

Sonogashira Coupling with Aqueous Ammonia

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(Received April 15, 2002; CL-020322)

The coupling reaction of terminal alkynes with organic halides, Sonogashira-(Hagihara) coupling, takes place with only 2 equivalents of dilute aqueous ammonia as an additive. The reaction of phenylacetylene and 4-iodoanisole in the presence of 1 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$, 2 mol% of CuI , and 2 equiv of aqueous ammonia in THF proceeds at room temperature for 6 h to afford the coupling product in a quantitative yield.

We herein report that the Sonogashira coupling can be carried out with dilute aqueous ammonia highly efficiently. The Sonogashira-(Hagihara) coupling, which is a C–C bond-forming reaction of terminal alkynes with organohalogen compounds in the presence of palladium(0)/copper(I) catalyst, has attracted much attention as a practical method to introduce an alkyne moiety into a wide range of organic molecules involving biologically and non-biologically important materials.¹ The reaction is, in general, carried out with large excess amounts of amine, which is generally a tertiary or secondary alkyl one, as a solvent or a co-solvent.² Otherwise, decreasing the amount of amine lowers the reactivity of the coupling considerably. Since it is recognized to be a significant progress to carry out the reaction with a reduced amount of amine accordingly, much effort has been paid recently to develop novel conditions.³ Krause showed that coupling of a terminal alkyne with several aromatic halides in the presence of a stoichiometric amount of triethylamine, however, the available halide had to possess an electron-withdrawing substituent on the aromatic ring.^{2b} On the other hand, use of a bulky and electron-donating phosphine as a ligand to improve the reactivity of transition metal-catalyzed coupling reactions was shown to be successful also for the Sonogashira coupling.^{4,5}

We envisaged that another solution for the problem in Sonogashira coupling was to develop a new class of activating agent instead of amines and revealed that silver(I) oxide (Ag_2O), tetrabutylammonium fluoride (TBAF), or tetrabutylammonium hydroxide (TBAOH) served as a surrogate of excess amine.⁶ During the course we learned unexpectedly that use of only two equivalents of dilute aqueous ammonia (ammonium hydroxide) promoted the coupling of terminal alkynes under mild conditions.

When a terminal alkyne (**1** $\text{R}=\text{Ph}$, **2** $\text{R}=\text{Me}_3\text{Si}$) was treated with 4-methoxy-1-iodobenzene (**3a**) at room temperature in the presence of 1 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$, 2 mol% of CuI , and 0.5 M aqueous ammonia (2 equiv to **3a**), the coupling product was obtained in excellent yields as shown in eq 1.⁶ During the reaction neither biaryl nor diyne through homocoupling was observed in a significant amount. Isolation and purification procedures were indeed quite simple to be carried out by usual aqueous work-up followed by silica gel chromatography, (distillation, or recrystallization). As far as we know, no successful example to undergo the Sonogashira coupling with ammonia was reported so far despite employing a readily available inexpensive reagent. Since

the Sonogashira reaction has been performed with highly basic secondary or tertiary alkyl amine in excess, the attempted reaction with ammonia might have been examined in a higher concentration and with a larger amount as much as possible. By contrast, the ammonia solution we employed herein was markedly dilute (0.5 M) and smaller amounts (two equivalents). It also turned out that the reaction with higher concentrations of ammonia inhibited the progress of the reaction.

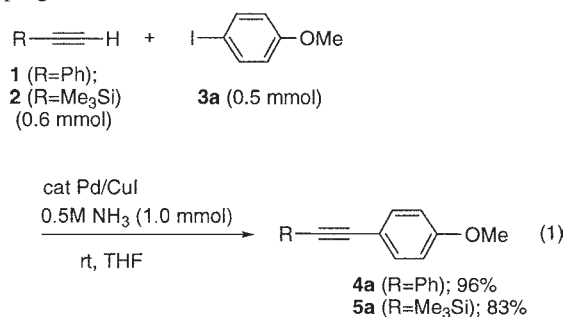


Figure 1 represents effect of the ammonia concentration toward the yield of the coupling product. Similar influence toward the concentration was observed in the reaction of both phenylethyne (**1**) and trimethylsilyl ethyne (**2**). The reaction with 0.5–2 M of ammonia was found to proceed smoothly. However, use of ammonia of higher than 4 M gradually decreased the yield and a commercially available conc NH_3 (28%; 14.9 M) afforded the coupling product in only 8% ($\text{R}=\text{Ph}$) and 17% ($\text{R}=\text{TMS}$) yields, respectively. It is also remarkable that addition of water to the above unreacted mixture using 14.9 M ammonia ($\text{R}=\text{Ph}$, after stirring at rt for 24 h) initiated the reaction to yield 90% of the coupling product after stirring for further 16 h.⁷

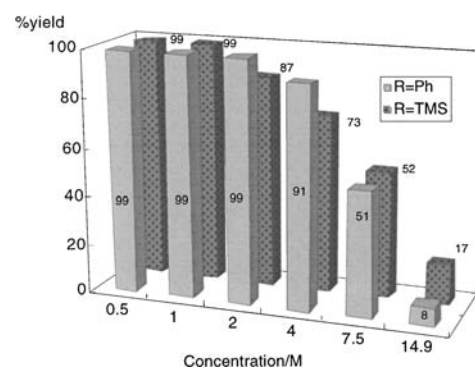


Figure 1. Relationship of the concentration of aqueous ammonia with the yield of the coupling reaction of $\text{R}-\text{C}\equiv\text{C}-\text{H}$ (**1a**; $\text{R}=\text{Ph}$ and **2**; $\text{R}=\text{TMS}$) with 4-methoxy-1-iodobenzene (**3a**) using 1 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$, 2 mol% of CuI , and two equiv of aq NH_3 .

