Substitution of acetylenic groups for halogen in the quinonoid ring

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The bromine or iodine atom in the quinonoid ring devoid of +M substituent in the position neighboring to the halogen is replaced by acetylenic groups on treatment with Cu^I acetylides, prepared either beforehand or *in situ*, in a mixture of DMSO and $CHCl_3$ in the presence of a Pd complex catalyst. A series of mono- and diacetylenic derivatives of 1,4-naphtho- and 1,4-benzoquinone were prepared.

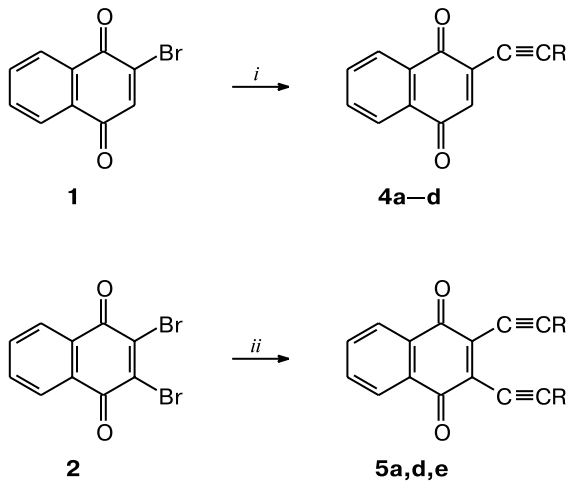
Key words: 2-bromo- and 2,3-dibromonaphthoquinones, 2,5-diiodo-1,4-benzoquinone, Cu^I acetylides, cross-coupling, alkynylquinones.

Quinones containing acetylenic substituents in the quinonoid ring are promising key intermediates in the preparation of heterocyclic quinones[1—3] and highly reactive unsaturated compounds.[4,5] There are two approaches to the synthesis of these acetylenylquinones: oxidation of acetylenic derivatives of some aromatic compounds to quinones[6,7] and the introduction of acetylenic substituents directly into the quinoid ring.[8] The implementation of the former is often complicated by the large number of stages, low accessibility of aromatic precursors, and insufficient selectivity of oxidants. The direct introduction of acetylenic substituents into the quinonoid ring is possible either through the addition of alkali metal acetylide to the carbonyl groups of dialkoxybenzoquinone followed by acidic hydrolysis and dehydration,[9] or through catalyzed substitution of halogen atoms on treatment with terminal acetylenes or metal acetylides.[8] The application of the alkynol route is limited exclusively by benzoquinone derivatives. The condensation of haloquinones, which seems *a priori* to be the most facile and efficient method, is hampered by the enhanced sensitivity of the quinonoid ring to the bases and nucleophiles used most often in these reactions.

Previously,[8] we found that haloquinones having a dialkylamino group or another substituent possessing a pronounced +M-effect in the position adjoining the halogen atom in the quinoid ring are less labile in the nucleophilic media and react with terminal acetylenes under usual Pd- and Cu-catalyzed cross-coupling conditions. In the present study we demonstrate the possibility and elucidate plausible conditions for the substitution of acetylenic groups for the halogen atoms in the quinonoid ring not deactivated by the neighboring +M substituent.

It was found that 2-bromo- (**1**) and 2,3-dibromo-1,4-naphthoquinone (**2**) react with cuprous acetylides **3** in a (1—2) : 1 DMSO—$CHCl_3$ mixture in the presence of $Pd(PPh_3)_2Cl_2$ at 35—50 °C to give the corresponding 2-acetylenyl- (**4**) and 2,3-diacetylenyl-1,4-naphthoquinones (**5**) in satisfactory yields (40—70%) (Scheme 1). The reaction time is 15—130 min. The reaction can be carried out not only with solid cuprous acetylides prepared beforehand but also with those obtained *in situ* from

Scheme 1



R = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**), $C(OH)Me_2$ (**d**), $C(OMe)Me_2$ (**e**)

Reagents: *i*. CuC≡CR (**3a—c**), $Pd(PPh_3)_2Cl_2$ or HC≡CR (**6d**), CuI, NEt_3, $Pd(PPh_3)_2Cl_2$; *ii*. HC≡CR (**6a,d,e**), CuI, NEt_3, $Pd(PPh_3)_2Cl_2$.

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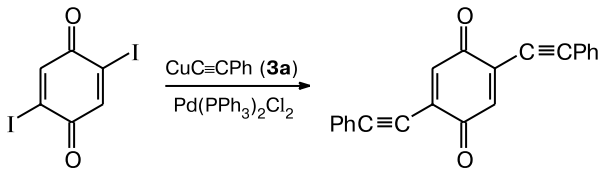
terminal acetylenes **6**, CuI, and Et_3N. This allows one to use acetylenic compounds forming no acetylides stable in the solid state, for example, tertiary α-acetylenic alcohols. This extends the scope of applicability of this reaction.

