The Regiospecific Substitution of Halogenated Quinones by Sulfonamides

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Sulfonamides of anthranilic esters react regiospecifically with halogenated benzo- and naphthoquinones in the presence of fluoride ions in dimethylformamide. Highly substituted products are thus made available for conversion to a wide variety of highly substituted acridones some of which are difficult to obtain by other means.

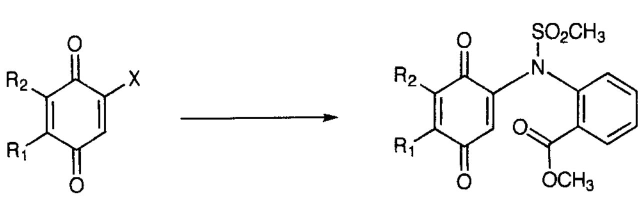
Most effective syntheses of acridones follow one of the numerous variations of a basic approach, the formation and cyclization of carboxydiphenylamines, aminobenzophenones or their derivatives.[1,2] The access to highly substituted starting materials needed for the duplication of patterns found in naturally occuring substances is favored by the ready availability of many anthranilic acids but can on occasion be limited by regiochemical considerations. In the latter case, improving the regioselectivity of the initial step would largely overcome this drawback.

The *ipso*-substitution of isomeric halogenated benzo- or naphthoquinones by anthranilates provides in principle the required flexibility for such a scheme. However the projected nucleophilic displacements do not usually occur regiospecifically unless strong electronic effects exerted by other substituents on the quinone assist the process.[3] A notable exception to this rule is provided by the fluoride-induced substitution by salicylates[4] which provides good yields of the regiospecific process even in the presence of competing effects. But, in general, *ipso*-substitution of halogenated quinones can be effected only with modest efficiency[5] except with the use of "hard" bases.[6]

Although borderline nucleophiles such as amines show notoriously poor selectivity in this respect,[3] an attempt was made to modify these reagents so as to approximate the nucleophilicity and behavior of salicylates. The corresponding acetamides were either unreactive or otherwise performed poorly. Much was expected of *N*-nitroanthranilates but these were cleaved by fluoride (giving, with benzoquinone **2**, < 50 % yield of the addition product[7]) and also, more surprisingly, in the presence of carbonate. Eventually, sulfonamides produced considerable *ipso*-substitution even in unfavorable circumstances and very little addition. No important difference was observed between methane-, *para*-toluene- or benzenesulfonamides (61–67 % in the case of benzoquinone **1**). Methanesulfonates were chosen for this study mainly on account of their better crystalline properties. In most cases, yields of *ipso*-substitution product are greater by about 5 %, an amount that corresponds to the readily isolated desulfonated product.

The process also seems subject to a delicate balance of effects in the sulfonamide and the presence of an electron-withdrawing group (i.e. methoxycarbonyl) on the *N*-phenyl moiety is required to effect *ipso*-substitution. Thus the reaction of methanesulfonamidobenzene with quinone **2** produced none of the desired displacement and only 24 % of the reoxidized addition compound, 3-anilino-2-chloro-6-methoxybenzoquinone.

The object of the present exercise concerns mainly the nature and structure of the quinonic substrates and their effect on the efficiency of the process. Bromoquinones consistently gave poorer yields than the chlorinated analogues by about 20 %, a result that may reflect the decreased electrophilic character of the adjacent carbon atom and suggests the use of fluoroquinones should the latter become readily available. 2-Chloro-5-methoxy- (**1**) or 2-bromo-6-phenylbenzoquinone (**8**) as well 2-chloro-8-methoxynaphthoquinone (**9**), in view of the electron densities involved,[8] were expected to give better conversions than the isomeric substances in which the electronic effects are not complementary. The experimental results largely bear out the prediction except that the use of a more readily available 2-bromo-6-phenylbenzoquinone tends to blur the issue (Scheme 1).



	X	R1	R2	Product	(Yield %)
1	Cl	OCH3	H	**11**	(74)
2	Cl	H	OCH3	**12**	(34)
3	Cl	OCH3	OCH3	**13**	(61)
4	Br	Br	H	**14**	(49)
5	Cl	Cl	H	**15**	(65)
6	Cl	H	Cl	**16**	(<5)
7	Cl	C6H5	H	**17**	(41)
8	Br	H	C6H5	**18**	(43)
9	Cl	8-methoxybenzo-		**19**	(85)
10	Cl	5-methoxybenzo-		**20**	(59)

Scheme 1

The modest yields obtained in some cases are largely compensated by the ease with which otherwise difficultly accessible substitution patterns are obtained. Some quinones bearing a polar substituent can sometimes be substituted[9] by nucleophiles directly. However, since this involves an oxidative step, yields are limited to less than 50% based on the starting quinones. Moreover, some earlier results have been shown to be more complex than originally claimed.[10] Finally, alkoxyl substituents are also known to be readily displaced by amines and other nucleophiles but the same constraints mentioned earlier also apply in this case.[11] The method proposed here is highly selective and allows the substitution of halogens in the presence of methoxyl groups. Compounds **11–20** could then be converted to acridones (with desulfonation) by standard procedures of reductive methylation,[12] saponification and cyclization ($POCl_3$).[1]

