The chemoselective alkynylation of dihaloquinolines by the Sonogashira—Hagihara reaction

I. P. Beletskaya, G. V. Latyshev, A. V. Tsvetkov, and N. V. Lukashev*

Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax: +7 (095) 939 3618. E-mail: beletska@org.chem.msu.ru; tsvet@org.chem.msu.su

Conditions for the regioselective Sonogashira—Hagihara alkynylation of 4-chloro-6-iodo(bromo)quinolines were found and 6-alkynyl-4-chloroquinolines were obtained in 90—100% yields.

Key words: alkynylation, dihaloquinolines, Sonogashira—Hagihara reaction.

The coupling reaction of terminal acetylenes with aryl and vinyl halides catalyzed by palladium complexes in the presence of a base and a catalytic amount of CuI (the Sonogashira—Hagihara reaction) is a widely used tool of fine organic synthesis.[1] Owing to experimental simplicity, high product yields, and the tolerance to a broad range of functional groups, this reaction can be regarded as one of the most convenient and versatile methods for the synthesis of arylacetylenes and enynes. During the last years, development of new catalyst systems allowed researchers to broaden the range of substrates for this reaction and to extend the reaction to highly hydrophilic compounds,[2] base-sensitive alkynes with electron-withdrawing substituents,[3] and some substrates traditionally "problematic" for palladium-catalyzed reactions such as vinyl chlorides[4] and aryl chlorides.[5]

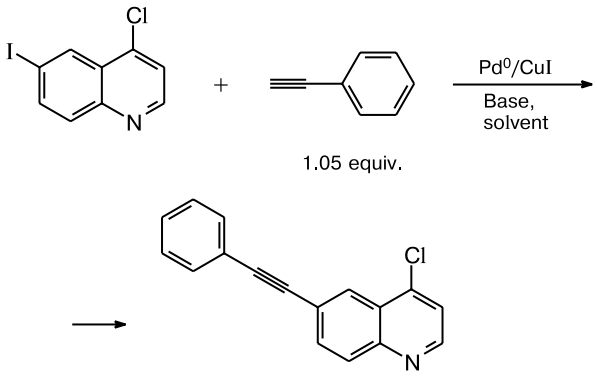
The use of dihalo derivatives of arenes and hetarenes as substrates for the regioselective introduction of substituents *via* cross-coupling markedly extends the scope of the method and opens up a facile synthetic approach to diverse classes of di- and polysubstituted aromatic or heteroaromatic compounds. This strategy was successfully used for the synthesis of materials with liquid-crystal properties,[6] natural products,[7] and biologically active compounds.[8] Conduction of consecutive substitution reactions using electron-deficient heterocycles containing two halogen atoms, one being located in a position activated toward a nucleophilic attack, is of particular interest. On the one hand, it is not always possible to predict *a priori* the relative reactivities of different C_{sp^2}—Hal bonds, for example in 4-chloro-6-iodoquinoline, in the cross-coupling. On the other hand, a subsequent cross-coupling step or aromatic nucleophilic substitution can be easily carried out for the resulting compound.

Readily accessible 4,6-dihaloquinolines[9] are interesting and convenient substrates for performing this sequence of transformations. Previously, we showed[10] that one or two halogen atoms in 4,6-dihaloquinolines can be replaced in a high yield by aryl groups using the Suzuki reaction. The purpose of this study is to develop a facile and convenient method for the synthesis of alkynylhaloquinolines by selective replacement of one halogen atom in dihaloquinolines.

Results and Discussion

For the attempt at selective monoalkynylation of 4,6-dihaloquinolines, we used as the model the reaction of 4-chloro-6-iodoquinoline with phenylacetylene (Scheme 1).

Scheme 1



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We found that the reaction of 4-chloro-6-iodoquinoline with a nearly stoichiometric amount of phenylacetylene in THF in the presence of 2 equiv. of Et_3N and a catalytic amount of $Pd(PPh_3)_4$ and CuI gives only the

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product of iodine replacement (according to ^{1}H NMR and elemental analysis data) in 81% yield. However, the presence of 19% of the unchanged starting dihaloquinoline appreciably hampers the isolation of the reaction product in a pure state. Despite the fact that the yield of the monoalkynylation product can be increased to nearly 100% by using an excess of phenylacetylene, this approach requires permanent monitoring of the reaction progress and is hardly suitable for more expensive alkynes.