It should be emphasized that the palladium catalyst should be used in any case; without the catalyst, the condensation does not take place (it has been demonstrated previously[10] that in the presence of palladium complexes, the temperature of cuprous phenylacetylide condensation with aryl halides can be markedly decreased). The choice of DMSO is due to the fact that bromides **1** and **2** are relatively stable in this solvent, as opposed to solvents traditional for cross-coupling (pyridine, DMF, Et_3N, and so on). However, the condensation of these compounds with cuprous acetylides **3** in DMSO is accompanied by significant resinification, which can be appreciably reduced by adding a second solvent component, $CHCl_3$.

Under these conditions, not only halo derivatives of polycyclic 1,4-quinones, such as bromonaphthoquinones **1** and **2**, but also halobenzoquinones, for example, 2,5-diiodo-1,4-benzoquinone (**7**) are condensed with cuprous acetylides (Scheme 2).

Scheme 2



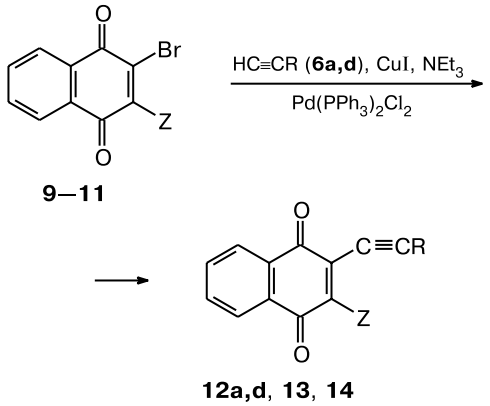
7 **8**

The condensation of diiodide **7** with cuprous phenylacetylide **3a** takes place even at 20 °C with self-heating and ends after 20 min; the yield of 2,5-di(phenylethynyl)-1,4-benzoquinone (**8**) reaches 84%.

The functional groups exhibiting no or weak +M-effect deactivate the neighboring position of the quinonoid ring with respect to a nucleophilic attack to a lesser extent than strong M-donors. Therefore, on the replacement of strong electron-donating groups (NR_2, NHR, NH_2, OH) by weaker ones (NHAc, NRAc, *etc.*), *vic*-functionally substituted haloquinones become able to undergo cross-coupling under the given conditions. Indeed, 2-substituted 3-bromo-1,4-naphthoquinones (**9—11**) condense with acetylides in DMSO—$CHCl_3$ similarly to bromide **1** to give the corresponding 2-substituted 3-acetylenyl-1,4-naphthoquinones (**12a,d**, **13**, **14**) (Scheme 3).

Acetylides were prepared *in situ* from terminal acetylenes (**6a,d**). The reactions of bromides **9** and **10** were carried out at 20—35 °C for 45—180 min. The greatest difficulties were encountered in the condensation of ethoxybromonaphthoquinone **11** with acetylide **3a**. For completion of the reaction, the addition of a large excess

Scheme 3



9—11 **12a,d**, **13**, **14**

R = Ph (**12a**, **13**, **14**), C(OH)Me_2 (**12d**);
Z = NHAc (**9**, **12a,d**), N(Ac)Ph (**10**, **13**), OEt (**11**, **14**)

of solid acetylide **3a** prepared beforehand was required; the condensation lasted for 6 h at 37 °C and was accompanied by substantial resinification. In the series of 2-substituted 3-bromo-1,4-naphthoquinones, the ethoxy group, which exerts a pronounced +M-effect, is apparently responsible for the limit of applicability of the method. As has been shown previously,[8] 3-bromo-2-ethoxy-1,4-naphthoquinone **11** reacts satisfactorily with terminal acetylenes under conditions used for condensation of stabilized 2-dialkylamino-3-bromo-1,4-naphthoquinones. However, the same bromide **11** retains the ability to be coupled with acetylides under specific conditions of condensation of reactive nonstabilized haloquinones.

It is noteworthy that the proposed cross-coupling procedure seems to be the only existing method for the replacement of a nondeactivated halogen atom in the quinoid ring.[11]

Experimental

^1H NMR spectra were recorded on a Bruker DPX-200 instrument (200 MHz) in $CDCl_3$ at 25 °C. The course of the reactions was monitored and the compound purity was checked by TLC on Silufol UV 254 plates.

