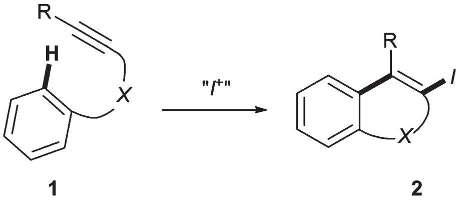
Intramolecular iodoarylation reaction of alkynes: easy access to derivatives of benzofused heterocycles†

José Barluenga,* Mónica Trincado, María Marco-Arias, Alfredo Ballesteros, Eduardo Rubio and José M. González

Received (in Cambridge, UK) 13th January 2005, Accepted 4th February 2005
First published as an Advance Article on the web 22nd February 2005
DOI: 10.1039/b500303b

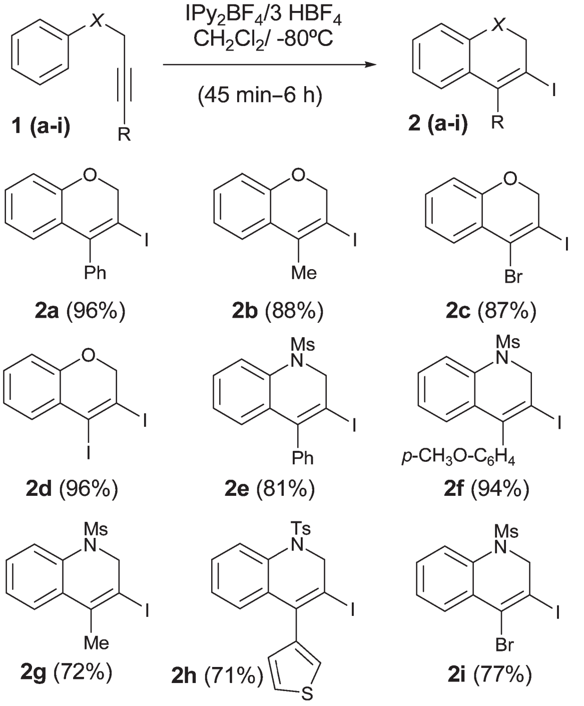
The iodoarylation reaction of heteroatom-tethered ω-arylalkynes offers an efficient and straightforward entry to heterocycles. As a result, both C–C ring-closing from readily available precursors, and concomitant selective iodination take place. The first related study conducted in water is presented.

The implementation of flexible, conceptually simple and synthetically promising approaches that bring about a rapid access to heterocycles is highly desirable, as there is widespread interest in their preparation. The use of organometallic catalysts and/or reagents to assist this task holds a prevailing position among the organic community.[1] The Friedel–Crafts reaction is well suited to promote the arylation reaction of alkenes; however, the related process using alkynes suffers from major limitations.[2] In this challenging scenario, transition metals have provided excellent results, overriding many of the otherwise encountered limitations.[3] We are engaged on a project aimed at uncovering the potential offered by iodonium ions in synthesis,[4] including several alternatives for making C–C bonds.[5] Herein, we describe a robust and versatile process for the construction of derivatives of benzofused heterocycles, based on a successful iodoarylation reaction of alkynes for the ring-closing step (Scheme 1), the heteroatom being just used as an easy tethering component for the assembling of the ω-arylalkyne precursor.



Scheme 1 Iodonium-mediated preparation of benzofused heterocycles by intramolecular arylation of an *X*-tethered alkyne (*X*: heteroatom).

First, the reactivity of different derivatives of phenyl propargyl ether as well as of related N-mesyl propargyl anilines was screened. Thus, following the above depicted approach, there is no need for additional substitution in the aromatic ring, the reaction giving rise to a smooth C–H functionalization. Our initial results are summarized in Scheme 2. Tetrafluoroborate of bis(pyridine)iodonium (IPy_2BF_4) was the reagent first tested as the source of iodonium ion, as it is a fine partner while searching for selective transformations.[6] The formed derivatives **2**[7] can be rationalized assuming initial formation of a vinyliodonium intermediate and its subsequent trapping by the arene, in a Friedel–Crafts type process.[8] Interestingly, though terminal alkynes failed to react, their masked halogenated forms were excellent partners, opening attractive synthetic possibilities for diversity oriented synthesis.[9] In this regard, compounds such as **2c** are particularly useful for further elaboration by merging the resulting halogenated structures of this approach with the potential of metal-catalyzed cross-coupling reactions (Scheme 3). Overall, this methodology renders an alternative and easy entry into a class of valuable tetrasubstituted cycloalkenes,[10] featuring structural motifs that are present in molecules used as ligands as potential selective estrogen modulators (SERMs).[11]