All melting points were taken for samples in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The IR spectra were determined on a Perkin-Elmer Model 1600 FT-IR spectrophotometer and NMR spectra were recorded with a Varian XL-200 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. ICN SiliTech 32–63 60A for flash chromatography were used throughout in a product-to-adsorbent ratio of 1:50–100. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Exact masses were provided by the Laboratoire de spectrométrie de masse, Université de Montréal, Qué. All new compounds gave satisfactory microanalyses: C ± 0.41, H ± 0.22, N ± 0.08 or HRMS ± 0.0013.

2-(*N*-Mesyl-2-methoxycarbonylanilino)quinones 11–20; General Procedure:

A detailed examination of the role of the various parameters and the effect of additives (crown ethers, molecular sieves, acid scavengers, etc) had led to the following general procedure: the halogenated quinone (1.0 mmol) and methyl *N*-mesylanthranilate (1.0 mmol) in dry DMF (10 mL) was added to a suspension of 50% CsF (1.5 mmol) on Celite and 18-crown-6 (0.1 mmol) in the same medium (10 mL) which had previously been heated to 45–65 °C for 1 h. The mixture was stirred at the same temperature for 2–8 h, cooled, poured into sat. aq NaCl (400 mL) and extracted with Et_2O (3 × 100 mL). The residue from the dried ($MgSO_4$) extracts was purified by flash chromatography using CH_2Cl_2/EtOAc 10:1 as eluent.

2-(N-Mesyl-2-methoxycarbonylanilino)-5-methoxy-1,4-benzoquinone (**11**): From 2-chloro-5-methoxybenzoquinone (**1**)[13] (45 °C, 5 h), mp 124.0–124.5 °C (benzene/hexanes).

IR (KBr): ν = 1736, 1672, 1659, 1592, 1354 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.45 (3 H, s, NSO_2CH_3), 3.83, 3.85 (2 × 3 H, 2 s, 2'-CO_2CH_3, 5-OCH_3), 5.95 (1 H, s, 6-H), 6.27 (1 H, s, 3-H), 7.43 (1 H, dt, *J* = 7.3, 1.8 Hz, 4'-H), 7.51–7.60 (2 H, m, 5', 6'-H), 7.92 (1 H, dd, *J* = 7.5, 1.8 Hz, 3'-H).

MS: *m*/*z* = 365 (2) (M^+), 170 (100).

2-(N-Mesyl-2-methoxycarbonylanilino)-6-methoxy-1,4-benzoquinone (**12**): From 2-chloro-6-methoxybenzoquinone (**2**)[13] (65 °C, 4 h), mp 145.0–146.0 °C (benzene/hexanes).

IR (KBr): ν = 1727, 1702, 1643, 1594, 1367 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.40 (3 H, s, NSO_2CH_3), 3.84, 3.86 (2 × 3 H, 2 s, 2'-CO_2CH_3, 6-OCH_3), 5.88 (1 H, d, *J* = 2.2 Hz, 5-H), 6.40 (1 H, d, *J* = 2.2 Hz, 3-H), 7.47 (1 H, dt, *J* = 7.0, 1.7 Hz, 4'-H), 7.54–7.63 (2 H, m, 5', 6'-H), 7.90 (1 H, dd, *J* = 7.6, 2.0 Hz, 3'-H).

MS: *m*/*z* = 286 (50) (M-79), 170 (100).

2-(N-Mesyl-2-methoxycarbonylanilino)-5,6-dimethoxy-1,4-benzoquinone (**13**): From 2-chloro-5,6-dimethoxybenzoquinone (**3**)[14] (65 °C, 6 h), mp 106.5–107.5 °C (benzene/hexanes).

IR (KBr): ν = 1730, 1674, 1645, 1592, 1361 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.41 (3 H, s, NSO_2CH_3), 3.85 (3 H, s, 2'-CO_2CH_3), 3.92, 4.02 (2 × 3 H, 2 s, 5, 6-OCH_3), 6.14 (1 H, s, 3-H), 7.39 (1 H, dd, *J* = 7.7, 1.7 Hz, 6'-H), 7.52 (1 H, dt, *J* = 7.5, 1.6 Hz, 4'-H), 7.58 (1 H, dt, *J* = 7.5, 1.9 Hz, 5'-H), 7.90 (1 H, dd, *J* = 7.2, 2.0 Hz, 3'-H).

MS: *m*/*z* = 396 (1) (M^+), 170 (100).

5-Bromo-2-(N-mesyl-2-methoxycarbonylanilino)-1,4-benzoquinone (**14**): From 2,5-dibromobenzoquinone (**4**)[15] (45 °C, 2 h), mp 164.5–165.0 °C (benzene/hexanes).

