O-Dihaloarenes as aryne precursors for nickel-catalyzed [2 + 2 + 2] cycloaddition with alkynes and nitriles†

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***o*-Dihaloarenes acting as aryne precursors react with acetylenes and nitriles catalyzed by the $NiBr_2$(dppe)/dppe/Zn system to give substituted naphthalene, phenanthridine or triphenylene derivatives depending on the reaction conditions in moderate to excellent yields with good tolerance of functional groups.**

In recent years, benzyne chemistry has attracted considerable attention, particularly in metal-catalyzed organic reactions employing arynes as π-components. A key to the relighted interest is the discovery of a mild method for the *in situ* generation of arynes at moderate temperature from *o*-silyl aryltriflate.[1] Although several methods for the generation of arynes are known, only very few of them are useful in transition metal-catalyzed organic reactions involving arynes as a substrate.[2,3] Our interest in metal-catalyzed benzyne reaction[4] and cyclization reactions with *o*-diiodoarenes[5] prompted us to explore the possibility of using *o*-diiodoarenes as a possible benzyne source for the catalytic cyclization reactions. In this paper, we report the synthesis of naphthalene derivatives *via* a nickel-catalyzed cyclization of substituted diiodobenzenes with alkynes or nitriles. The catalytic reaction likely involves a nickel-assisted generation of benzyne as a key step. Controlled synthesis of polysubstituted naphthalene, phenanthridine and triphenylene derivatives is important due to the unique electronic, and biological properties of these compounds. A vast number of biologically active natural products[6,7] and antibiotics possess a simple naphthalene skeleton. Also, naphthalene compounds have found application as chiral reagents,[6] semiconductors, and various electronic devices.[8,9] In spite of the wide usage, polysubstituted naphthalenes are difficult to prepare.[10]

Treatment of 1,2-diiodobenzene **1a** with diethylacetylene **2a** in the presence of Ni(dppe)Br_2, dppe (bis(diphenylphosphino)ethane) and zinc powder in acetonitrile at 100 °C for 48 h afforded 1,2,3,4-tetraethylnaphthalene **3a** in 94% yield. The structure of **3a** that is derived from one molecule of **1a** and two molecule of **2a** was confirmed by its ^1H, ^{13}C NMR and mass data.

The above optimized catalytic reaction conditions were obtained by studying the effect of solvent and metal complex used on the reaction of **1a** with **2a**. In the absence of either nickel catalyst or zinc powder, no cycloaddition product **3a** was observed. The nickel complex with monodentate phosphine ligand such as PPh_3 provided lower yield of product **3a** but higher yields in triphenylene. Thus, $NiBr_2(PPh_3)_2$ and $NiCl_2(PPh_3)_2$ gave **3a** in 35 and 33% yields, respectively, with a substantial amount of triphenylene. Nickel complexes $NiBr_2(L_2)$ where L_2 are dppm, dppe, dppp and dppb gave **3a** in 56, 76, 61 and 44% yields, respectively. $NiBr_2$(dppe) was found to be the best catalyst in this investigation producing **3a** in 76% yield with a trace of triphenylene. Palladium and cobalt complexes $Pd(PPh_3)_4$, $Pd(dba)_2$, $PdCl_2(PPh_3)_2$ and CoI_2(dppe) are inactive for this reaction. The catalytic reaction was more favorable using polar solvents. For example, THF, DMF and CH_3CN afforded **3a** in 71, 68 and 76% yields, respectively, but nonpolar solvents toluene and *o*-xylene gave only **3a** in lower yields of 53 and 47%, respectively. This study indicated that CH_3CN was the best solvent when Ni(dppe)Br_2 was used as the catalyst.

The effect of temperature on the product yield was also investigated. No desired product **3a** was formed and large amount of **2a** was recovered, if the reaction temperature was below 60 °C. The product yields increased as the reaction temperature increased. However, the reaction became complicated and gave a lower yield of **3a** for temperatures >100 °C. The best reaction temperature appears to be around 100 °C. The presence of extra dppe significantly diminished the self cyclotrimerization of alkyne **2a**. The reaction with additional dppe provided **3a** in 94% yield and trace triphenylene. As a result, we employed Ni(dppe)Br_2, dppe and zinc in acetonitrile at 100 °C as the catalyst system for the following cycloaddition of *o*-diiodoarenes with disubstituted alkynes.

