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1,3-Dibromo-5,5-dimethylhydantoin, a useful reagent for *ortho*-monobromination of phenols and polyphenols

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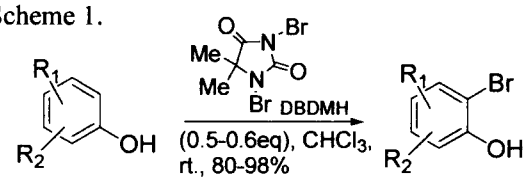
Ortho-monobromination of phenols and polyphenols by 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) is described. A simple addition of commercially available DBDMH to phenols and polyphenols in chloroform at room temperature resulted in a good to excellent yield of corresponding *ortho*-monobromo derivatives.

Keywords: *ortho-monobromination, phenol, polyphenol, DBDMH.*

Introduction

Aromatic bromination with bromine is one of the most widely used and extensively studied electrophilic aromatic substitution reactions.[1] Owing to low reactivity, highly toxicity, and handling inconvenience due to the liquid behavior of bromine, some other alternative brominating agents such as NBS,[1] tetrabromocyclohexadienone[2] have been developed. For the bromination of phenols, bromine in halogenated hydrocarbons[3] or AcOH[4] is often the reagent of choice. However, for many substances, mixtures of mono- and poly-brominated compounds are obtained.[5] For selective monobromination of less hazardous reagents like dioxane dibromide,[6] phenols and other active aromatics, milder and DBU hydrobromide perbromide,[7] tetrabromocyclohexadienone,[2] tetraalkylammoniumtribromides[8] have developed. These reagents yield selectively *para*-brominated phenols unless the *para*-position is substituted. Several methods for *ortho*-bromination of phenols have been appeared,[9] but some of them required low temperature or other uses very unstable brominating agents and most of them suffers from the formation of dibromo derivatives.[10]

Scheme 1.



R_1, R_2= Me, OMe, OBn, CO_2Me, OH, etc.

There are several reports of bromination of aromatics using N-bromosuccinamide (NBS)[10] or

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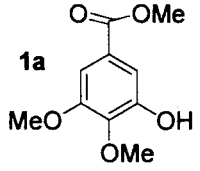
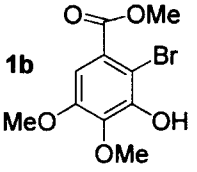
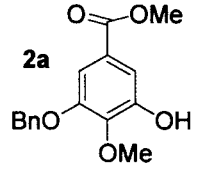
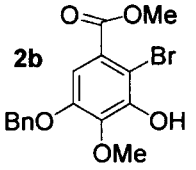
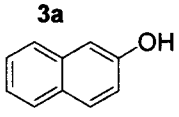
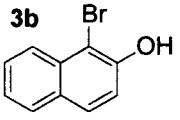
by DBDMH in the presence of $HBF_4 \cdot Et_2O$[11] or other strong acids such as methyltrifluoroacetic acid.[12] Monobromination of carboxylic acid by DBDMH in aqueous NaOH has been reported,[13] but it is not applicable for other aromatics except carboxylic acids. Herein, we report a very simple and convenient method for the *ortho*-monobromination of phenols and polyphenols using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (Scheme 1).