As summarized in Table 1, the reaction with several terminal alkynes and aryl halides was examined. The reaction with

Table 1. Coupling of terminal alkynes with aqueous ammonia^a

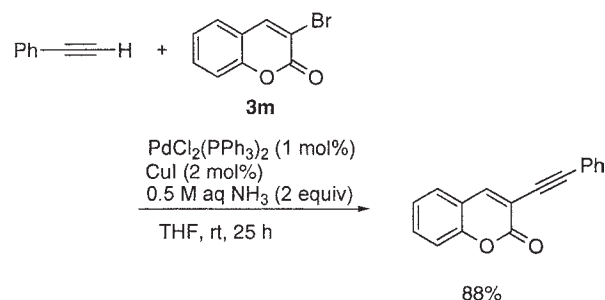
Alkyne	Aryl halide	Time/ h	Yield/ %
C ₆ H ₅ -C≡C-H (1a)	4-MeOC ₆ H ₄ -I (3a)	6	96
	4-MeCOC ₆ H ₄ -I (3b)	18	88
	4-MeCOC ₆ H ₄ -Br (3c)	30	92 ^b
	4-MeOCOC ₆ H ₄ -Br (3d)	24	91 ^b
	1-Naphthyl-OTf (3e)	9	78 ^b
	4-NCC ₆ H ₄ -OTf (3f)	6	75 ^b
4-MeOC ₆ H ₄ -C≡C-H (1b)	3a	6	75
4-O ₂ NC ₆ H ₄ -C≡C-H (1c)	3a	8	44
<i>n</i> -C ₆ H ₁₃ -C≡C-H (5)	3a	48	81 ^c
Me ₃ Si-C≡C-H (2)	4-O ₂ NC ₆ H ₄ -I (3g)	48	91
	3a	5	83
	3-MeOC ₆ H ₄ -I (3h)	6	75
	2-MeOC ₆ H ₄ -I (3i)	3	62
	4-MeC ₆ H ₄ -I (3j)	10	65
	C ₆ H ₅ -I (3k)	5	59
	3g	7	72
	3b	9	67
	3c	24	52 ^{b,c}
	4-NCC ₆ H ₄ -Br (3l)	48	57 ^b
	3e	13	62 ^b

^aUnless noted the reaction was carried out with alkyne (0.6 mmol), halide (0.5 mmol), and 0.5 M aqueous ammonia (1.0 mmol) in the presence of 1 mol% of PdCl₂(PPh₃)₂ and 2 mol% of CuI at room temperature in THF. ^bThe amount of PdCl₂(PPh₃)₂ loaded was 3 mol%. ^cThe yield was estimated by ¹H NMR.

arylalkynes **1a–c** bearing an electron-withdrawing or -donating substituent on the aromatic ring proceeded. An alkyne with an alkyl substituent, 1-octyne (**5**) also underwent the reaction although it required a longer period compared with aryl alkynes **1**. Worthy of note is that trimethylsilyl ethyne (**2**), which reaction has been unsuccessful to undergo the coupling in our previous studies using TBAF or TBAOH,⁶ could affect the reaction with various aryl halides. In addition to aryl iodides, the coupling reaction with bromide also proceeded although it took a slightly longer reaction period. It is remarkable that triflate also reacted under similar conditions.

The coupling with aqueous ammonia was then employed for a new class of organic electrophile, 3-bromocoumarin (**3m**), which was potentially applicable for the synthesis of various coumarin derivatives with an alkynyl substituent. The reaction of phenylethyne (**1a**) and **3m** under the conditions as shown in Scheme 1 resulted in giving the corresponding coupling product in 88% yield. Since coumarins have been employed as an efficient fluorescent dye as well as biologically active compounds, efficient synthetic method for such derivatives appears to be of much interest. Indeed, the combinatorial generation and screening of the coumarin libraries were recently demonstrated by Bäuerle,⁸ in which several derivatives with an alkynyl substituent were synthesized by the Sonogashira coupling.

In summary, dilute aqueous ammonia was found to serve as an effective additive for the coupling reaction of terminal alkynes. The coupling reaction was revealed to be sensitive to the concentration of ammonia. There is no doubt that ammonia is



most inexpensive amine reagent and use of large excess amounts is not required. Consequently, the reaction would be alternatively practical to the conventional Sonogashira coupling using excess amine as an activator as well as a solvent.⁹

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- Concentration of aqueous ammonia has become 0.5 M subsequently by the addition of water.
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- Typical experimental procedure: To PdCl₂(PPh₃)₂ (70 mg, 0.1 mmol), CuI (38 mg, 0.2 mmol), and 4-methoxy-1-iodobenzene (2.34 g, 10.0 mmol) in 60 mL of THF was added phenylethyne (1.32 mL, 12.0 mmol) at room temperature under an argon atmosphere. A 0.5 M solution of aqueous ammonia (40 mL, 20.0 mmol) was then added dropwise and stirring was continued for 6 h at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether (60 mL × 2). The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate = 10 : 1) to furnish 2.04 g of 1-phenyl-2-(4-methoxyphenyl)ethyne (98%).