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Investigations into the Bromination of Substituted Phenols using Diethyl Bromomalonate and Diethyl Dibromomalonate

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Substituted 4-bromophenols can be synthesised efficiently by heating the corresponding phenol in either neat diethyl bromomalonate or diethyl dibromomalonate. We discuss the regioselectivity of such reactions and comment on the scope and limitation of this procedure.

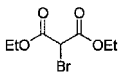
Electrophilic bromination of substituted phenols is well documented.[1] A wide variety of efficient electrophilic brominating reagents have been used,[2] such as Br_2[3] and *N*-bromosuccinimide (NBS)[4] which appear to be the most commonly used method. The presence of additives, such as strong acids[5] are generally required to catalyze the reaction and basic amines[6] to control the regioselectivity. Consequently, many of these methods require the reaction to be performed in either acidic or basic conditions.[6] We were interested in developing a novel bromination procedure that could be performed under much milder conditions. We chose to investigate the use of diethyl bromomalonate (**1**) and dibromomalonate (**2**) as electrophilic brominating reagents, primarily due to their commercial availability and structural similarity to the less reactive *N*-bromosuccinimide (NBS), but more importantly because the near neutral conditions would be preserved due to formation of the relatively non-acidic by-product diethyl malonate or diethyl bromomalonate (**1**). The use of such reagents are rare, but there is a report where both react efficiently with very labile ester enolates.[7] Herein, we report our study into the use of both reagents as electrophilic Br-sources with phenol derivatives and comment on the scope and limitation of this procedure. The optimum conditions for efficient bromination were found to require direct heating of the substituted phenol in either neat diethyl bromomalonate (**1**) (1 molar amount) or diethyl dibromomalonate (**2**) (0.5 molar amount) at 100 °C for 2 days; for example, treatment of simple phenol (**3**) under such conditions gave exclusively the 4-bromophenol (**4**) in good yield [82% in both cases using either (**1**) or (**2**)]. Both reagents behave similarly, giving the same regioisomer in good yield, but the reaction times were marginally shorter for the more electrophilic dibromomalonate (**2**). It is quite remarkable that efficient Br transfer occurs using the diethyl bromomalonate (**1**) [to give phenol (**4**)] due to the presence of the mildly acidic proton, but the rate is presumably slower than the dibromomalonate cases due to competing H-transfer. The progress of the both reactions can easily be monitored by TLC, by the formation of the by-products diethyl malonate and diethyl bromomalonate (**1**).

The remaining substituted phenols (**5**), (**8**), (**10**), (**13**) and (**16**) behaved similarly. Bromination of the 1-napthanol (**5**) gave a mixture of 4-bromo- and 2,4-dibromophenol (**6**) and (**7**) respectively in good yield (Table 1). Bromination always occurs within the same aromatic ring as the directing OH group. This mixture can be prevented if an electron-donating group was positioned in both rings. Whereas, treatment of 1,5-dihydroxynapthalene diol (**8**) under our standard conditions gave the 4-bromophenol (**9**) in very poor yield, presumably due to additional *peri*-strain within the transition state.

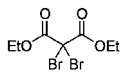
Bromination can efficiently occur at the C2 position when more favored C4 position was blocked. Treatment of the symmetrical phenol hydroquinone (**10**) with diethyl bromomalonate (**1**) and diethyl dibromomalonate (**2**) gave a mixture of monobromophenol (**11**) (major) and dibromophenol (**12**) (minor) in 85–91% yield. The isomeric phenol, resorcinol (**13**) and the 2,2′-biphenyl diol (**16**) were identical giving the 4-bromophenol (**14**) and 5-bromo-2,2′-biphenyl diol (**17**) in excellent yield (Table 1).

Attempts at brominating less nucleophilic phenols, such as the deactivated *ortho*-, *meta*- and *para*-nitrophenols proved un-

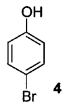
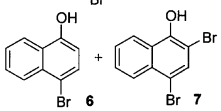
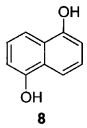
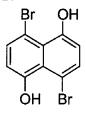
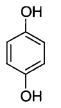
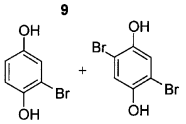
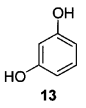
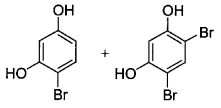
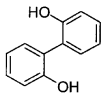
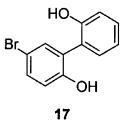
Table 1. The Synthesis and Yield(%) of Bromophenols