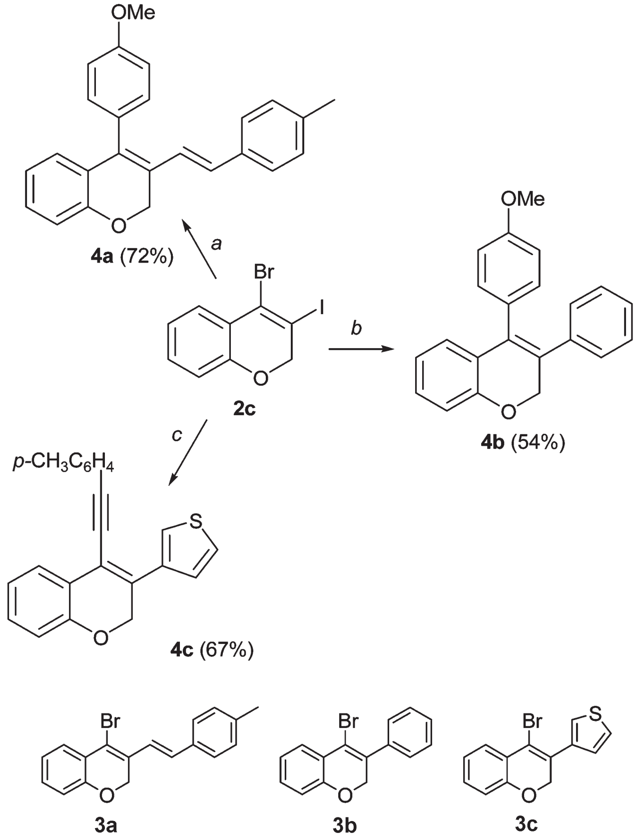
Scheme 2 Cyclization of compounds **1** (*X*: O, NTs, NMs) using iodoarylation reactions for the ring-closing step.

Furthermore, as depicted in Scheme 4, the cyclization allows for additional substitution at the propargylic position retaining chiral information included in **1j**,[12] as well as for carrying out more than one ring-closing step, as in the cases of **6** and **8**.

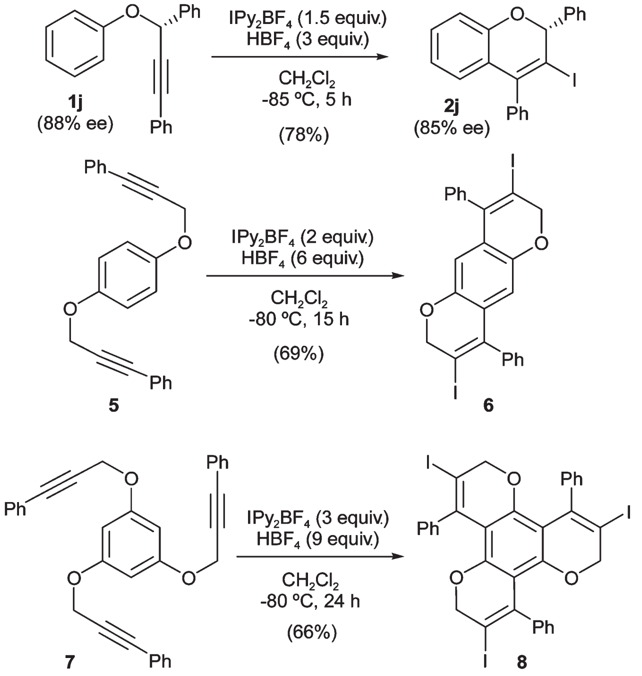
---

† Electronic supplementary information (ESI) available: experimental procedures, characterization data for compounds **2**, **4**, **6**, **8** (including ^1H and ^{13}C NMR spectra). See http://www.rsc.org/suppdata/cc/b5/b500303b/

