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N-Methylpyrrolidin-2-one hydrotribromide (MPHT) a mild reagent for selective bromination of carbonyl compounds: synthesis of substituted 2-bromo-1-naphtols

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Abstract—The reaction of the *N*-methylpyrrolidin-2-one hydrotribromide complex (MPHT) with substituted-1-tetralones has been investigated. This safety reagent proved to be successful for selective α,α-dibromination of tetralones. Moreover, under base-free conditions, several 2-bromo-1-naphtols were obtained from tetralones in a 'one pot' sequence in good to excellent yields.

Bromination of carbonyl compounds is an important transformation, as the resulting α-brominated products are versatile intermediates in organic synthesis.[1] Although the α-bromination of ketones is now well documented,[2] the α,α-dibromination reaction has received little attention. The most commonly used reagent for this transformation requires elemental bromine,[3] which have several environmental drawbacks. The handling of liquid bromine, due to its hazardous nature, is troublesome and special equipment and care are needed for the transfer of these materials in large scale. In order to overcome these problems, alternative methods for preparing α,α-dibromoketones have been developed such as $HBr–H_2O_2$,[4] 1,3-dibromo-5,5-dimethylhydantoin,[5] polymer supported brominating reagents,[6] KBr–$KBrO_3$–Dowex[7] or dioxane–dibromide–silica gel under microwave irradiation.[8] While these reactions are suitable methods, in the case of robust substrates, it would be useful to have alternative sources of bromine that offer advantages of safety, selectivity, mild reaction conditions and stability.

As a part of our programme aimed at the development of new and selective reagents for the preparation of α-halogenated carbonyl compounds,[9] we had previously improved the synthesis of a crystalline bromine complex *N*-methylpyrrolidin-2-one hydrotribromide (MPHT, $[NMP]_2HBr_3$) **1** (Fig. 1) and determined its structure by means of single-crystal X-ray diffraction methods.[10] This complex is insensitive to moisture and showed a remarkable stability at room temperature. Even though no decrease in free bromine titre could be detected when exposed to air for several months, nothing is known about its reactivity.

An important aspect of our ongoing research on the synthetic utility of **1** as soft acting brominating reagent in organic synthesis led us to investigate its reactivity with carbonyl compounds. Herein, we report the results of this study and the use of complex MPHT **1** for the selective preparation of α,α-dibrominated tetralones **3** suitable substrates for the construction of substituted 2-bromo-1-naphtols **4**.

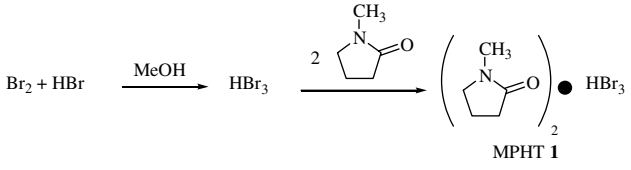

Figure 1. Synthesis of MPHT **1**.

