A Smooth and Practicable Azido-Iodination Reaction of Alkenes Based on IPy_2BF_4 and Me_3SiN_3

José Barluenga,* Mónica Álvarez-Pérez, Francisco J. Fañanás, José M. González

Instituto Universitario de Química Organometálica “Enrique Moles”, Unidad Asociada al CSIC, Universidad de Oviedo,
Julian Clavería 8, 33071 Oviedo, Spain
Tel. and Fax: (+34) 98-510-3450, e-mail: barluenga@sauron.quimica.uniovi.es

Received March 2, 2001; Accepted March 30, 2001

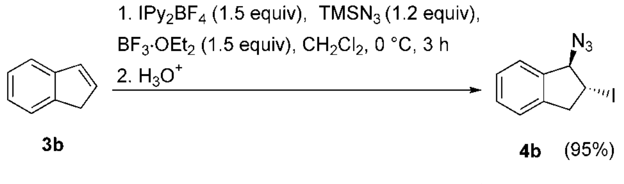
Abstract: The reaction of alkenes with IPy_2BF_4 and Me_3SiN_3 under the influence of $BF_3 \cdot OEt_2$ provides a mild an efficient entry to vicinal azidoiodoalkanes. Besides the simplicity of the experimental protocol and the convenience found in the handling of the reagents, the use of stoichiometric amounts of the azide source is remarkable, and overrides the known and always troublesome dependence on large excesses of azide to accomplish this synthetically valuable transformation.

Keywords: alkenes; azides; azido-iodination; electrophilic additions; synthetic methods

Addition reactions to alkenes promoted by electrophiles offer a straightforward entry to saturated derivatives bearing vicinal functionality[1] and, to this purpose, halogenation reactions are central processes.[2] Seminal work from Hassner[3] showed that β-iodoalkyl azides can be readily prepared from alkenes by addition of iodine(I) azide, providing simple access to introduce nitrogen functionality into organic compounds.[4] However, the explosive character of the iodine azide[5] has been considered a major disadvantage of this process, constraining its synthetic usefulness.[6] Recently, new solution[6] and polymer-bound[7] protocols have been introduced to override these limitations. These processes rely on the capability of iodine(III) reagents to create haloazide-like species from iodide via oxidation and ligand transfer steps. Moreover, the combination of reagents NaN_3/NaI/CAN led to complementary azido-iodides, according to an anti-Markovnikov addition mode.[8]

This renewed interest prompted us to investigate the convenience of bispyridineiodonium(I) tetrafluoroborate **1** (IPy_2BF_4)[9] to promote azido-iodination reactions of alkenes, on the basis of its already established power to behave as a fine source of electrophilic iodonium ions.[10] Interestingly, we have found that it gives rise to an efficient, selective, and simple conversion of alkenes into β-iodoalkyl azides using trimethylsilyl azide[11] **2** ($TMSN_3$) as an appropriate supplier of the required azide nucleophile.

Initial studies conducted using cycloalkenes **3** as starting materials provided evidence of the merit of this approach. Thus, a CH_2Cl_2 solution of **1** (1.5 equiv) was treated with **2** (1.2 equiv) and boron trifluoride diethyl etherate (1.5 equiv) at 0 °C, followed by rapid addition of indene **3b**. Upon stirring the mixture for 3 hours keeping the temperature constant, simple hydrolysis and isolation steps[12] led to the exclusive formation of *trans*-1-azido-2-iodoindane **4b**[13] in 95% yield, as depicted in Scheme 1.



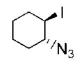
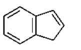
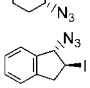
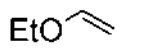
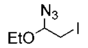
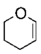
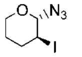
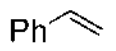
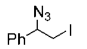
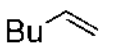
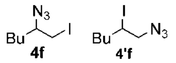
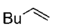
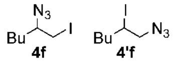
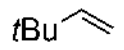
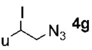
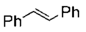
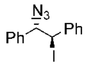
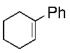
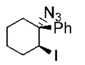
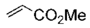
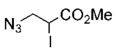
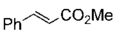
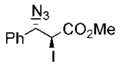
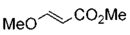
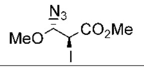
Scheme 1. Representative azido-iodination of indene.

