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REGIOSPECIFIC SYNTHESIS OF BROMOJUGLONE DERIVATIVES

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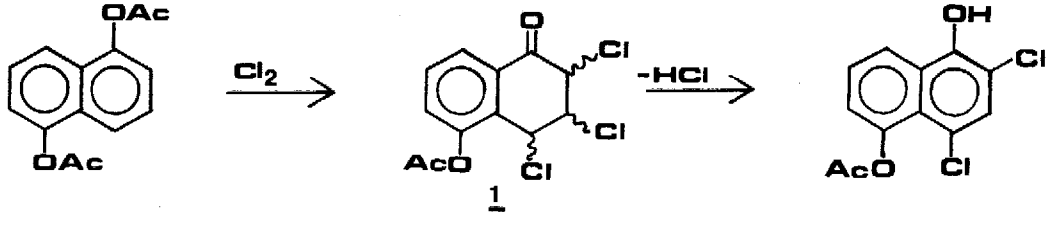
Abstract: A large yield highly regiospecific one step procedure for the synthesis of 2- and 3-bromo-5-acetoxy-1,4-naphthoquinone has been achieved from the reaction between N-bromosuccinimide and 1,5- and 1,8-diacetoxynaphthalene, respectively.

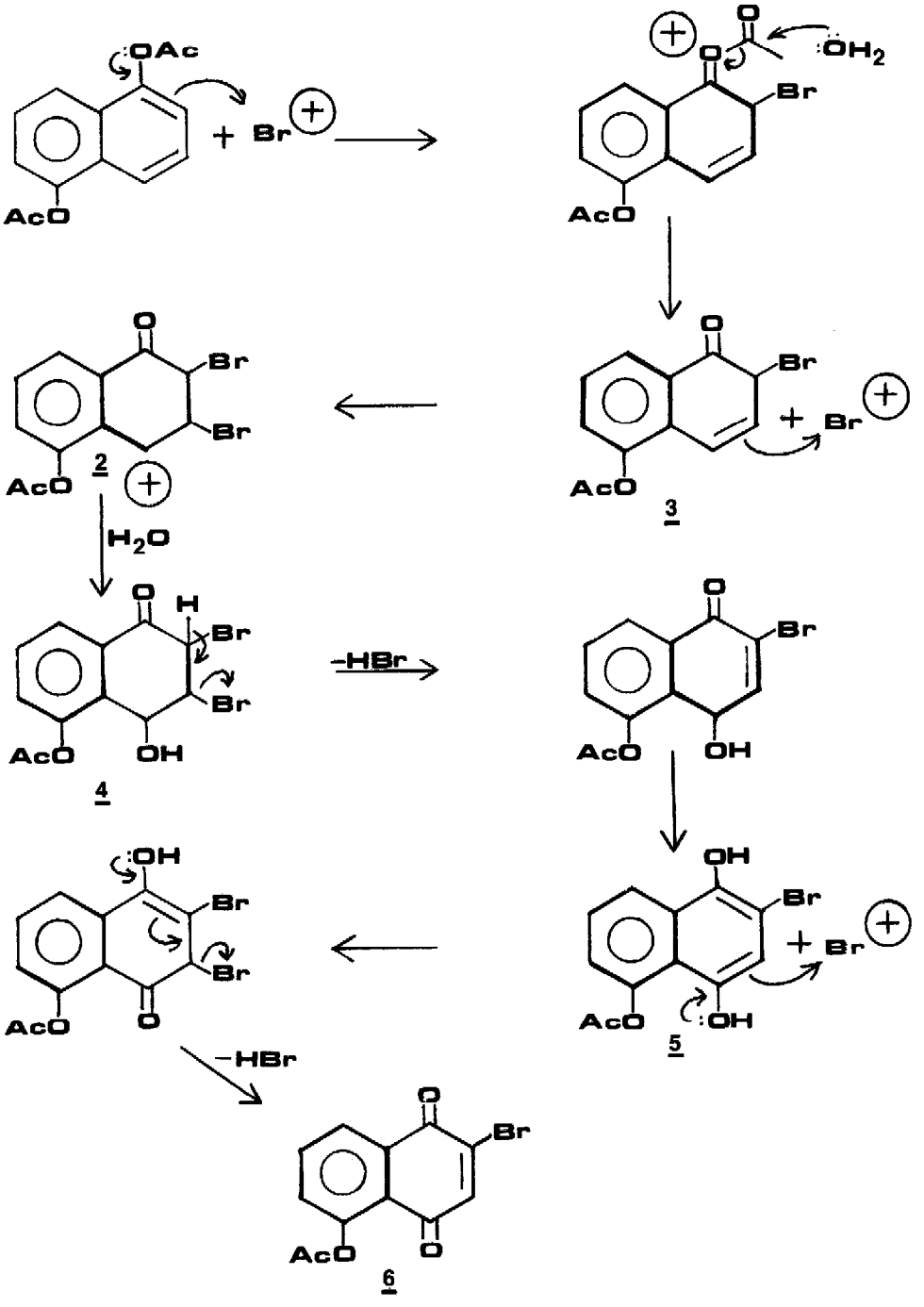
The utility of halogen atoms as control elements directing the regiochemistry of the Diels-Alder reactions with chlorojuglone derivatives makes the synthesis of halojuglone compounds from inexpensive starting materials highly desirable.[1] Rapoport has synthesized 2- and 3-bromo-5-methoxy-1,4-naphthoquinone by multi-step procedures while Bhatt has prepared 2-chloro-1,4-naphthoquinone from 1-naphthol, hydrogen peroxide and hydrochloric acid.[2,3] We wish to report a novel one step synthesis of the acetates of 2- and 3-bromojuglone from the reaction between N-bromosuccinimide and the diacetates of 1,5- and 1,8-dihydroxynaphthalene, respectively.