2-Phenylethynyl-1,4-naphthoquinone (4a). ***A.*** Triethylamine (3.30 g, 32.7 mmol, 4.5 mL), phenylacetylene **6a** (4.20 g, 41.2 mmol, 4.5 mL), $Pd(PPh_3)_2Cl_2$ (75 mg), and bromide **1** (7.10 g, 30.0 mmol) were added successively with stirring under Ar to CuI (17.20 g, 90.1 mmol) in DMSO (100 mL) and $CHCl_3$ (70 mL). The mixture was heated for 50 min at 35—36 °C until the initial **1** disappeared and poured into 300 mL of $CHCl_3$, the resulting mixture was filtered, and the filtrate was washed many times with water and dried with $CaCl_2$. After removal of the solvent, the residue was triturated with ether (20 mL), and the precipitate was filtered off and dissolved in $CHCl_3$ (30 mL). Ethanol (25 mL) was added to the solution, and $CHCl_3$ was evaporated *in vacuo* to give 4.30 g (56%) of phenylethynylnaphthoquinone **4a**, m.p. 147—148 °C (from CCl_4).[6]

B. A mixture of bromonaphthoquinone **1** (2.20 g, 9.3 mmol), cuprous phenylacetylide **3a** (1.60 g, 9.7 mmol), and $Pd(PPh_3)_2Cl_2$ (20 mg) in DMSO (20 mL) and $CHCl_3$ (10 mL) was stirred under argon for 75 min at 35—37 °C. Acetylene **4a** was isolated as described above; yield 1.30 g (54%).

2-(4-Nitrophenylethynyl)-1,4-naphthoquinone (4b). Bromonaphthoquinone **1** (0.60 g, 2.5 mmol) was condensed with acetylide **3b** (0.70 g, 3.3 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (10 mg) in a mixture of DMSO (10 mL) and $CHCl_3$ (5 mL) for 15 min at 35—37 °C. (Nitrophenylethynyl)naphthoquinone **4b** was isolated similarly to acetylene **4a**; the yield was 0.53 g (69%) (Table 1).

2-(4-Methoxyphenylethynyl)-1,4-naphthoquinone (4c). Cuprous 4-methoxyphenylacetylide prepared from acetylene **6c** (0.80 g, 6.1 mmol), CuI (1.50 g, 12.4 mmol), and Et_3N (0.55 g, 5.4 mmol, 0.74 mL) in a mixture of DMSO (15 mL) and $CHCl_3$ (8 mL) were condensed with bromonaphthoquinone **1** (1.20 g, 5.1 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (12 mg) for 70 min at 40—41 °C as described in the synthesis of acetylene **4a** (method *A*). The yield of quinone **4c** was 0.75 g (51%) (see Table 1).

2-(3-Hydroxy-3-methylbutynyl)-1,4-naphthoquinone (4d). The reaction of bromide **1** (2.40 g, 10.1 mmol), 2-methylbut-3-yn-2-ol (**6d**) (1.30 g, 15.5 mmol, 1.5 mL), CuI (3.80 g, 19.9 mmol), Et_3N (1.10 g, 10.9 mmol, 1.48 mL), and $Pd(PPh_3)_2Cl_2$ (40 mg) in a mixture of DMSO (40 mL) and $CHCl_3$ (30 mL) was carried out as described for the preparation of acetylenylquinone **4a** (method *A*) at 45—47 °C for 60 min. The product in ether was filtered through a small SiO_2 layer, the solvent was removed, and the product was recrystallized in dibutyl ether and filtered off. Recrystallization from hexane gave 1.20 g (49%) (see Table 1).

2,3-Di(phenylethynyl)-1,4-naphthoquinone (5a). *A.* The compound was prepared similarly to 2-phenylethynylnaphtho-

