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

Alain Bekaert, Olivier Provot*, Olimihamina Rasolojaona, Mouâd Alami* and Jean-Daniel Brion

Laboratoire de Chimie Thérapeutique, BioCIS-CNRS (UMR 8076), Université Paris-Sud, Faculté de Pharmacie, rue J.B. Clément 92296 Châtenay-Malabry Cedex, France

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 $\text{HBr-H}_2\text{O}_2$,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 program 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, $[\text{NMP}]_2\text{HBr}_3$) **1** (Figure 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 titer 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**.

The synthesis of MPHT complex **1** was achieved readily in 87% yield¹¹ under a slightly modified Daniels' procedure¹² 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**

* **Keywords** : halogenation; MPHT; 1-tetralones; 2-bromo-1-naphtols. * Corresponding authors. E-mail : olivier.provot@cep.u-psud.fr ; mouad.alami@cep.u-psud.fr

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 CH₂Cl₂, toluene, dioxane and DMF gave unsatisfactory yields of **3a**.

The results of the dibromination reaction of various substituted tetralones **2** with the MPHT complex **1** in CH₃CN 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-naphthol **4f**.

Since 2-bromo-1-naphthol derivatives are interesting reagents for metal catalyzed coupling reaction¹⁵ and particularly for the synthesis of heterocyclic products¹⁶, it would be useful to transform the dibrominated tetralones **3** into their corresponding 2-bromo-1-naphthols **4**. To this end, tetralones **3** were reacted for 30 minutes at room temperature with an excess of Et₃N (10 equiv) in CHCl₃, and the expected 2-bromo-1-naphthols **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 -bromonaphthol 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 Et₃N (3 mL / 1 mmol of tetralone **2a**) at 80°C for 18h. Under these conditions, the dibromination-dehydrobromination process does not occurred and starting material was recovered unchanged, probably owing to an undesirable reaction between NEt₃ and electrophilic MPHT. However, by adding Et₃N 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-naphthol **4a** was isolated in 76% isolated yield after stirring for 30 min at room temperature.

To examine if the presence of Et₃N is necessary for the dehydrobromination step, we performed the reaction of tetralone **2a** with the MPHT complex **1** (2 equiv) in boiling CH₃CN for a prolonged reaction time (18h). 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-naphthol **4a** in a one step sequence in 78% yield. These base free conditions have been applied successfully to the preparation α -bromonaphthol 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 bromonaphthol **4f** under microwave irradiation.

For a complete understanding of this dehydrobromination reaction, we have stirred the α,α -dibrominated tetralone **3a** in CH₃CN for 18 hours 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 CH₃CN in the presence of N-Methyl-2-pyrrolidin-2-one (4 equiv), the expected 2-bromo-1-naphthol **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 prolonged 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.

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-naphthol **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 naphthol derivative **4d** (**Figure 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 CH₂Cl₂, 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 the selective mono and/or dibromination of various substituted tetralones. Moreover, under base-free conditions, in boiling CH₃CN, 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-naphthol 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.

Acknowledgments

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- 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°C and 15°C. Elemental bromine, 60 mL, was then added by the dropping funnel (2 drops per second) and the solution was stirred for 10 minutes. Then, N-Methylpyrrolidin-2-one, 250 mL, was added by the dropping funnel (2 drops per second). The mixture was stirred for 1 hour at 10°C and orange crystals were collected, washed with Et₂O (4 x 50 mL) and dried under vacuum to give 440 g of MPHT **1** as orange crystals (yield = 87 %). mp. 122-124°C. ¹H NMR (CDCl₃, 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 (bs, 1H). ¹³C NMR (CDCl₃, 200 MHz) δ 18.3, 31.4, 33.3, 52.8, 178.3. IR cm⁻¹ : 3339, 1640, 1420, 1228.
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- All new compounds were characterized by ¹H, ¹³C NMR and IR.
3c: mp. 85°C. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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.
3d: mp. 88-90°C. ¹H NMR (CDCl₃, 200 MHz) δ 2.90 (m, 4H), 4.10 (s, 3H), 7.40 (m, 2H), 7.85 (d, 1H, J = 1 Hz). ¹³C NMR (CDCl₃, 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.
3e: mp. 83°C. ¹H NMR (CDCl₃, 200 MHz) δ 2.95 (m, 4H), 3.80 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 7.40 (s, 1H). ¹³C NMR (CDCl₃, 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.
3f: ¹H NMR (CDCl₃, 200 MHz) δ 3.30 (m, 4H), 7.50 (t, 1H, J = 8 Hz), 8.00 (dd, 1H, J = 8 Hz, J = 1 Hz), 8.35 (dd, 1H, J = 8 Hz, J = 1 Hz). ¹³C NMR (CDCl₃, 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.
4c: mp. 87°C. ¹H NMR (CDCl₃, 200 MHz) δ 3.85 (s, 3H), 5.80 (bs, 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). ¹³C NMR (CDCl₃, 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.
4d: mp. 60°C. ¹H NMR (CDCl₃, 200 MHz) δ 3.95 (s, 3H), 5.35 (bs, 1H), 7.10-7.25 (m, 3H), 7.45 (d, 1H, J = 2 Hz), 7.70 (d, 1H, J = 9 Hz). ¹³C NMR (CDCl₃, 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.
4e: mp. 75°C. ¹H NMR (CDCl₃, 200 MHz) δ 3.90 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 5.00-5.50 (bs, 1H), 7.15 (s, 1H), 7.20 (d, 1H, J = 9 Hz), 7.40 (d, 1H, J = 9 Hz). ¹³C NMR (CDCl₃, 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.
4f: mp. 70-72°C. ¹H NMR (CDCl₃, 200 MHz) δ 6.05 (s, 1H), 7.30 (dd, 1H, J = 8.5 Hz, J = 8.0 Hz), 7.55 (d, 1H, J = 9 Hz), 7.70 (d, 1H, J = 9 Hz), 7.80 (dd, 1H, J = 8 Hz, J = 1 Hz), 8.20 (d, 1H, J = 8.5 Hz). ¹³C NMR (CDCl₃, 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.
4g: mp. 142°C. ¹H NMR (CDCl₃, 200 MHz) δ 3.90 (s, 3H), 5.80 (bs, 1H), 7.05-7.20 (dd, 1H, J = 9 Hz, J = 2.5 Hz), 7.45 (d, 1H, J = 2.5 Hz), 7.55 (s, 1H), 7.85-7.95 (d, 1H, J = 9 Hz). ¹³C NMR (CDCl₃, 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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