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Synthesis of Polycyclic Benzonitriles via a One-Pot Aryl Alkylation/Cyanation Reaction

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The cyanation of aryl halides and pseudohalides using palladium has emerged as one of the most reliable and efficient methods for the synthesis of the aryl−cyanide bond.[1] Despite these advances, the use of this valuable cross-coupling reaction in a tandem process is largely unknown.[2] Recently, we have reported a norbornene-mediated palladium-catalyzed tandem process for the synthesis of fused aromatic heterocycles.[3,4] Our approach toward developing a tandem reaction relies on using the inherent reactivity of norbornene to initiate a competitive C−H functionalization pathway, so that C−C and C−CN bond formation can occur sequentially. Herein, we describe the application of this sequence to the rapid synthesis of complex and sterically hindered bi- and tricyclic benzonitriles.

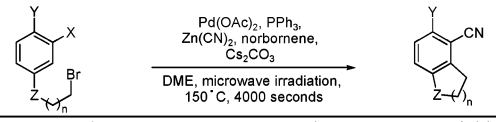
Initial exploration of the reaction focused on the synthesis of oxygen-containing ring systems. While preliminary experiments yielded a mixture of both cyclized and uncyclized benzonitriles, the formation of the uncyclized benzonitriles could be suppressed by careful variation of the reaction temperature. Under the optimized conditions [aryl halide (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (22 mol %), Cs_2CO_3 (2 equiv), norbornene (3 equiv), and $Zn(CN)_2$ (1 equiv) in DME (0.05 M) under microwave irradiation at 150 °C for 4000 s], substrate **1** was transformed into the five-membered ring oxacycle **2** in 91% yield (Table 1, entry 1).[5] Lowering the catalyst loading to 5 mol % palladium gave **2** in 63% yield. Extension to larger ring systems was also possible under these conditions affording the desired six- and seven-membered rings in 78% and 62% yields, respectively (entries 2 and 3). Next, the nitro- (**7**) and methoxy-(**9**) containing aryl iodides were subjected to the reaction conditions to ascertain the effect of different ortho blocking substituents on the yield of the reaction. Gratifyingly, both substrates furnished the corresponding benzonitriles in good yields (entries 4 and 5); demonstrating that both electron-withdrawing and electron-donating ortho blocking substituents are tolerated under the reaction conditions. All attempts using substrates lacking an ortho substituent were found to give complex mixtures.

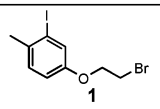
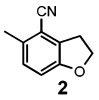
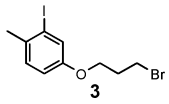
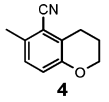
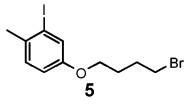
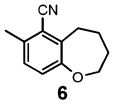
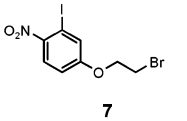
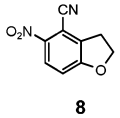
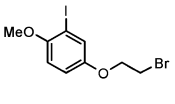
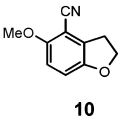
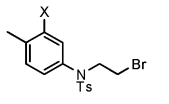
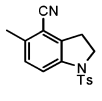
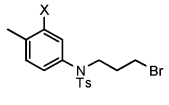
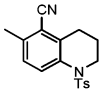
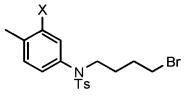
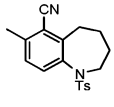
The synthesis of nitrogen-containing heterocyclic benzonitriles also proved to be very efficient. Five- and six-membered ring products were generated in 78% and 79% yields, respectively (entries 6−7), while seven-membered ring formation occurred in a lower 67% yield (entry 8). We also investigated the feasibility of using aryl bromides under the optimized reaction conditions. To our delight **11b** underwent cyclization to give **12** in 57% yield (entry 9). Similar results were obtained for the transformation of **13b** and **15b.** Although there was a substantial drop in the yield, these results demonstrate the potential for using aryl bromides in the reaction.

The successful preparation of bicyclic substrates led us to extend the reaction scope to include tricyclic benzonitriles through a double ortho-alkylation/cyanation sequence (Table 2).

While the 5,6,5-ring system product **18** was prepared in 88% yield (entry 1), larger 6,6,6- and unsymmetrical 5,6,6-ring systems were generated in 75% and 56% yields, respectively (entries 2 and 3). In addition, fully substituted tricyclic benzonitrile **24** was prepared in 74% yield from the corresponding *p*-methoxy aryl iodide **23** (entry 4).

