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EFFECT OF THE USE OF BULKY ALKYLPHOSPHINES IN THE SONOGASHIRA COUPLING WITH AQUEOUS AMMONIA‡

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‡ This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

Abstract – The Sonogashira coupling of terminal alkynes and aryl bromides with aqueous ammonia catalyzed by the in situ formed palladium complex of a bulky alkylphosphine furnishes the coupling product at room temperature. One-pot reaction of the Sonogashira coupling and the following intramolecular cyclization with 2-hydroxy or 2-amino aryl bromide leads to a facile synthesis of benzofuran and indole derivatives.

INTRODUCTION

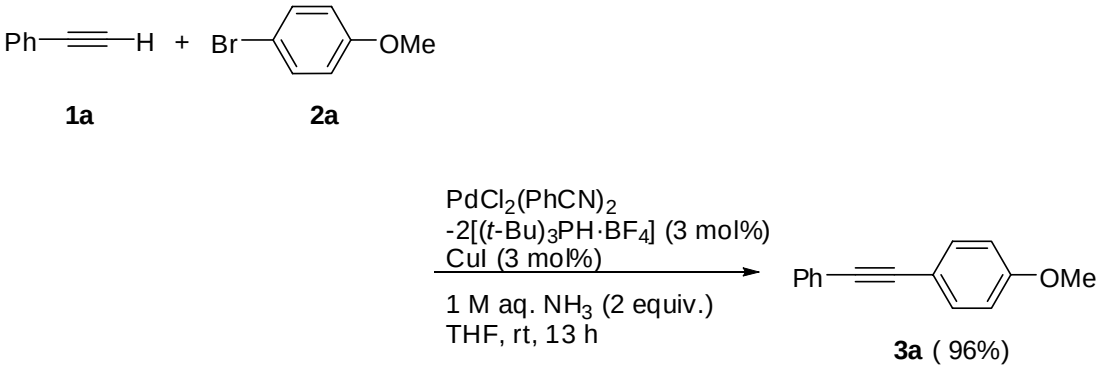
Sonogashira coupling, which is the reaction of terminal alkynes with organic halides, is of considerable interest since construction of the organic framework bearing a carbon-carbon triple bond moiety is highly important in the design of advanced organic materials as well as biologically active compounds.[1] We have recently shown that the Sonogashira coupling reaction takes place with aqueous ammonia under mild conditions.[2] Since one of the major drawback of the conventional Sonogashira conditions using large excess of organic amines as a solvent or a cosolvent is isolation and purification procedures for the removal of such amines, the reaction with not a large excess amount of aqueous ammonia improves feasibility of the reaction procedure particularly in the preparation of a laboratory scale.

On the other hand, a variety of transition metal-catalyzed coupling reactions have been shown to proceed under milder conditions when a bulky alkylphosphine such as tri-*t*-butylphosphine is employed as a ligand of the palladium catalyst.[3-8] Furthermore, the in situ formation of the palladium complex was performed by the reaction of palladium with *t*-$Bu_3PH{\cdot}BF_4$, which enabled the reaction to avoid the use of easily oxidized alkylphosphines as a ligand for the coupling reactions.[9] These findings prompted us to

examine the effect of the bulky alkylphosphine in the Sonogahsira reaction with aqueous ammonia. We herein report that the coupling reaction with unactivated aryl bromides takes place at room temperature.

RESULTS AND DISCUSSION

The reaction of phenylethyne **1a** with 4-methoxy-1-bromobenzene **2a** with 1 M of aqueous ammonia (2 equiv. to **2a**) in the presence of 3 mol% of $PdCl_2(PhCN)_2$, 6 mol% of $(t\text{-}Bu)_3PH{\cdot}BF_4$, and 3 mol% of CuI was carried out in THF at room temperature to afford the corresponding coupling product **3a** in 96% yield (Scheme 1). The reaction has been unsuccessful at room temperature when the similar reaction is carried out with $PdCl_2(Ph_3P)_2$ as a catalyst showing that an enhanced reactivity is observed in the reaction of aqueous ammonia.[2c]