The *cis*-diastereoisomer was not observed in the crude reaction mixture on the basis of ^1H NMR analysis (400 MHz). Furthermore, formation of the vicinal diazide[14] was not detected. These facts are relevant features of the herein reported procedure.[15] In the same way, cyclohexene gave **4a** in high yield, as a single *trans*-stereoisomer. Although the reactions were carried out on a 4 mmol scale as a routine basis, 5.4 g of **4a** were easily prepared in one batch from the reaction of 25 mmol of **3a** (see Table 1).[16] Thus the meth-

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/asc/ or from the author.

1615-4150/01/34301-335–337 $ 17.50-.50/0

Table 1. Iodoazidation of alkenes using IPy_2BF_4 [a]

Entry	Alkene **3**	T (°C)	t (h)	Product **4**	Yield (%)[b]
1	 **3a**	0	3	 **4a**	84 (86)[c]
2	 **3b**	0	3	 **4b**	95
3	 **3c**	0	2.5	 **4c**	74
4	 **3d**	0	3	 **4d**	75[d]
5	 **3e**	0	3	 **4e**	90
6	 **3f**	0	3	 **4f** **4'f**	80[e]
7	 **3f**	–40	72	 **4f** **4'f**	90[f]
8	 **3g**	0	2.5	 **4g**	70
9	 **3h**	–40	96	 **4h**	47
10	 **3i**	20	1.5	 **4i**	90
11	 **3j**	20	36	 **4j**	45[g]
12	 **3k**	–10	14	 **4k**	72[h]
13	 **3l**	–20	67	 **4l**	75[i]

[a] All the reactions have been carried out on a 4 mmol scale.
[b] Isolated yield after flash column chromatography.
[c] In brackets yield corresponding to 25 mmol scale.
[d] 20 : 1 mixture of diastereoisomers.
[e] 2 : 1 mixture of regioisomers.
[f] 5 : 1 mixture of regioisomers.
[g] Triflic acid has been used instead of boron trifluoride.
[h] IPy_2OTf was used.
[i] 22 : 1 mixture of diastereoisomers.

od is also of interest to prepare moderate amounts of azido-iodinated derivatives in a practicable manner. It nicely compares to the more demanding polymer-bound hypervalent iodine(III) process that relies on larger excesses of the azide source,[17] and requires longer reaction times to produce the desired addition compounds; these facts could possibly allow competitive side reactions to take place.[15]

On this ground, we have explored the scope of the IPy_2BF_4/$TMSN_3$-based method. The results are summarized in Table 1 and reveal a general process with respect to the electronic demand of the substituents in **3**, enabling neutral, electron-rich, and electron-deficient alkenes **3** to undergo the azido-iodination reaction in good to excellent yields. Full control over the regioselectivity was realized in addition reactions to enol ethers (entries 3 and 4). Adducts bearing N_3 on the carbon next to oxygen were exclusively obtained, probably as a consequence of the polarity that could be developed upon activation of **3** by attack of electrophilic iodine. In the case of 3,4-dihydro-2*H*-pyran (entry 4) the product with *trans*-stereochemistry is almost exclusively obtained, reflecting again an *anti*-addition of iodine and the azide across the alkene. The regioselectivity in addition reactions to neutral mono-substituted alkenes was investigated and found to depend on the nature of the substitution on the alkene. The phenyl group behaves as a strong director giving only **4e**, arising from incorporation of N_3 at the benzylic position; this is again in agreement with the expected outcome for an ionic process. However, under related conditions **3f** led to addition products as a mixture of regioisomers, the Markovnikov isomer **4f** being the major component (80% combined yield, 2:1 molar ratio for **4f** to **4'f**). This ratio can be nicely modulated simply by adjusting the reaction temperature (entry 7); at –40 °C a slower (72 h) but still efficient (90% yield) reaction was noticed, resulting in higher amount of the Markovnikov component (5:1 molar ratio for **4f** to **4'f**). Not only electronic but steric hindrance also plays a role as evidenced in addition reactions to 3,3-dimethyl-1-butene **3g**; the corresponding *anti*-Markovnikov addition isomer **4g** was formed as the sole reaction product in fairly good yield.[18] The azido-iodination of *trans*-1,2-diphenylethene required a low reaction temperature to give a clean transformation. Although obtained only in moderate yield, **4h**[3a] was diastereoselectively formed according to an *anti*-addition mode. Trisubstituted alkenes can be equally azido-iodinated using this reaction, as demonstrated by the regio- and diastereoselective synthesis of **4i**. The fact that α,β-unsaturated esters undergo azido-iodination by IPy_2BF_4/$TMSN_3$ significantly expands the scope of the process, adding interest for the synthesis of modified β-amino acids. They reacted under related conditions to those previously described for more reactive alkenes,[19] and furnished the regioisomer with the azide moiety attached to the β-carbon (entries 11–13). Moreover, only one diastereoisomer was formed in the azido-iodination of methyl (*E*)-cinnamate **3k**, corresponding to an *anti*-addition of N_3 and I.[20] The push-pull substituted alkene (*E*)-3-methoxy-2-propenoate **3l** yields **4l** (entry 13)[21] as the major component (22 : 1 mixture of stereoisomers).

