RAPID AND TOTAL BROMINATION OF AROMATIC COMPOUNDS USING TsNBr₂ WITHOUT ANY CATALYST

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GRAPHICAL ABSTRACT

Abstract N,N-Dibromo-p-toluenesulfonamide (TsNBr₂) has been found to be a new reagent for bromination of aromatic compounds. The reaction is extremely fast and goes into completion instantaneously at ambient temperature to produce exclusively the corresponding polybrominated product. This procedure is applicable to various phenols, anisole, and anilines to give corresponding polybrominated compound as a single product in excellent yield.

Keywords Aniline; anisole; bromination; phenol; tribromophenol; TsNBr₂

INTRODUCTION

In recent years, bromoaromatics are finding extensive applications in organic synthesis as versatile precursors for construction of carbon–carbon bond via transition-metal-mediated coupling reactions. They are also used as important synthetic intermediates for the manufacture of pharmaceuticals, agrochemicals, and specialty chemicals. Polybrominated phenols such as tribromophenol (TBP) is used as an intermediate in the preparation of flame retardants such as brominated epoxy resins. Moreover, many bromo compounds exhibit antitumor, antibacterial, antifungal, antineoplastic, antiviral, and antioxidizing properties.
tribromophenol (TBPNa) is used as fungicide and wood preservative. In nature, TBP has been found in ocean sediments as a metabolite of marine fauna. Although bromination with elemental bromine is a well-known reaction due to the hazardous effect of bromine, several brominating agents were utilized, including N-bromosuccinimide (NBS), tetraalkylammonium tribromides, DBUH·Br₃, cetyltrimethylammonium tribromide, pyridinium tribromide, LiBr/ceric ammonium nitrate, dioxanedibromide, pyridinium hydrobromide perbromide, DBU hydrobromide perbromide, tetramethylcyclohexadienone, tetraalkylammonium bromides, hexamethylenetetramine tribromide, 1-butyl-3-methylpyridinium tribromide, ZrBr₄/diazene mixture, metal bromides/oxidants, AlBr₃ in the presence of NH₄VO₃ and bromochromates. However, in many cases, the products contain a mixture of ortho and para products or a mixture of mono- and poly-brominated compounds. Moreover, it is difficult to achieve exclusive formation of polybrominated products. Even use of an excess reagent results in a mixture of mono- and polybrominated compounds. Very recently, Liu et al. reported a method for mono- and dibromination of arenes using a combination of I₂O₅ and KBr.

A most popular brominating agent, NBS, brominates in the aromatic nucleus when no radical initiator is present. Generally, acidic catalysts such as H₂SO₄, TsOH, silica gel, and HZSM-5 are used with NBS for the bromination of activated aromatic substrate. Other activators such as microwave or ultrasound, ultraviolet (UV) radiation, or ionic liquids have also been reported for NBS-assisted bromination of activated aromatics. Bromination with NBS is favored by polar solvents such as propylene carbonate, DMF, and CH₃CN. However, in the case of bromination of phenol in CH₃CN, NBS gives a mixture of substrate, monobrominated phenol, and corresponding dibrominated phenol with longer time period.

RESULTS AND DISCUSSION

We have recently reported few efficient protocols for various transformations using N,N-dibromo-p-toluenesulfonamide (TsNBr₂). As a continuation of our work on TsNBr₂, we report herein a rapid procedure for bromination of phenols and anilines (Scheme 1).

Initial experiments to study the feasibility of the reagent for bromination reaction were carried out by taking phenol as a model substrate. The reaction was carried out as follows:

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\begin{align*}
R \text{ (OH, OMe or NH₂)} & \xrightarrow{\text{TsNBr}_2} \text{PhBr} \xrightarrow{\text{CH₃CN, rt}} \text{PhBr}_2 \\
& \text{Instantaneous}
\end{align*}
\]

Scheme 1. Bromination of aromatics using TsNBr₂.
out by adding TsNBr2 to the organic solution of phenol (1 mmol) in acetonitrile (2 mL) at room temperature. The reaction was found to complete instantaneously to produce the corresponding bromo products. After 10 min of exposure, the reaction mixture was treated with sodium thiosulfate and subjected to the usual workup procedure. When 0.5 mmol of TsNBr2 was added, the reaction produced a mixture of 4-bromophenol (40%) and 2,4,6-tribromophenol (10%) along with unreacted phenol (Table 1). When 1 mmol of TsNBr2 was used, the reaction produced a mixture of 4-bromo and tribromophenol. No unreacted phenol was found. Further increment of the amount of TsNBr2 to 1.5 mmol led to the formation of 2,4,6-tribromo phenol exclusively with 87% isolated yield (Table 1). The reaction was also carried out at low temperature (0°C). In both cases 2,4,6-tribromo phenol was obtained with similar yield in an instantaneous reaction.

