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The nickel-catalyzed Sonogashira–Hagihara reaction

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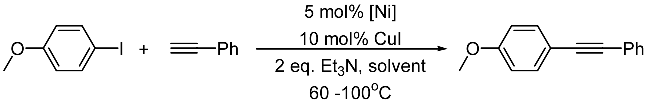
Abstract—The Sonogashira–Hagihara coupling of terminal acetylenes with aryl iodides in the presence of a nickel catalyst and CuI was investigated. The reaction proceeds rapidly in aqueous dioxane in the presence of $Ni(PPh_3)_2Cl_2$ with high yields of disubstituted tolanes being obtained. The reaction seems to be an inexpensive alternative to the palladium-catalyzed process.

The Sonogashira–Hagihara[1] reaction of terminal alkynes with aryl halides catalyzed by Pd complexes in the presence of a catalytic amount of CuI and an amine base is a powerful and versatile method for acetylene synthesis. This method has been successfully applied in the syntheses of natural compounds,[2] biologically active molecules,[3] new organic materials for optical and microelectronic applications;[4] dendrimeric, oligomeric, and polymeric materials,[5] macrocycles with acetylene links,[6] polyalkynylated molecules, and, generally, as a route to new intriguing molecular architectures.[7]

It is not surprising that an impressive variety of modifications have so far been developed for this reaction including the phase transfer,[8] aqueous,[9] solventless,[10] copper-free versions,[11] the use of a variety of promoters[12] and solvents,[13] etc. Particularly interesting are the reactions catalyzed only by Cu complexes without Pd (the Castro-type reaction) at relatively low temperatures.[14]

On the other hand, nickel, being a well-established partner of palladium in other cross-coupling reactions, has so far been missing in the context of Sonogashira–Hagihara reactions. The probable reason being inactivation due to coordination to the triple bond.[15] We have successfully accomplished the nickel-catalyzed reaction of copper acetylides with 4-nitroiodobenzene[16] and extended our investigations into the possibility of using nickel catalysts for the Sonogashira–Hagihara reaction. Below we report the results confirming that such a reaction does indeed take place giving disubstituted alkynes in high yields.

We studied the influence of different conditions on the yield of 4-methoxytolane in the model reaction of 4-iodoanisole with phenylacetylene in the presence of different nickel complexes and catalytic amounts of CuI. The readily available nickel complex, $Ni(PPh_3)_2Cl_2$ was selected as a precursor of the Ni-catalyst.



The Pd-catalyzed Sonogashira–Hagihara reaction is well-known to readily take place in THF.[13a] In our case low yields of coupled products were obtained in anhydrous THF, dioxane or MeCN (Table 1, entries 1–3). Even in piperidine, which is known to be a highly favourable media for the Pd-catalyzed Sonogashira–Hagihara reaction,[13c] only traces of the product were obtained (Table 1, entry 4). On the other hand, the Ni catalyzed reaction was found to proceed smoothly in aqueous dioxane (Table 1, entry 7). Other aqueous solvents were less efficient (Table 1, entries 5 and 6).

The yields of the coupled products strongly depend on the nickel catalyst used. Various Ni complexes with both mono- and bidentate ligands, as well as simple Ni salts have been studied (Table 2). Ni complexes with bidentate ligands (dppf, dppb, dppe) (Table 2, entries 3–5), or the electron rich monodentate ligand Ph_2PMe (Table 2, entry 6) or the phosphine free Ni derivatives failed to give the desired coupled product (Table 2, entries 7 and 8). Meanwhile, a readily available cheap complex $Ni(PPh_3)_2Cl_2$ showed high activity and gave a 78% yield of the coupled product. Prior reduction of Ni(II) to Ni(0) using $LiBH_4$ lowered the yield to 59%.

Keywords: Sonogashira–Hagihara coupling; nickel catalyst; tolanes.

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Table 1. Influence of solvent on the yield of the coupling of 4-iodoanisole with phenylacetylene[a]

Entry	Solvent/T	Conversion (%)	Entry	Solvent/T	Conversion (%)
1	THF, 65°C	16	5	THF:H_2O,[c] 64°C	5
2	Acetonitrile, 80°C	34	6	Acetonitrile:H_2O,[c] 80°C	53
3	Dioxane, 100°C	8	7	Dioxane:H_2O,[c] 100°C	78
4	Piperidine, 20°C[b]	5			

[a] 5 mol% $Ni(PPh_3)_2Cl_2$, 10 mol% CuI, 2 equiv. Et_3N, reflux for 2 h.

[b] 5 mol% $Ni(PPh_3)_2Cl_2$, 10 mol% CuI, 2 h.