Although no mechanistic work has been undertaken, the results described are fully compatible with an electrophilic addition process. An initial formation of a cyclic iodonium ion, followed by its subsequent capture by azide would lead to the formation of the adducts with the noted regio- and stereochemistry. The already established ability of the reaction medium to liberate fluoride might be responsible for the N-Si bond activation.[22]

In summary, a new approach to synthesize valuable azido-iodinated derivatives from the known addition path is established. It allows an efficient, easy, and clean introduction of nitrogen and iodine into organic compounds from commercial reagents. The solid and air-stable IPy_2BF_4 reagent emerges as a powerful and easy to manipulate iodonium source for this purpose, overcoming many previously noticed limitations. It is noteworthy that it requires lower amounts of the azide source than other established alternatives, overriding side reactions and minimizing the risk associated to handling the resulting reaction mixtures. On this basis, this new reaction represents the alternative of choice to prepare moderate amounts of azido-iodinated compounds.

Experimental Section

Typical Procedure (Compound 4b)

A solution of IPy_2BF_4 (2.23 g, 6 mmol) in CH_2Cl_2 (20 mL) was treated at 0 °C with $TMSN_3$ (0.56 g, 0.64 mL, 4.8 mmol) under a nitrogen atmosphere. To the resulting yellow solution $BF_3 \cdot OEt_2$ (0.85 g, 0.76 mL, 6 mmol) was added dropwise whereupon the color changed to dark red. Then indene (0.46 g, 0.46 mL, 4 mmol) was added at once. The mixture was stirred for 3 h at the same temperature. The reaction mixture was quenched with a 5% solution of sodium thiosulfate pentahydrate (20 mL) and extracted with dichloromethane (2×10 mL). The combined organic layers were washed with water (2×10 mL) and dried over anhydrous sodium sulfate. Solvents were removed under vacuum and the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 20:1) to yield **4b** (1.08 g, 95%) as a white solid (mp: 54–56 °C).

Acknowledgements

This work was supported by DGICYT (Grant PB97–1271). M. A. thanks the Spanish M.E.C. for a fellowship.

References and Notes

[1] (a) P. B. D. De la Mare, R. Bolton, *Electrophilic Additions to Unsaturated Systems,* 2nd edn., Elsevier, New York, **1982**; (b) E. Block, A. L. Schwan in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 329–362.

[2] (a) Review: J. Rodriguez, J.-P. Dulcère, *Synthesis* **1993**, 1177–1205; (b) S. L. Neidleman, J. Geigert, *Biohalogenation: Principles, Basic Roles and Applications,* Ellis Horwood, Chichester, **1986**.

[3] (a) F. W. Fowler, A. Hassner, L. A. Levy, *J. Am. Chem. Soc.* **1967**, *89*, 2077–2082; (b) A. Hassner, *Acc. Chem. Res.* **1971**, *4*, 9–16; (c) A. Hassner, W. Dehaen, *J. Org. Chem.* **1990**, *55*, 2243–2245.