Keywords: Halogenation; MPHT; 1-Tetralones; 2-Bromo-1-naphtols.
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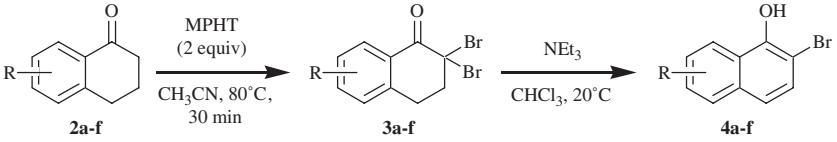
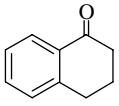
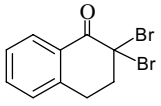
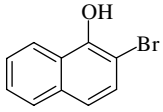
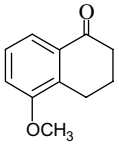
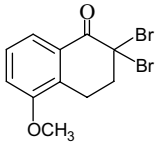
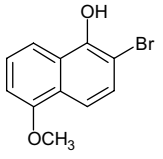
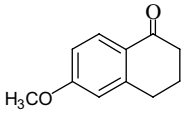
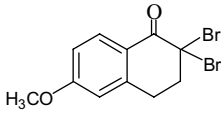
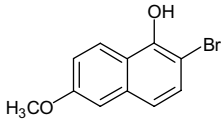
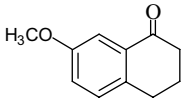
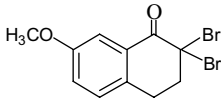
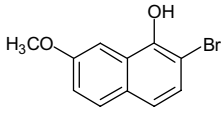
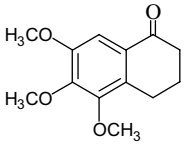
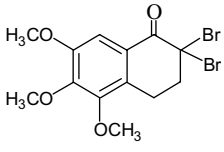
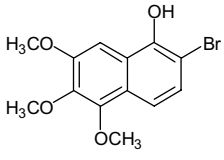
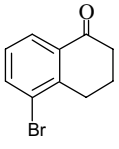
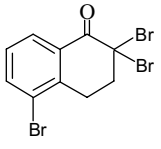
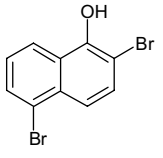
The synthesis of MPHT complex **1** was achieved readily in 87% yield[11] under a slightly modified Daniels' procedure[12] using a HBr solution (30% in acetic acid) instead of gaseous HBr.

The reactivity of the MPHT complex **1** was evaluated with several 1-tetralones in order to prepare the α,α-dibrominated compounds. First, we investigated this reaction in CH_3CN, solvent that we have previously found to be efficient in α-iodination of ketones.[9] Thus, reaction of tetralone **2a** with the MPHT complex **1** (2 equiv) at room temperature gave the desired α,α-dibrominated tetralone **3a** in very low yield (10%). The effect of temperature was then examined and we found that heating the reaction at 50 °C provided the expected tetralone **3a** in 79% yield after stirring for 12 h. However, when the reaction was run at 80 °C, we were pleased to observe complete conversion of the starting material **2a** within 30 min and **3a** was isolated in 90% yield (Table 1, entry 1). Of the several solvents tested, MeCN gave the highest yield of α,α-dibrominated tetralone **3a**. The other solvents including CH_2Cl_2, toluene, dioxane and DMF gave unsatisfactory yields of **3a**.

Table 1. Bromination of tetralones **2** with MPHT complex **1**: synthesis of 2-bromo-1-naphtols **4**



Entry	Tetralones **2**	α,α-Dibrominated tetralones **3**	Yield[a,b] (%) **2** → **3**	2-Bromo-1-naphtols **4**	Yield[a,b] (%) **3** → **4**
1	 **2a**	 **3a**	90	 **4a**	91
2	 **2b**	 **3b**	76	 **4b**	92
3	 **2c**	 **3c**	64	 **4c**	88
4	 **2d**	 **3d**	85	 **4d**	94
5	 **2e**	 **3e**	80	 **4e**	90
6	 **2f**	 **3f**	39[c]	 **4f**	56

[a] Isolated yield. All new compounds exhibited satisfactory spectral properties[14] and microanalyses (C ±0.40, H ±0.31).
[b] α,α-Dibromotetralone and bromophenol derivatives synthesized are new compounds except those of entries 1 and 2.
[c] 20% of bromonaphtol **4f** were also obtained.

The results of the dibromination reaction of various substituted tetralones **2** with the MPHT complex **1** in CH_3CN are summarized in Table 1. Under these optimized conditions,[13] good yields of dibrominated tetralones **3** were obtained except when the reaction is carried out from tetralone **2f**. In this case, 39% of tetralone **3f** were isolated together with 20% of 2-bromo-1-naphtol **4f**.