Results and discussion

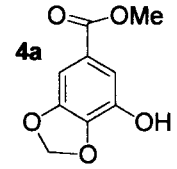
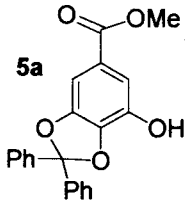
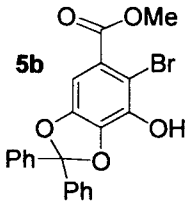
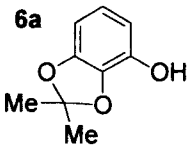
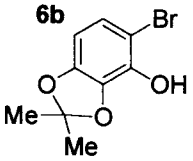
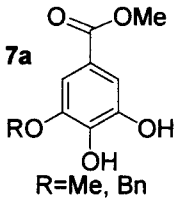
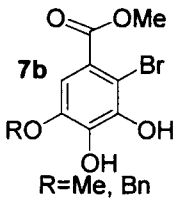
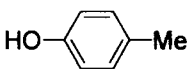
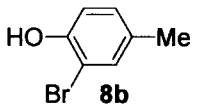
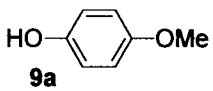
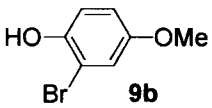
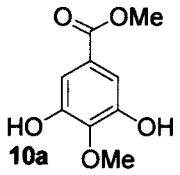
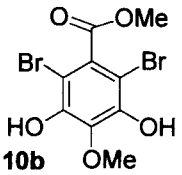
All the reactions were carried out in ordinary chloroform at room temperature. The yield in DMF was worst and the starting material was remained unreacted after long period of time. Results of the bromination of variety of phenols and polyphenols by DBDMH are summarized in Table 1. Most of the phenols and polyphenols gave the single bromo- derivative, whereas some of them yielded small amount of dibromo derivatives (entry 8 and 9). Treatment of **1a** with DBDMH yielded the corresponding 2-Br derivative in 92.5% yield and high purity compared to the reported Br_2/*iso*-Pr_2NH/toluene method (68% isolated yield, lit.[14] 74%). But unfortunately, similar treatment of **2a** with DBDMH yielded the mixture of mono-, dibromo derivative and the unreacted starting material, which was difficult to separate by column chromatography. Then, the Br_2/*iso*-Pr_2NH method was examined for **2a** and resulted in a mixture of mono- and dibromo components in 1.5:1 ratio with only 61% yield. In the presence of different organic acids[12] such as methylsulfonic acid, DBDMH also yielded a mixture of bromides and some other unknown compound. Changing the solvent to DMF, treatment with excess DBDMH for short reaction time was also failed. Then, suddenly it was found that if DBDMH is added at once instead of in portion, the reaction goes smoothly and yielded pure monobromo derivative in surprisingly high yield (98%). Whereas, for all other reactions the DBDMH was added in several portions and it was not so much sensitive to the mode of addition (at once or in portion).

Table 1. Bromination of phenols and polyphenols by DBDMH.

Entry	Phenol/ Polyphenol	Condition	Product	Isolated yield
1	**1a** 	DBDMH (0.52 eq), 5 h, rt.	**1b** 	Single product, 92.5%; lit.[15] 74%
2	**2a** 	DBDMH (0.50 eq),, 16h, rt.	**2b** 	Single product, 98%
3	**3a** 	DBDMH (0.53 eq), 15min, rt.	**3b** 	Single product, 91%

(Continued)

Table 1 (Continued)

Entry	Phenol/ Polyphenol	Condition	Product	Isolated yield
4	 **4a**	DBDMH (0.51 eq), 10 h, rt.	 **4b**	Single product, 95%
5	 **5a**	DBDMH (0.51 eq), 2 h, rt.	 **5b**	Single product, 97%
6	 **6a**	DBDMH (0.51 eq), 1.5 h, rt	 **6b**	Single product, 77%
7	 **7a** R=Me, Bn	DBDMH (0.51 eq), 24 h, rt.	 **7b** R=Me, Bn	Single product R= Me, 98% R= Bn, 95%
8	 **8a**	DBDMH (0.52 eq), 30 min, rt.	 **8b**	Mono-Br, 85% di-Br (15%)
9	 **9a**	DBDMH (0.52 eq), 12 h, rt.	 **9b**	Mono-Br , 75% di-Br, trace
10	 **10a**	DBDMH (1.20 eq), 2 h, rt.	 **10b**	Di-bromo, 98%

Phenols that have two identical positions for bromination (**8a**, **9a** and **10a**), getting the pure monobromo derivative is somewhat difficult. For example, a mixture of mono- and dibromo ester of **10a** was obtained (85:15) upon treatment of **10a** with 0.58 mole equivalent of DBDMH. Thus the suitability of the reagent for the dibromination was also checked. For instance, treatment of **10a** with 1.20 equiv. of DBDMH yielded the corresponding dibromo ester **10b** in excellent yield (entry 10). So, DBDMD is also an excellent reagent for the preparation of dibromo derivative of compounds like **10a**.

In conclusion, we can say that DBDMH is an excellent reagent for the monobromination of phenols and polyphenols at the *ortho*-position to the hydroxy group because of its stable solid state, commercial availability, simplicity of the reaction, clean reaction product, easy workup, and of course the high yield and purity of product.

