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Aryne Insertion into I−I σ-Bonds

Diego Rodríguez-Lojo, Agustín Cobas, Diego Peña, Dolores Pérez,* and Enrique Guitián*

Centro de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), and Departamento de Química Orgánica, Universidade de Santiago, 15782 Santiago de Compostela, Spain

enrique.guitian@usc.es; dolores.perez@usc.es

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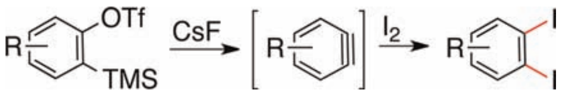
ABSTRACT



A new protocol for the efficient synthesis of *o*-diiodoarenes has been developed. This method allows the synthesis of substituted and polycyclic *o*-diiodoarenes, which are difficult to obtain by classical methods. This diiodination process involves the formal insertion of arynes into the I−I *σ*-bond.

The insertions of arynes into σ-bonds are interesting processes from both theoretical and synthetic points of view. Formally, the insertion of an aryne into an A−B σ-bond involves cleavage of the A−B bond and the formation of an arene derivative, which incorporates A and B at the *ortho* positions. A wide spectrum of insertions involving σ-bonds linking a great variety of atoms (C−C, C−Si, Si−Si, Sn−Sn, B−Si, C−O, C−N, C−Cl, etc.) have been reported.[1,2]

o-Diiodoarenes are valuable synthetic intermediates, but the majority of these compounds are not commercially available. Additionally, there is no general, efficient, and straightforward route to *o*-diiodoarenes.[3] Direct iodination of arenes with reagents such as HgO/I_2, I_2/HIO_4, I_2/H_2SO_4, and ICl works reasonably well at activated positions. In other cases, however, harsh conditions are required and this leads to mixtures of regioisomers.[4] Synthetic routes from more highly functionalized precursors, such as *o*-dibromoarenes,[5] *o*-bis(trimethylsilyl)arenes,[6] *o*-iodoanilines,[7] and aryne−metal complexes,[8] have been developed, but the synthesis of these compounds is not always easy.

It has been known that benzyne (**1a**), generated from benzenediazonium 2-carboxylate,[9] diphenyliodonium 2-carboxylate,[9] or 1-aminobenzo-triazole,[10] inserts into the I−I σ-bond (Scheme 1). These reactions give moderate yields for benzyne, but far lower yields are obtained for substituted and polycyclic arynes.[9,11]

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(1) (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (c) Gallo, R. D. C.; Rezende, H. V.; Muzzi, R. M.; Raminelli, C. *Quim. Nova* **2009**, *32*, 2437. (d) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199.

(2) For more recent examples, see: (a) C—C insertion: Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 5691. (b) C—N insertion: Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (c) B—B insertion: Yoshida, H.; Okada, K.; Kawashima, S.; Tanino, K.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 1763. (d) C═O insertion: Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956. (e) C—C insertion: Yoshida, H.; Morishita, T.; Ohshita, J. *Chem. Lett.* **2010**, *39*, 508. (f) C—O insertion: Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117. (g) C—H insertion: Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (h) Sn—H insertion: Lakshmi, B. V.; Wefwelscheid, U. K.; Kazmaier, U. *Synlett* **2011**, 345. (i) C—O insertion: Łaczkowski, K. Z.; García, D.; Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Org. Lett.* **2011**, *13*, 960. (j) Bi—S insertion: Chen, J.; Murafuji, T. *Organometallics* **2011**, *30*, 4532.

(3) Waldvogel, S. R.; Wehming, K. M. *Sci. Synth.* **2007**, *31a*, 235.

(4) See for example: (a) Dallacker, F.; Adolphen, G. *Ann. Chem.* **1966**, *691*, 134. (b) Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 128. (c) Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. *Synthesis* **1995**, 1273.

(5) Suzuki, H.; Kondo, A.; Inouye, M.; Ogawa, T. *Synthesis* **1985**, 121.

