Multicomponent Reactions

Three-Component Coupling of Arynes and Organic Bromides**

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Arynes have been versatile tools in synthetic organic chemistry for the facile construction of benzoannulated structures and multisubstituted arenes.^[1] Despite the labile and transient character arising from the highly strained C=C bonds, the use of a suitable combination of nucleophiles and electrophiles allows arynes to serve as connectors between these two components, thus leading to various three-component coupling reactions of high synthetic significance; in the reaction zwitterions (1,n-dipoles) generated from the arynes and nucleophiles act as key intermediates.^[2,3] In view of the fact that almost all three-component coupling reactions reported so far employ classic electrophiles (e.g., carbonyl compounds, sulforylimines, and CO_2) as the third component,^[4] there should be a number of unexploited three-component coupling reactions with potential synthetic utility that would be made feasible by employing a new type of third component. We report herein that 1,3- or 1,4-dipoles generated in situ from arynes can be captured by alkynyl (or polyfluoroaryl) bromides, which serve as a source of bromine cations and alkynyl (or polyfluoroaryl) anions,^[5] thus leading to the direct construction of functionalized bromoarenes having diverse structures.

We first conducted the reaction of benzyne (from 1a and KF/[18]crown-6),^[6] 1,1,3,3-tetramethylbutyl isocyanide (tOctNC; 2a), and phenylethynyl bromide (3a) in DME at 0°C, and observed that two C-C bonds and a C-Br bond formed all in one pot to give the three-component coupling product 4a in 88% yield (Scheme 1).^[7] As described in Scheme 2, the reaction would be triggered by formation of the zwitterion (1,3-dipole) 5 from benzyne and 2a.^[8] Subsequent nucleophilic attack of the aryl anionic moiety on the bromo moiety of **3a** produces the phenylacetylide **7** and an aryl-Br bond in 8 through the bromine at complex $6^{[9]}$ with subsequent C-C bond formation between 7 and the nitrilium cation 8 to furnish 4a. Products derived from various alkynyl bromides bearing a substituted aryl (4b-4d), thienyl (4e), or enynyl (4f) moieties were obtained. The doubly coupled product 4g was produced from 1,4-bis(bromoethynyl)benzene in 66% yield (Scheme 1). The reaction was also applicable to aliphatic alkynyl bromides whose acetal or

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propargylic ether moiety remained intact (4h-4j), and moreover, the functionalized iodoarene 4k could be synthesized by use of phenylethynyl iodide.^[10] Next, we examined the threecomponent coupling with substituted arynes. The respective products from dimethylbenzynes (41 and 4m) and cyclo-



Scheme 1. Three-component coupling of arynes, an isocyanide, and alkynyl halides. Reaction conditions: aryne precursor (0.30 mmol, 2 equiv), isocyanide (0.23 mmol, 1.5 equiv), alkynyl halide (0.15 mmol, 1 equiv), KF (0.60 mmol, 4 equiv), [18]crown-6 (0.60 mmol, 4 equiv), DME (2 mL). Yields are of isolated products. [a] 1a (4 equiv), 2a (3 equiv), alkynyl bromide (1 equiv), KF (8 equiv), [18]crown-6 (8 equiv). [b] 1a (1 equiv), 2a (1 equiv), alkynyl iodide (1 equiv), KF (4 equiv), [18]crown-6 (2 equiv). DME = 1,2-dimethoxyethane, Tf=tri-fluoromethanesulfonyl, TMS=trimethylsilyl.



