

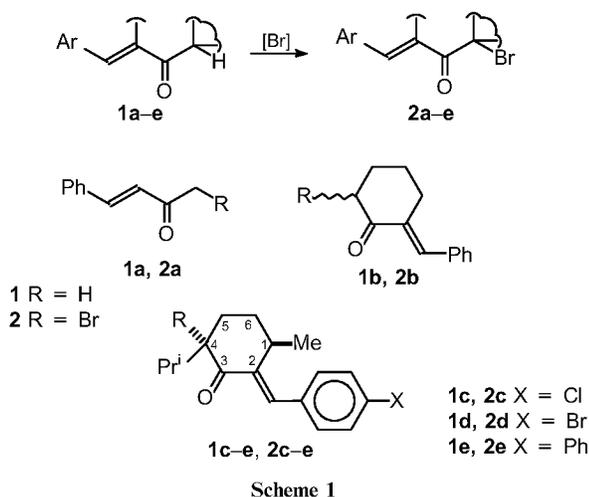
Bromination of 2-Arylideneketones

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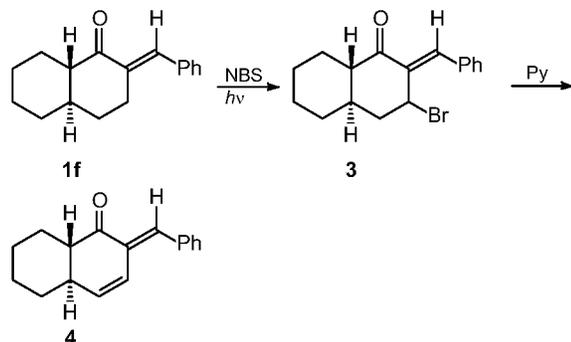
It is shown that the acid catalysed bromination of α,β -unsaturated ketones by NBS occurs in the α' -position in high yield; this reaction with chiral (1*R*,4*R*)-2-arylidene-*p*-menthanones is diastereoselective and results in 1*R*,4*S*-diastereoisomers.

α' -Halogeno- α,β -unsaturated ketones are useful intermediates in organic synthesis. The bromination of benzylideneacetone **1a** on the methyl group (Scheme 1) without a side reaction (bromine addition on the double bond) was first carried out using pyrrolidone hydrotribromide.¹ Several other reagents were subsequently successfully used.²⁻⁷

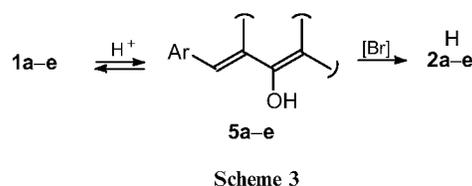


However, most of the brominating agents used in work cited in the literature are not available. At the same time, the successful use of such a well-known reagent as NBS for α' -bromination of the α,β -unsaturated ketones, has not been described to date. So, NBS does not react with benzylideneacetone **1a** in the absence of free radical source, and in the presence of the latter dibromide (from addition to the double bond) was the main product.⁸ The bromination of the 2-benzylidene-1-decalone **1f** by NBS under irradiation and subsequent dehydrobromination without separation of the bromo-derivative **3** results in the corresponding dienone **4** (yield 61%, conversion 74%), and thus proceeds through the intermediate formation of 3-bromo-2-benzylidenedecalone as the main allylic bromination product (Scheme 2).⁹ The synthesis of the 4-bromo-2-arylidene-*p*-menthanones **2c-e** (Scheme 1) in moderate yields (21–31%) by bromination of **1c-e** with NBS in the presence of Bz_2O_2 has been described.¹⁰

It is well known that in the presence of acids (including Lewis acids) NBS is involved in electrophilic substitution reactions with activated substrates.¹¹ Also well known is that,



in heterolytic bromination of carbonyl-containing compounds, the ketone enolisation step is the rate determining one and the subsequent interaction with an electrophile occurs at a high rate.^{12,13} In the preliminary synthesis of enolic derivatives (enolborinates, alkyl and trimethylsilyl ethers) the bromination by NBS proceeds very vigorously and does not require either free radical sources or the presence of acids.¹⁴ The direct bromination of α,β -unsaturated ketones with a series of reagents other than NBS is, in most cases, also an acid catalysed process^{1-3,5-7} and, as in the case of saturated ketones, proceeds through the intermediate formation of respective dienols **5a-e** (Scheme 3). Therefore, an attempt to use NBS for bromination of α,β -unsaturated ketones in acid catalysis conditions seems to be reasonable.



In this work, we wish to report on the acid catalysed bromination of the arylidene ketones **1a-e** by NBS. It turns out that this reaction occurs with an equimolar reactant ratio under mild conditions: at somewhat elevated temperature with catalytic amounts of strong acids, the best being conc. $HClO_4$. Yields and melting points for crude and purified compounds are listed in Table 1.

This is a simple and convenient method, permitting easy isolation of product. The crude bromo-derivatives obtained under optimal conditions (Table 1, entries 2, 3, 5, 9 and 11) are single compounds (according to TLC).[†] For **1b** the yield and m.p. stay the same with the use of reagents other than NBS with similar product purification methods: 88%, 82–84 °C; 94%, 85–86 °C.^{2,4} Bromination of **1c-e** by NBS under these conditions leads to higher yields of **2c-e** (Table 1) than in the presence of Bz_2O_2 (21–34%).¹⁰

In the reaction studied the bromo-derivative yield in the same solvent depends significantly on the acid catalyst nature, as shown with **2c**, and increases symmetrically with the rising proton-donating ability of the acids: $HClO_4 > H_2SO_4 \gg HCl$ (see Table 1, entries 5, 7 and 8).¹⁵ The strong dependence of the bromo-derivative yield on the acidity of catalyst used is due obviously to the differentiating effect of dioxane.