*barluenga@uniovi.es

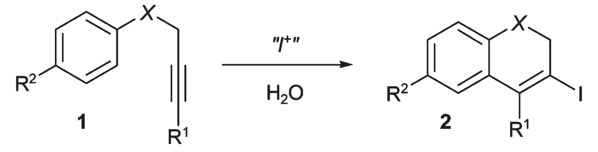


Scheme 3 *Reagents and conditions:* (a) i: **2c** (1 equiv.), p-MeC$_6$H$_4$(CH=CH$_2$) (1.5 equiv.), Pd(OAc)$_2$ (2.3 mol%), P(o-MeC$_6$H$_4$)$_3$ (3 mol%), NEt$_3$, 120 °C (sealed tube), 10 h. ii: **3a** (1 equiv.), p-MeOC$_6$H$_4$B(OH)$_2$ (1.1 equiv.), Pd(Ph$_3$)$_4$ (2 mol%), Na$_2$CO$_3$ (3 equiv.), C$_6$H$_6$–EtOH, 80 °C, 48 h (b) i: **2c** (1 equiv.), C$_6$H$_5$B(OH)$_2$ (1.1 equiv.), Pd(dba)$_2$ (0.5 mol%), PPh$_3$ (1 mol%), KOH (1.1 equiv.), C$_6$H$_6$–EtOH, 80 °C, 15 h. ii: **3b** (1 equiv.), p-MeOC$_6$H$_4$B(OH)$_2$ (1.1 equiv.), Pd(PPh$_3$)$_4$ (2 mol%), Na$_2$CO$_3$ (3 equiv.), C$_6$H$_6$–EtOH, 80 °C, 48 h. (c) i: **2c** (1 equiv.), 3-[B(OH)$_2$]thiophene (1.1 equiv.), Pd(dba)$_2$ (0.5 mol%), PPh$_3$ (1 mol%), KOH (1.1 equiv.), C$_6$H$_6$–EtOH, 80 °C, 15 h. ii: **3c** (1 equiv.), p-MeC$_6$H$_4$(C≡CH) (1.5 equiv.), Pd(OAc)$_2$ (2 mol%), P(o-MeC$_6$H$_4$)$_3$ (3 mol%), CuI (15 mol%), NEt$_3$, 120 °C (sealed tube), 15 h.



Scheme 4 Chromenes upon iodoarylation of alkynes: retention of stereochemistry and multiple ring-closing reactions.

Table 1 Intramolecular iodoarylation reaction of alkynes in water



Entry	R^1	R^2	X	*"I$^+$"*[a]	**Product**	Yield (%)[b]
1	Ph	H	O	A	**2a**	50
2	Ph	H	CH$_2$	A	**2k**	52[c]
3	Ph	H	CH$_2$	B	**2k**	90
4	Ph	H	O	B	**2a**	75[d]
5	Me	H	CH$_2$	B	**2l**	—[e]
6	*n*-Bu	H	CH$_2$	B	**2m**	35[f]
7	Ph	OMe	O	B	**2n**	55[g]
8	Ph	OMe	O	B[h]	**2n**	90[i]

[a] Method A: NaI (1 equiv.), H$_2$O$_2$ (6 equiv. of H$_2$O$_2$, 30% aqueous solution), H$_2$SO$_4$ (8 equiv.), H$_2$O (15 mL/1 mmol **1**), 40 °C, 5 h. Method B: I$_2$ (2 equiv.), H$_2$O (15 mL/1 mmol **1**), rt, 2 h. [b] Isolated yield referred to **1**. [c] Reaction for 20 h. [d] 3 equiv. of I$_2$ used. [e] 1-[(E)-3,4-diiodopent-3-enyl]benzene **9** was formed (95%). [f] 1-[(E)-3,4-diiodooct-3-enyl]benzene **10** was the major product isolated from the reaction mixture. [g] 4-phenyl chromane **11** was also formed and isolated (30%). [h] Amberlyst®-15wet (1g of resin/1 mmol of **1**) was incorporated as additive to the reaction. [i] **11** was formed as by-product (9%).

In connection with our interest in organic processes in water,[13] we were attracted by the stimulating problem of developing C–C bond forming reactions in that media.[14] Initial and promising results were gathered using conditions based on our previous work on iodohydroxylation of alkenes, Table 1 (entries 1–2).[13a]

Thus, NaI can be activated to give both carbo- and heterocyclization reactions involving a scantly reported iodoarylation of alkynes now, for the first time, taking place in water.[15] Alongside this study we also used iodine as the source for the electrophile. Running the reaction in water,[16] cyclization was observed in variable yield, as a function of the alkyne substituent. For simple alkyl groups, the cyclization outcome was dramatically dependent on the length of the chain (entries 5[17] and 6), whereas satisfactory results were accomplished if the alkyne bore an aryl group (entries 3 and 4).

