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Microwave-Assisted Suzuki Cross-Coupling Reaction, a Key Step in the Synthesis of Polycyclic Aromatic Hydrocarbons and Their Metabolites

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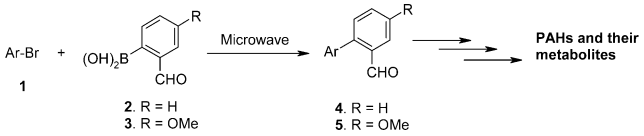

A highly efficient and general method for Suzuki cross-coupling reaction en route to the synthesis of polycyclic aromatic hydrocarbons (PAHs) and their metabolites has been developed. Microwave irradiation of aryl bromides **1** and boronic acids (**2** and **3**) using polyurea microencapsulated palladium catalyst (Pd EnCat 30) gave the coupling adducts **4** and **5** in excellent yields in just 20 min compared to ∼24 h under thermal conditions, corresponding to a ∼72-fold increase in reaction rate.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants[1] that require metabolic activation to electrophilic reactive species in order to exert their mutagenic and tumorigenic activity.[2] The diol epoxides derived from PAHs having a sterically hindered fjord region[3] [e.g., benzo[*c*]-phenanthrene (B[*c*]P), benzo[*c*]chrysene (B[*c*]C), benzo[*g*]-chrysene (B[*g*]C), dibenzo[*a,l*]pyrene (DB[*a,l*]P), and dibenzo-[*c,mno*]chrysene (DB[*c,mno*]C)] and those having a methyl group in the bay region[4] [e.g., 7,12-dimethylbenz[*a*]anthracene (DMBA)] are relatively potent carcinogens. In connection with metabolism study and determination of mutagenicity and tumorigenicity, the synthetic standards of PAHs and their metabolites are required. This need has led to a continuous development of new and efficient methods for their synthesis. Most prominent methods commonly used involve Suzuki cross-coupling reactions[5−13] and photochemical reactions.[1,10,13,14] The former has recently been used extensively because it allows for a larger scale and is by far the most versatile synthetic method for the generation of biaryl compounds.[15] We have previously reported the successful use of Suzuki cross-coupling reactions to generate key intermediates for the synthesis of PAHs and their metabolites.[9−13] However, this coupling is associated with extended reaction times and requires up to 24 h of refluxing. In pursuit of our previous investigations toward developing more efficient methods for the synthesis of PAH derivatives, we optimized the Suzuki reaction conditions under microwave irradiation. It was envisaged that the microwave irradiation would enhance the rate of reaction, thereby reducing time.

TABLE 1. Optimization of Reaction Conditions

entry	reaction conditions	time/temp (°C)	conv (%)
1	$Pd(PPh_3)_4$, CsF, DME	1 h/120	90
2	$Pd(OAc)_2$, K_2CO_3, dioxane/water (5:1)	20 min/120	85
3	Pd EnCat 30 (5 mol %), Bu_4NH_4OAc, EtOH	10 min/120	90
4	Pd EnCat 30 (10 mol %), Bu_4NH_4OAc, EtOH	20 min/ 120	>98

The conditions were optimized for the reaction of 9-bromophenanthrene with 2-formylphenylboronic (**2**) (Table 1). Microwave irradiation resulted in 90% conversion[16] in 1 h at 120 °C, using $Pd(PPh_3)_4$ and CsF in DME (entry 1), the reaction

* To whom correspondence should be addressed. Phone: (717) 531-0003 ext 285016. Fax: (717) 531-0244.