[c] 3:1 ratio.

Table 2. Influence of the type of Ni catalyst employed on the yields of 4-methoxytolane[a]

Entry	Catalyst	Conversion (%)	Entry	Catalyst	Conversion (%)
1	$Ni(PPh_3)_2Cl_2$	78	5	$Ni(dppe)Cl_2$	0
2	$Ni(PPh_3)_2Cl_2/LiBH_4$	59	6	$Ni(Ph_2PMe)_2Cl_2$	5
3	$Ni(dppf)Cl_2$	0	7	$Ni(acac)_2$	0
4	$Ni(dppb)Cl_2$	0	8	$NiCl_2{\cdot}6H_2O$	0

[a] 5 mol% of Ni catalyst, 10 mol% CuI, 2 equiv. Et_3N, dioxane:H_2O = 3:1, reflux for 2 h.

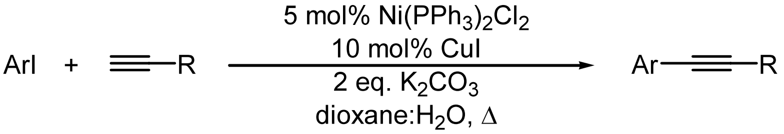
An essential improvement can be achieved by using K_2CO_3 (2 equiv.) as a base in place of Et_3N, which gave 94% yield of the coupled product (91% isolated yield).

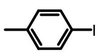
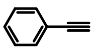
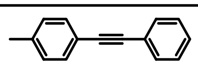
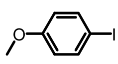
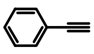
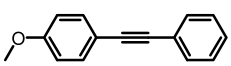
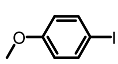
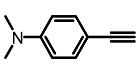
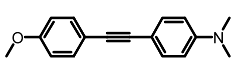
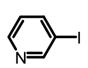
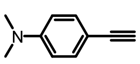
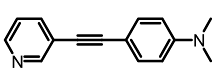
The cross-coupling of various aryl halides with acetylenes has been studied under optimal conditions (Table 3).

The catalytic system discovered gave high yields of the coupled products between arylacetylenes and aryl iodides possessing both donor and acceptor substituents (Table 3). However, the reaction of phenylacetylene with 3-bromoquinoline was very slow giving only 27% yield of product in 21 h. Alkylacetylenes, which are less reactive in the Sonogashira–Hagihara reaction, reacted very slowly. The reaction of propargylic alcohol with 4-iodoanisole gave only 12% yield of coupled product in 2 h. The reaction is highly selective, as no product of oxidative coupling (diacetylene) has been observed.

Although the Sonogashira–Hagihara reactions can be realized using Cu catalysts,[14] they are less efficient in the absence of $Ni(PPh_3)_2Cl_2$ in the system described above. The addition of PPh_3, which is necessary for reaction in the Cu-catalyzed system, resulted in further retardation of the reaction under the conditions studied.

Table 3. Synthesis of tolanes via the nickel-catalyzed Sonogashira reaction[a]



Entry	ArHal	RC≡CH	product	yield, % [b]
1 [c]				100
2				91
3				86
4				93

[a] 5 mol% $Ni(PPh_3)_2Cl_2$, 10 mol% CuI, 2 eq. K_2CO_3, dioxane:H_2O (3:1), reflux for 2 h.

[b] isolated yield.

[c] 4 h.

All novel compounds were isolated and characterised by ^{1}H NMR and elemental analyses.

Typical procedure: In a flask equipped with a reflux condenser with an argon inlet 3-iodopyridine (61.5 mg, 0.3 mmol), 4-ethynyl-*N*,*N*-dimethylaniline (52.2 mg, 0.36 mmol), potassium carbonate (82.8 mg, 0.6 mmol), copper(I) iodide (5.7 mg, 30 μmol, 10 mol%) and $Ni(PPh_3)_2Cl_2$ (9.8 mg, 15 μmol, 5 mol%) were mixed under an argon atmosphere in 1.5 mL of dioxane and 0.5 mL of water. The mixture was stirred at reflux for 2 h, then filtered through a pad of silica and evaporated under reduced pressure. *N*,*N*-Dimethyl-4-(3-pyridinylethynyl)aniline (61.8 mg, 93%) was isolated by column chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.72 (1H, m), 8.48 (1H, m), 7.74 (1H, m), 7.40 (2H, m), 7.23 (1H, m), 6.65 (2H, m) 2.99 (6H, s); mp 133°C. Anal. found: C, 80.98; H, 6.50; N, 12.39. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60%.

Acknowledgements

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