COMMUNICATION

ChemComm
www.rsc.org/chemcomm

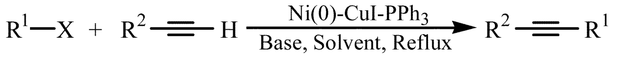
The Sonogashira coupling reaction catalyzed by ultrafine nickel(0) powder

Lei Wang,*[ab] Pinhua Li[a] and Yicheng Zhang[a]
[a] *Department of Chemistry, Huaibei Coal Teachers College, Huaibei, Anhui 235000, P. R. China;*
Fax: 86-561-309-0518; Tel: 86-561-380-2069. E-mail: leiwang@hbcnc.edu.cn
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China*

Received (in Cambridge, UK) 15th November 2003, Accepted 15th December 2003
First published as an Advance Article on the web 27th January 2004

The Sonogashira coupling reaction catalyzed by ultrafine nickel(0) powder has been developed; terminal alkynes couple with aryl, alkenyl iodide and aryl bromide in the presence of cuprous iodide, triphenylphosphine, potassium hydroxide and ultrafine particle nickel(0) to provide the corresponding cross-coupling products with high yields.

Transition metal-catalyzed cross-coupling reactions of organometallic compounds with organic electrophiles rank among the most useful processes for forming carbon–carbon bonds.[1] The palladium-catalyzed coupling of terminal acetylenes with aryl and vinyl halides (the Sonogashira reaction) is one of the important and widely used procedures for the preparation of terminal and internal alkynes in organic syntheses.[2] The reaction generally proceeds in the presence of a homogeneous palladium catalyst, which makes the recovery of the metal tedious if not impossible and might result in high palladium contamination of the product. Because of its cheap availability and high catalytic activity, Ni(0) has been used in Suzuki coupling, Negishi reaction, Kumada coupling, and amination reactions in the last two decades.[3] To the best of our knowledge, there is one report on the Sonogashira reaction catalyzed by $Ni(PPh_3)_2Cl_2$, but this approach is limited by the narrow choice of reactants (only aryl iodides and aromatic terminal alkynes).[4] Here, we report an ultrafine particle nickel(0) catalyzed Sonogashira reaction of terminal alkynes with aryl iodides, vinyl iodide and aryl bromides in heterogeneous catalytic conditions, and the Ni(0) catalyst can be recycled without change of activity.



$$R^1{-}X + R^2{\equiv}H \xrightarrow[\text{Base, Solvent, Reflux}]{\text{Ni(0)-CuI-PPh}_3} R^2{\equiv}R^1$$

First, our studies were directed towards exploring the reaction conditions for the reaction of aryl iodides with terminal alkynes catalyzed by nickel(0).† The results are summarized in Table 1. Phenylacetylene and *p*-iodotoluene were chosen as model compounds for the initial investigation.

As can be seen from Table 1, the solvent plays a very important role in the coupling reaction. A low yield of coupled product was obtained in THF (entry 6, Table 1), and moderate to good yields were obtained in DMSO, dioxane, acetonitrile and DMF (entries 2–5, Table 1). When isopropanol serves as solvent, and potassium hydroxide as base, a quantitative yield of product was isolated (entry 1, Table 1). In addition, the Sonogashira reaction requires the presence of a base. Of the bases, including organic and inorganic bases we tested, potassium hydroxide was the most effective (entries 7–12, Table 1). The ultrafine nickel(0) powder (*ca*. 100 nm diameter), triphenylphosphine and cuprous iodide are all essential to the reaction. No reaction occurs in the absence of nickel(0) powder, triphenylphosphine or cuprous iodide. Meanwhile, the particle size of metallic nickel powder has a strong effect on the reaction. When 100 mesh nickel(0) powder was used for the reaction, only a trace of the product was generated, and when a submicron nickel(0) powder was used, 57% yield of the product was obtained (entries 13–14, Table 1).

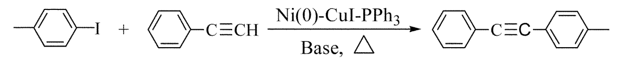
Under optimized conditions, the coupling results of a variety of terminal alkynes with organic halides are shown in Table 2. Aromatic terminal alkynes and aliphatic terminal alkynes were successfully coupled with aromatic, heteroaromatic and vinyl iodides. Aryl bromides with terminal alkynes formed moderate to good yields of coupling products under unoptimized reaction conditions. Substituent effects of aromatic terminal alkynes and aromatic iodides were also examined. The results indicate that the reaction is relatively insensitive to the electronic characteristics of a substituent as well as its location.

Since potassium hydroxide is an effective desilylating reagent for trimethylsilyl-substituted acetylene,[5] we used the trimethylsilyl derivatives of aryl terminal alkynes as starting materials to react with aromatic iodides in a one-pot Sonogashira coupling reaction. 1-Phenyl-2-(trimethylsilyl)acetylene coupled with *p*-iodotoluene to generate the corresponding cross coupling product in excellent yield (95%) under the reaction conditions. We also investigated the Sonogashira coupling-cyclization of *o*-iodophenol with phenylacetylene to produce a 75% yield of 2-phenylbenzo[*b*]furan (Scheme 1).