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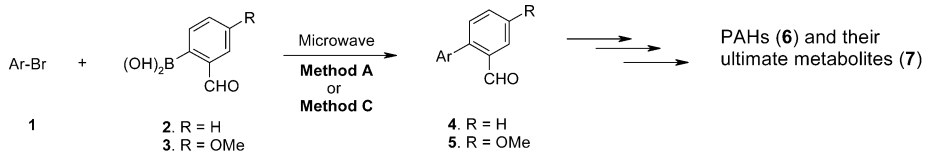
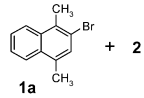
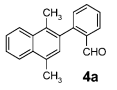
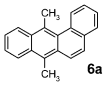
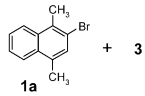
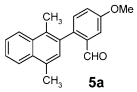
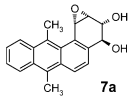
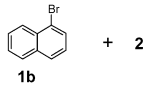
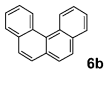
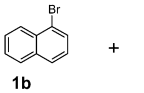
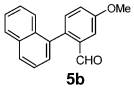
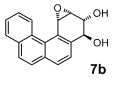
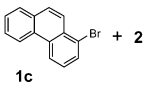
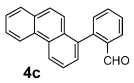
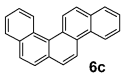
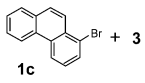
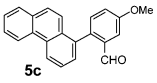
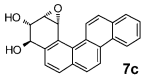
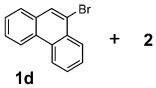
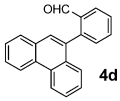
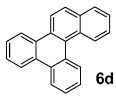
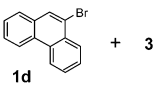
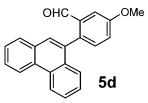
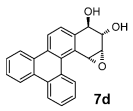
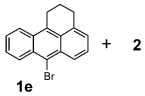
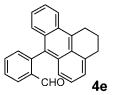
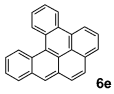
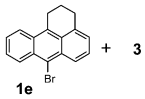
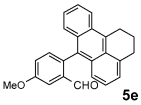
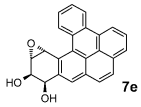
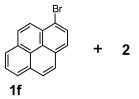
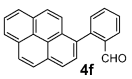
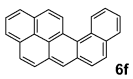
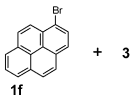
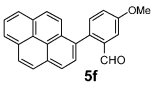
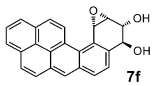
TABLE 2. Microwave-Assisted Suzuki Cross-Coupling Reactions Using Pd EnCat 30 (Method C) or $Pd(PPh_3)_4$ (Method A) as Catalysts



1

2. R = H
3. R = OMe

4. R = H
5. R = OMe

entry	reactants	product[a]	reaction time: microwave/ Method[b]	reaction time: thermal[ref.]	yield: micro -wave	yield: thermal[ref.]	mp (°C)	precursor for
1	 1a + 2	 4a	1 h / A	N/A	79%	N/A	85-87	 6a
2	 1a + 3	 5a	1 h / A	20 h[6]	81%	87%[11]	104-106 lit.[11] 104-105	 7a
3	 1b + 2	 4b	20 min. / C	12-18 h[8]	90%	95%[8]	87-88 lit.[8] 86-87	 6b
4	 1b + 3	 5b	20 min. / C	18 h[7]	91%	100%[7]	114-115 lit.[7] 115-116	 7b
5	 1c + 2	 4c	20 min. / C	12-18 h[8]	92%	92%[8]	viscous oil lit.[8] oil	 6c
6	 1c + 3	 5c	20 min. / C	5 h[11]	83%	66%[11]	127-128 lit.[11] 126-127	 7c
7	 1d + 2	 4d	20 min. / C	12-18 h[8]	89%	92%[8]	130-132 lit.[8] 109-110	 6d
8	 1d + 3	 5d	20 min. / C	18 h[7]	93%	100%[7]	118-119 lit.[7] 118.5-119	 7d
9	 1e + 2	 4e	1 h / A	24 h[9]	76%	61%[9]	207-208 Lit.[9] 206-208	 6e
10	 1e + 3	 5e	1 h / A	24 h[9]	80%	65%[9]	210-212 lit.[9] 213-214	 7e
11	 1f + 2	 4f	20 min. / C	20[10]	84%	73%[10]	149-150 lit.[10] 149-150	 6f
12	 1f + 3	 5f	20 min. / C	20[10]	78%	92%[10]	202-203 lit.[10] 201-202	 7f

[a] All the products (except **4a**) were characterized by comparison with the published data.[7−11] [b] See the Experimental Section.