(6) Grützmacher, H.-F.; Lohmann, J. *Liebigs Ann. Chem.* **1970**, *733*, 88.

(7) (a) Dunoguês, J.; N'Gabe, D.; Laguerre, M.; Duffaut, N.; Calas, R. *Organometallics* **1982**, *1*, 1525. (b) Berris, B. C.; Hovakeemian, G. H.; Lai, Y. H.; Mestdagh, H.; Vollhardt, K. P. C *J. Am. Chem. Soc.* **1985**, *107*, 5670.

(8) Buchwald, S. L.; Lucas, E. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, *111*, 397.

(9) Friedman, L.; Logullo, F. M. *Angew. Chem., Int. Ed.* **1965**, *4*, 239.

(10) Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchell, M. B. *Tetrahedron* **2000**, *56*, 1013.

(11) Perry, R. J.; Turner, S. R. *J. Org. Chem.* **1991**, *56*, 6573.

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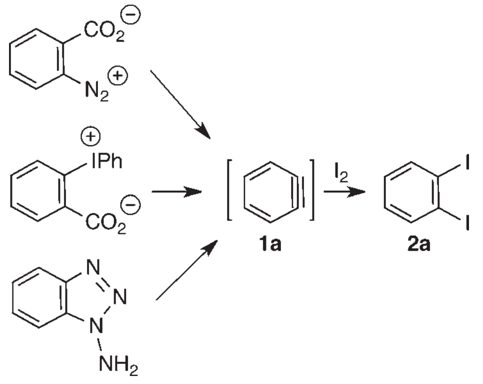
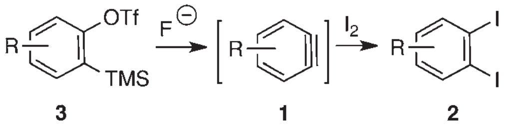
Scheme 1. Previous Benzyne Insertions into I—I σ-Bond



In recent years, however, many classical aryne reactions have been revisited using Kobayashi's method for aryne generation,[12] i.e. the treatment of *o*-(trimethylsilyl)aryl triflates with fluoride, and this approach has led to a general improvement in yields.[13] Bearing in mind our long experience in the use of this method,[14] we envisaged that this approach could be applied to aryne insertions into I—I bonds (see Scheme 2).

Scheme 2. New Diiodination Method

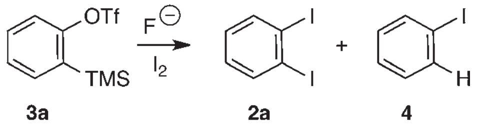


We report here the results of an experimental study of aryne insertion into I—I σ-bonds and its use for the synthesis of *o*-diiodoarenes, which are valuable synthetic intermediates.

In order to assess the feasibility of the transformation we tested the reaction between iodine and benzyne, generated from *o*-(trimethylsilyl)phenyl triflate (**3a**),[12,15] and several fluoride sources in different solvents. The results of selected experiments are shown in Table 1. A key requirement for the success of the insertion is the use of a dry solvent and an anhydrous fluoride source. The use of Bu_4NF containing variable amounts of water[16] led to mixtures of **2a** and **4** (entries 1—3 and 5—7). It is interesting to note that an excess of fluoride with respect to iodine is required; otherwise **3a** is recovered unchanged (entry 4).

The best selectivity for the diiodinated products was obtained in acetonitrile with a 1/2.5/5 molar ratio of the reactants **3a**, I_2, and an anhydrous fluoride source (CsF or $BnMe_3NF$) (entries 8 and 9), respectively.