After obtaining an acceptable reaction condition from the initial experiments, we extended the procedure to varieties of substituted phenols (Table 2). However, total bromination of substituted phenols could be achieved using 1 mmol of TsNBr2 per mole of the substrate. It can be seen from Table 2 that different kinds of phenolic substrates undergo total bromination reactions instantaneously at room temperature. 2-Naphthol produced the corresponding 1,3-dibromo product in 76% yield. However, in the case of 2-aminophenol, the yield of corresponding brominated product is relatively poor (Table 2, entry 9). When the reaction was extended to anisol, 77% of corresponding tribromoanisole was obtained after 2 h of reaction.

The success of the method with phenols encouraged us to extend the reaction to anilines (Table 3). Initial reaction with aniline was encouraging. The reaction was completed instantaneously with 90% yield of the desired tribromo aniline in the presence of 1.5 equivalents of TsNBr2. In this case, however, the addition of TsNBr2 should be done at 0°C for better yield. It is necessary to add the brominating agent at low temperature to subside the exothermicity. Then the process was extended to variety of anilines and the results are summarized in Table 3.

It can be seen from Table 3 that different kind of anilines could be converted to corresponding polybrominated product in excellent yield.

**EXPERIMENTAL**

TsNBr2 (1 mmol) was added at 0°C to a solution of the aromatic compound (1 mmol) in acetonitrile (2 mL). After 10 min of stirring at room temperature, sodium...
Table 2. Bromination of phenols using TsNBr₂

| Entry | Substrate (a) | TsNBr₂ (equiv) | Product (b) | Yield\(^a\) (%) |
|-------|---------------|----------------|-------------|-----------------|
| 1     |               | 1.5            |             | 87              |
| 2     |               | 1              |             | 85              |
| 3     |               | 1              |             | 78              |
| 4     |               | 1.5            |             | 84              |
| 5     |               | 1              |             | 82              |
| 6     |               | 1              |             | 76              |
| 7     |               | 1              |             | 87              |
| 8     |               | 1              |             | 95              |
| 9     |               | 1              |             | 69              |
| 10\(^b\) |               | 1.5          |             | 77              |

\(^a\) Isolated yield after chromatographic purification.

\(^b\) Reaction time is 2 h.
thiosulfate (200 mg approx.) was added and stirred for 10 min. The reaction was taken up in ethyl acetate, dried over NaSO₄, and concentrated. The crude product was purified by flash chromatography or silica gel (230–400 mesh) with a mixture of petroleum ether and ethyl acetate as eluent.

2,6-Dibromo-4-chloro-5-methylphenol

IR (KBr, cm⁻¹): 3430, 1595, 1442, 1380, 1308, 1219, 1171, 1028, 969, 854, 771, 707, 646; ¹H NMR (CDCl₃, 400 MHz) δ: 7.32 (s, 1H), 5.73 (s, 1H), 2.3 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ: 148.4, 136.2, 131.2, 126.1, 113.4, 106.4, 21.0; GCMS (m/z %): 302 (M⁺ +2, 75), 300 (M⁺, 98), 265 (58), 221 (63), 139 (21), 111 (100), 75 (83), 38 (24). Elemental analysis: C, 27.56%; H, 1.89%; O, 6.29%.

CONCLUSION

In conclusion, we have developed an efficient method for bromination of phenol and anilines. The reaction completes instantaneously to produce corresponding polybrominated product in excellent yield.
FUNDING

Financial support from the Department of Science and Technology (Grant Nos. SR/S1/RFPC-07/2006 and SR/S1/OC-43/2011) is gratefully acknowledged. I. S. and P. C. thank the Council for Scientific and Industrial Research for a senior research fellowship.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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