Therefore, we undertook a systematic search for the optimal conditions of chemoselective monoalkynylation of 4-chloro-6-iodoquinoline.

A study of the influence of the nature of catalyst precursors on the yield of the monoalkynylation product showed that Pd^0 and Pd^{II} complexes with PPh_3 exhibit similar activities (Table 1, runs *1*, *2*). The use of palladium complexes with bidentate phosphine ligands (see Table 1, runs *4*—*6*) results in a lower product yield and a somewhat lower chemoselectivity of the reaction. The low yield observed with $Pd(OAc)_2$ as the catalyst (see Table 1, run *3*) is apparently due to its instability under the reaction conditions.

The behavior of the reaction depends substantially on the nature of the solvent. When THF is replaced by dioxane (Table 2, run *2*), the yield slightly increases (probably, due to the higher boiling point of the solvent). The use of MeCN or Et_3N as the solvent (see Table 2, runs *3*, *4*) resulted in an almost complete conversion of 4-chloro-6-iodoquinoline over a short period of time.

A significant acceleration of the reaction is attained by using water as a co-solvent (see Table 2, runs *5*, *6*). The replacement of Et_3N by K_2CO_3 does not influence the reaction rate or the product yield (Table 3, run *2*). However, the use of K_3PO_4 as the base (see Table 3, run *3*) substantially increases the reaction time (2 h instead of 5 min). However, it should be noted that a decrease in the process rate does not result in a lower product yield.

It was found that the reaction of 6-bromo-4-chloroquinoline with phenylacetylelene also proceeds selectively, giving rise, under the same conditions (see Table 3, run *1*), to the substitution product of Br in a high yield (98%) over a short period (5 min).

The reaction carried out without a copper co-catalyst is markedly retarded (the yield is only 33% after 4 h) (Table 4, run *1*). It is of interest that, unlike CuI, which does not exhibit a catalytic activity, the soluble complex $Cu(PPh_3)_3Br$ (see Table 4, run *3*) has an activity compa-

Table 1. Effect of the catalyst on the yield of the monoalkynylation product of 4-chloro-6-iodoquinoline[a]

Run	Catalyst (mol.%)	Yield (%)
1	$Pd(PPh_3)_4$ (5)	81
2	$Pd(PPh_3)_2Cl_2$ (5)	80
3	$Pd(OAc)_2$ (5)	32
4	$Pd(dppf)Cl_2$ (5)	68
5	$Pd(dppb)Cl_2$ (5)	67[b]
6	$Pd(OAc)_2$ (5)/dppe (10)	59[c]

Note. dppf is 1,1′-bis(diphenylphosphino)ferrocene, dppb is 1,4-bis(diphenylphosphino)butane, dppe is 1,2-bis(diphenylphosphino)ethane.
[a] Reaction conditions: 1.05 equiv. of PhC≡CH, 2 equiv. of Et_3N, 10 mol.% CuI, THF, 65 °C, 4 h.
[b] The yield of the dialkynylation product was 3%.
[c] The yield of the dialkynylation product was 4%.

Table 2. Effect of the solvent on the yield of the monoalkynylation product **1**[a]

Run	Solvent	Reaction time /min	Yield (%)
1	THF	240	81
2	Dioxane	240	91
3	MeCN	15	96 (93[b])
4	Et_3N	15	98
5	MeCN—H_2O[c]	5	98
6	Dioxane—H_2O[c]	5	97

[a] Reaction conditions: 5 mol.% $Pd(PPh_3)_4$, 10 mol.% CuI, 1.05 equiv. of PhC≡CH, 2 equiv. of Et_3N, refluxing.
[b] The isolated yield.
[c] Ratio 3 : 1.