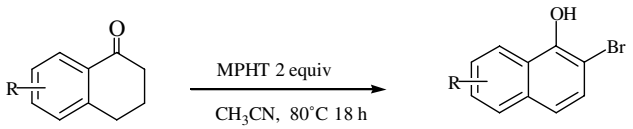
Since 2-bromo-1-naphtol derivatives are interesting reagents for metal catalyzed coupling reaction[15] and particularly for the synthesis of heterocyclic products,[16] it would be useful to transform the dibrominated tetralones **3** into their corresponding 2-bromo-1-naphtols **4**. To this end, tetralones **3** were reacted for 30 min at room temperature with an excess of Et_3N (10 equiv) in $CHCl_3$, and the expected 2-bromo-1-naphtols **4** were obtained in good to high yields (Table 1).

In order to simplify this transformation from the point of view of the synthetic chemist, our aim was also to obtain α-bromonaphtol derivatives **4** in a one-pot procedure without isolation of the intermediate α,α-dibrominated products **3**. Thus, we investigated the reaction of tetralone **2a** with MPHT complex (2 equiv) in acetonitrile in the presence of an excess of Et_3N (3 mL/1 mmol of tetralone **2a**) at 80 °C for 18 h. Under these conditions, the dibromination–dehydrobromination process does not occurred and starting material was recovered unchanged, probably owing to an undesirable reaction between NEt_3 and electrophilic MPHT. However, by adding Et_3N in the media after completion of the dibromination step (disappearance of tetralone **2a** after 30 min as judged by TLC) we were pleased to observe that, the expected 2-bromo-1-naphtol **4a** was isolated in 76% isolated yield after stirring for 30 min at room temperature.

To examine if the presence of Et_3N is necessary for the dehydrobromination step, we performed the reaction of tetralone **2a** with the MPHT complex **1** (2 equiv) in boiling CH_3CN for a prolongated reaction time (18 h). In these base-free conditions, we observed a fully dehydrobromination of the intermediate α,α-dibrominated tetralone **3a** to give the expected 2-bromo-1-naphtol **4a** in a one-step sequence in 78% yield. These base-free conditions have been applied successfully to the preparation α-bromonaphtol derivatives **4** from tetralones **2** (Scheme 1).

Moreover, we were pleased to observe that tetralone **2f** has been transformed successfully (95% vs 60%) into its corresponding bromonaphtol **4f** under microwave irradiation.

For a complete understanding of this dehydrobromination reaction, we have stirred the α,α-dibrominated tetralone **3a** in CH_3CN for 18 h at 80 °C. The result of this experiment showed a partial thermal dehydrobromination of **3a** producing **4a** in only 25% yield. However, if the experiment is carried out in CH_3CN in the presence of *N*-methyl-2-pyrrolidin-2-one (4 equiv), the expected 2-bromo-1-naphtol **4a** was obtained in an excellent isolated yield (90%). This result clearly indicated that in the case of dibromination–dehydrobromination process, the MPHT complex acted first, as a safe and selective brominating agent and subsequently, the NMP liberated in the media promoted the thermal dehydrobromination step, when reactions were performed for a prolongated reaction time (80 °C). Under these thermal and base-free conditions (2 equiv of **1**), it should be noted that no products resulting from bromination of activated aromatic ring could be detected.



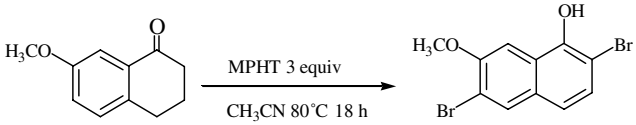
2a R = H — **4a** 78%[a]
2b R = 5-OMe — **4b** 70%[a]
2d R = 7-OMe — **4d** 87 %[a]
2f R = 5-Br — **4f** 60 %[a]
2f R = 5-Br — **4f** 95 %[b]

Scheme 1. One pot synthesis of 2-bromo-1-naphtols under base-free conditions. [a]Isolated yield (Ref. 17). [b]Isolated yield after irradiation in microwave for 1 h at 140 °C.

Interestingly, we showed if an excess of MPHT was used, selective electrophilic aromatic bromination on the aryl ring occurred. Thus, reaction of 7-methoxytetralone **2d** with the MPHT complex **1** (3 equiv) in acetonitrile at 80 °C for a night, provided selectively 2,6-dibromo-7-methoxy-1-naphtol **4g** in 83% yield. The MPHT complex acted this time at first, as a α,α-dibrominating agent, then assisted the dehydrobromination step and finally permitted the bromination of the intermediary naphtol derivative **4d** (Fig. 2).