Scheme 2. Proposed mechanism for the reaction of isocyanides.

alkane-condensed arynes (**4n** and **4o**) were afforded in high yields, and the reaction of 3-methoxybenzyne took place with perfect regioselectivity, thus leading to the sole formation of **4p** in 69% yield.^[11]

Besides alkynyl halides, bromopentafluorobenzene (9a) and 1-bromo-2,6-difluorobenzene (9b) proved to serve as a source of bromine cations and aryl anions to give the products **10a** and **10b**, respectively, when reacted with benzyne and *t*OctNC (Scheme 3). The present reaction exhibits broad substrate scope for isocyanides, and thus the products arising from isocyanides having 1-adamantyl (**10c**), *t*Bu (**10d**), Cy (**10e**), or 2,6-di(isopropyl)phenyl (**10f**) substituents readily underwent the three-component coupling.^[12]

The resulting *ortho*-iminobromoarene **10 a** could be directly converted into multisubstituted isoquinolines, which constitute an important class of biologically active compounds such as berberine,^[13] palmatine,^[14] and papaverine^[15] (Scheme 4). By treating **10 a** with diphenylacetylene (**11 a**) in the presence of $[Pd(tBu_3P)_2]$ and sodium carbonate in DMF at



Scheme 3. Three-component coupling of benzyne, isocyanides, and polyfluoroaryl bromides. Reaction conditions: aryne precursor (0.27 mmol, 1.8 equiv), isocyanide (0.23 mmol, 1.5 equiv), aryl bromide (0.15 mmol, 1 equiv), KF (0.54 mmol, 3.6 equiv), [18]crown-6 (0.54 mmol, 3.6 equiv), DME (2 mL). Yields are of isolated products.



Scheme 4. Synthesis of isoquinolines from 10a. DMF = N,N'-dimethyl-formamide.

100 °C, the isoquinoline **12a** was produced in 72 % yield.^[16] The annulation could be applied to electron-rich and electron-deficient diarylacetylenes to furnish the variously substituted triarylisoquinolines **12b–12d**, albeit in moderate yield.

In view of the fact that organic halides are an excellent third component for capturing 1,3-dipoles, we further investigated the reaction of 1,*n*-dipoles derived from arynes and other nucleophiles, and found that cyclic ethers performed well in the three-component coupling.^[17] The three-component coupling was found to selectively proceed when benzyne was treated with **3a** in THF at 0°C, thus providing a 78% yield of 1-bromo-2-(6-phenylhex-5-ynyloxy)benzene (**13a**) (Scheme 5).

A variety of alkynyl bromides were efficiently coupled with benzyne and THF to give the products (13b-13f), and furthermore an electrophilic cyano group in (4-cyanophenyl)ethynyl bromide (13g) was tolerable throughout the reaction despite the intermediacy of aryl and alkynyl anionic species (Scheme 6), thus showing the high functional group compatibility of the reaction. In addition, **9a** and 1-bromo-2,3,5,6-tetrafluorobenzene (**9c**) gave the corresponding products (**13h** and **13i**) in 82 and 78% yield, respectively, whereas the reaction of 1-bromo-2,4,6-trifluorobenzene (**9d** \rightarrow **13j**) or **9b** (no reaction) resulted in lower yields. Similar to the case of **4g**, dual installation of the 1,4-dipole into both of the C–Br bonds of 1,4-dibromotetrafluorobenzene readily occurred to provide a 90% yield of **13k**.^[18]

Finally, we found that oxetane could be transformed into the three-component coupling product **14a** in the reaction with benzyne and **3a** (Scheme 7). Other alkynyl bromides (**14b–14d**) also smoothly reacted with benzyne and oxetane, and the reaction of 3,3-dimethyloxetane furnished a 50% yield of **14e**. In marked contrast, the use of a three- or sixmembered cyclic ether (cyclohexene oxide or tetrahydropyran) in the reaction with benzyne and **3a** did not afford the three-component coupling product at all.^[19]

Synthetic utility of the three-component coupling was demonstrated by the total synthesis of a benzo[b]oxepinebased nonsteroidal estrogen, which is a new candidate or lead compound for treatment and prevention of an estrogendeficient syndrome such as osteoporosis, Alzheimer's, and cardiovascular diseases (Scheme 8).^[20] Thus, oxetane was regioselectively coupled with 4-chloro-5-methoxybenzyne (from **15**) and (4-benzyloxyphenyl)ethynyl bromide (**16**) to produce **17**,^[21] which was then transformed into a vicinal