IR (KBr): ν = 1732, 1680, 1658, 1589, 1355 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.42 (3 H, s, NSO_2CH_3), 3.85 (3 H, s, 2'-CO_2CH_3), 6.44 (1 H, s, 3-H), 7.31 (1 H, s, 6-H), 7.43 (1 H, dd, *J* = 7.4, 1.8 Hz, 6'-H), 7.53 (1 H, dt, *J* = 7.5, 1.7 Hz, 4'-H), 7.62 (1 H, dt, *J* = 7.5, 2.0 Hz, 5'-H), 7.95 (1 H, dd, *J* = 7.5, 2.0 Hz, 3'-H).

MS: *m*/*z* = 415/413 (2/2) (M^+), 170 (100).

5-Chloro-2-(N-mesyl-2-methoxycarbonylanilino)-5-chloro-1,4-benzoquinone (**15**): From 2,5-dichlorobenzoquinone (**5**) (65 °C, 2 h), mp 158.0–158.5 °C (benzene/hexanes).

IR (KBr): ν = 1733, 1681, 1662, 1587, 1355 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.40 (3 H, s, NSO_2CH_3), 3.82 (3 H, s, 2'-CO_2CH_3), 6.38 (1 H, s, 3-H), 7.01 (1 H, s, 6-H), 7.40 (1 H, dd, *J* = 7.4, 1.8 Hz, 6'-H), 7.47–7.64 (2 H, m, 4', 5'-H), 7.93 (1 H, dd, *J* = 7.3, 2.0 Hz, 3'-H).

MS: *m*/*z* = 371/369 (1/2) (M^+), 292/290 (40/100).

2-(N-Mesyl-2-methoxycarbonylanilino)-5-phenyl-1,4-benzoquinone (**17**): From 2-chloro-5-phenylbenzoquinone (**7**)[16] (45 °C, 5 h), mp 119.5–120.5 °C (Et_2O).

IR (KBr): ν = 1728, 1668, 1649, 1586, 1359 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.46 (3 H, s, NSO_2CH_3), 3.88 (3 H, s, 2'-CO_2CH_3), 6.45 (1 H, s, 3-H), 6.89 (1 H, s, 6-H), 7.44 (5 H, s, C_6H_5-H), 7.45–7.66 (3 H, m, 4', 5', 6'-H), 7.96 (1 H, dd, *J* = 7.2, 2.0 Hz, 3'-H).

2-(N-Mesyl-2-methoxycarbonylanilino)-6-phenyl-1,4-benzoquinone (**18**): From 2-bromo-6-phenylbenzoquinone (**8**)[17] (45 °C, 6 h), mp 156.0 °C (benzene/hexanes).

IR (KBr): ν = 1726, 1678, 1646, 1582, 1359 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.44 (3 H, s, NSO_2CH_3), 3.85 (3 H, s, 2'-CO_2CH_3), 6.24 (1 H, d, *J* = 2.5 Hz, 3-H), 6.79 (1 H, d, *J* = 2.5 Hz, 6-H), 7.43–7.57 (7 H, m, 4',6'-H, C_6H_5-H), 7.62 (1 H, dt, *J* = 7.5, 1.9 Hz, 5'-H), 7.95 (1 H, dd, *J* = 7.5, 1.9 Hz, 3'-H).

MS: *m*/*z* = 411 (3) (M^+), 332 (100).

2-(N-Mesyl-2-methoxycarbonylanilino)-8-methoxy-1,4-naphthoquinone (**19**): From 2-chloro-8-methoxynaphthoquinone (**9**) (45 °C, 7 h), mp 174.5–175.5 °C (benzene/hexanes).

IR (KBr): ν = 1728, 1676, 1657, 1586, 1354 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.46 (3 H, s, NSO_2CH_3), 3.82 (3 H, s, 2'-CO_2CH_3), 3.96 (3 H, s, 8-OCH_3), 6.42 (1 H, s, 3 H), 7.26 (1 H, dd, *J* = 6.8, 2.8 Hz, 7-H), 7.38–7.62 (5 H, m, 4', 5', 6', 5, 6-H), 7.89 (1 H, dd, *J* = 7.5, 2.0 Hz, 3'-H).

MS: *m*/*z* = 415 (5) (M^+), 336 (100).

2-(N-Mesyl-2-methoxycarbonylanilino)-5-methoxy-1,4-naphthoquinone (**20**): From 2-chloro-5-methoxynaphthoquinone (**10**) (65 °C, 8 h), mp 155.0 °C (benzene/hexanes).

IR (KBr): ν = 1713, 1682, 1651, 1583, 1360 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.46 (3 H, s, NSO_2CH_3), 3.83 (3 H, s, 2'-CO_2CH_3), 3.96 (3 H, s, 5-OCH_3), 6.47 (1 H, s, 3 H), 7.29 (1 H, d, *J* = 8.1 Hz, 6-H), 7.45–7.77 (5 H, m, 4',5',6',7,8-H), 7.92 (1 H, dd, *J* = 7.2, 2.0 Hz, 3'-H).

MS: *m*/*z* = 415 (1) (M^+), 336 (100).

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