



Mild and Regiospecific Nuclear Iodination of Methoxybenzenes and Naphthalenes with *N*-Iodosuccinimide in Acetonitrile

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
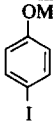

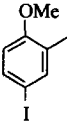

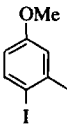
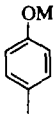
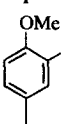
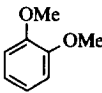
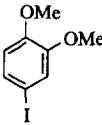
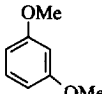
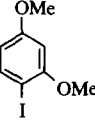
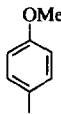
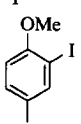
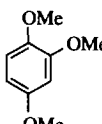
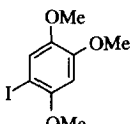
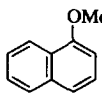
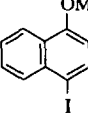
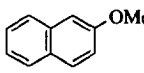
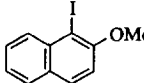
Abstract: A wide range of methoxy substituted benzenes and naphthalenes were regiospecifically iodinated at *para* position with *N*-iodosuccinimide in acetonitrile under mild conditions in excellent yields. Methylanisoles afforded only nuclear iodination products.
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Iodination of aromatic compounds has been the subject of numerous studies¹ due to the interest of iododerivatives as substrates for reactions involving C-C bond formation mainly mediated by transition metals.² These derivatives have been used in the synthesis of many interesting natural products³ and bioactive compounds.⁴ Concerning iodination procedures, the moderate reactivity of iodine with aromatic substrates determined the use of different activating agents⁵ to effectively succeed in the goal. Iodonium donating reagents⁶ and other more sophisticated procedures⁷ have also been employed. The wide range of methods described so far revealed the lack of an efficient and general enough procedure.

We recently reported the use of *N*-bromosuccinimide (NBS) in acetonitrile as a mild and excellent nuclear brominating reagent for methoxybenzenes and naphthalenes.⁸ Seeking for further extension of these results we thought of *N*-iodosuccinimide (NIS) as iodination agent. We report in this letter the ability of NIS to achieve nuclear iodination of activated aromatic compounds under very mild conditions and in good to excellent yields. Whereas NCS and NBS have been extensively used for many years⁹ as halogenating agents for aromatic substrates under different conditions, aromatic iodinations using *N*-iodoamides have been used in a lesser extent.¹⁰

Methoxy aromatic derivatives used in this study were commercially available. These compounds were submitted to reaction with NIS in CH₃CN at different temperatures.¹¹ The results are collected in the Table. As can be seen, the products obtained in all cases resulted from the regiospecific iodination of the aromatic ring and their structures were easily determined from their ¹H-NMR spectra and by comparison with the literature data. The observed regiochemistry was the result of reaction through the presumably more electron rich and less sterically encumbered aromatic ring position. Thus, *para* positions of methoxybenzenes (entries 1, 5 and 6) and 4- and 1- position of methoxynaphthalenes (entries 9 and 10) were exclusively iodinated, whereas the *ortho*-iodination only occurred when the *para* position was occupied (entries 4 and 7). As was found with NBS, chain iodination products were not detected in the reactions of NIS with methylanisoles under refluxing acetonitrile (entries 2-4).

Table. Iodination of Methoxybenzenes and Naphthalenes with NIS in CH₃CN.

Entry	Substrate	Equiv NIS	T (°C)	Time (h)	Product	Crude yield (%)
1		1.5	82	6		95
2		1.5	82	8		96
3		1.5	82	2		90
4		1.5	82	8		90
5		1.5	82	18		85
6		1.1	20	5		90
7		1.1	20	16		95
8		1.1	20	4		95
9		1.5	82	6		97
10		1.5	82	24		96

The reactivity of the substrates seems to be associated to the electronic density of the aromatic rings. Thus, iodination of 1,3- and 1,4-dimethoxybenzene (entries 6 and 7) and 1,2,4-trimethoxybenzene (entry 8) took place at rt whereas the reactions of methoxybenzenes and naphthalenes (entries 1-4 and 9-10) and 1,2-dimethoxybenzene (entry 5) required refluxing acetonitrile to be completed. It is noteworthy that the activating effect of the substituents is only additive when they are not arranged on adjacent carbons. Thus, the influence of a second electron-donating substituent situated on a vicinal carbon on the reactivity is scarce (compare entries 1 with 2 and 6 with 8) or even negative (compare entries 1 with 5) when iodination can take place on a free *para* position. In the case of 1,2-dimethoxybenzene (entry 5), this could be a consequence of the lower activation of the reactive position 4 due to the OMe group situated at C-2 (*meta*).