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Scheme 5. Three-component coupling of benzyne, THF, and alkynyl (or polyfluoroaryl) bromides. Reaction conditions: (for alkynyl bromide) aryne precursor (0.40 mmol, 2 equiv), alkynyl bromide (0.20 mmol, 1 equiv), KF (0.80 mmol, 4 equiv), [18]crown-6 (0.80 mmol, 4 equiv), THF (2 mL); (for aryl bromide) aryne precursor (0.30 mmol, 1.5 equiv), aryl bromide (0.20 mmol, 1 equiv), KF (0.60 mmol, 3 equiv), [18]crown-6 (0.60 mmol, 3 equiv), THF (2 mL). Yields are of isolated products. [a] 1a (3 equiv), aryl bromide (1 equiv), KF (6 equiv), [18]crown-6 (6 equiv). THF = tetrahydrofuran.



Scheme 6. Proposed mechanism for the reaction of THF.

diborylalkene **18** through the platinum-catalyzed diborylation using bis(pinacolato)diboron ((pin)B–B(pin)).^[22] An intramolecular Suzuki–Miyaura coupling at the aryl–Br bond of **18** accompanied by base-induced proto-deborylation afforded the benzo[*b*]oxepine **19**, whose alkenyl moiety was hydrogenated along with removal of the benzyl moiety to give **20**. Finally, the target benzoxepine **21** could be obtained by the dechlorination using Na/*t*BuOH (24% overall yield based on oxetane).^[23]



Scheme 7. Three-component coupling of benzyne, oxetanes, and alkynyl bromides. Reaction conditions: aryne precursor (0.40 mmol, 2 equiv), oxetane (0.20 mmol, 1 equiv), alkynyl halide (0.40 mmol, 2 equiv), KF (0.80 mmol, 4 equiv), [18]crown-6 (0.80 mmol, 4 equiv), DME (2 mL). Yields are of isolated products.



Scheme 8. Synthesis of benzo[b]oxepine: a) **15** (2 equiv), oxetane (1 equiv), **16** (2 equiv), KF (4 equiv), [18]crown-6 (4 equiv), DME, -15 °C, 27 h. b) **17** (1 equiv), (pin)B-B(pin) (1.1 equiv), [Pt(PPh₃)₄] (8 mol%), DMF, 80 °C, 22 h. c) **18** (1 equiv), Cs₂CO₃ (1.2 equiv), [Pd-(tBu₃P)₂] (5 mol%), H₂O (33 equiv), DME, 80 °C, 24 h. d) Cs₂CO₃ (1.2 equiv), H₂O (33 equiv), DME, 80 °C, 24 h. e) **19** (1 equiv), H₂ (4 atm), 10% Pd/C (30 mol%), MeOH, RT, 48 h. f) **20** (1 equiv), Na (14 equiv), tBuOH (5 equiv), THF, 70 °C, 65 h.

In conclusion, we have disclosed a novel three-component coupling reaction of arynes, isocyanides (or cyclic ethers), and organic halides, where in situ-generated 1,3- or 1,4-dipoles are effectively captured by halogen cations and alkynyl (or polyfluoroaryl) anions. Moreover, the resulting functionalized bromoarenes have been demonstrated to be versatile intermediates in synthesizing multisubstituted isoquinolines and benzo[b]oxepine of pharmacological activity. Further studies on aryne-based multicomponent coupling reactions of this type as well as on application of the present methodology to the total synthesis of biologically active compounds are in progress.



Experimental Section

General procedure for the three-component coupling of arynes, isocyanides, and alkynyl halides: A Schlenk tube equipped with a magnetic stirring bar was charged with KF (0.60 mmol) and [18]crown-6 (0.60 mmol). The tube was evacuated at room temperature for 1 h with stirring before addition of DME (1 mL) and an alkynyl bromide (0.15 mmol) under an argon atmosphere. Then an isocyanide (0.23 mmol), an aryne precursor (0.30 mmol), and DME (1 mL) were added at 0 °C, and the resulting mixture was stirred at 0 °C. The mixture was diluted with ethyl acetate and filtered through a Celite plug. The organic solution was washed three times with brine and dried over MgSO₄. Evaporation of the solvent followed by recycling preparative HPLC gave the product.

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