conditions that we[9−13] and others[5c,6−8] have used earlier under conventional thermal conditions. The conversion could not be improved even after keeping the reaction for longer time at 140 °C or by using 1.5 equiv of boronic acid **2**. In an attempt to achieve better conversion in less time, we investigated the use of $Pd(OAc)_2$ in the presence of K_2CO_3 in dioxane/water 5:1 (entry 2). Under these conditions, the reaction went to about 85% conversion in 20 min at 120 °C. The TLC showed additional spots of impurities compromising the yield of the reaction. Next, we exploited the use of palladium-microencap-

(16) (a) The conversion percentage was determined by normal phase HPLC monitored at 254 nm (solvent system: THF/hexanes (5:95) at 1.0 mL min^{-1}; column: LiChrosorb Si 60 10 μm (250 × 4 mm)]. (b) The isolated yield of this reaction after column purification was 82%.

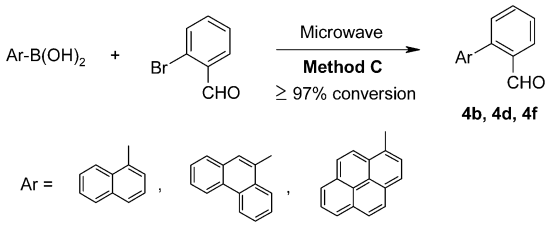
sulated catalyst, Pd EnCat 30, in the presence of tetrabutylammonium acetate in ethanol.[17] Using 5 mol % of Pd EnCat 30 (entry 3) with these reagents at 120 °C, the reaction showed 90% conversion in 10 min. The percentage conversion could not be improved by enhancing the reaction time, temperature or by using excess of boronic acid. However, using 10 mol % of Pd EnCat 30 in the presence of tetrabutylammonium acetate in ethanol led to up to 95% conversion in 10 min. Increasing the reaction time to 20 min under the above conditions led to >98% conversion (entry 4). The compound was purified by silica gel column chromatography to yield the product in 89% yield. The product was characterized on the basis of NMR and MS. In all of the above cases, the workup procedures consisted of only filtration followed by purification by silica gel column chromatography.

Once the reaction conditions were optimized, they were used for coupling of several aryl bromides **1** with 2-formylphenylboronic acid (**2**) and 2-formyl-5-methoxyphenylboronic acid[6] (**3**) to obtain the key intermediates (**4** and **5**) for the synthesis of DMBA (**6a**) B[*c*]P (**6b**), B[*c*]C (**6c**), B[*g*]C (**6d**), DB[*a*,*l*]P (**6e**), DB[*c*,*mno*]C (**6f**) and their corresponding ultimate carcinogens, the diol epoxides **7a**−**f**. The experimental details, results, and the literature data comparison are summarized in Table 2. The reaction conditions using Pd EnCat 30 with Bu_4NH_4OAc (method C) worked extremely well (>98% conversion) for all of the substrates except for the reactions of 7-bromo-5,6-dihydro-4*H*-benz[*de*]anthracene (**1e**) and 2-bromo-1,4-dimethylnaphthalene (**1a**). We determined that the reactions of **1e** with boronic acids **2** and **3** by method C gave only 25−30% conversion. The conversion percentage was not improved even after the reaction mixture was irradiated for up to 1 h at 140 °C under these conditions. Altering the reaction conditions using Pd EnCat 30 in the presence of K_2CO_3 in a mixture of toluene/water/EtOH (4:2:1)[17] did not improve the conversion percentage significantly. In an attempt to enhance the yield, we tried the reactions of **1e** with boronic acids **2** and **3** with $Pd(OAc)_2$ or $Pd(PPh_3)_4$ as catalysts. The use of $Pd(OAc)_2$ (method B) resulted in even diminished conversion (~10%) and more sloppy reactions. The best results were obtained by conducting the coupling using $Pd(PPh_3)_4$ as a catalyst in the presence of CsF in DME (method A). Under these conditions, a satisfactory 90% conversion was achieved in about 1 h leading to about 76−80% isolated yields (Table 2, entries 9 and 10). Similarly, the reactions of 2-bromo-1,4-dimethylnaphthalene (**1a**) with boronic acids **2** and **3** worked best (~90% conversion) when $Pd(PPh_3)_4$ was employed as a catalyst in the presence of CsF in DME. The coupling reactions in the presence of Pd EnCat 30 (60−70% conversion) or $Pd(OAc)_2$ (40−50% conversion) were less efficient. All the products were characterized by ^1H NMR and MS and by comparison of the spectral data and melting points with the literature values.

