Polyiodination on Benzene at Room Temperature A Regioselective Synthesis of Derivatives.

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Summary: Reaction of IPy_2BF_4 with benzene and CF_3SO_3H in CH_2Cl_2 gives regioselectively polyiodinated compounds at room temperature, providing a definitely easy synthetic entry to those rarely accessible benzene derivatives.

Straightforward methods to preparare polyiodinated arenes are scarce,¹ and should compete with multistep synthesis based on anilines.² The direct and regioselective polyiodination of benzene, the representative aromatic substratum, had not been solved yet.

In this letter, we report the first method to achieve those elusive transformations at room temperature. The method is based on the reaction in CH_2Cl_2 of benzene, bis(pyridine) iodonium(I) tetrafluoroborate ³ (IPy₂BF₄) and CF₃SO₃H (triflic acid) (Scheme 1, Table).

$$\bigcap_{\text{CH}_2\text{Cl}_2, \text{ rt}} \frac{\text{n IPy}_2\text{BF}_4, 2\text{n CF}_3\text{SO}_3\text{H}}{\text{CH}_6\text{-m}\text{I}_m (1-6)}$$

Scheme 1

The reaction takes place by mixing the reagents under nitrogen and stirring the resulting mixture at room temperature. The yields (calculated from pure isolated compounds and referred to benzene) and the structures of the compounds synthesized, are depicted in Scheme 2. Reaction time, molar ratio of the reagents, and the amount of solvent were crucial variables to determine the nature of the products (1-6), and were the only elements used to drive the reactions. In all the cases, the molar ratio triflic acid:IPy₂BF₄ was 2:1. Specific conditions to prepare the reported polyiodinated compounds are briefly outlined in the Table. The reaction was stopped by addition of water. Conventional isolation and purification techniques provided polyiodinated arenes in pure form. The monoiodination had been previously established.³ Benzene was quantitatively converted to a mixture of diiodobenzene isomers (*para:ortho*=87:13), from where 79% of pure regioisomer 2 was isolated.

| Compound | Reaction time (h) | benzene:IPy ₂ BF ₄ molar ratio | benzene (moles.l ⁻¹) |
|----------|----------------------|---|-------------------------------------|
| 1 | 1 | 1:1.1 | 2x10 ⁻¹ |
| 2 | 2 | 1:2.1 | 2x10 ⁻¹ |
| 3 | 4 | 1:3 | 4x10 ⁻² |
| 4 | б | 1:5 | 4x10 ⁻² |
| 5 | 12 | 1:18 | 2x10 ⁻² |
| 6 | 14 | 1:30 | 1x10 ⁻² |
| | | | |

Table Preparation of polyiodinated benzene derivatives (Schemes 1 and 2)

Scheme 2

The yield for 1,2,4-triiodobenzene 3 is moderate but, it should be noted that the crude reaction contains a 1:1 mixture of 2 and 3, and only traces of 4, compounds that are easily separated and obtained in pure form in multigram scale by distillation under high vacuum. Also, conditions has been established for the regioselective preparation of 3 from the recycled diiodo derivative; thus, an overall higher yield synthesis of 3 from benzene is conceivable. Most significantly, the room temperature synthesis of the highly iodinated derivatives 4, 5 and 6, isolated by simple filtration after hydrolysis, took place with excellent yields, higher than those found in the literature.⁴ The difference of solubility of the final products was a helpful tool to achieve the polyiodination of benzene with the observed regioselectivity.

It is worth remarking the absence in the literature⁵ of procedures being suitable for both, simple monoiodination and regioselective polyiodination, in the herein shown range. Known procedures, either fail to monoiodinate arenes bearing electon-withdrawing groups, or require strong experimental conditions resulting in the loss of control over the extent of the polyiodination.

We have explored the reaction using other starting arenes, in view of the unusual power of the reagent allowing the quantitative periodination of benzene to take place under mild conditions, and for the purpose of preparing aromatic building blocks useful for selective assembly of molecular structures that might exhibit interesting behaviours.⁶ We examined the reaction of the 1,3,5-isomers of trichloro-, tribromo-, and trimethyl-benzene (mesitylene), and of the 1,2,4-tribromobenzene (Scheme 3). Influences of the substituent on the reaction conditions have been noted. Thus, mesitylene $(4 \times 10^{-2} \text{ M})$ is periodinated, affording 7 in 92% yield, at 20°C in 15 minutes, for a ratio arene: $IPy_2BF_4 = 6:1$. A similar reaction of 1,3,5-tri-bromobenzene furnished 87% isolated yield of 8, but now the reaction was stirred for overnight, and a 40:1 molar ratio of the iodinating agent was used. Under related conditions 1,3,5-trichlorobenzene affords 9 only in 36% yield, and 10, can be isolated in 64% yield from the parent bromoarene.



Scheme 3

The starting compounds for the obtention of mixed perhalobenzenes have shown lower reactivity compared with related process in the preparation of periodobenzene, but the resulting periodinated arenes are more soluble in the reaction medium. Taking advantage of this fact, one can reduce the value of the arene: IPy_2BF_4 ratio employed. For instance, a value 1:20 of that ratio, furnished 8 in 85% yield when the arene was 2×10^{-2} M, and it suggests ways to optimize the process. Control over the reaction in these cases is also possible and the diiododerivatives are accessible (11, 98% yield, arene: $IPy_2BF_4 = 1:2.1$, mesitylene 4×10^{-2} M, 15 minutes at room temperature; and 12, 89% yield, arene: $IPy_2BF_4 = 1:5$, 1,3,5-tribromobenzene 4×10^{-2} M, overnight at room temperature). All compounds (1-12) gave satisfactory spectarl data (i.r., MS, ¹H and ¹³C NMR) and match previously reported physical properties.

In summary, for the first time a procedure has been established to direct and regioselectively polyiodinate benzene at room temperature. Yields, mild experimental conditions, and control over the nature of products by simply tuning experimental conditions, are attractive features of this approach. The reaction can be succesfully applied to other arenes. Work is in progress to optimize results, to further expand the scope and determine applications of this polyiodination method.

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