We have also checked the influence of solvent polarity on the reactivity. When these reactions were performed using CCl₄, the reactivity observed was lower than in CH₃CN. Thus, the reaction of the most reactive substrates in the Table (1,3-dimethoxy- and 1,2,4-trimethoxybenzenes) required four days in refluxing CCl₄ to be completed, whereas the less reactive ones (2-methyl- and 2-methoxyanisole) were recovered unaltered after 5 days in the same conditions. These results evidenced the important role of the solvent polarity to achieve an efficient iodination with NIS. A similar effect was observed in bromination with NBS,⁸ where the reactions in CH₃CN were faster than in CCl₄.

The regioselectivity observed (*para* iodination preferred when possible) revealed the influence of steric grounds on the reaction. The different reactivity of the studied aromatic substrates (the more electron rich reacted faster) and the effect of solvent polarity on the efficiency of the reaction suggested an aromatic electrophilic halogenation-type mechanism, with the succinimide anion acting as leaving group at the first step (formally a S_N2 reaction at halogen) and as a base in the subsequent deprotonation of the Wheland intermediate.¹² The lower reactivity of NIS with respect to NBS could be explained by assuming that the nucleophilic attack on iodine is less favoured than on bromine due to the higher size and lower positive charge density of the former.¹³

In order to take advantage of this highly regioselective iodination in a controlled mixed dihalogenation, we performed the reaction of 4-iodo-3-methylanisole with NBS/CH₃CN.¹⁴ Unfortunately, the method was not preparatively useful and after 3 days at rt we obtained a complex mixture where 6-bromo-4-iodo-3-methylanisole and 4-bromo-3-methylanisole were detected as major components in a similar proportion, indicating that the reactivity of C-4 adjacent to the methyl substituent was as large as that of the less hindered C-6 contiguous to the methoxy group. The well contrasted higher reactivity of the system NBS/H₂SO₄^{9e} did not allow us to achieve the regioselective bromination. The reaction of the above substrate with NBS/*p*-TsOH¹⁵ at rt yielded a *ca.* 60:40 mixture of the 2-bromo and 6-bromo derivatives.

In conclusion, the regiospecific nuclear iodination of aromatic methoxy derivatives can be efficiently achieved with NIS in CH₃CN. These results broaden the range of application of *N*-halosuccinimides and provide a mild and controlled entry into substituted aromatic iododerivatives widely used in organic synthesis. We are now extending the utilization of this method in the iodination of highly functionalized aromatic derivatives in order to evaluate its compatibility with a range of functional groups.

Acknowledgement: We thank *Dirección General de Investigación Científica y Técnica* (Grants PB92-0161 and PB92-0162) and *Comunidad Autónoma de Madrid* (CAM, Grants AE00144/94 and AE00244/95) for financial support. Two of us (MAT and GS) thanks CAM for a fellowship.

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11. Representative procedure: to a solution of 1 mmol of the aromatic compound in 4 mL of CH₃CN, NIS was added and the reaction was stirred at the desired temperature. After the time required in each case, the solvent was evaporated and ether was added. The ethereal phase was washed with aqueous NaHSO₃ solution and water. After workup, the crude iodoaromatic was obtained pure by ¹H-NMR.
12. See: March, J. In *Advanced Organic Chemistry: Reactions, Mechanism and Structure*, 4th ed.; John Wiley & Sons: New York, 1992; pp 501-521 and references cited therein.
13. We have also checked that NCS is much less reactive than NBS (almost complete chlorination of 1,2,4-trimethoxybenzene with NCS at refluxing CCl₄ required 4 days, whereas the same substrate was completely brominated with NBS/CCl₄ in 4 hours at 20°C. This would indicate that the differences in the nucleophilic carbon attack to Cl and Br (presumably higher for Cl) is not able to compensate the large difference in reactivity imposed by the respective bond energies (N-Cl > N-Br).
14. 4-Bromo-3-methylanisole was recovered unaltered after 6 days of treatment with NIS in refluxing acetonitrile.
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(Received in UK 25 March 1996; revised 16 April 1996; accepted 19 April 1996)