Finally, it is noteworthy that the use of a stoichiometric amount of the MPHT complex **1**, exclusively monobromination of tetralones **2** occurred. Thus, in CH_2Cl_2, α-bromination of **2a** with the MPHT complex **1** (1 equiv) provided the corresponding α-bromoketone at room temperature in 80% yield, comparable with those obtained to bromination with elemental bromine (e.g., 72→99%).[18]

In summary, we have examined the synthetic potential of the MPHT complex **1** in the bromination reactions of various tetralones. This complex, which could be prepared in large amounts (multi-moles scale) and could be stored several months at room temperature, permitted



2d — **4g** 83%

Figure 2. A one-pot synthesis of **4g** from **2d**.

the selective mono- and/or dibromination of various substituted tetralones. Moreover, under base-free conditions, in boiling CH_3CN, the *N*-methylpyrrolidin-2-one liberated in the media assisted and completed the thermal dehydrobromination of intermediary dibrominated tetralones to lead in a one-pot sequence to the expected 2-bromo-1-naphtol derivatives.

The ease of MPHT use in selective bromination(s) and subsequent dehydrobromination(s) together with its crystalline state, make it very attractive in organic chemistry. Other selective bromination reactions with aliphatic ketones and electrophilic aromatic bromination are now in progress in our laboratory.

