dissolved in 4:1 *t*-BuOH/H_2O (100 mL) and to this was added NaH_2PO_4 (4.53 g; 37.98 mmol), 2-methyl-2-butene (2 M in THF; 34 mL; 68 mmol), and $NaClO_2$ (80%; 1.36 g; 12.04 mmol). The reaction mixture was stirred at room temperature for 2 h after which the volatiles were removed in vacuo. The crude residue was partitioned between EtOAc (200 mL) and water (150 mL) and the aqueous phase was acidified to pH 4 with HOAc and extracted with EtOAc (2×200 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo giving 2.97 g of acid **10g** (97% for 2 steps) which was >95% pure by HPLC. Data for **9g**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (2H, d, 8.5 Hz, Ar–*H*), 7.31 (2H, d, 8.2 Hz, Ar–*H*), 4.81 (2H, s), 2.42 (3H, s). Data for **10g**: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.89 (2H, d, 8.4 Hz, Ar–*H*), 7.42 (2H, d, 8.1 Hz, Ar–*H*), 2.39 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 166.7, 159.9, 155.7, 141.6, 129.9, 126.8, 122.8, 89.1, 21.1; MS (ESI): *m*/*z* (% relative intensity, assignment) 236.2 + 238.2 (100, $[M+H-CO_2]^+$).

20. ArgoGel® amine resin with an initial loading capacity of ~0.4 mmol/g was coupled with bis-Fmoc lysine under standard conditions (DIC, HOBt, DCM) followed by removal of the Fmoc protecting groups (30% piperidine/DMF) to increase the theoretical loading to ~0.8 mmol/g.
21. The purity of the crude cleavage product **15** was determined by the peak integral at 254 nm in the HPLC chromatogram. The yield was determined as the weight of the purified product (purified by standard silica gel chromatography; elution with 4:1 hexanes/EtOAc) divided by the theoretical yield. The theoretical yield was calculated as [Mol. Wt. of product] × [weight of resin used] × [theoretical loading of **14** based on double loading with lysine (initial loading of 0.8 mmol/g) and taking into account weight corrections; (theoretical loading of **14** = 0.51 mmol/g)]. Data for **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.26 (6H, m, Ar–*H*), 7.05 (1H, dd, 8.2, 1.9 Hz, Ar–*H*), 7.0–6.9 (4H, m, Ar–*H*), 6.76 (1H, d, 8.2 Hz, Ar–*H*), 5.98 (2H, s, OCH_2O), 4.56 (2H, d, 6.0 Hz, NCH_2Ph), 3.85 (3H, s, CH_3); MS (ESI): *m*/*z* (% relative intensity, assignment) 429.1 (100, $[M+H]^+$), 856.6 (12, $[2M+H]^+$), 878.9 (28, $[2M+Na]^+$).