Table 3. Effect of a base on the yield of the monoalkynylation product **1**[a]

Run	Base[b]	Reaction time /min	Yield (%)
1	Et_3N	5	97
2	K_2CO_3	5	98
3	K_3PO_4	120	100

[a] Reaction conditions: 5 mol.% $Pd(PPh_3)_4$, 10 mol.% CuI, 1.05 equiv. of PhC≡CH, dioxane—H_2O (3 : 1), 100 °C.
[b] 2 equiv.

Table 4. Reaction of 4-chloro-6-iodoquinoline with phenyalacetylene in the presence of palladium and copper catalysts*

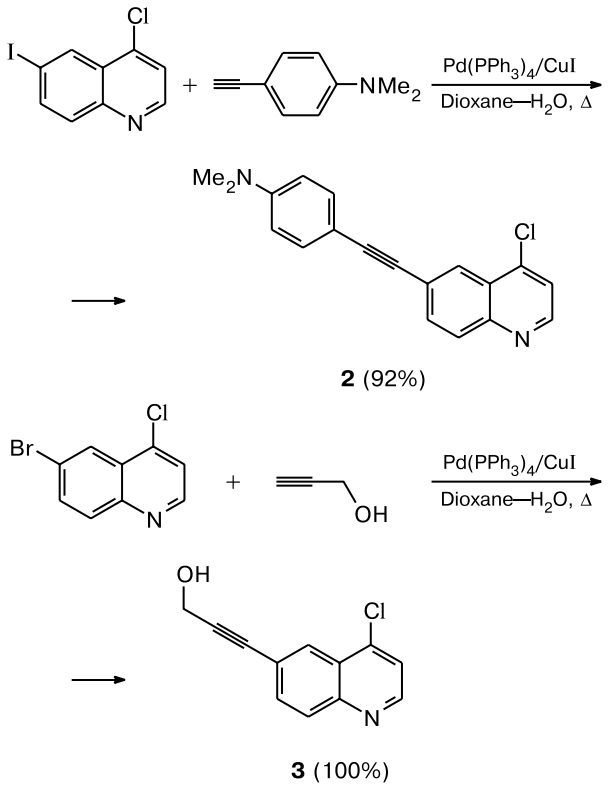
Run	Catalyst (mol.%)	Yield of product **1** (%)
1	$Pd(PPh_3)_4$ (5)	33
2	CuI (10)	1
3	$Cu(PPh_3)_3Br$ (10)	38

* Reaction conditions: 1.05 equiv. of PhC≡CH, MeCN—H_2O (3 : 1), 80 °C, 4 h.

rable to that of $Pd(PPh_3)_4$ (in the absence of a copper cocatalyst).

The selective replacement of a halogen atom in 6-halo-4-chloroquinolines can be extended to other alkynes; the reactions afford 6-alkynyl-4-chloroquinolines **2** and **3** in high preparative yields (Scheme 2).

Scheme 2



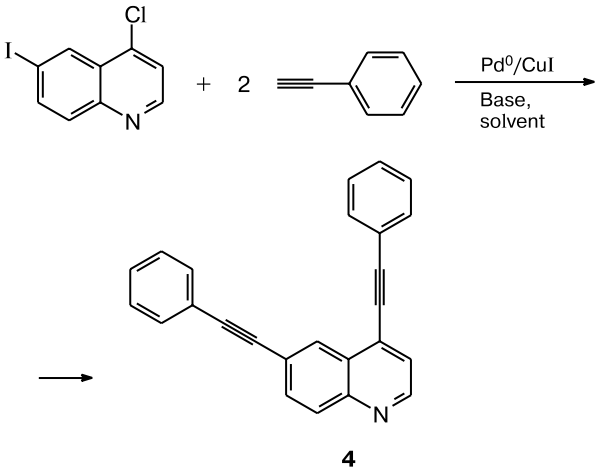
We attempted to perform a successive dialkynylation of 4-chloro-6-iodoquinoline by introducing it into the reaction with a twofold amount of phenylacetylene (2.2 equiv.) (Scheme 3).

The reaction carried out in an aqueous dioxane in the presence of 4 equiv. of Et_3N, 5 mol.% $Pd(PPh_3)_4$, and 10 mol.% CuI affords a mixture of 4,6-bis(phenylethynyl)quinoline **4** (83%) and 6-monoalkynylated compound **1** (15%). The use of other water—organic mixtures does not increase the yield of the disubstitution product (Table 5).