Table 1. Optimization of Benzyne Iodination



entry	I_2 equiv	F^- source	F^- equiv	solvent	ratio **2a:4**[a]
1	1	Bu_4NF	1.1	THF	75:25
2	2	Bu_4NF	2.2	THF	55:45
3	4	Bu_4NF	4.1	THF	68:32
4	16	Bu_4NF	4.1	THF	NR[b]
5	2.5	Bu_4NF	5.0	CH_3CN	76:24
6	2.5	Bu_4NF	5.0	CH_2Cl_2	79:21
7	2.5	Bu_4NF	5.0	DEE[c]	80:20
8	2.5	CsF[d]	5.0	CH_3CN	100:0
9	2.5	$BnMe_3NF$[d]	5.0	CH_3CN	100:0

[a] Ratio calculated (GC) at 100% of conversion. [b] NR: no reaction. [c] DEE: 1,2-diethoxyethane. [d] Anhydrous.

In an optimized procedure for diiodination a solution of *o*-(trimethylsilyl)aryl triflate (**3a**, 1 equiv) and iodine (2.5 equiv) in acetonitrile is stirred under argon with dry cesium fluoride (5 equiv) at rt for 16 h. It can be seen from the results in Table 2 that this protocol was applied to benzyne as well as substituted and polycyclic arynes. The reaction of benzyne precursor **3a** gave a good yield of *o*-diiodobenzene (**2a**, entry 1, 81%), and this is an improvement on previous results (54—67% yield).[9] Significantly, on using this procedure 4-methyl-1,2-diiodobenzene (**2b**, entry 2) was isolated in 76% yield, which represents a remarkable increase in the yield obtained by diazotization of 5-methylanthranilic acid in the presence of iodine (8%[11] or 30%[9]).

Compounds **2c**—**2h** and **2j** (entries 3—8 and 10) had not previously been prepared by aryne insertions into I_2 using the procedures outlined in Scheme 1. On using our procedure these *o*-diiodoarenes were obtained in good yield. Furthermore, 2,3-diiodonaphthalene (**2i**), which had previously been prepared from the corresponding 3-naphthalenediazonium 2-carboxylate in only 0.5% yield,[11] was obtained in 69% yield from **3i**.

Even tetraiodoarenes can be obtained in one pot by double insertion processes involving bisaryne precursors (entries 11—13). 1,2,4,5-Tetraiodobenzene (**2k**), 2,3,6,7-tetraiodonaphthalene (**2l**), and 1,2,5,6-tetraiodonaphthalene (**2m**) were obtained in 49%, 40%, and 30% yield,

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[12] Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

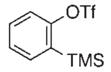
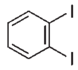
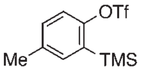
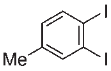
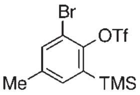
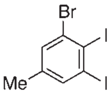
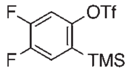
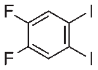
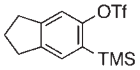
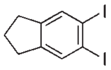
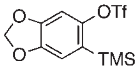
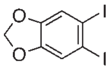
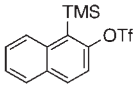
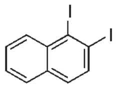
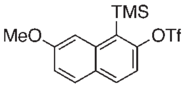
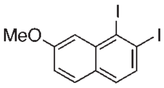
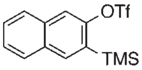
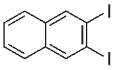
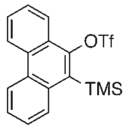
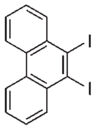
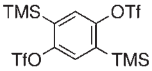
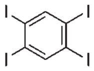
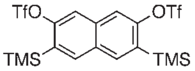
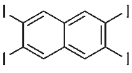
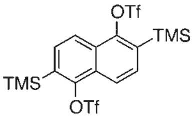
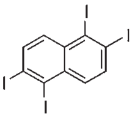
[13] (a) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

[14] (a) Criado, A.; Peña, D.; Cobas, A.; Guitián, E. *Chem.—Eur. J.* **2010**, *16*, 9736. (b) Rodríguez, D.; Peña, D.; Guitián, E. *Org. Biomol. Chem.* **2010**, *8*, 3386. (c) Criado, A.; Gómez-Escalonilla, M. J.; Fierro, J. L. G.; Urbina, A.; Peña, D.; Guitián, E.; Langa, F. *Chem. Commun.* **2010**, 7028.