The recyclability of the nickel(0) powder catalyst was also examined. After carrying out a reaction and isolating the product, additional potassium hydroxide, cuprous iodide and triphenylphosphine were added to the nickel catalyst and the reaction repeated. Only minor decreases in product yields were observed through seven repetitive cycles.

In conclusion, a novel and reliable procedure for the synthesis of arylacetylenes *via* a Sonogashira coupling reaction has been developed which involves the use of ultrafine nickel(0) powder as catalyst. The reaction is an inexpensive alternative to the palladium-catalyzed process, and results in high yields of the desired product.

Table 1 Optimization reaction conditions for Sonogashira coupling[a]

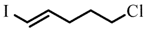


Entry	Solvent (*T*/°C)	Base	Yield[b] (%)
1	Isopropanol (80)	KOH	98
2	DMSO (120)	KOH	58
3	Dioxane (100)	KOH	70
4	DMF (100)	K_2CO_3	80
5	Acetonitrile (80)	KOH	75
6	THF (70)	KOH	23
7	Acetonitrile (80)	K_3PO_4	82
8	Isopropanol (80)	KF	25
9	Isopropanol (80)	NaOH	89
10	Isopropanol (80)	K_3PO_4	80
11	Isopropanol (80)	K_2CO_3	71
12	Isopropanol (80)	$(C_2H_5)_3N$	10
13	Isopropanol (80)	KOH	Trace[c]
14	Isopropanol (80)	KOH	57[d]

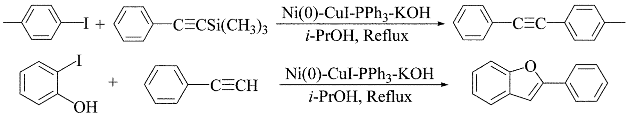
[a] Phenylacetylene (102 mg, 1.00 mmol), *p*-iodotoluene (218 mg, 1.00 mmol), Ni (*ca*. 100 nm activated powder from Aldrich, 6 mg, 0.10 mmol), CuI (10 mg, 0.052 mmol), triphenylphosphine (79 mg, 0.30 mmol), and base (3 mmol) in solvent (4 mL) for 5 h. [b] Isolated yield. [c] Ni (100 mesh) was used instead of Ni (*ca*. 100 nm) powder. [d] Ni (submicron powder) was used instead of Ni (*ca*. 100 nm) powder.

DOI: 10.1039/b314246a

Table 2 Ultrafine nickel(0) powder catalyzed Sonogashira coupling reaction[a]

Entry	R^{1}X	R^{2}C≡CH	Solvent/base (T/°C)	Yield[b] (%)
1	p-CH$_3$C$_6$H$_4$I	n-C$_8$H$_{17}$C≡CH	Isopropanol/KOH (80)	94
2	C$_6$H$_5$I	n-C$_6$H$_{13}$C≡CH	Isopropanol/KOH (80)	92
3	C$_6$H$_5$I	C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	95
4	p-CH$_3$C$_6$H$_4$I	C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	98
5	p-CH$_3$OC$_6$H$_4$I	C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	96
6	p-H$_2$NC$_6$H$_4$I	C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	90
7	p-O$_2$NC$_6$H$_4$I	C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	88
8	o-FC$_6$H$_4$I	n-C$_8$H$_{17}$C≡CH	Isopropanol/KOH (80)	93
9	p-CH$_3$COC$_6$H$_4$I	n-C$_8$H$_{17}$C≡CH	Isopropanol/K$_2$CO$_3$ (80)	92
10	C$_6$H$_5$I	p-CH$_3$C$_6$H$_4$C≡CH	Isopropanol/KOH (80)	91
11	C$_6$H$_5$I	p-FC$_6$H$_4$C≡CH	Isopropanol/KOH (80)	95
12	C$_6$H$_5$I	o-ClC$_6$H$_4$C≡CH	Isopropanol/KOH (80)	90
13	2-Iodothiophene	C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	89
14		C$_6$H$_5$C≡CH	Isopropanol/KOH (80)	85
15	p-CNC$_6$H$_4$Br	n-C$_8$H$_{17}$C≡CH	DMF/K$_2$CO$_3$ (120)	56
16	2-Bromopyridine	C$_6$H$_5$C≡CH	DMF/K$_2$CO$_3$ (120)	71
17	3-Bromopyridine	n-C$_8$H$_{17}$C≡CH	DMF/K$_2$CO$_3$ (120)	63

[a] Terminal alkyne (1.00 mmol), organic halide (1.00 mmol), Ni (*ca.* 100 nm diameter size activated powder, 6 mg, 0.10 mmol), CuI (10 mg, 0.052 mmol), triphenylphosphine (79 mg, 0.30 mmol), and base (3 mmol) in solvent (4 mL) at the given reaction temperature with stirring for 5 h. [b] Isolated yields.



Scheme 1

We thank the National Natural Science Foundation of China (No. 20372024, 20172018) and the Excellent Scientist Foundation of Anhui Province, China (No. 2001040) for support of this research.