The nickel-catalyzed cycloaddition reaction was successfully extended to various disubstituted acetylenes and the results are listed in Table 1. Thus, **1a** reacted smoothly with dipropyl, dimethoxymethyl, dialkoxycarbonyl and diaryl acetylenes, **2b–g**, to provide the corresponding cycloaddition products **3b–g** in moderate to excellent yields (entries 2–7). The substituted diiodobenzene **1b–d** bearing dimethyl, dimethoxy and dioxole moieties on the aryl ring also underwent cyclization with alkynes. Thus, treatment of **1b** with **2a** and **2f** afforded **3h** and **3i** in 66 and 94% yields, respectively (entries 8, 9). The reaction of **1c** with **2a** and **2f** gave **3j** and **3k** in 68 and 96% yields, respectively (entries 10, 11). Diiobenzodioxole **1d** reacted with **2a** and **2d** to afford **3l** and **3m** in 63 and 58% yields, respectively (entries 12, 13). Diiodobenzene **1e** with four electron-withdrawing fluoro groups also underwent the nickel-catalyzed cycloaddition reaction with **2a** and **2d** to give **3n** and **3o** in slightly lower yields (entries 14, 15). These results demonstrate that the nickel-catalyzed cycloaddition reaction has excellent tolerance of functional groups. Under the same

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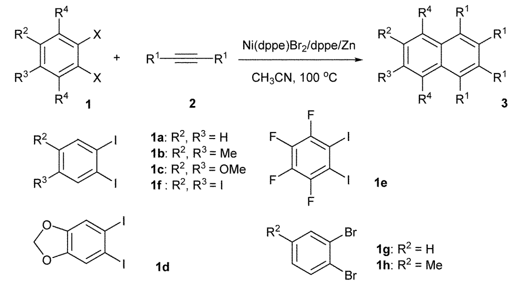
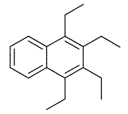
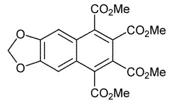
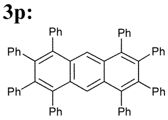
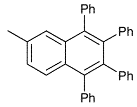
Table 1 Results of nickel-catalyzed cycloaddition of *o*-diiodoarenes with disubstituted alkynes[a]



Entry	1	2	3	Yield (%)[b]
1	**1a**	**2a**: $R^1 = Et$	**3a**: 	94
2	**1a**	**2b**: $R^1 = n$-Pr	**3b**	71
3	**1a**	**2c**: $R^1 = CH_2OMe$	**3c**	73
4	**1a**	**2d**: $R^1 = CO_2Me$	**3d**	81
5	**1a**	**2e**: $R^1 = CO_2Et$	**3e**	75
6	**1a**	**2f**: $R^1 = Ph$	**3f**	96
7	**1a**	**2g**: $R^1 = p$-tolyl	**3g**	77
8	**1b**	**2a**: $R^1 = Et$	**3h**	66
9	**1b**	**2f**: $R^1 = Ph$	**3i**	94
10	**1c**	**2a**: $R^1 = Et$	**3j**	68
11	**1c**	**2f**: $R^1 = Ph$	**3k**	96
12	**1d**	**2a**: $R^1 = Et$	**3l**	63
13	**1d**	**2d**: $R^1 = CO_2Me$	**3m**: 	58
14	**1e**	**2a**: $R^1 = Et$	**3n**: R^2, R^3, $R^4 = F$	69
15	**1e**	**2d**: $R^1 = CO_2Me$	**3o**: R^2, R^3, $R^4 = F$	72
16	**1f**	**2f**: $R^1 = Ph$	**3p**: 	64
17	**1g**	**2a**: $R^1 = Et$	**3a**	58
18	**1g**	**2f**: $R^1 = Ph$	**3f**	83
19	**1h**	**2a**: $R^1 = Et$	**3q**: $R^2 = Me$	51
20	**1h**	**2f**: $R^1 = Ph$	**3r**: 	85

[a] Unless stated otherwise, all reactions were carried out using *o*-diiodoarene (**1**) (0.50 mmol), acetylene (**2**) (3.0 mmol), $NiBr_2$(dppe) (10.0 mol%), dppe (10.0 mol%) and Zn (3.0 equiv.) in CH_3CN (1.0 mL) at 100 °C under N_2 for 48 h.[b] Isolated yields based on 1,2-diiodoarene.