[15] Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

[16] Commercially available Bu_4NF solutions in THF (1.0 M) were used. Although the initial water content of this solution is 5 wt % (approx.), the level of water could be higher due to the hygroscopic character of the salt.

Table 2. Synthesis of Di- and Tetraiodoarenes **2**^{a}

entry	aryne precursor **3**^{b}		iodoarene **2**, yield	
1	**3a**			**2a**, 81%
2	**3b**			**2b**, 76%
3	**3c**			**2c**, 55%
4	**3d**			**2d**, 80%
5	**3e**			**2e**, 73%
6	**3f**			**2f**, 78%
7	**3g**			**2g**, 82%
8	**3h**			**2h**, 70%
9	**3i**			**2i,** 69%
10	**3j**			**2j**, 68%
11	**3k**			**2k**, 49%
12	**3l**			**2l**, 40%
13	**3m**			**2m**, 30%

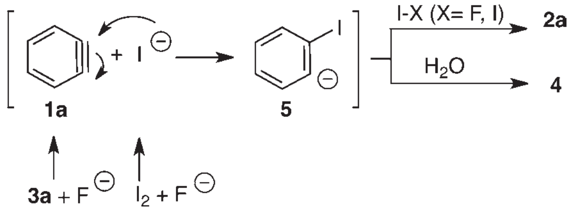
^{a} Reaction conditions: *o*-(Trimethylsilyl)aryl triflate (**3**, 1 equiv), I_2 (2.5 equiv), CsF (5 equiv), CH_3CN, rt, 16 h. ^{b} See Supporting Information

respectively. Isolation problems due to the low solubility of these compounds led to lower yields.

We also became interested in the mechanism of the insertion reaction, particularly after the remarkable mechanistic proposal by Hoffmann,[1] who pointed out that the insertion reaction begins with the nucleophilic attack of benzyne (**1a**) to iodine, to afford a 2-iodophenylcation.[17] The reactivity of iodine is compatible with this mechanism since it can act as either a nucleophile or an electrophile. However, most theoretical and experimental studies highlight the highly electrophilic character for benzyne.[18,19] In fact, inter- and intramolecular additions to arynes of a broad variety of polar species such as water, alcohols, amines, etc. have been interpreted as nucleophilic additions to an electrophilic aryne.[1] In this context the mechanistic proposal by Hoffmann, in which benzyne acts as a nucleophile, is controversial.

To account for our experimental results we propose a new mechanism outlined in Scheme 3. First, fluoride would react with iodine to generate iodide. Excess fluoride, if available, would react with **3a** to form benzyne (**1a**). Nucleophilic attack of iodide to benzyne would afford carbanion **5**, which could be iodinated to **2a**. By contrast, in the presence of a proton source such as H_2O, carbanion **5** would lead to iodobenzene (**4**) through protonation.

Scheme 3. Mechanistic Proposal for the Insertion



In summary, a new procedure for the efficient insertion of arynes into the I–I σ-bond has been developed. This method is applicable to arynes bearing electron-donating or -withdrawing substituents, to polycyclic arynes, and even to bisarynes. From the synthetic point of view, this procedure opens up a short and efficient route for the synthesis of *o*-diiodoarenes and related tetraiodoarenes under mild reaction conditions.

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Supporting Information Available. Experimental details and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Hoffmann's mechanistic proposal is based on experimental results obtained by Friedman, although there is a discrepancy between the product named by this group and the chemical formula drawn by Hoffmann. See refs 1 and 9 for details.

(18) Rondan, G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron* **1979**, *35*, 3237.

(19) Domingo, L. R.; Pérez, P.; Contreras, R. *Eur. J. Org. Chem.* **2006**, *2*, 498.

The authors declare no competing financial interest.