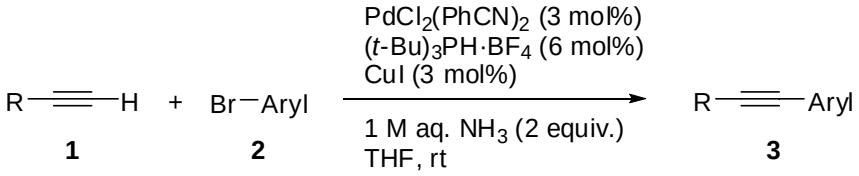


Scheme 1

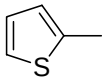
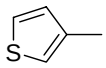
The reaction was examined with several unactivated aryl bromides and terminal alkynes as summarized in Table 1. Phenylethyne **1a** and unactivated aryl bromides such as bromobenzene **2b**, 4-methyl-1-bromobenzene **2c**, 4-*N*,*N*-dimethylamino-1-bromobenzene **2d**, 2-bromothiophene **2e**, and 3-bromothiophene **2f** underwent the coupling reaction at room temperature to afford the corresponding internal alkynes **3** in moderate to excellent yields. The reaction of 1-octyne **1b** also proceeded at room temperature although a longer reaction period was necessary to achieve the reasonable yield.

The reaction was revealed to be effective when a base-sensitive compound is employed as a substrate.[10] Coupling of vinylidene bromide **4** and **1a** with aqueous ammonia afforded the dialkynylated product **5** in 69% yield, along with the formation of diyne **6**, which was generated by base-promoted dehydrobromination of monoalkynylated product, was obtained in only 7% yield.[11] By contrast, the reaction with stoichiometric triethylamine as an activator resulted to produce a significant amount of **6** (32% yield) as shown in Scheme 2.

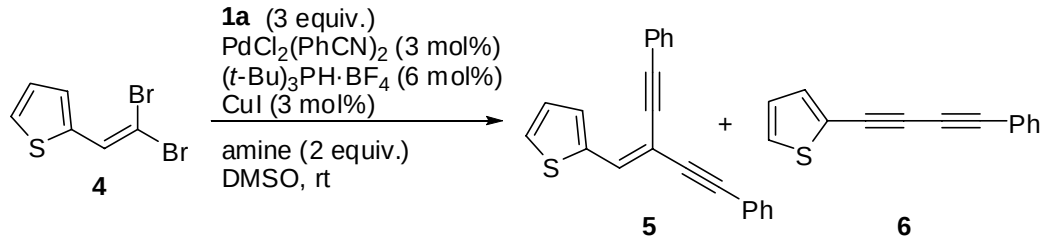
Table 1 Sonogashira coupling of terminal alkynes **1** with unactivated aryl bromides **2**[a]



1 **2** **3**

R	Aryl	time (h)	**3**, yield (%)
Ph (**1a**)	4-$MeOC_6H_4$ (**2a**)	13	**3a**, 96
	Ph (**2b**)	12	**3b**, quant.
	4-MeC_6H_4 (**2c**)	12	**3c**, quant.
	4-$Me_2NC_6H_4$ (**2d**)	16	**3d**, quant.
	 (**2e**)	16	**3e**, 61
	 (**2f**)	24	**3f**, 67
n-hexyl (**1b**)	**2a**	96	**3g**, 83

[a] The reaction was carried out with **2** (0.5 mmol) and **1** (0.6 mmol) in the presence of 3 mol% of $PdCl_2(PhCN)_2$, 6 mol% of $(t\text{-}Bu)_3PH{\cdot}BF_4$ and 3 mol% of CuI in THF with 1 M of aqueous ammonia (1 mmol) at rt.