1



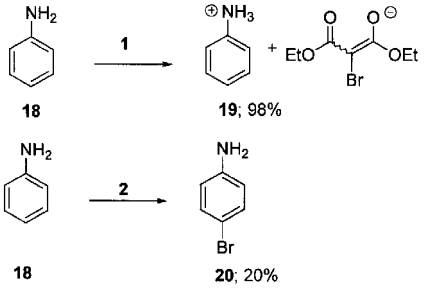
2

Entry	Starting material	Product	Reagent	Yield/%
1	 **3**	 **4**	**1** **2**	82 82
2	 **5**	 **6** + **7**	**1** **2**	**6**; 48, **7**; 51 **6**; 32, **7**; 45
3	 **8**	 **9**	**1**	8
4	 **10**	 **11** + **12**	**1** **2**	**11**; 80, **12**; 11 **11**; 68, **12**; 17
5	 **13**	 **14** + **15**	**1** **2**	**14**; 67, **15**; 23 **14**; 91, **15**; 0
6	 **16**	 **17**	**1** **2**	**17**; 99 **17**; 99

successful — even on prolonged heating — and were re-isolated in near quantitative yield. The question remained whether the phenol or the phenolate was the active component in this reaction. By comparison, reacting the *protected* phenol in the form of anisole with both electrophilic bromomalonates (**1**) and (**2**) gave only recovered starting material, presumably indicating that formation of the more nucleophilic phenolate was responsible for the addition to poor electrophilic brominating reagents.

Discrimination between these reagents can be seen by using more basic aromatic systems, such as aniline (**18**). With diethyl bromomalonate (**1**), deprotonation occurs to give the ammonium salt (**19**) in near quantitative yield, whereas partial bromination does occur with dibromomalonate (**2**) to give 4-bromoaniline (**20**) (20%) (Scheme 1). The yield was much lower than the corresponding phenol (82%) due to the formation of the acidic by-product **1** which subsequently protonates the original aniline. Attempts at brominating less nucleophilic alkyl-substituted aromatics, such as toluene, also proved unsuccessful and gave recovered starting material in near quantitative yield.

In conclusion, we have shown that substituted 4-bromophenols can be synthesised efficiently in good yield by heating the corresponding phenol in either neat diethyl bromomalonate (**1**) or diethyl dibromomalonate (**2**). The reaction was shown to be particularly sensitive to the substitution pattern, and the presence of both electron withdrawing groups (such as NO_2) and protecting the phenolic OH group, which have been shown to hinder this electrophilic bromination reaction. Both reagents are similarly high yielding, but the less reactive bromomalonate (**1**) appears to be the better reagent due to the ease of purification.



Scheme 1.

Experimental

General Procedure with Diethyl Bromomalonate (1): Hydroquinone (**10**) (0.46 g, 4.18 mmol) was added to a stirred solution of diethyl dibromomalonate (1.0 g, 0.71 ml, 4.18 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 CH_2Cl_2 to give 2-bromophenol (**11**) (0.64 g, 80%) as a white needles, mp 106–109 °C (CH_2Cl_2); R_f [CH_2Cl_2] 0.1; IR ($CHCl_3$) 3600–3000 (broad OH), 1577 and 1560 cm^{-1} (C=C). ^1H NMR (250 MHz, DMSO-d_6) δ 9.30 (1 H, s, OH), 9.0 (1 H, s, OH), 6.90 (1 H, d, J = 1.5, CH; Ar), 6.85 (1 H, d, J = 6.0 and 1.5 Hz, CH; Ar). ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 152.6, 146.9, 119.2, 117.2, 115.7 and 109.4. Found: m/z, 187.9402. Calcd for $C_6H_5BrO_2$ M, 187.9473. MS m/z 189.9 (100, M^{81}) and 187.9 (100, M^{79}); and dibromophenol (**12**) (0.13 g, 11%) as white needles, mp 159–162 °C; R_f [CH_2Cl_2] 0.2; IR ($CHCl_3$) 3600–3000 (broad OH), 1580 and 1560 cm^{-1} (C=C); ^1H NMR (250 MHz, DMSO-d_6) δ 9.75 (2 H, s, 2 × OH) and 7.05 (2 H, s, 2 × CH; Ar); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 147.6, 119.7 and 108.6. Found m/z, 265.8579. Calcd for $C_6H_5Br_2O_2$ M, 265.8578. MS m/z 267.9 (100, M^{81}) and 265.9 (100, M^{79}).

General Procedure with Diethyl Bromomalonate (2): Hydroquinone (**10**) (0.35 g, 3.14 mmol) was added to a stirred solution of diethyl bromomalonate (0.5 g, 0.3 ml, 1.6 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 CH_2Cl_2 to the 2-bromophenol (**11**) (0.40 g, 68%) and 2,5-dibromophenol (**12**) (0.14 g, 17%), identical to that obtained previously.

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