SHORT PAPER

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Synthesis of substituted 2-bromo phenols using a novel bromination-dehydrobromination reaction

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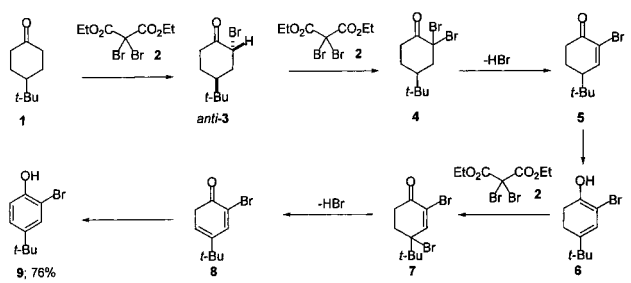
Substituted 2-bromo-phenols can be synthesised by heating substituted cyclohexanones in neat diethyl dibromomalonate at 100°C. We discuss the efficiency of such a procedure and comment on the possible mechanism.

The synthesis of substituted cyclohexanones by the formal reduction of the phenols is well known.[1] The reverse functional group transformation of substituted cyclohexanones into the corresponding phenol is much rarer.[2] There are some reports that this can be efficiently achieved by consecutive dehydrogenation[3] or dehydrohalogenation[4] involving the cyclohexanone framework. We were originally interested in the development of a enol-bromination reaction performed under neutral conditions, rather than the usual harsh acidic conditions.[5] We chose to use the little known[6] brominating reagent, diethyl dibromomalonate **2**[7] primarily due to the required neutral conditions being preserved throughout the reaction by the formation of the relatively non-acidic by-product diethyl bromomalonate. Herein, we report a novel procedure for the synthesis of 2-bromo substituted phenols and comment on the relationship between substitution pattern of the cyclohexanone and the positional isomer formed, all of which helps to elucidate to the mechanism of the title reaction.

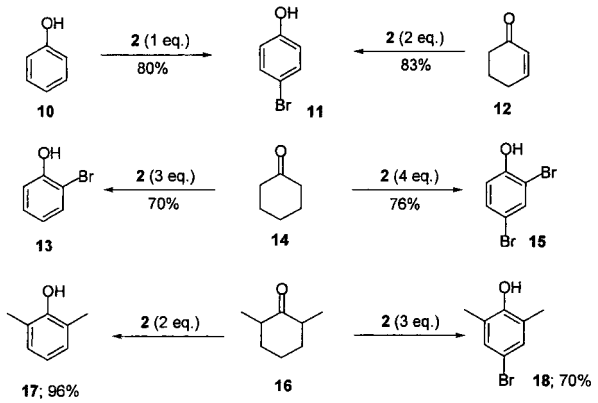
Whilst attempting to synthesise the 2-bromo ketone *anti*-**3** by heating a solution of 4-*tert*-butyl cyclohexanone 1 in an excess of diethyl dibromomalonate **2** (3 equivalents)[4] at 100°C, the required bromide *anti*-**3** was not isolated, but to our surprise the substituted 2-bromo phenol **9** was formed in 76% yield as shown in Scheme 1. Clearly, the reaction must proceed *via* an efficient series of HBr eliminations to account for the loss of **2** equivalents of HBr to give **5**, then **8**, tautomerisation of which leads to the more thermodynamically stable aromatic phenol **9**. The reaction certainly does proceed *via* both the bromide *anti*-**3** and dibromide **4**, as these can be formed as a partially separable mixture (ratio 1:2) in 72% yield by performing the reaction at a lower temperature to prevent HBr elimination – by heating both reagents in CCl_4 for 12 h. These intermediates can be re-subjected under the original reaction conditions to give the 2-bromophenol **9** in 70 % yield (Scheme 2). The reaction rate can be further increased by the addition of a catalytic amount of HCl, which presumably increases the rate of initial enol formation, thus lowering the reaction time to 12 hours. However, the reaction does become auto-catalytic after HBr elimination from the dibromide **4**.

