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Mild and regioselective iodination of aromatic compounds with *N*,*N*′-diiodo-*N*,*N*′-1,2-ethanediylbis(*p*-toluenesulphonamide)

Ramin Ghorbani-Vaghei*

Department of Chemistry, Faculty of Science, Bu-Ali Sina University, Hamadan, Iran

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Abstract—*N*,*N*′-Diiodo-*N*,*N*′-1,2-ethanediylbis(*p*-tolouenesulphonamide) [NIBTS] and catalytic trifluoroacetic acid can be used for the regioselective iodination of aromatic compounds in acetonitrile under mild conditions in excellent yields.

Aromatic iodides have long been used in organic synthesis as versatile intermediates that can be transformed to a variety of functional groups.[1] They can be easily functionalized through metal catalyzed cross-coupling reactions.[2] These derivatives have been used in the synthesis of many interesting natural products[3] and also bioactive materials.[4] The moderate reactivity of iodine with aromatic substrates requires the addition of activating agents for its utilization and recently direct iodination methods have been developed by using the following iodonium donating reagents: iodine-tetrabutylammonium peroxydisulfate,[5] BuLi-F_3CCH_2I,[6] iodine-nitrogen dioxide,[7] iodine-F-TEDA-BF_4,[8] NIS,[9] iodine-diiodine pentoxide,[10] bis(sym-collidine)iodine(I) hexafluorophosphate,[11] iodine monochloride,[12] bis(pyridineiodonium(I)tetrafluoroborate - CF_3SO_3H,[13] NIS-CF_3SO_3H,[14] iodine-silver sulfate,[15] iodine-mercury salts,[16] NaOCl-NaI[17] and NIS-CF_3CO_2H.[18] However, most of these methods require hazardous or toxic reagents or long reaction times.[9]

Herein, a convenient method for iodination of aromatic compounds using a new reagent [NIBTS] **1** (Scheme 1) that is prepared from *N*,*N*′-1,2-ethanediylbis(*p*-toluenesulphonamide)[19] and catalytic trifluoroacetic acid is reported.

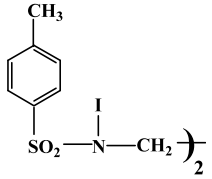
The advantages of NIBTS are as follows:

1. The preparation of NIBTS is easy.
2. NIBTS is stable for six months under atmospheric conditions.
3. After the reaction of NIBTS with a substrate, the sulphonamide is recovered and can be reused many times without decreasing the yield.

The reaction of aromatic compounds with NIBTS in refluxing acetonitrile afforded iodo-compounds without side products (Scheme 2).

However, this reaction does not proceed in the absence of trifluoroacetic acid and it is probable that the active species for this iodination is probably the 'in situ' formed iodine trifluoroacetate which can act as a very reactive electrophile. The following mechanism for the reaction (Scheme 3) is suggested.

The results of the iodination of representative aromatic compounds are presented in Table 1.



NIBTS 1

Scheme 1.

* Corresponding author. Fax: (+98) 811 8272404; e-mail: ghorbani@basu.ac.ir

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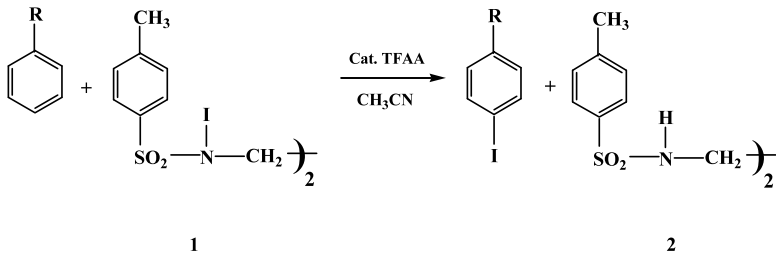
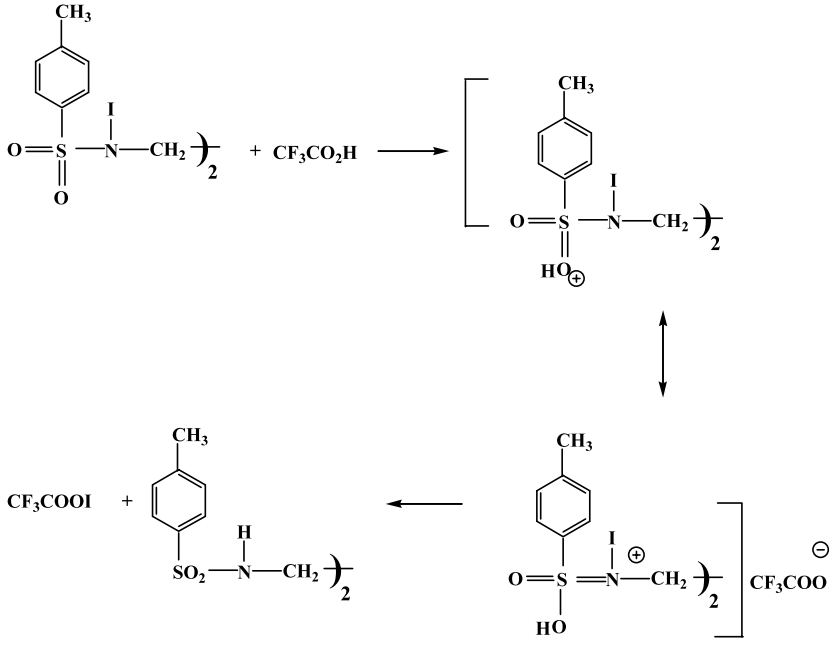