The use of other bases, instead of Et_3N, also does not increase the degree of conversion of compound **1** into product **4** (Table 6).

The incomplete conversion of alkynylchloroquinoline is apparently caused by side processes that lead to consumption of phenylacetylene. Indeed, the repeated addition of the catalyst to the reaction mixture does not induce an increase in the product yield, while the addition

Scheme 3



of a fresh portion of phenylacetylene results in the formation of compound **4** in a quantitative yield. The reaction can also be brought to completion (conversion 98%) when 4 equiv. of phenylacetylene are taken from the very beginning.

The method for the synthesis of alkynylquinolines that we developed in combination with the selective arylation of dihaloquinolines described in our previous publica-

Table 5. Effect of the solvent on the yield of the product of dialkynylation of 4-chloro-6-iodoquinoline*

Run	Solvent (ratio)	Reaction time/h	Yield of product **4** (%)
1	Dioxane—H_2O (3 : 1)	4	83
2	Dioxane—H_2O (19 : 1)	4	80
3	THF—H_2O (3 : 1)	4	70
4	MeCN—H_2O (3 : 1)	7	70

* Reaction conditions: 2.2 equiv. of PhC≡CH, 5 mol.% $Pd(PPh_3)_4$, 10 mol.% CuI, 4 equiv. of Et_3N, 4 h, refluxing.

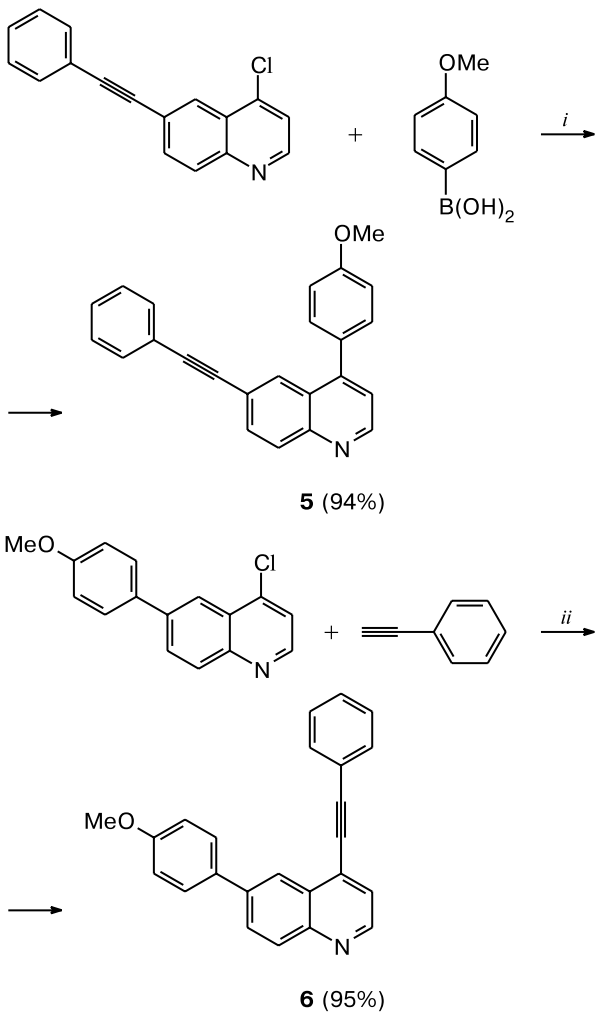
Table 6. Effect of the base on the yield of the product of dialkynylation of 4-chloro-6-iodoquinoline[a]

Run	Base	Yield (%)
1	Et_3N	83
2	DABCO[b]	65
3	K_2CO_3[c]	52

[a] Reaction conditions: 2.2 equiv. of PhC≡CH, 5 mol.% $Pd(PPh_3)_4$, 10 mol.% CuI, dioxane—H_2O (3 : 1), 4 h, 100 °C.
[b] 3 equiv.
[c] 3 equiv. (reaction with 6-bromo-4-chloroquinoline).

tion[10] permits easy synthesis of alkynylarylquinolines in high yields using an arylation—alkynylation reaction sequence (Scheme 4).