[4] For a recent review on the synthesis of β-haloazides, see: D. Savoia, *Methoden Org. Chem. (Houben-Weyl,)* 4th edn., **1996**, Vol. E21/9, Thieme, Stuttgart, pp. 5192–5203.

[5] (a) K. Dehnicke, *Angew. Chem.* **1976**, *88*, 612–613; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 553–554; (b) P. Buzek, T. M. Klapötke, P. von. R. Schleyer, I. C. Tornieporth-Oetting, P. S. White, *Angew. Chem.* **1993**, *105*, 289–290; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 275–277.

[6] A. Kirschning, A. Hashem, H. Monenschein, L. Rose, K.-U. Schöning, *J. Org. Chem.* **1999**, *64*, 6522–6526.

[7] A. Kirschning, H. Monenschein, C. Schmeck, *Angew. Chem.* **1999**, *111*, 2720–2722; *Angew. Chem. Int Ed. Engl.* **1999**, *38*, 2594–2596.

[8] V. Nair, T. G. George, V. Sheeba, A. Augustine, L. Balagopal, L. G. Nair, *Synlett* **2000**, 1597–1598.

[9] IPy_2BF_4 is a commercial reagent from either Novabiochem or Aldrich.

[10] (a) For a brief overall view on early applications, see: J. Barluenga, *Pure Appl. Chem.* **1999**, *71*, 431–436; (b) For a recent publication: G. Espuña, G. Arsequell, G. Valencia, J. Barluenga, M. Pérez, J. M. González, *Chem. Commun.* **2000**, 1307–1308.

[11] For the use of $TMSN_3$ in related azidobromination of alkenes, see: G. A. Olah, Q. Wang, X.-Y. Li, G. K. S. Prakash, *Synlett* **1990**, 487–489.

[12] Though we have not had any explosion while preparing these azidoiodides, care should be taken since azides are potentially explosive compounds.

[13] All compounds **4** were fully characterized by IR, MS, ^1H and ^{13}C NMR, elemental analysis and/or HRMS data. See supporting information for representative data.

[14] For a synthesis of vicinal diazides from alkenes using hypervalent iodine reagents, see: R. M. Moriarty, J. S. Khosrowshahi, *Tetrahedron Lett.* **1986**, *27*, 2809–2812.

[15] In the literature, the polymer-bound approach clearly appears as a powerful synthetic alternative to previously established procedures. However, our approach offers higher control over the selectivity as competitive side-reactions were suppressed.

[16] The experimental protocol was slightly modified to avoid fluoroiodination reaction as a side process. In this case, a 200 mL solution containing the iodinating reagent in CH_2Cl_2 was added over a period of 4 h to a mixture of the rest of the components in 90 mL of the same solvent. Once the addition was completed, the reaction mixture was stirred for 2 h, and then standard work-up afforded **4a** in 86% yield.

[17] The polymer-bound reagent is well suited for automated high throughput synthesis where use and access of reagents does not represent a constraint and convenience of work-up is relevant.

[18] For a similar behavior, see ref. [3a] and related references cited therein.

[19] More difficult reactions have been noticed in related IPy_2BF_4-promoted additions to alkenes for electron-withdrawing groups such as in fluoro-iodination reactions, see: J. Barluenga, P. J. Campos, J. M. González, J. L. Suárez, G. Asensio, *J. Org. Chem.* **1991**, *56*, 2234–2237.

[20] Compound **4k** matches data previously described for this structure. For a discussion of several reaction paths in the azidoiodination of α,β-unsaturated systems, see: R. C. Cambie, J. L. Jurlina, P. S. Rutledge, B. E. Swedlund, P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1* **1982**, 327–333.

[21] The stereochemistry was tentatively assigned on the basis of that established for **4k**.

[22] (a) J. Barluenga, I. Llorente, L. J. Alvarez-García, José M. González, P. J. Campos, M. R. Díaz, S. García-Granda *J. Am. Chem. Soc.* **1997**, *119*, 6933–6934; (b) See also ref. [20]