The introduction of the 2-bromo substituent is more than likely due to E2 elimination of dibromide **4**, to give the intermediate vinyl bromide **5**. But the question still remained whether the introduction of a bromide substituent could have occurred *via* direct electrophilic substitution of the phenol. In fact, bromination of the simple phenol **10** under such conditions does occur, to give the complementary positional isomer 4-bromo phenol **11** in 80 % yield, in comparison to cyclohexanone **14** giving 2-bromo phenol **13** in 70% yield. By using an excess of dibromo malonate **2** (4 equivalents), further bromination can occur to give the 2,4-dibromo phenol **15** in good yield (76%). It does appear that the 4-bromo substituent occurs after formation of the phenolic ring, since the simple enone **12** gave exclusively the 4-bromo phenol in 83% yield. Non-brominated phenols can efficiently be synthesised if the corresponding C2 and C6 positions in the required phenol were previously substituted. For example, refluxing 2,6-dimethyl cyclohexanone **16** under our standard conditions with **2** equivalents of dibromo malonate **2** gave the 2,6-dimethylphenol **17** in near perfect yield. Repeating the reaction with an excess of dibromide malonate (3 equivalents) leads exclusively to the 4-bromo phenol **18** in 70% yield (Scheme 2).

The remaining substituted cyclohexanones **19**, **21** and **23** behaved similarly (Scheme 3). The 2- and 4-positional isomers of methyl cyclohexanone **19** and **21** gave the 2-bromo substituted phenols **20** and **22** respectively in reasonable yield. Whereas the 3-methyl cyclohexanone **23** gave for the first time a mixture of partially separable (ratio 1:1) positional isomeric bromides **24** and **25** in 76% yield. This was unsurpris-



Scheme 1



Scheme 2

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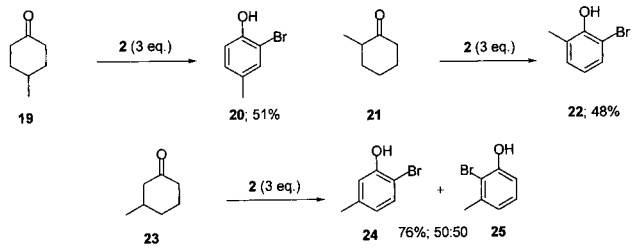
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 3

ing since this 3-methyl substituent would have little control over regioselective enol formation.

In conclusion, we have shown that substituted 2-bromo phenols can be synthesised efficiently in good yield by a series of tandem dehydrobromination reactions involving substituted cyclohexanones. The reaction is relatively easy to perform by heating the corresponding cyclohexanone derivative in neat diethyl dibromomalonate (3 equivalents). The course of the reaction can be easily monitored by the formation of the byproduct diethyl bromomalonate.

The nearest analogue to this work is the dehydrobromination of simple cyclohexanones and cyclohexenones using other related Br-sources like NBS[8] and Br.[9] These methods are slightly different since they allow efficient aromatisation to occur without Br incorporation. In our case, by using an alternative Br-source, diethyl dibromomalonate **2**, incorporation does occur exclusively at the C2 position. This has been shown to occur before aromatisation, rather than by direct electrophilic bromination on the phenol ring.

Typical procedure: 4-*tert*-butyl cyclohexanone **4** (0.24 g, 1.6 mmol) was added to a stirred solution of diethyl dibromomalonate (1.0 g, 0.6 ml, 3.14 mmol). This solution was heated at 100 °C for 2 days and allowed to cool to room temperature. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane to give 2-bromo-4-*tert*-butyl phenol **9** (0.25 g, 60 %) as a colourless oil; R_f [CH_2Cl_2] 0.62; ν_{max}($CHCl_3$)/cm^{-1} 3600–3000 (broad OH), 1577 and 1560 (C=C); δ_H(250 MHz, $CDCl_3$) 7.42 (1 H, d, *J* 2.2, CH; Ar) 7.20 (1 H, dd, *J* 8.4 and 2.3, CH; Ar), 6.9 (1 H, d, *J* 8.4, CH; Ar), 5.40 (1 H, s, OH) and 1.32 (9 H, s, *tert*-Bu); δ_C(67.5 MHz, $CDCl_3$) 153.2, 150.0, 145.1, 129.2, 128.8, 126.3, 63.1 and 31.5 (Found M^+, 228.0183. $C_{10}H_{13}BrO$ requires M, 228.0150); *m/z* 230.1 (100 %, ^{81}M) and 228.1 (100% ^{79}M).

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