Acknowledgements

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11. *Preparation of MPHT*: To a 2 L round bottomed flask, cooled in an ice bath and equipped with a dropping funnel and a condenser, were added, successively, 200 mL of MeOH and 250 mL (one drop per second) of HBr (30% in acetic acid) while maintaining the internal temperature between 10 and 15 °C. Elemental bromine, 60 mL, was then added by the dropping funnel (two drops per second) and the solution was stirred for 10 min. Then, *N*-methylpyrrolidin-2-one, 250 mL, was added by the dropping funnel (two drops per second). The mixture was stirred for 1 h at 10 °C and orange crystals were collected, washed with Et_2O (4×50 mL) and dried under vacuum to give 440 g of MPHT **1** as orange crystals (yield = 87%). Mp 122–124 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.25 (m, 4H), 2.90 (t, 4H, $J = 8$ Hz), 3.00 (s, 6H), 3.75 (t, 4H, $J = 7.2$ Hz), 14.6 (br s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 18.3, 31.4, 33.3, 52.8, 178.3. IR cm^{-1}: 3339, 1640, 1420, 1228.
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13. *General procedure for the α,α-dibromination of tetralones with MPHT* **1**: In a round bottomed flask, a solution of tetralone **2** (1 mmol) in CH_3CN (10 mL) was stirred in an oil bath at 80 °C and then MPHT (2 mmol) was added dropwise (each drop was added only after the previous drop had completely decolourized). The mixture was then stirred for 30 additional minutes at this temperature. The reaction mixture was cooled to 20 °C and treated with a saturated $Na_2S_2O_3$ solution. The organic layer was washed with HCl 10% (3×10 mL) and dried over $MgSO_4$. Removal of the solvent yielded a crude product, which was purified by silica gel flash chromatography to afford **3** (see Table 1 for yields).
14. All new compounds were characterized by ^{1}H, ^{13}C NMR and IR.
Compound **3c**: Mp 85 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.90 (s, 4H), 3.70 (s, 3H), 6.65 (d, 1H, $J = 2.1$ Hz), 6.85 (dd, 1H, $J = 8.3$, 2.1 Hz), 8.05 (d, 1H, $J = 8.3$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 29.5, 46.0, 55.6, 67.8, 112.3, 114.5, 120.2, 132.4, 144.7, 164.4, 183.0. IR cm^{-1}: 1684, 1596, 1494.
Compound **3d**: Mp 88–90 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.90 (m, 4H), 4.10 (s, 3H), 7.40 (m, 2H), 7.85 (d, 1H, $J = 1$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 28.4, 46.0, 55.5, 67.3, 111.5, 123.0, 128.0, 129.8, 134.6, 158.8, 184.1. IR cm^{-1}: 1498, 1283.
Compound **3e**: Mp 83 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.95 (m, 4H), 3.80 (s, 3H), 3.82 (s, 3H), 3.90, (s, 3H), 7.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 23.1, 45.6, 56.0, 60.6, 60.8, 67.2, 107.4, 122.2, 129.9, 145.6, 149.8, 152.8, 185.1. IR cm^{-1}: 1691, 1589, 1485.
Compound **3f**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.30 (m, 4H), 7.50 (t, 1H, $J = 8$ Hz), 8.00 (dd, 1H, $J = 8$, 1 Hz), 8.35 (dd, 1H, $J = 8$, 1 Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 30.0, 44.3, 65.6, 124.2, 128.5, 129.0, 129.1, 138.0, 140.9, 183.1. IR cm^{-1}: 1699, 1586, 1559.
Compound **4c**: Mp 87 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.85 (s, 3H), 5.80 (br s, 1H), 6.95 (d, 1H, $J = 2$ Hz), 7.05 (m, 2H), 7.25 (d, 1H, $J = 8.5$ Hz), 8.05 (d, 1H, $J = 8.5$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 55.2, 101.6, 105.7, 118.4, 119.6, 120.1, 123.9, 128.9, 135.2, 148.2, 158.3. IR cm^{-1}: 3530, 1622, 1595.
Compound **4d**: Mp 60 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.95 (s, 3H), 5.35 (br s, 1H), 7.10–7.25 (m, 3H), 7.45 (d, 1H, $J = 2$ Hz), 7.70 (d, 1H, $J = 9$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 55.3, 100.5, 104.7, 119.5, 121.0, 125.5, 125.8, 128.8, 129.1, 147.0, 157.9. IR cm^{-1}: 3497, 1626, 1591.
Compound **4e**: Mp 75 °C. ^{1}H NMR($CDCl_3$, 200 MHz): δ 3.90 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 5.00–5.50 (br s, 1H), 7.15 (s, 1H), 7.20 (d, 1H, $J = 9$ Hz), 7.40 (d, 1H, $J = 9$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 55.8, 60.1, 61.4, 97.2, 105.2, 115.2, 124.5, 126.0, 129.1, 152.1, 152.6, 152.9, 162.2. IR cm^{-1}: 3497, 1629, 1590.
Compound **4f**: Mp 70–72 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.05 (s, 1H), 7.30 (dd, 1H, $J = 8.5$, 8.0 Hz),

7.55 (d, 1H, $J = 9$ Hz), 7.70 (d, 1H, $J = 9$ Hz), 7.80 (dd, 1H, $J = 8$, 1 Hz), 8.20 (d, 1H, $J = 8.5$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 105.2, 120.5, 122.2, 122.6, 125.6, 126.3, 129.4, 130.8, 132.4, 148.2. IR cm^{-1}: 3406, 1616, 1583.

Compound **4g**: Mp 142 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.90 (s, 3H), 5.80 (br s, 1H), 7.05–7.20 (dd, 1H, $J = 9$, 2.5 Hz), 7.45 (d, 1H, $J = 2.5$ Hz), 7.55 (s, 1H), 7.85–7.95 (d, 1H, $J = 9$ Hz). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 55.4, 101.0, 103.7, 113.1, 120.4, 126.0, 126.7, 128.4, 128.7, 146.9, 158.3. IR cm^{-1}: 3441, 1585, 1497.

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17. *General procedure for the synthesis of 2-bromo-1-naphtols under base-free conditions*: In a round bottomed flask, a solution of tetralone **2** (1 mmol) and MPHT (2 mmol) in CH_3CN (10 mL) was stirred in an oil bath at 80 °C for 18 h. The reaction mixture was cooled and treated as above (Ref. 13).
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