Iranian Journal of Organic Chemistry 3 (2009) 160-162

A simple iodination protocol *via in situ* generated ICl using $NaIO_4$/NaCl/Silica sulfuric acid

Saeed Taghvaei–Ganjali,[a] Mahbobeh Ghasemian-Dazmiri,[a] Maasoumeh Hosseinzadeh,[b] Abolfazl Hosseini[b] and Mohammad A. Khalilzadeh[b*]
[a]*Department of Chemistry, Islamic Azad University, North of Tehran branch, Iran*
[b]*Department of Chemistry, Islamic Azad University, Qaemshahr, Iran*

Abstract: $NaIO_4$/NaCl in the presence of silica sulfuric acid is a mild, cheap, and non-toxic reagent for the iodination of phenols in fair to excellent yields by a very simple isolation protocol. The scope of the procedure is exemplified by the iodination of phenol to 2,4,6-triiodophenol in 92% yield.

Keywords: NaIO4/NaCl; Mild iodination; Phenols; Silica sulfuric acid

Introduction

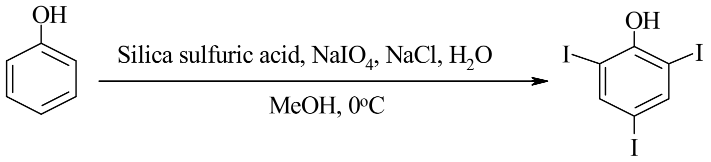
The iodination of phenols and other aromatic compounds is the subject of continuing interest in organic chemistry due to the extensive use of iodinated derivatives as versatile intermediates or building blocks in a variety of synthetic transformations, in medicinal chemistry, and in the biomedical sciences, e.g., as imaging agents in non-invasive medical diagnostic techniques [1,2]. The biological importance of iodophenols is illustrated by the thyroid hormones which derive biogenetically from the phenolic amino acid tyrosine via repeated iodination steps [3]. The methodologies currently available to organic chemists for the preparation of iodophenols and iodinated aromatic amines and heteroarenes are based on a broad range of iodinating agents such as iodine/HgO [4], iodine/tetrabutylammonium peroxydisulphate [5], *n*-BuLi/CF_3CH_2I [6], NIS/CF_3SO_3H [7], NIS [8], ICl [9], $KBrO_3$/KI [10], $IPyBF_4$ [11] or iodidecoupled with oxone [12], polymethylhydrosiloxane [13], diiodine pentoxide [14], Ag_2SO_4 [15], $NaIO_4$ [16], HIO_4 [17], NaOCl [18], urea/H_2O_2 [19], HIO_3 [20] and catalytic ceric ammonium nitrate [21]. These iodinating systems rely for their activity on the presence of Lewis acids or strong oxidizing agents to overcome the problems relating to the low electrophilicity of molecular iodine that renders direct iodination difficult compared to chlorination or bromination. Despite the broad choice of options, however, many iodination methodologies are cumbersome, costly, harsh, involve use of toxic heavy metals, or do not perform equally well on sensitive aromatic substrates. The development of quick, inexpensive, widely applicable, and environmentally benign iodinating agents is therefore still an active area of research. On this basis the $NaIO_4$/NaCl in the presence of silica sulfuric acid was probed on a variety of substrates and we report here its application for the iodination of phenols, and heterocyclic substrates, in fair to excellent yields.

Results and discussion

We report here a practical aromatic iodination. A combination of $NaIO_4$ and NaCl in the presence of silica sulfuric acid has been found to be an excellent reagent for the efficient iodination of phenols and heterocyclic compounds such as α-naphthol, 4-ethoxy pyridine, imidazole and pyridine or its derivatives (Scheme 1).
These reactions are carried out at $0^{o}C$ for phenols and reflux conditions for heterocyclic compounds using 75% aqueous methanol as a solvent. A variety of phenol and heteroaromatic compounds were investigated for the reaction with $NaIO_4$ and NaCl in the presence of silica sulfuric acid (Table 1).

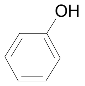
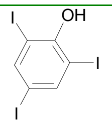
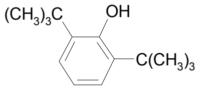
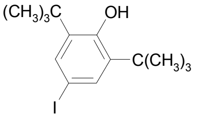
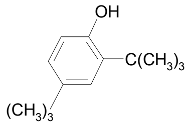
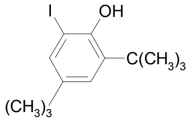
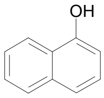
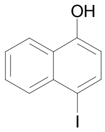
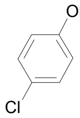
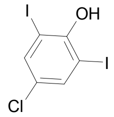
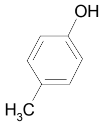
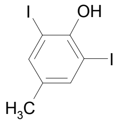
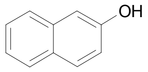
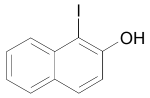
---

*Corresponding author. Tel.: +(98) 11252-34338; Fax: +(98) 11252-42002; E-Mail: *m.khalilzadeh@hotmail.com*



Scheme 1

Table 1: Iodination of hydroxy aromatics by $NaIO_4/NaCl$ in the presence of silica sulfuric acid