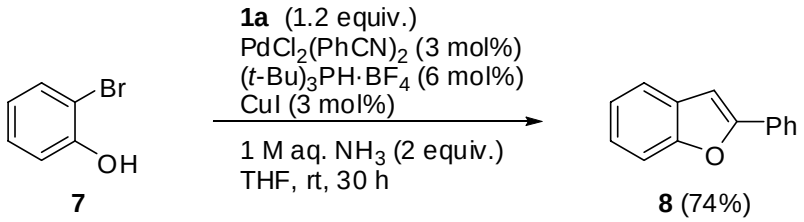
4 **5** **6**

1 M aq. NH_3 (90 h)	69%	7%
NEt_3 (24 h)	50%	32%

Scheme 2

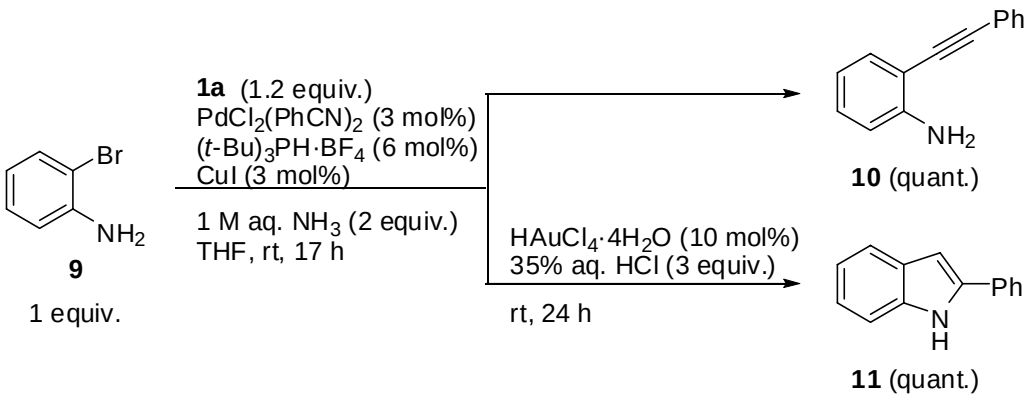
The utility of the Sonogashira coupling reaction of aryl bromide with aqueous ammonia is highlighted by the tandem coupling and following intramolecular cyclization leading to benzofuran and indole in a one-pot manner at room temperature. Since benzofuran and indole derivatives are versatile intermediates in the preparation of biologically important molecules, a facile and preparative method for such compounds is of much interest.

The reaction of 2-bromophenol **7** with **1a** with 1 M aqueous ammonia in the presence of 3 mol% of $PdCl_2(PhCN)_2$ and 6 mol% of $(t\text{-Bu})_3PH{\cdot}BF_4$, and 3 mol% of CuI at room temperature for 30 h afforded the corresponding benzofuran derivative **8** in 74% yield as shown in Scheme 3.



Scheme 3

The coupling reaction was carried out with 2-bromoaniline **9** under similar conditions to afford the coupling product **10**, while no cyclized product was obtained at all. However, the cyclization was achieved by the addition of 10 mol% of $HAuCl_4$ after the Sonogashira coupling was confirmed to be complete.[12] Stirring at room temperature for 24 h afforded indole **11** in a quantitative yield (Scheme 4). Although the tandem coupling and cyclization reaction strategy has been studied extensively in the synthesis of indole derivatives, the reactions of both steps at room temperature are worthy to note arbeit additional reagent is necessary for the cyclization.[13]



Scheme 4

In summary, effect of the enhanced reactivity in the use of bulky alkylphosphines was shown to be observed in the Sonogashira coupling with aqueous ammonia to undergo the reaction at room temperature with in situ formed tri-*t*-butylphosphine complex of the palladium catalyst. The reaction would be highly

effective for the reaction of base-sensitive substrate due to the weak basicity of the dilute ammonia.

EXPERIMENTAL

General: Infrared spectra were measured by Perkin-Elmer FT-IR spectrometer SPECTRUM 1000 apparatus. ^{1}H and ^{13}C NMR spectra were measured by Brucker Avance 500 spectrometer at Center for Supports to Research and Education Activities of Kobe University. Elemental analyses were performed at the Elemental Analyses Center of Chemical Resources Laboratory, Tokyo Institute of Technology using Yanako MTCHN Corder. HRMS analyses were carried out with JEOL MStation JMS 700 of Tokyo Institute of Technology. Column chromatography was carried out with Wakogel C-200. All the reactions were performed under nitrogen atmosphere using standard Schlenk technique. THF and DMSO (anhydrous grade) were purchased from Wako Pure Chemicals Co. Ltd and stored in a Schlenk tube. $HAuCl_4 \cdot 4H_2O$ was purchased from Tanaka Kikinzoku Co. Ltd. Other chemicals were purchased and used without further purification.

