

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

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Received (in Cambridge, UK) 13th January 2005, Accepted 4th February 2005

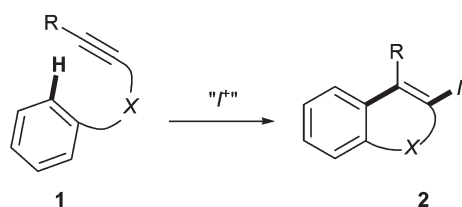
First published as an Advance Article on the web 22nd February 2005

DOI: 10.1039/b500303b

The iodoarylation reaction of heteroatom-tethered ω -aryl-alkynes 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.

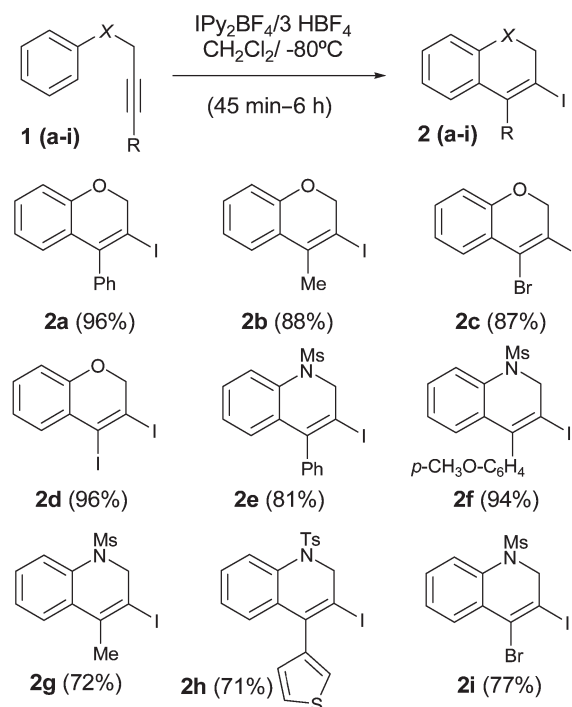
The implementation of flexible, conceptually simple and synthetically promising approaches that bring about a rapid access to heterocycles is highly desirable, as there is widespread interest in their preparation. The use of organometallic catalysts and/or reagents to assist this task holds a prevailing 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.

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 (IPy₂BF₄) was the reagent first tested as the source of iodonium



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

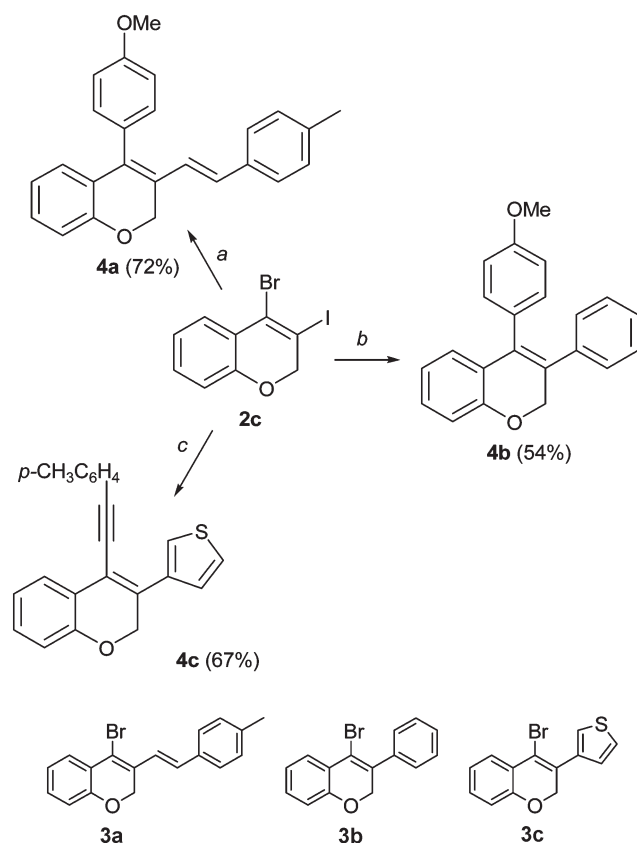
† Electronic supplementary information (ESI) available: experimental procedures, characterization data for compounds **2**, **4**, **6**, **8** (including ¹H and ¹³C NMR spectra). See <http://www.rsc.org/suppdata/cc/b5/b500303b/> *barluenga@uniovi.es



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

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 vinylidonium 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 tetra-substituted cycloalkenes,¹⁰ featuring structural motifs that are present in molecules used as ligands as potential selective estrogen modulators (SERMs).¹¹

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**.