Entry	Starting material	Product	Yield(%)
1			92
2			90
3			90
4			88
5			92
6			85
7			87

From a mechanistic point of view, we think that the active species for this iodination is probably the ‘in situ formed’ iodine chloride which can act as a very reactive electrophile, allowing iodination in short reaction times at at reflux or at room temperature (Scheme 2).

$$HIO_4 + SiO_2 \xrightarrow{\text{Reductive decomposition}} I_2$$
$$8NaCl + HIO_4 + 8H_2SO_4 \longrightarrow 4Cl_2 + 4H_2O + 8NaHSO_4 + HI$$
$$I_2 + Cl_2 + H^+ \longrightarrow 2\ I\text{-}Cl$$
$$8\ I\text{-}Cl + HIO_4 + 8H_2SO_4 \longrightarrow 8IOSO_3H + 4Cl_2 + 4H_2O + HI$$

Scheme 2

The product was obtained with iodination at the electron rich *ortho* or *para* positions. When the o-position was blocked with a substituent, only iodination took place at the *p*-position. Interestingly, 2,6-ditertiobuthyl phenol was used the product was 2,6-diiodo phenol (Table 1, entries 2). Iodination did not occur on the side chains, that is, $–OCH_2CH_3$ or $–CH_3$. The iodination reaction only occurred on the hydroxy-substituted aromatic ring due to the electron density at the *ortho/para* positions, and not on another aromatic centre (Table 1, entries 1–3).

Conclusion

In summary, the iodination procedure is very simple; the required reagents are easily handled without any special apparatus and the starting material can be used without any activation or modification.

Experimental procedures

M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-, and ^{13}C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. All chemicals were obtained from *Fluka* and were used without further purification.

General procedure

To a stirred solution of sodiom periodate (3 mmol, 0.69 g) in 4 mL water was added silica sulfuric acid (0.5 g) and stirred for 10 minutes at reflux or at room temperature. Then, a solution of sodium chloride (0.35 g) was added slowly to the previous mixture. The phenol and heteroaromatic compounds (3 mmol) was dissolved in water/methanol (3 ml) and added to the above mixture. After the appropriate time (reaction was monitored by TLC and GC), the reaction mixture was filtered and the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography (SiO_2; *n*-hexane**s**/EtOAc 8:1) to afford pure desired products. The products were characterized from their physical constants and NMR, IR, and GC–MS spectra.

Acknowledgement

Financial support of this work from the Research Council of Mazandaran and Azad University is gratefully acknowledged.

References

[1] Kung, H. F.; Newman, S.; Choi, S.-R.; Oya, S.; Hou, C.; Zhuang, Z.-P.; Acton, P. D.; Ploessl, K.; Winkler, J.; Kung, M.-P. *J. Med. Chem.* **2004**, *47*, 5258-5264.

[2] Bennacef, I.; Tymciu, S.; Dhilly, M.; Lasne, M.-C.; Debruyne, D.; Perrio, C.; Barre, L. *Bioorg. Med. Chem.* **2004**, *12*, 4533-4541.

[3] Dunn, A. D.; Corsi, C. M.; Myers, H. E.; Dunn, J. T. *J. Biol. Chem.* **1998**, *273*, 25223-25229.

[4] Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H.; Tokuda, M. *Synthesis* **1997**, 23-25.

[5] Yang, S. G.; Kim, Y. H. *Tetrahedron Lett.* **1999**, *40*, 6051-6054.

[6] Blackmore, I. J.; Boa, A. N.; Murray, E. J.; Dennis, M.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 6671-6672.

[7] Olah, G. A.; Wang, Q.; Sandford, G.; Surya Prakash, G. K. *J. Org. Chem.* **1993**, *58*, 3194-3195.

[8] Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081-4084.

[9] Mukaiyama, T.; Kitagawa, H.; Matsuo, J.-I. *Tetrahedron Lett.* **2000**, *41*, 9383-9386.

[10] Sathiyapriya, R.; Karunakaran, R. J. *J. Chem. Res.* **2006**, 575-576.

[11] Barluenga, J.; Alvarez-Gutierrez, J. M.; Ballesteros, A.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1281-1283.

[12] Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 2319-2324.

[13] Das, B.; Holla, H.; Srinivas, Y.; Chowdhury, N.; Bandgar, B. P. *Tetrahedron Lett.* **2007**, *48*, 3201-3204.

[14] Brazdil, L. C.; Fitch, J. L.; Cutler, C. J.; Haynik, D. M.; Ace, E. R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 933-936.

[15] Sy, W.-W. *Tetrahedron Lett.* **1993**, *34*, 6223-6224.

[16] Kraszkiewicz, L.; Sosnowski, M.; Skulski, L. *Synthesis* **2006**, 1195-1199.

[17] Suzuki, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2871-2873

[18] Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287-5291.

[19] Pavlinac, J.; Zupan, M.; Stavber, S. *Org. Biomol. Chem.* **2007**, *5*, 699-707.

[20] Patil, B. R.; Bhusareb, S. R.; Pawar, R. P.; Vibhute, Y. B. *Tetrahedron Lett.* **2005**, *46*, 7179-7181.

[21] Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V. S. *Tetrahedron Lett.* **2007**, *48*, 81-83.