Experimental

General: 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) was purchased from TCI, Japan and was used as it was. All the reactions were carried out in the ordinary chloroform and inert atmosphere was not maintained. Reaction was monitored by GC-MS and flash chromatography was performed on silica gel (Merck, 60N, spherical, neutral, 40-50 mash). IR was recorded on a Thermo Nicolet Avatar 360T2 instrument using either ATR. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded by JEOL AL 300 instrument. GC-MS was studied in a SHIMADZU GCMS-QP5000 instrument.

The starting materials phenols **1-3a, 5a,7a** and **10a** were prepared from gallic acid.[15] Compound **6a** was also prepared form pyrogallol by treating it with acetone and montmorrilonite K10 in CH_3CN at room temperature.[16]

General procedure for the bromination by DBDMH:

Solid DBDMH (0.50-0.52 mole equiv.) was added in part into the solution of starting material (Ar-OH) in $CHCl_3$ (5-7 ml/ mmol) at room temperature. Upon addition of the DBDMH, the solution became red or deep brown colored, the next portion of DBDMH was added after the disappearance of color and so on. The progress of the reaction was monitored by GC-MS, and sometimes can easily be understood by observing the persistence of the color of the reaction mixture (in case of slight excess DBDMH was used). After completion of the reaction, removal of the solvent followed by the separation of the solid byproduct (derived from DBDMH) by simple filtration provided the almost pure bromide. For the compounds with low solubility, 10% aq. sodium hydrosulfite ($Na_2S_2O_4$) solution was added into the reaction mixture, stirred for 5 min. Organic layer was separated, dried over $MeSO_4$ and concentrated in evaporator yielded the almost pure product. Passing through a small chromatographic column, it gave the pure products.

References

1. Larock, R. C. *Comprehensive Organic Transformation*; Wiley-VCH: New York, 1999, 2nd ed., 619; Smith, M. B; March, J. *March's Advanced Organic Chemistry*; Wiley: New York, 2001, 5th ed., 704.
2. Calo, V.; Ciminale, F.; Lopez, L.; Todesco, P. E. *J. Chem. Soc. C.* **1971**, 3652; Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7150.
3. Torii, S.; Tanaka, H.; Siroi, T.; Akada, M. *J. Org. Chem.* **1979**, *44*, 3305; Weller, D.; Stirchak, F. P.; Yokoyama, A. *J. Org. Chem.* **1984**, *49*, 2061; Kelly, S. M.; Schadt, H. *Helv. Chim. Acta* **1985**, *68*, 813.
4. Coburn, C. E.; Anderson, D. K.; Swenton, J. S. *J. Org. Chem.* **1983**, *48*, 1455.
5. Berg, S. S.; Newbery, G. *J. Chem. Soc.* **1949**, 642; Zhan, S. L.; Zhang, C. Z. *Chinese*

Chem. Lett. **1992**, *3*, 29; Chang, J.; Chen, R.; Guo, R.; Dong, C.; Zhao, K. *Helv. Chim. Acta.* **2003**, *86*, 2239.

6. Yanovskaya, L.; Terentyev, A. P.; Belenky, L. I. *J. Gen. Chem.* **1952**, *22*, 1635.
7. Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740.
8. Bisarya, S. C.; Rao, R. *Synth. Commun.* **1993**, *23*, 779.
9. Calò, V.; Lopez, L.; Pesce, G.; Ciminale, F.; Todesco, P. E. *J. Chem. Soc. Perkin Trans. 2,* **1974**, 1189; Calò, V.; Lopez, L.; Pesce, G.; Todesco, E. *J. Chem. Soc. Perkin Trans. 2,* **1974**, 1192.
10. Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1579.
11. Oberhauser, T. *J. Org. Chem.* **1997**, 4504.
12. Eguchi, H.; Kawaguchi, H.; Yoshinaga, S.; Nishida, A.; Nishiguchi, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* **1994**, 1918.
13. Aurrbach, J; Weissman, S. A.; Blacklock, J. T.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett.* **1993**, *34*, 931.
14. Peter, W.; Weiner, W. S. *J. Org. Chem.* **1999**, *64*, 5321.
15. Alam, A.; Takaguchi, Y.; Ito, H.; Yushida, T.; Tsuboi, S. *Tetrahedron* **2005**, in press.
16. Cole, E. R.; Crank, G.; Minh, H. T. H. *Aust. J. Chem.* **1980**, *33*, 675.