In connection with other studies we reacted several equivalents of bromine with 1,5-dihydroxy naphthalene in a water, acetic acid mixture and isolated small amounts of an acetylated bromojuglone derivative. We were unable to make this reaction proceed in high yield. P.B.D. de la Mare[4] showed that the chlorination of 1,5-diacetoxynaphthalene in anhydrous methylene chloride gave 2,4-dichloro-1-hydroxy-5-acetoxynaphthalene via the intermediate trichlorotetralone derivative 1. Also, the bromination of 1,5-diacetoxynaphthalene in glacial acetic acid with two equivalents of bromine produced the corresponding dibromohydroxynaphthalene acetate.[5a] These observations suggested that halogenation of 1,5-diacetoxynaphthalene in the absence of halide ion and in the presence of water, which can intercept the intermediate 2 (Scheme I), should form a halojuglone derivative. Thus, the reaction between N-bromosuccimide dissolved in water, acetic acid and 1,5-diacetoxynapthalene gave 2-bromo-5-acetoxy-1,4-naphthoquinone in excellent yield (Table I).



1

SCHEME I



The regiospecific substitution of the halogen atom ortho to an acetoxy group in the reactant is demonstrated further by the formation of 3-bromo-5-acetoxy-1,4-naphthoquinone 7 from the reaction between N-bromosuccimide and 1,8-diacetoxynaphthalene. The 2- and 3-bromojuglone acetates have similar but distinct melting points, spectral data, and liquid chromatographic properties. The hydrolysis[5b] of the 2- and 3-bromojuglone acetates have the corresponding known 2- and 3-bromojuglones 8 and 9 whose melting points differ by 36°. The cmr data[6] for the acetates and the hydrolysis products are shown in Table II. The 2- and 3-bromoacetates can be distinguished by reverse phase liquid chromatography.[7] Analysis of each crude product after one recrystallization showed no trace of the other isomer.

1-Naphthylacetate and 1-naphthol gave 2-bromo-1,4-naphthoquinone, which is also the product upon reaction of 2-aceto-1-naphthol. The loss of the acetyl group probably arises from addition of water to the acetyl carbonyl of a dibromo intermediate corresponding to 4 in Scheme I. The success with 1-naphthol led to reacting 1,5-dihydroxynaphthalene. The several products which formed proved impossible to separate.