Table 1. Acetylenic derivatives of naphthoquinone

Compound	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR (δ, *J*/Hz)	IR, ν/cm^{-1}
		C	H	N			
4b	203—205 (decomp., $CHCl_3$—ethanol)	70.83 / 71.29	3.07 / 2.99	4.95 / 4.62	$C_{18}H_9NO_4$	7.24 (s, 1 H, H(3)); 7.75—7.85 (m, 2 H, H(6), H(7)); 7.77 (d, 2 H, H(2′), H(6′), *J* = 8.5); 8.10—8.25 (m, 2 H, H(5), H(8)); 8.26 (d, 2 H, H(3′), H(5′), *J* = 8.5)	1665, 1685 (C=O); 2210 (C=C)
4c	153—154 (decomp., ether)	78.90 / 79.15	4.22 / 4.19	—	$C_{19}H_{12}O_3$	3.84 (s, 3 H, Me); 6.90 (d, 2 H, H(3′), H(5′), *J* = 8.5); 7.12 (s, 1 H, H(3)); 7.56 (d, 2 H, H(2′), H(6′), *J* = 8.5); 7.70—7.90 (m, 2 H, H(6), H(7)); 8.05—8.15 (m, 2 H, H(5), H(8))	1660, 1680 (C=O); 2200, 2230 (C≡C)
4d	82—83 (dibutyl ether)	75.02 / 74.99	4.98 / 5.03	—	$C_{15}H_{12}O_3$	1.64 (s, 6 H, Me); 3.14 (s, 1 H, OH); 7.05 (s, 1 H, H(3)); 7.70—7.75 (m, 2 H, H(6), H(7)); 8.00—8.05 (m, 2 H, H(5), H(8))	1680 (C=O); 2210, 2230 (C≡C); 3520 br (OH)
5a	>150 (decomp., ethanol)	87.07 / 87.13	3.95 / 3.94	—	$C_{26}H_{14}O_2$	7.30—7.45 (m, 6 H, 4 H Ph_m, 2 H Ph_p); 7.60—7.70 (m, 4 H, 4 H Ph_o); 7.70—7.80 (m, 2 H, H(6), H(7)); 8.10—8.20 (m, 2 H, H(5), H(8))	1675 sh, 1695 (C=O); 2200 (C≡C)
5d	140—141 (decomp., $CHCl_3$—hexane)	74.42 / 74.52	5.54 / 5.63	—	$C_{20}H_{18}O_4$	1.67 (s, 12 H, Me); 3.90 (s, 2 H, OH); 7.70—7.80 (m, 2 H, H(6), H(7)); 8.00—8.10 (m, 2 H, H(5), H(8))	1675 sh, 1715 (C=O); 2230 (C≡C); 3470 br, 3610 (OH)
5e	78—80 (benzene—hexane)	75.16 / 75.41	6.23 / 6.33	—	$C_{22}H_{22}O_4$	1.58 (s, 12 H, Me); 3.50 (s, 6 H, OMe); 7.70—7.80 (m, 2 H, H(6), H(7)); 8.05—8.15 (m, 2 H, H(5), H(8))	1675 (C=O); 2220 (C≡C)
12a	186—187 (decomp., ethanol)	76.17 / 76.18	4.06 / 4.16	4.40 / 4.44	$C_{20}H_{13}NO_3$	2.33 (s, 3 H, COMe); 7.10—7.40 (m, 3 H, 2 H Ph_m, 1 H Ph_p); 7.50—7.65 (m, 2 H, 2 H Ph_o); 7.70—7.80 (m, 2 H, H(6), H(7)); 7.99 (s, 1 H, NH); 8.05—8.20 (m, 2 H, H(5), H(8))	1660 (C=O); 1720 (NC=O); 2205 (C≡C); 3375 (NH)
12d	172—173 (decomp., $CHCl_3$—hexane)	68.70 / 68.68	5.05 / 5.09	4.95 / 4.71	$C_{17}H_{15}NO_4$	1.24 (s, 6 H, Me); 2.29 (s, 3 H, COMe); 7.65—7.85 (m, 2 H, H(6), H(7)); 7.98 (s, 1 H, NH); 8.05—8.15 (m, 2 H, H(5), H(8))	1670 (C=O); 1725 (NC=O); 2215 (C≡C); 3380 (NH); 3500 (OH)
13	195.5—196.5 (decomp., $CHCl_3$—ether)	79.63 / 79.78	4.30 / 4.38	3.65 / 3.58	$C_{26}H_{17}NO_3$	2.16 (s, 3 H, COMe); 7.30—7.55 (m, 10 H, Ph); 7.70—7.80 (m, 2 H, H(6), H(7)); 8.05—8.20 (m, 2 H, H(5), H(8))	1680 (C=O); 2195 (C=C)

quinone (**4a**) (method *A*) from 2,3-dibromonaphthoquinone (**2**) (1.00 g, 3.2 mmol), phenylacetylene (**6a**) (1.00 g, 10 mmol), CuI (1.30 g, 6.8 mmol), and Et_3N (0.70 g, 8.0 mmol, 0.95 mL) in the presence of $Pd(PPh_3)_2Cl_2$ (8 mg) in a mixture of DMSO (10 mL) and $CHCl_3$ (5 mL) (40—42 °C, 40 min); yield 0.60 g (53%) (see Table 1).