General procedure for the Sonogashira coupling of terminal alkynes (1) with aryl bromides (2): To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PhCN)_2$ (5.8 mg, 0.015 mmol), (t-Bu)$_3$PH·BF_4 (8.7 mg, 0.030 mmol), CuI (2.9 mg, 0.015 mmol), THF (1 mL) and 1 M aqueous ammonia (1 mL, 1.0 mmol). Then, **2** (0.50 mmol) and **1** (0.60 mmol) were added, and the reaction resulting mixture was stirred at rt for the period stated in Table 1. After the reaction was confirmed to be complete by the TLC analysis, the mixture was poured into a mixture of Et_2O and water to observe that two phases were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), then the combined organic layers were washed with water (15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding coupling product **3**.

Reaction of phenylethyne (1a) with 2-(thiophen-2-yl)-1,1-dibromoethene (4): To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PhCN)_2$ (5.8 mg, 0.015 mmol), (t-Bu)$_3$PH·BF_4 (8.7 mg, 0.030 mmol), CuI (2.9 mg, 0.015 mmol), DMSO (3 mL) and 1 M aqueous ammonia (2 mL, 2.0 mmol) under a nitrogen atmosphere. 2-(Thiophen-2-yl)-1,1-dibromoethene **4** (134.0 mg, 0.50 mmol) and phenylethyne **1a** (164.7 μL, 1.5 mmol) were then added and the reaction mixture was stirred at rt. After the period shown in eq 2, the mixture was poured into water and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was then washed with water (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to leave a crude oil, which was purified by column chromatography on silica gel (n-hexane) to afford dialkynylated compound **5** as a yellow solid (69%). Mp 128-130 ˚C; ^{1}H

NMR ($CDCl_3$, 500 MHz): δ 7.08 (dd, *J* = 5.2, 3.7 Hz, 1H), 7.33-7.36 (m, 4H), 7.38-7.43 (m, 5H), 7.52-7.54 (m, 2H), 7.64-7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 87.2, 88.7, 89.0, 97.6, 100.3, 122.95, 122.98, 126.7, 128.3, 128.37, 128.4, 128.6, 128.8, 131.0, 131.63, 131.64, 136.7, 140.0; IR (KBr): 1490, 2196, 3022, 3068, 3093 cm^{-1}. Anal. Calcd for $C_{22}H_{14}S$: C, 85.12; H, 4.55; S, 10.33. Found: C, 84.72; H, 4.40; S, 10.44. HRMS (EI, *m*/*z*) Calcd for $C_{22}H_{14}S$: 310.0816. Found: 310.0826.

2-Phenylbenzo[*b*]furan (8)[14]: To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PhCN)_2$ (5.8 mg, 0.015 mmol), (*t*-Bu)$_3$PH·BF_4 (8.7 mg, 0.030 mmol), CuI (2.9 mg, 0.015 mmol), THF (1 mL) and 1 M aqueous ammonia (1 mL, 1.0 mmol) under a nitrogen atmosphere. 2-Bromophenol **7** (58.0 μL, 0.50 mmol) and phenylethyne **1a** (65.9 μL, 0.60 mmol) were added and the mixture was stirred at rt for 30 h. The resulting mixture was poured into water and extracted with Et_2O (2 × 10 mL). The extracts were washed with water (15 mL), dried over anhydrous K_2CO_3 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane) to afford **8** (71.8 mg, 74%).

2-(Phenylethynyl)aniline (10)[15]: 2-(Phenylethynyl)aniline **10** was prepared similarly to **3** from 2-bromoaniline **9** (>99% yield).

2-Phenylindole (11)[15]: To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PhCN)_2$ (5.8 mg, 0.015 mmol), (*t*-Bu)$_3$PH·BF_4 (8.7 mg, 0.030 mmol), CuI (2.9 mg, 0.015 mmol), THF (1 mL) and 1 M aqueous ammonia (1 mL, 1.0 mmol) under a nitrogen atmosphere. 2-Bromoaniline **9** (56.6 μL, 0.50 mmol) and phenylethyne **1a** (65.9 μL, 0.60 mmol) were added, and the mixture was stirred at rt. After the Sonogashira coupling was completed, the reaction mixture was acidified with 35% hydrochloric acid (0.13 mL, 1.5 mmol), and was stirred at rt for 24 h after the addition of $HAuCl_4·4H_2O$ (20.6 mg, 0.050 mmol). The resulting mixture was basified with saturated Na_2CO_3 aqueous solution, and extracted with Et_2O (2 × 10 mL), then the extract was washed with water (15 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (30:1 *n*-hexane:EtOAc) to afford **11** (96.6 mg, 100%).

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