Scheme 4



Reagents and conditions: *i*. 2 mol.% $Pd(PPh_3)_4$, K_2CO_3, dioxane—H_2O (3 : 1), Δ. *ii*. 5 mol.% $Pd(PPh_3)_4$, 10 mol.% CuI, Et_3N, dioxane—H_2O (3 : 1), Δ.

Experimental

The reactions were monitored by TLC on Silufol UV-254 plates and by ^{1}H NMR spectroscopy. The yields of the products of alkynylation of 4,6-dihaloquinolines were determined by ^{1}H NMR spectroscopy (except for the runs where the products were isolated). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian VXR 400 spectrometer operating at 400 MHz. The chemical shifts are given in the δ scale and referred to HMDS. Commercial chemicals (Aldrich) were used. 6-Bromo- and 6-iodo-4-chloroquinolines were prepared by a known procedure.[9]

4-Chloro-6-phenylethynylquinoline (1). 4-Chloro-6-iodoquinoline[9] (43.4 mg, 0.15 mmol), phenylacetylene (16.1 mg, 0.158 mmol), Et_3N (42 μL, 0.3 mmol), CuI (2.9 mg, 15 μmol, 10 mol.%), and $Pd(PPh_3)_4$ (8.7 mg, 7.5 μmol, 5 mol.%) in 2 mL of MeCN were mixed under argon in a flask equipped with a reflux condenser. The reaction mixture was refluxed until 4-chloro-6-iodoquinoline disappeared (according to TLC), cooled, diluted with CH_2Cl_2, and filtered through a silica gel layer (3 cm), and the solvents were evaporated under reduced pressure. The product was isolated by column chromatography on silica gel using a light petroleum—Et_2O mixture for elution. Yield 36.8 mg (93%), m.p. 75—76 °C. Found (%): C, 76.98; H, 4.09; N, 5.00. $C_{17}H_{10}ClN$. Calculated (%): C, 77.42; H, 3.82; N, 5.31. ^{1}H NMR, δ: 7.36 (m, 3 H); 7.49 (d, 1 H, J = 4.7 Hz); 7.58 (m, 2 H); 7.84 (dd, 1 H, J = 8.7 Hz, J = 1.8 Hz); 8.07 (d, 1 H, J = 8.7 Hz); 8.39 (d, 1 H, J = 1.8 Hz); 8.75 (d, 1 H, J = 4.7 Hz).

4-Chloro-6-(4-dimethylaminophenylethynyl)quinoline (2) was synthesized in a similar way from 4-chloro-6-iodoquinoline[9] (43.4 mg, 0.15 mmol) and 4-dimethylaminophenylacetylene (22.9 mg, 0.158 mmol) in 2 mL of a dioxane—water (3 : 1) mixture in a yield of 42.3 mg (92%), m.p. 108—109 °C. Found (%): C, 74.36; H, 4.99; N, 9.08. $C_{19}H_{15}ClN_2$. Calculated (%): C, 74.38; H, 4.93; N, 9.13. ^{1}H NMR, δ: 3.00 (s, 6 H); 6.67 (m, 2 H); 7.46 (m, 3 H); 7.82 (dd, 1 H, J = 8.7 Hz, J = 1.8 Hz); 8.04 (d, 1 H, J = 8.7 Hz); 8.34 (d, 1 H, J = 1.8 Hz); 8.73 (d, 1 H, J = 4.7 Hz).

4-Chloro-6-(3-hydroxyprop-1-ynyl)quinoline (3) was synthesized in a similar way from 6-bromo-4-chloroquinoline[9] (60.6 mg, 0.25 mmol) and prop-2-ynol (14.7 mg, 0.262 mmol) in a yield of 54.3 mg (100%), m.p. 136—138 °C. Found (%): C, 66.61; H, 3.69; N, 6.61. $C_{12}H_8ClNO$. Calculated (%): C, 66.22; H, 3.70; N, 6.44. ^{1}H NMR, δ: 3.49 (br.s, 1 H); 4.56 (d, 2 H, J = 6.1 Hz); 7.50 (d, 1 H, J = 4.7 Hz); 7.74 (dd, 1 H, J = 8.7 Hz, J = 1.8 Hz); 8.05 (d, 1 H, J = 8.7 Hz); 8.32 (d, 1 H, J = 1.8 Hz); 8.76 (d, 1 H, J = 4.7 Hz).