An interesting effect was noticed in the cyclization of the propargyl ether derivative of p-methoxyphenol. Improved selectivity towards the formation of the desired chromene[18] **2n**, as well as a better yield was accomplished upon screening several additives. Best results were obtained using a solid acid-resin (see entries 7 and 8); in the same way, addition of sulfuric acid gave a similar result.

In summary, a versatile entry to heterocycles has been established on the basis of an efficient iodoarylation of alkynes. The convenience of this simple but powerful approach is amplified by further considering the use of the resulting adducts in cross-coupling reactions, that results in a superb combination for the rapid preparation of derivatives. Preliminary evidence on the feasibility of conducting related chemistry in water, under an air atmosphere, are also timely presented and should open interesting opportunities for future developments of reactions taking place at this important interface. Further work, dealing with several points brought about by this communication, is in progress.

This research was partly supported by The Principality of Asturias (PR-01-GE-9) and by The Spanish DGI (MCT-01-BQU-3853). M. T. wants to thank Spanish M.E.C. for a fellowship. Generous support from Merck Sharp & Dohme (UK) is also gratefully acknowledged.

José Barluenga,* Mónica Trincado, María Marco-Arias,
Alfredo Ballesteros, Eduardo Rubio and José M. González
Instituto Universitario de Química Organometálica "Enrique Moles"-Unidad Asociada al C.S.I.C., Universidad de Oviedo, C/Julián Clavería, 8, 33006-Oviedo, Spain. E-mail: barluenga@uniovi.es; Fax: +34 985103450; Tel: +34 985103450

Notes and references

1 (*a*) J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Amsterdam, 2000; (*b*) R. J. Sundberg, *Indoles*, Academic Press, London, 1996; (*c*) for recent reviews, see: I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127; (*d*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285.

2 For a recent advance, showing the merit of ionic liquids to conduct the alkenylation of arenes by reaction with alkynes in the presence of metal triflates, see: (*a*) C. E. Song, D.-u. Jung, S. Y. Choung, E. J. Roh and S.-g. Lee, *Angew. Chem. Int. Ed.*, 2004, **43**, 6183; (*b*) for recent acid-promoted intramolecular carbocyclizations, see: K. Y. Koltunov, S. Walspurger and J. Sommer, *Chem. Commun.*, 2004, 1754; (*c*) L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 10204.

3 Metal-catalyzed hydroarylation of alkynes: (*a*) C. A. Merlic and M. E. Pauly, *J. Am. Chem. Soc.*, 1996, **118**, 11319; (*b*) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura and Y. Fujiwara, *Science*, 2000, **287**, 1992; (*c*) H. Inoue, N. Chatani and S. Murai, *J. Org. Chem.*, 2002, **67**, 1414; (*d*) B. Martín-Matute, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *J. Am. Chem. Soc.*, 2003, **125**, 5757; (*e*) M. T. Reetz and K. Sommer, *Eur. J. Org. Chem.*, 2003, 3485; (*f*) S. J. Pastine, S. W. Youn and D. Sames, *Tetrahedron*, 2003, **59**, 8859; (*g*) N. Tsukada, T. Mitsuboshi, H. Setoguchi and Y. Inoue, *J. Am. Chem. Soc.*, 2003, **125**, 12102; (*h*) C. Nieto-Oberhuber, M. Paz-Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2004, **43**, 2402; (*i*) Z. Shi and C. He, *J. Org. Chem.*, 2004, **69**, 3669; (*j*) V. Mamane, P. Hannen and A. Fürstner, *Chem. Eur. J.*, 2004, **10**, 4556; (*k*) E. Fillion, R. J. Carson, V. E. Trépanier, J. M. Goll and A. A. Remorova, *J. Am. Chem. Soc.*, 2004, **126**, 15354.

4 For recent work, see: J. Barluenga, F. J. González-Bobes, M. C. Murguía, S. R. Ananthoju and J. M. González, *Chem. Eur. J.*, 2004, **10**, 4206.

5 For recent examples, see for instance: (*a*) J. Barluenga, H. Vázquez-Villa, A. Ballesteros and J. M. González, *J. Am. Chem. Soc.*, 2003, **125**, 9028; (*b*) J. Barluenga, H. Vázquez-Villa, A. Ballesteros and J. M. González, *Org. Lett.*, 2003, **5**, 4121; (*c*) J. Barluenga, M. Trincado, E. Rubio and J. M. González, *J. Am. Chem. Soc.*, 2004, **126**, 3416.