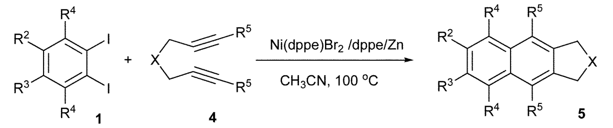
conditions, 1,2,4,5-tetraiodobenzene (**1f**) reacted with four equivalents of diphenyl acetylene (**2f**) to provide octaphenylanthracene in 64% yield (entry 16). Presumably, **1f** underwent [2 + 2 + 2] cycloaddition twice with **2f** consuming 4 equivalents of **2f**.

In addition, *o*-dibromoarenes **1g,h** also successfully reacted with **2a** and **2f** to give the corresponding products **3a**, **3f**, **3q** and **3r** in 51–85% yield (entries 17–20).

The nickel-catalyzed reaction can be smoothly extended to various diynes to furnish the corresponding naphthalenes (Table 2). Thus, **1a** reacts with 1,6-heptadiyne (**4a**) and 1,7-octadiyne (**4b**) to provide the naphthalene products, **5a** and **5b**, in 63 and 39% yields, respectively (entries 1, 2). Similarly, terminal diynes, **4c–e**, underwent cycloaddition with **1a** to produce naphthalene derivatives **5c–e** in moderate yields (entries 3–5). The reaction of internal diynes, **4f–i**, with **1a** resulted in higher yields of the corresponding naphthalene products **5f–i** (entries 6–8). This is probably because of the lower reactivity of self cyclization of the internal diynes. In a similar manner, the more electron rich 1,2-diiodoarenes **1b–d** reacted with internal diynes to afford naphthalene products in 81–84% yields (entries 10–12). On the other hand, diiodobenzene **1e** bearing electron-withdrawing fluoro groups reacted with **4f** to give naphthalene derivatives **5m** in lower 51% yield (entry 13).

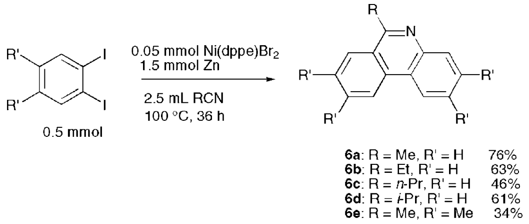
The foregoing results reveal that the present catalytic reaction can tolerate various functional groups on the acetylene, diyne and *o*-diiodoarene. Diaryl acetylenes (Table 1) and terminal diaryl diynes (Table 2) gave higher yields of the [2 + 2 + 2] cycloadducts because they are less reactive in forming homocyclotrimerization products. Diiodoarenes

Table 2 Results of nickel-catalyzed cycloaddition of *o*-diiodoarenes with diynes[a]



Entry	1	4	5	Yield (%)[b]
1	**1a**	**4a**: $R^5 = H$, $X = CH_2$	**5a**	63
2	**1a**	**4b**: $R^5 = H$, $X = (CH_2)_2$	**5b**	39
3	**1a**	**4c**: $R^5 = H$, $X = O$	**5c**	57
4	**1a**	**4d**: $R^5 = H$, $X = (MeO_2C)_2C$	**5d**	56
5	**1a**	**4e**: $R^5 = H$, $X = (CN)_2C$	**5e**	64
6	**1a**	**4f**: $R^5 = Ph$, $X = CH_2$	**5f**	86
7	**1a**	**4g**: $R^5 = p$-tolyl, $X = CH_2$	**5g**	85
8	**1a**	**4h**: $R^5 = p$-anisyl, $X = CH_2$	**5h**	77
9	**1a**	**4i**: $R^5 = p$-acetylphenyl, $X = CH_2$	**5i**	69
10	**1b**	**4f**: $R^5 = Ph$, $X = CH_2$	**5j**	81
11	**1c**	**4f**: $R^5 = Ph$, $X = CH_2$	**5k**	83
12	**1d**	**4f**: $R^5 = Ph$, $X = CH_2$	**5l**	84
13	**1e**	**4f**: $R^5 = Ph$, $X = CH_2$	**5m**	51