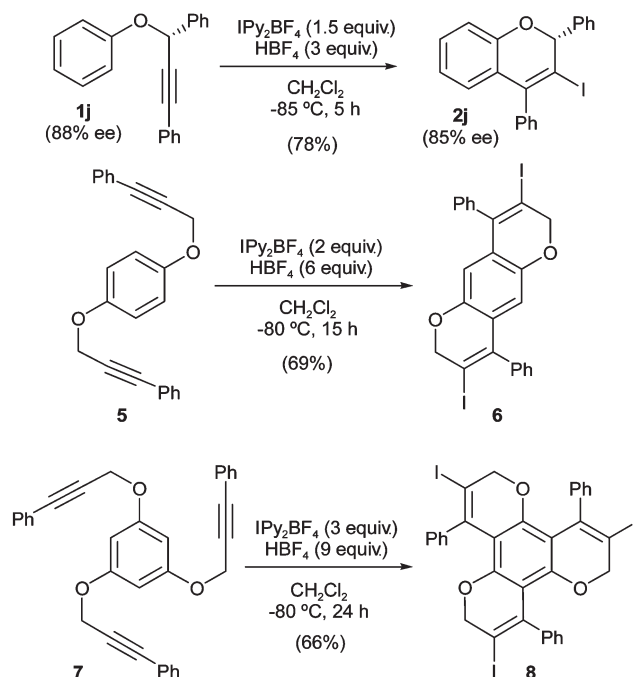


Scheme 3 Reagents and conditions: (a) i: **2c** (1 equiv.), *p*-MeC₆H₄(CH=CH₂) (1.5 equiv.), Pd(OAc)₂ (2.3 mol%), P(*o*-MeC₆H₄)₃ (3 mol%), NEt₃, 120 °C (sealed tube), 10 h. ii: **3a** (1 equiv.), *p*-MeOC₆H₄B(OH)₂ (1.1 equiv.), Pd(PPh₃)₄ (2 mol%), Na₂CO₃ (3 equiv.), C₆H₆-EtOH, 80 °C, 48 h. (b) i: **2c** (1 equiv.), C₆H₅B(OH)₂ (1.1 equiv.), Pd(dba)₂ (0.5 mol%), PPh₃ (1 mol%), KOH (1.1 equiv.), C₆H₆-EtOH, 80 °C, 15 h. ii: **3b** (1 equiv.), *p*-MeOC₆H₄B(OH)₂ (1.1 equiv.), Pd(PPh₃)₄ (2 mol%), Na₂CO₃ (3 equiv.), C₆H₆-EtOH, 80 °C, 48 h. (c) i: **2c** (1 equiv.), 3-[B(OH)₂]thiophene (1.1 equiv.), Pd(dba)₂ (0.5 mol%), PPh₃ (1 mol%), KOH (1.1 equiv.), C₆H₆-EtOH, 80 °C, 15 h. ii: **3c** (1 equiv.), *p*-MeC₆H₄(C≡CH) (1.5 equiv.), Pd(OAc)₂ (2 mol%), P(*o*-MeC₆H₄)₃ (3 mol%), CuI (15 mol%), NEt₃, 120 °C (sealed tube), 15 h.

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 scanty 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 5¹⁷ 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 chromene¹⁸ **2n**, as well as a better yield was accomplished upon screening several



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	"T" ^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	<i>n</i> -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.), H₂O₂ (6 equiv. of H₂O₂, 30% aqueous solution), H₂SO₄ (8 equiv.), H₂O (15 mL/1 mmol **1**), 40 °C, 5 h. Method B: I₂ (2 equiv.), H₂O (15 mL/1 mmol **1**), rt, 2 h. ^b Isolated yield referred to **1**. ^c Reaction for 20 h. ^d 3 equiv. of I₂ 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 chromene **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%).

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.

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