Scheme 2.



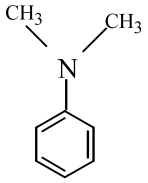
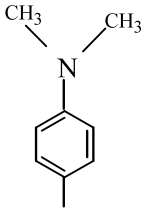
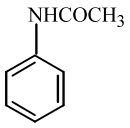
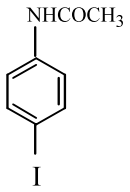
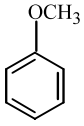
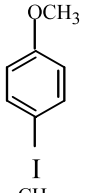
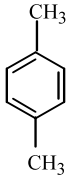
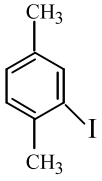
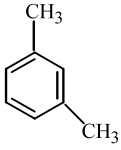
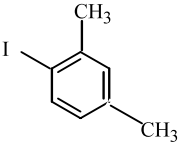
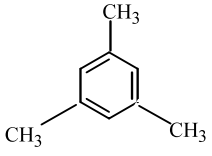
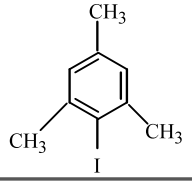
Scheme 3.

The products of reaction with NIBTS were isolated simply by filtering off the sulfonimide **2** and evaporating the solvent from the filtrate. The method has advantages in terms of yields, simplicity of reaction conditions, short reaction times and lack of side products. The recovered starting material **2**, was re-iodinated and used many times without reducing the yield.

Procedure for the preparation of *N*,*N*′-diiodo-*N*,*N*′-1,2-ethanediylbis(*p*-toluenesulphonamide) 1: *N*,*N*′-1,2-ethanediylbis(*p*-toluenesulphonamide) (1 g, 0.006 mol) was dissolved in a slight molar excess of sodium hydroxide solution (6 M) at room temperature and was transferred to a beaker. Iodine (10 g) dissolved in carbon tetrachloride (15 ml) was added to the solution with vigorous stirring at −10°C and immediately a yellow precipitate was formed. The product (yellow precipitate) was collected on a Buchner funnel and washed with distilled cold water (10 ml) and then dried in a vacuum desicator at room temperature for 6 h. The reaction gives **1** in (0.9 g, 90%). IR (KBr): ν 1600, 1460, 1340, 1150 cm^{-1}. ^1H NMR (DMSO-d^6): δ 2.40 (s, 6H), 2.70 (s, 4H), 7.50–7.76 (m, 8H). ^{13}C NMR (DMSO): δ 20.2 (CH_3), 45.1 (CH_2), 126.20–141.19 (4 peaks for the aromatic carbons).

General procedure for iodination of aromatic compounds with NIBTS: To a solution of 1 mmol of the aromatic compound in 5 ml of CH_3CN, 0.5 mmol of NIBTS and five drops of trifluoroacetic acid were added, then the mixture was refluxed for the specified time (Table 1). After completion of the reaction, the insoluble sulfonamide **2** was removed by filtration and washed with cold acetonitrile (10 ml). The solvent was then evaporated and ether was added. The ethereal phase was washed with aqueous $NaHSO_3$ and water. After work-up, the crude iodoaromatic was obtained pure as shown by ^1H NMR.

Table 1. Iodination of aromatic compounds with NIBTS and CF_3CO_2H

Entry	Substrate	Product[a]	Time (h)	Temp. (°C)	Yield (%)	M.P.[B.P.] (°C)	Lit.M.P.[B.P.] (°C)
1			2	81	92	75-76	77[20]
2			3	81	90	182-184	184-185[21a]
3			3	81	91	48-50	50-53[21b]
4			4.5	81	93	[224-6 d]	[227-8 d][21b]
5			4.5	81	91	[229 d]	[231 d][21b]
6			5	81	92	28-30	30.5-31[22]

[a] Products were characterized by their physical properties, comparison with authentic samples and by spectroscopic methods.

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