The stoichiometry of the reaction is 3 equivalents of N-bromosuccinimide per equivalent of diacetoxynaphthalene. In practice 4-equivalents of NBS gave better yields. When 2,4-dibromo-5-acetoxy-1-naphthol was reacted with 2 equivalents of N-bromosuccinimide in water, acetic acid, no naphthoquinone was produced, although a tribromoacetoxy naphthalenone was isolated in low yield. Thus, compounds brominated in the para position relative to an acetoxy group in the reactant do not appear to be intermediates in the formation of the product bromonaphthoquinone. A possible mechanism for the oxidation by N-bromosuccinimide is shown in Scheme I. Bromination of the diacetate formed the bromoketone 3 after deacetylation by water. Bromonium ion and 3 produced the carbonium ion 2 which was trapped by water to provide the dibromide 4 which in turn loses hydrogen bromide followed by tautomerization to afford the bromide 5. The reaction of 5 with a third equivalent of bromonium ion with subsequent elimination of hydrogen bromide gave the product 6.

General Method

A solution of 0.005 moles of substrate dissolved in 50 ml of warm acetic acid was added over a period of 5 min. to a solution of N-bromosuccinimide (0.02 moles) dissolved in 50 ml of acetic acid and 100 ml of water. The resulting solution was stirred at 55-60° for lengths of time (generally 30-45 min.) dependent on the substrate. Subsequently, 100 ml of water were added to the solution, followed by extraction with dichloromethane (6x50 ml). The combined extracts were washed with water (4x100 ml), saturated $NaHCO_3$ (5x100 ml), saturated NaCl (1x100 ml), dried over $MgSO_4$, and evaporated to afford the product quinones. The bromoquinones may be recrystallized from ethanol although if the ethanolic solution was allowed to rise above 50° the bromoquinones badly discolored.

Table I. Oxidation of Naphthalene Derivatives with N-Bromosuccinimide

Substrates	Time	Products[a]	Yields	M.P.
1,5-Diacetoxynaphthalene	45 min.	2-bromo-5-acetoxy-1-4-naphthoquinone	>90%	154.5-156°
1,8-Diacetoxynaphthalene	45 min.	3-bromo-5-acetoxy-1,4-naphthoquinone	>90%	149-150°
1-Naphthylacetate[b]	30 min.	2-bromo-1,4-naphthoquinone	50%	131-132°
1-Naphthol[c]	30 min.	"	85%	
2-Aceto-1-naphthol	30 min.	"	84%	

a) Identity of products was established on the basis of ir, nmr, ms, m.p. and conversion to other derivatives.

b) Yields are low due to an inefficient isolation procedure.

c) 1-Naphthol added dropwise over 30 min. at 45°C.

Table II. ^{13}C-NMR (22.63 MHz) Spectral Data[6]

Atom	6	7	8	9
C-1	177.5(s)	176.3(s)	176.0(s)	181.7(s)
C-2	138.5(s)	139.5(d)	140.9(s)	141.5(d)
C-3	141.5(d)	141.2(s)	140.3(d)	142.4(s)
C-4	180.9(s)	181.6(s)	187.5(s)	183.1(s)
C-5	149.9(s)	150.9(s)	161.8(s)	162.2(s)
C-6	130.4(d)	130.3(d)	125.2(d)	124.6(d)
C-7	134.9(d)	135.7(d)	136.5(d)	137.3(d)
C-8	126.4(d)	125.4(d)	120.9(d)	119.8(d)
C-9	132.7(s)	133.9(s)	130.8(s)	131.9(s)
C-10	123.3(s)	122.9(s)	114.7(s)	114.2(s)
C-11	169.2(s)	169.3(s)	---	---
C-12	20.99(q)	20.99(q)	---	---

References

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6. Our cmr assignments are based on those made for juglone acetate: M. Kobayashi, Y. Terui, K. Tori, and N. Tsuji, Tetrahedron Letters, 619 (1976).

7. We wish to acknowledge Denis Foerst of the Environmental Research Center, Environmental Monitoring and Support Laboratory, Cincinnati, OH for performing the liquid chromatographic analysis which was conducted on a Waters Model 440 liquid chromatograph using 5 μm Li Chrosorb RP-2, 4.6 mm x 25 cm column at 1300 psi and a flow rate of 1.00 mL/min with 37% acetonitrile and 63% 0.65 μm Milli-Q filtered distilled water as eluent. The retention time for 6 was 17.7 min and for 7 was 16.6 min.

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