[a] Unless stated otherwise, all reactions were carried out using *o*-diiodoarene (**1**) (0.50 mmol), diyne (**4**) (1.5 mmol), $NiBr_2$(dppe) (10.0 mol%), dppe (10.0 mol%) and Zn (3.0 equiv.) in CH_3CN (1.0 mL) at 100 °C under N_2 for 48 h.[b] Isolated yields based on 1,2-diiodoarene.

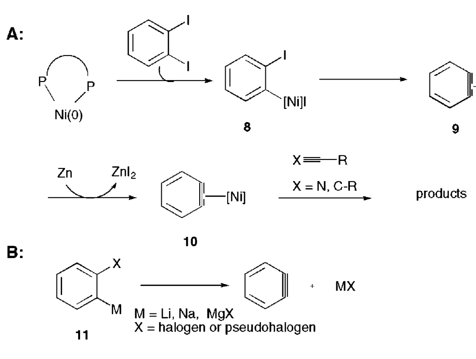


Scheme 1

consisting of electron-donating groups provided better yields on reaction with diphenyl acetylene than with dialkyl and dialkoxycarbonyl acetylenes.

To our surprise, when diiodobenzene was heated in the presence of $NiBr_2$(dppe) and zinc without additional dppe, the reaction produced a new [2 + 2 + 2] cyclization product, phenanthridine, in addition to the expected triphenylene. The yield of phenanthridine increased as the relative amount of solvent increased. As shown in Scheme 1, with the same amounts of the nickel catalyst, zinc metal, diiodobenzene and acetonitrile used in Table 1, the catalytic reaction provided triphenylene as the major product in about 60% yield. However, as the amount of acetonitrile solvent was increased from 1.0 to 2.5 ml, phenanthridine, **6a**, became the major product in 76% yield. It is clear from the structure of **6a** that the new cocyclotrimerization product is from two molecules of diiodobenzene and an acetonitrile molecule. Under similar reaction conditions, other nitriles also underwent cocyclotrimerization with diiodoarenes to give the corresponding phenanthridine[11] derivatives **6b–e** in moderate to good yields.

Compared with the known benzyne chemistry,[12,13] the results of the above nickel-catalyzed reactions strongly suggest that the products including triphenylenes, naphthalenes and phenanthridines are likely due to [2 + 2 + 2] cycloaddition of arynes with alkynes or nitriles. As shown in Scheme 2(A), the aryne intermediate is probably generated from the oxidative addition of *o*-dihaloarene to a nickel(0) complex to give **8**, followed by a β-halogen elimination to afford **9**. Reduction of **9** gives Ni–aryne complex **10**. The latter then reacts with alkynes or nitriles to afford the final organic products. However, the detailed pathways are not yet clear. It is noteworthy that the stoichiometric reactions of *o*-dihaloarenes with nickel(0) complex to give complexes similar to **8** and further reaction with sodium metal to give nickel–benzyne complexes has been reported previously.[12,13] In addition, the reaction of *o*-dihaloarenes with alkaline metals, magnesium or *n*-butyl lithium to give benzynes, are known and are widely used in organic synthesis (Scheme 2(B)).[1] The pathway for the formation of benzynes in these reactions involves the elimination reaction of intermediate **11**,[1b,11] similar in structure to **8**, to yield benzynes and a metal salt.



Scheme 2

Another possible pathway for the nickel-catalyzed synthesis of naphthalene derivatives shown in Tables 1 and 2 involves stepwise insertion of two alkyne moieties into the oxidative addition product of *o*-dihaloarene with nickel(0) (see intermediate **8**) followed by cyclization. Although this pathway cannot be excluded totally, it is difficult to explain the regiochemistry of product **5** shown in Table 2.

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