Table 1. Synthesis of Bicyclic Benzonitriles via Palladium-Catalyzed Tandem Alkylation/Cyanation Reaction[a]

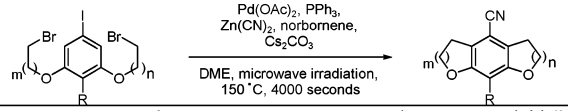


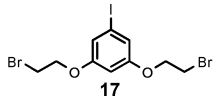
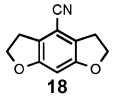
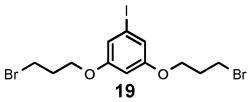
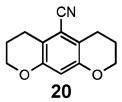
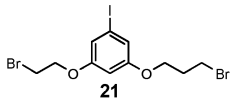
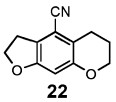
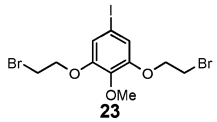
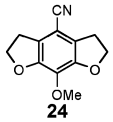
entry	substrate	product	yield (%)[b]
1	 **1**	 **2**	91
2	 **3**	 **4**	78
3	 **5**	 **6**	62
4	 **7**	 **8**	73
5	 **9**	 **10**	83
6	 **11a, X=I** **11b, X=Br**	 **12**	78 57[c]
7	 **13a, X=I** **13b, X=Br**	 **14**	79 55[c]
8	 **15a, X=I** **15b, X=Br**	 **16**	67 47[c]

[a] All reactions were run under the following conditions: aryl halide (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (22 mol %), Cs_2CO_3 (2 equiv), norbornene (3 equiv), and $Zn(CN)_2$ (1 equiv) in DME (0.05 M) were heated in a sealed tube at 150 °C for 4000 s under microwave irradiation. [b] Isolated yield. [c] Yield from aryl bromide.

10.1021/ja064742p CCC: $33.50

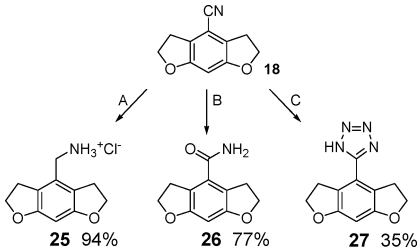
Table 2. Synthesis of Tricyclic Benzonitriles via Palladium-Catalyzed Tandem Alkylation/Cyanation Reaction[a]



entry	substrate	product	yield (%)[b]
1	 **17**	 **18**	88
2	 **19**	 **20**	75
3	 **21**	 **22**	56
4	 **23**	 **24**	74

[a] All reactions were run under the following conditions: iodoarene (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (22 mol %), Cs_2CO_3 (2 equiv), norbornene (3 equiv), $Zn(CN)_2$ (1 equiv) in DME (0.05 M) were heated in a sealed tube at 150 °C for 4000 s under microwave irradiation. [b] Isolated yield.

Scheme 1. Modification of Benzonitrile Product



(A) $LiAlH_4$ (1 equiv), THF, 0 °C to room temp, 6 h, then HCl in ether; (B) H_2O_2 (7.5 equiv), NaOH (0.6 equiv), 95% EtOH, 60 °C, 8 h; (C) NaN_3 (12 equiv), NH_4Cl (12 equiv), DMF, 220 °C microwave irradiation, 25 min.

To demonstrate the synthetic utility of the resulting benzonitrile moiety, **18** was converted into three common functional groups, showing the versatility of our nitrile containing products (Scheme 1). Reduction using lithium aluminum hydride, followed by formation of the hydrochloride salt resulted in 94% yield of **25**. Conversion of the benzonitrile functionality to the corresponding amide could be carried out using basic hydrogen peroxide in 77% yield. Finally, preparation of tetrazole **27** was achieved in modest yield using sodium azide and ammonium chloride in DMF under microwave irradiation.[6]

In summary, we have developed an approach toward the synthesis of highly substituted benzonitriles via a palladium-catalyzed intramolecular alkylation/intermolecular cyanation reaction. This method has been applied toward the synthesis of a variety of synthetically useful bicyclic and tricyclic benzonitrile products. Studies toward the tandem intermolecular alkylation/intermolecular cyanation reaction are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The reaction could also be carried out in a sealed tube at 150 °C using conventional heating for 4000 seconds to give **2** in a 77% yield.

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