Thus, we have revealed new possibilities of NBS use for the effective α' -bromination of the α,β -unsaturated ketones.

In the process of acid catalysed bromination of **1c-e** through dienols **5c-e**, both 1*R*,4*S*- and 1*R*,4*R*-configurations may occur. The bromo-derivatives isolated **2c-e** are identical to those previously synthesised using NBS in the presence of Bz_2O_2 .¹⁰ Their structure and 1*R*,4*S*-configuration were

[†] Typical procedure: An equimolar mixture of α,β -unsaturated ketone and NBS (ca. 10 mmol) in the appropriate solvent (30–40 ml), to which 1–2 drops of acid were added, was maintained at the temperature as indicated in Table 1 until reaction was completed (check by TLC). The reaction mixture was then diluted with water, filtered (for compounds **2b-e**) and dried. Crude products were purified by recrystallisation from propan-2-ol or hexane. For **2a**, the oil after dilution was extracted with dichloromethane, dried over $MgSO_4$ and isolated by column chromatography on silica gel.

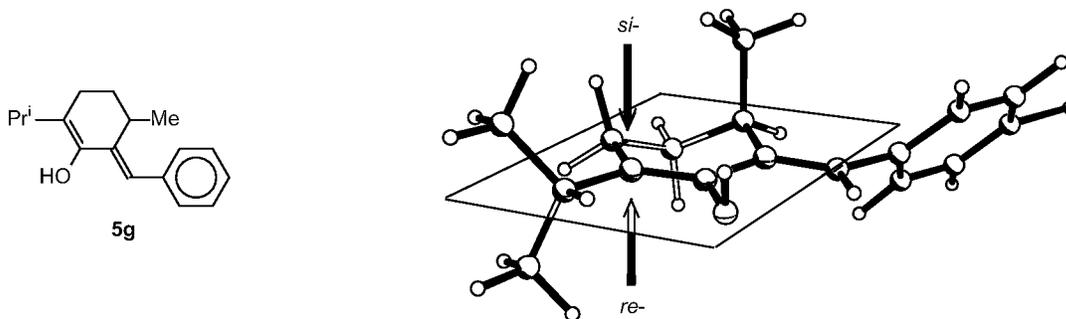


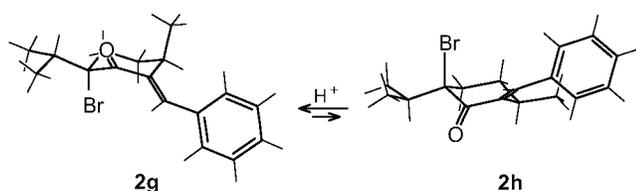
Fig. 1 Diastereofacial surface of the model dieneol **5g**.

Table 1 Acid catalysed bromination of the arylideneketones **1a–e** by NBS.

Entry	Product	Catalyst	Solvent	Reaction temperature/°C	Reaction time/h	Yield (%) ^a	M.p./°C ^a		
1	2a	HClO ₄	dioxane	20	3	no react.	–		
2				55	1	– (55)	– (44–46)		
3	2b	HClO ₄	dioxane	20	1.5	97 (55)	83–85 (89–90)		
4			CH ₂ Cl ₂			90	82–83		
5	2c	HClO ₄	dioxane	40	3	97 (66)	93–100 (108–110)		
6			CH ₂ Cl ₂			79 (53)	93–100		
7			H ₂ SO ₄			dioxane	5	81 (52)	92–97
8			HCl			dioxane	12	no react.	–
9	2d	HClO ₄	dioxane	40	3	93 (72)	113–116 (123–125)		
10			THF	40	0.1	70 (43)	112–116 (123–125)		
11	2e	HClO ₄	dioxane	40	5	98 (66)	135–140 (143–144)		

^a Data for crude compounds; in parentheses – for purified compounds.

proved by NMR and IR spectroscopy¹⁶ and X-ray analysis.¹⁷ Thus, acid catalysed bromination by NBS of 2-arylidene-*p*-menthanones is essentially diastereoselective.



Scheme 4

If the acid catalysed ketone bromination is thermodynamically controlled so that an equilibrium between the diastereoisomeric bromides is possible (Scheme 4), the diastereoselectivity observed can be explained by the energetic preference of 1*R*,4*S*-diastereoisomers over their 1*R*,4*R*-analogues (modelling by molecular mechanics, MMX force field).¹⁷ For a model compound 1*R*,4*S*-4-bromo-2-benzylidene-*p*-menthan-3-one **2g** the E_{st} value is 2.2 kcal mol⁻¹ lower than for the most favourable 1*R*,4*R*-diastereoisomer conformation **2h**.

In addition, the kinetically controlled bromination of compounds **1** can not be excluded so the diastereoselectivity observed may be explained by relatively lesser hindrance of the *re*-diastereofacial surface of the model dieneol **5g** electrophile attack (from molecular mechanics simulations, Fig. 1).

Thus, for the reaction in question, both thermodynamic and kinetic controls led to the products with 1*R*,4*S*-configuration, and it is difficult to judge definitively on the causes of such high diastereoselectivity. The synthesis of 1*R*,4*R*-diastereoisomeric bromo-derivatives and their study in the reaction conditions under consideration should lead to more definite conclusions.

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