The use of Pd EnCat 30 has led to substantial reduction in reaction time (20 min) compared to the reported conventional thermal conditions (up to 24 h), corresponding to up to 72-fold rate increase. The reactions were also more expeditious and cleaner than the other microwave conditions tried herein. The reaction yields were better than or comparable to those reported under thermal conditions (see Table 2). In addition to significantly facilitating the Suzuki coupling reaction, the advantages of Pd EnCat 30 are that it can be recycled and reused, thus reducing the expense and palladium-related toxicity especially at a larger scale.[17]

(17) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem. Eur. J.* **2006**, *12*, 4407 and references cited therein.

SCHEME 1



To demonstrate the versatility of the Pd EnCat 30 catalyzed Suzuki coupling among boronic acids, we performed a few reactions with the reverse combination, i.e., the reaction of 2-bromobenzaldehyde with aryl boronic acids (Scheme 1) in place of 2-formylphenylboronic acid (**2**) with aryl bromides (**1**) as described above (Table 2). The reactions of naphthalene-1-boronic acid, phenanthrene-9-boronic acid, and pyrene-1-boronic acid[10] with 2-bromobenzaldehyde using method C led to ≥97% conversion and gave isolated yields of **4b**, **4d**, and **4f** similar to those obtained earlier (Table 2).

In conclusion, an efficient method has been developed for the microwave-assisted Suzuki cross-coupling reaction using Pd EnCat 30 as a catalyst. The products **4** and **5** are the key intermediates for the syntheses of PAHs **6** and PAH-diol epoxides **7**, and these transformations have been reported previously.[7−11] These results establish for the first time the application of microwave irradiation in the synthesis of environmental pollutant PAHs and their ultimate carcinogens.

Experimental Section

General Method for Suzuki Cross-Coupling Reactions. Method A. The aryl halide (0.5 mmol) and boronic acid (0.55 mmol) were dissolved in ethylene glycol dimethyl ether (5 mL) in a microwave vial. $Pd(PPh_3)_4$ (0.02 mmol) and cesium fluoride (1.25 mmol) were added, and the reaction mixture was irradiated in a microwave apparatus at 120 °C, 250 W for 1 h. After the reaction mixture was cooled to ambient temperature, the product was filtered, the filtrate was concentrated, and the crude mixture was purified by silica gel column chromatography using hexane/ethyl acetate (96/4) as eluent.

Method B. The aryl halide (0.5 mmol) and boronic acid (0.55 mmol) were dissolved in dioxane/water (5:1, 5 mL) in a microwave vial. Palladium acetate (0.02 mmol) and potassium carbonate (1.25 mmol) were added, and the reaction mixture was irradiated in a microwave apparatus at 120 °C, 250 W for 20 min. After the reaction mixture was cooled to ambient temperature, the product was purified as described in method A.

Method C. The aryl halide (0.5 mmol) and boronic acid (0.55 mmol) were dissolved in ethanol (5 mL) in a microwave vial. Pd EnCat 30 (10 mol %) and tetrabutylammonium acetate (1.5 mmol) were added, and the reaction mixture was irradiated in a microwave apparatus at 120 °C, 250 W for 20 min. The product was purified as described in method A.

2-(2-Formylphenyl)-1,4-dimethylnaphthalene (4a): ^1H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.73 (s, 3H), 7.23 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.62−7.67 (m, 2H), 7.70 (dt, J = 7.5 and 1.5 Hz, 1H), 8.09−8.16 (m, 3H), 9.82 (s, 1H); HRMS (EI) calcd for $C_{19}H_{16}O$ 260.1187, found 260.1194.

Acknowledgment. This study was supported by NCI Contract NO2-CB-56603 and by the Penn State Cancer Institute of the Penn State College of Medicine.

Supporting Information Available: Copies of ^1H NMR spectra for compounds **4a**, **5a**, **4b**, **5b**, **4c**, **5c**, **4d**, **5d**, **4e**, **5e**, **4f**, and **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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