B. Dibromide **2** (6.00 g, 19.0 mmol) was condensed with cuprous phenylacetylide (**3a**) (7.60 g, 46.0 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (60 mg) in DMSO (60 mL) at 40—42 °C for 50 min to give 2.30 g (34%) of **5a**.

2,3-Di(3-hydroxy-3-methylbutynyl)-1,4-naphthoquinone (5d). The compound was prepared from dibromide **2** (1.60 g, 5.1 mmol), 2-methylbut-3-yn-2-ol (**6d**) (1.60 g, 19.0 mmol, 1.85 mL), CuI (2.50 g, 13.1 mmol), Et_3N (1.10 g, 10.9 mmol, 1.48 mL), and $Pd(PPh_3)_2Cl_2$ (15 mg) in a mixture of DMSO (20 mL) and $CHCl_3$ (15 mL) (50 °C, 130 min). The crude product was dissolved in $CHCl_3$ and precipitated with hexane; the yield of glycol **5d** was 0.80 g (49%) (see Table 1).

2,3-Di(3-methoxy-3-methylbutynyl)-1,4-naphthoquinone (5e) was prepared similarly to diacetylene **5d** from dibromide **2** (2.40 g, 7.6 mmol) and 2-methoxy-2-methylbutyne (**6e**) (2.90 g, 30 mmol) (50 °C, 4 h). Yield 1.06 g (40%) (see Table 1).

2,5-Di(phenylethynyl)-1,4-benzoquinone (8). Catalyst $Pd(PPh_3)_2Cl_2$ (6 mg) was dissolved in a mixture of DMSO (10 mL) and $CHCl_3$ (10 mL) at 55 °C under argon, the solution was cooled to 20 °C, diiodide **7** (0.50 g, 13.9 mmol) and cuprous phenylacetylide **3a** (0.60 g, 36.4 mmol) were added, and the mixture was stirred for 20 min, while its temperature rose spontaneously to 28 °C. Diacetylene **8** (0.36 g, 84%) was isolated by the usual procedure, m.p. ~238—240 °C (with decomp., CCl_4).[7]

2-Acetylamino-3-phenylethynyl-1,4-naphthoquinone (12a) was prepared similarly to acetylenylquinone **4a** from 2-acetylamino-3-bromo-1,4-naphthoquinone (**9**) (2.90 g, 10.0 mmol) phenylacetylene (**6a**) (1.50 g, 15.0 mmol), CuI (3.00 g, 15.7 mmol), Et_3N (1.30 g, 12.9 mmol, 1.75 mL), and $Pd(PPh_3)_2Cl_2$ (30 mg) in a mixture DMSO (50 mL) and $CHCl_3$ (35 mL) (20—22 °C, 75 min); yield 2.50 g (81%) (see Table 1).

2-Acetylamino-3-(3-hydroxy-3-methylbutynyl)-1,4-naphthoquinone (12d) The reaction of bromide **9** (1.20 g, 3.0 mmol) and 2-methylbut-3-yn-2-ol (**6d**) (0.60 g, 7.1 mmol, 0.7 mL) under conditions used in the synthesis of acetylenylquinone **12a** (reaction time 45 min) gave 0.60 g (50%) of compound **12d** (see Table 1).

2-*N*-Acetyl(phenylamino)-3-phenylethynyl-1,4-naphthoquinone (13). 2-*N*-Acetyl(phenylamino)-3-bromo-1,4-naphthoquinone (**10**) (0.74 g, 2.0 mmol) was condensed with acetylene **6a** (0.41 g, 4.0 mmol) using the same reactant and solvent ratios as in the preparation of **12a**; the reaction temperature was 36 °C and the reaction time was 3 h. The yield of quinone **13** was 0.32 g (41%) (see Table 1).

3-Phenylethynyl-2-ethoxy-1,4-naphthoquinone (14). 3-Bromo-2-ethoxy-1,4-naphthoquinone (**11**) (0.50 g, 1.8 mmol), phenylacetylene (**6a**) (0.46 g, 4.5 mmol), CuI (0.95 g, 5.0 mmol), Et_3N (0.36 g, 3.6 mmol, 0.48 mL), and $Pd(PPh_3)_2Cl_2$ (8 mg) in DMSO (10 mL) and $CHCl_3$ (6.5 mL) were stirred for 3.5 h at 36—37 °C, phenylacetylide **3a** (0.45 g, 2.7 mmol) was added, and the mixture was stirred for additional 2 h. Chromatography on Al_2O_3 in $CHCl_3$ followed by crystallization from a mixture of ether and hexane gave 0.18 g (34%) of compound **14**, m.p. 105.5—106 °C (from a $CHCl_3$—EtOH mixture).[8]

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