4,6-Bis(phenylethynyl)quinoline (4) was synthesized in a similar way from 4-chloro-6-iodoquinoline[9] (43.4 mg, 0.15 mmol), phenylacetylene (61.2 mg, 0.6 mmol), Et_3N (84 μL, 0.6 mmol), CuI (2.9 mg, 15 μmol, 10 mol.%), and $Pd(PPh_3)_4$ (8.7 mg, 7.5 μmol, 5 mol.%) in 1.5 mL of dioxane and 0.5 mL of H_2O. Yield 44.3 mg (90%), m.p. 143 °C. ^{1}H NMR, δ: 7.36, 7.42 (both m, each 3 H); 7.55 (d, 1 H, J = 4.5 Hz); 7.60, 7.68 (both m, each 2 H); 7.83 (dd, 1 H, J = 8.7 Hz, J = 1.8 Hz); 8.07 (d, 1 H, J = 8.7 Hz); 8.49 (d, 1 H, J = 1.8 Hz); 8.86 (d, 1 H, J = 4.5 Hz). The substance is partially resinified over a period of 1—2 days at ~20 °C, which precluded the preparation of an analytical grade sample.

6-(4-Anisyl)-4-phenylethynylquinoline (6) was synthesized in a similar way from 6-(4-anisyl)-4-chloroquinoline (50 mg, 0.186 mmol) and phenylacetylene (38 mg, 0.372 mmol) in a yield of 61 mg (95%), m.p. 141 °C. Found (%): C, 85.64; H, 4.98; N, 4.31. $C_{24}H_{17}NO$. Calculated (%): C, 85.94; H, 5.11; N, 4.18. ^{1}H NMR, δ: 3.86 (s, 3 H); 7.04 (m, 2 H); 7.41 (m, 3 H); 7.55 (d, 1 H, J = 4.4 Hz); 7.64, 7.69 (both m, each 2 H); 7.97 (dd, 1 H, J = 8.9 Hz, J = 2.0 Hz); 8.14 (d, 1 H, J = 8.9 Hz); 8.46 (d, 1 H, J = 2.0 Hz); 8.84 (d, 1 H, J = 4.4 Hz).

4-(4-Anisyl)-6-phenylethynylquinoline (5). 4-Chloro-6-phenylethynylquinoline (50 mg, 0.19 mmol), 4-anisylboronic acid (38 mg, 0.25 mmol), K_2CO_3 (78.7 mg, 0.57 mmol), and $Pd(PPh_3)_4$ (4.4 mg, 3.8 μmol) in 1.5 mL of dioxane and 0.5 mL of H_2O were mixed under argon in a flask equipped with a reflux condenser. The reaction mixture was refluxed for 2 h, cooled,

diluted with CH_2Cl_2, and filtered through a silica gel layer (3 cm), and the solvents were evaporated under reduced pressure. The product was purified by column chromatography on silica gel in a light petroleum—Et_2O mixture (1 : 1). Yield 59.4 mg (94%), m.p. 139 °C. Found (%): C, 86.02; H, 5.15; N, 4.11. $C_{24}H_{17}NO$. Calculated (%): C, 85.94; H, 5.11; N, 4.18. ^{1}H NMR, δ: 3.87 (s, 3 H); 7.05 (m, 2 H); 7.28 (d, 1 H, J = 4.4 Hz); 7.31 (m, 3 H); 7.43, 7.51 (both m, each 2 H); 7.79 (dd, 1 H, J = 8.8 Hz, J = 1.7 Hz); 8.10 (d, 1 H, J = 8.8 Hz); 8.12 (d, 1 H, J = 1.7 Hz); 8.67 (d, 1 H, J = 4.4 Hz).

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