Notes and references

† The synthesis of phenyl-*p*-tolylacetylene is representative. Phenylacetylene (102 mg, 1.00 mmol), *p*-iodotoluene (218 mg, 1.00 mmol), nickel (*ca.* 100 nm diameter activated powder from Aldrich, 6 mg, 0.10 mmol), triphenylphosphine (79 mg, 0.30 mmol), cuprous iodide (10 mg, 0.052 mmol), and potassium hydroxide (168 mg, 3.00 mmol) were added in a round-bottomed flask containing isopropanol (4 mL). The reaction mixture was stirred at 80 °C for 5 h. After complete reaction, the mixture was vacuum filtered using a sintered glass funnel and the product was purified by flash chromatography to generate 188 mg of phenyl-*p*-tolylacetylene (98% yield).

1 (*a*) K. Tamao, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and L. Fleming, Pergamon Press, Elmsford, NY, 1991, vol. 3, pp. 435–480; (*b*) D. W. Knight, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and L. Fleming, Pergamon Press, Elmsford, NY, 1991, vol. 3, pp. 481–520; (*c*) K. Sonogashira, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and L. Fleming, Pergamon Press, Elmsford, NY, 1991, vol. 3, pp. 521–549; (*d*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*e*) J. K. Still, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508; (*f*) E.-i. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821; (*g*) E.-i. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340; (*h*) E. Erdik, in *Organozinc Reagents in Organic Synthesis*, CRC Press, Boca Raton, FL, 1996, pp. 271–334; (*i*) H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, 1974, **96**, 1133; (*j*) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158; (*k*) K. Tamao and M. Kumada, in *The Chemistry of the Metal–Carbon Bond*, ed. F. R. Hartley, Wiley, New York, 1987, vol. 4, p. 820.

2 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467; (*b*) Y. Tohda, K. Sonogashira and N. Hagihara, *J. Chem. Soc., Chem. Commun.*, 1975, 54; (*c*) G. B. Jones, J. M. Wright, G. W. Ploured II, G. Hynd, R. S. Huber and J. E. Mathews, *J. Am. Chem. Soc.*, 2000, **122**, 1937; (*d*) S.-X. Liu, C. Michel and M. Schmittel, *Org. Lett.*, 2000, **2**, 3959; (*e*) W. Shen and S. A. Thomas, *Org. Lett.*, 2000, **2**, 2857; (*f*) G. W. Kabalka, L. Wang, V. Namboodiri and R. M. Pagni, *Tetrahedron Lett.*, 2000, **41**, 5151; (*g*) K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed.*, 1991, **30**, 1387; (*h*) M. de Kort, V. Correa, A. R. Valentijin, G. A. van der Marel, B. V. L. Potter, C. W. Taylor and J. H. van Boom, *J. Med. Chem.*, 2000, **43**, 3295; (*i*) P. Lang, G. Magnin, G. Mathis, A. Burger and J.-F. Biellmann, *J. Org. Chem.*, 2000, **65**, 7825; (*j*) G. Wegner and K. Müllen, *Electronic Materials—the Oligomer Approach*, Wiley-VCH, Weinheim, 1998; (*k*) H. S. Nalwa and S. Miyata, *Nonlinear Optics of Organic Molecules and Polymers*, CRC Press, Boca Raton, FL, 1997; (*l*) M. Inouye, K. Takahashi and H. Nakazumi, *J. Am. Chem. Soc.*, 1999, **121**, 341.

3 (*a*) B. H. Lipshutz and H. Ueda, *Angew. Chem., Int. Ed.*, 2000, **39**, 4492; (*b*) B. H. Lipshutz, S. Tasler, W. Chrisman, B. Spliethoff and B. Tesche, *J. Org. Chem.*, 2003, **68**, 1177; (*c*) B. H. Lipshutz and P. A. Blomgren, *J. Am. Chem. Soc.*, 1999, **121**, 5819; (*d*) D. K. Rayabarapu and C.-H. Cheng, *J. Am. Chem. Soc.*, 2002, **124**, 5630; (*e*) D. J. Spielvogel and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 3500; (*f*) V. Percec, J.-Y. Bae and D. H. Hill, *J. Org. Chem.*, 1995, **60**, 1060; (*g*) S. Saito, S. Oh-tani and N. Miyaura, *J. Org. Chem.*, 1997, **62**, 8024; (*h*) B. H. Lipshutz, T. Tomioka, P. A. Blomgren and J. A. Sclafani, *Inorg. Chim. Acta*, 1999, **296**, 164.

4 I. P. Beletskaya, G. V. Latyshev, A. V. Tsvetkov and N. V. Lukashev, *Tetrahedron Lett.*, 2003, **44**, 5011.

5 (*a*) W. B. Austin, N. Bilow, W. J. Kellegan and K. S. Y. Lau, *J. Org. Chem.*, 1981, **46**, 2280; (*b*) A. Arcadi, S. Cacchi, M. D. Rosario, G. Fabrizi and F. Marinelli, *J. Org. Chem.*, 1996, **61**, 9280.