6 For an example of unusual selectivity for the *ortho*-iodination in the aromatic substitution reaction, see: G. Espuña, G. Arsequell, G. Valencia, J. Barluenga, J. Alvarez-Gutiérez, A. Ballesteros and J. M. González, *Angew. Chem. Int. Ed.*, 2004, **43**, 325.

7 The structures of compounds **2** were established on the basis of their NMR (^{1}H and ^{13}C) spectroscopic and MS data. All new compounds **2** gave satisfactory elemental analysis and/or HRMS data, according to the proposed structures.

8 For an intermolecular arylation reaction of alkynes, see: (*a*) J. Barluenga, M. A. Rodríguez, J. M. González and P. J. Campos, *Tetrahedron Lett.*, 1990, **31**, 4207; (*b*) In a recent report using ICl, it was assumed that the iodoarylation processes should be applicable only to cyclize electron-rich and conjugated biaryl alkyne fragments, see: T. Yao, M. A. Campo and R. C. Larock, *Org. Lett.*, 2004, **6**, 2677. Clearly, this is not mandatory in our system, nor was it in our related previous work.

9 (*a*) D. S. Tan, M. A. Foley, M. D. Shair and S. L. Schreiber, *J. Am. Chem. Soc.*, 1998, **120**, 8565; (*b*) K. C. Nicolau, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G.-Q. Cao, R. L. Affleck and J. E. Lillig, *J. Am. Chem. Soc.*, 2000, **122**, 9954; (*c*) M.-S. Schiedel, C. A. Briehn and P. Bäuerle, *Angew. Chem. Int. Ed.*, 2001, **40**, 4677.

10 For the preparation of related tetrasubstituted cycloalkenes and their use as precursors for the synthesis of *cis*-3,4-disubstituted chromanes upon hydrogenation, see: P. S. Bury, L. S. Christiansen, P. Jacobsen, A. S. Jørgensen, A. Kanstrup, L. Nærum, S. Bain, C. Fledelius, B. Gissel, B. S. Hansen, N. Korsgaard, S. M. Thorpe and K. Wassermann, *Bioorg. Med. Chem.*, 2002, **10**, 125.

11 Recent reviews on SERMs: (*a*) V. C. Jordan, *J. Med. Chem.*, 2003, **46**, 883; (*b*) V. C. Jordan, *J. Med. Chem.*, 2003, **46**, 1081.

12 This is a relevant characteristic in order to further apply this methodology to the synthesis of compounds with structures related to those present in some SERMs. All compounds **1**, were prepared according to standard procedures.

13 (*a*) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros and J. M. González, *Chem. Eur. J.*, 2004, **10**, 1677; (*b*) J. Barluenga, M. Marco-Arias, F. J. González-Bobes, A. Ballesteros and J. M. González, *Chem. Commun.*, 2004, 2616.

14 For a recent review on stereoselective organic reactions in water, see: (*a*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (*b*) for a recent example of enzymatically triggered halonium-promoted C–C bond-forming reactions in water, see: J. N. Carter-Franklin and A. Butler, *J. Am. Chem. Soc.*, 2004, **126**, 15060.

15 For early work on intramolecular iodoarylation of alkynes, see: (*a*) J. Barluenga, J. M. González, P. J. Campos and G. Asensio, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1546; (*b*) for an elegant development *en route* to prepare fused polycyclic aromatic compounds, see: M. B. Goldfinger, K. B. Crawford and T. M. Swager, *J. Am. Chem. Soc.*, 1997, **119**, 4578.

16 When the reaction of **1k** with iodine (2 equiv.) was conducted in CH_2Cl_2 (15 mL/1 mmol of alkyne) **2k** was obtained in 30% isolated yield.

17 For the obtention of diiodoalkenes from alkynes, see: (*a*) R. A. Hollins and M. P. A. Campos, *J. Org. Chem.*, 1979, **44**, 3931; (*b*) N. Hénaff, S. K. Stewart and A. Whiting, *Tetrahedron Lett.*, 1997, **38**, 4525.

18 For related synthesis of chromenes, see: (*a*) X. García, P. Ballester and J. M. Saá, *Tetrahedron Lett.*, 1991, **32**, 7739; (*b*) N. Cesad, A. A. Clifford and C. M. Rayner, *Tetrahedron Lett.*, 2001, **42**, 323; (*c*) W. Zhao and E. M. Carreira, *Org. Lett.*, 2003, **5**, 4153.