

Regioselective Synthesis of Substituted Naphthalenes: A Novel de Novo Approach Based on a Metal-Free Protocol for Stepwise Cycloaddition of *o*-Alkynylbenzaldehyde Derivatives with Either Alkynes or Alkenes

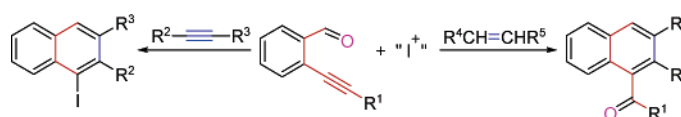
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ABSTRACT

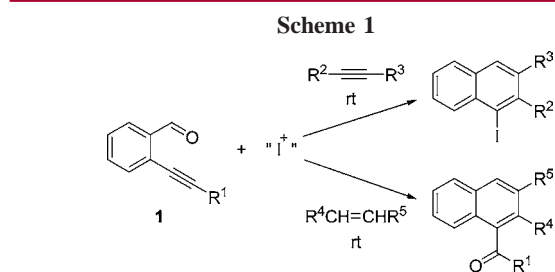


Iodonium ions, *o*-alkynyl-substituted carbonyl compounds, and alkynes react to give 1-iodonaphthalene derivatives featuring interesting substitution patterns. The reaction with alkenes instead of acetylenes affords related naphthyl ketone derivatives. These two metal-free processes are conducted at room temperature and furnish products in a regioselective manner.

The reactivity of carbon–metal bonds has been largely exploited for the regioselective elaboration of substituted naphthalenes.¹ Thus, at the same time the basic aromatic core is assembled, a site-selective functionalization of naphthalene is achieved, rendering straightforward access to otherwise difficult substitution patterns.² Recently, we have shown that iodonium ions are a simple alternative to metal compounds to accomplish valuable C–C bond forming reactions.³ Herein, we present recent findings on the preparation of substituted naphthalene compounds upon treatment of *o*-(alkynyl)-benzaldehyde derivatives **1** with bis(pyridine) iodonium tetrafluoroborate (IPy₂BF₄)⁴ and subsequent addition of either an alkyne **2** or an alkene **5** (Scheme 1).

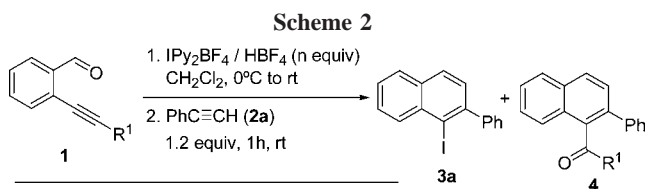
The cocyclization of acetylenic aldehydes **1** with different alkynes **2** mediated by IPy₂BF₄ was initially explored. Representative data are summarized in Scheme 2.⁵

In a standard protocol, HBF₄ is added to generate in solution a reactive form of the iodonium ion, by neutralizing pyridine ligands.⁶ On this basis, a facile and regioselective assembling of iodinated naphthalenes **3** was noticed upon



mixing reagents at 0 °C, allowing the reaction mixture to rise up to room temperature before adding **2a**, and further stirring the mixture for 1 h. Variable amounts of naphthyl

(1) For recent examples, see: (a) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680. (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (c) Viswanathan, G. S.; Wang, M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2138. (d) Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505. (e) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518.



1	HBF ₄ (equiv)	Yield (%) ^a	3 : 4 ratio ^b
1a (R ¹ = Ph)	1.1	62	1 : 1 (3a : 4a)
1b (R ¹ = Bu)	1.1	72	5 : 1 (3a : 4b)
1a (R ¹ = Ph)	2.2	72	1 : 1 (3a : 4a)
1b (R ¹ = Bu)	2.2	76	10 : 1 (3a : 4b)

^a Yield based on the combined isolated amount of pure compounds **3** and **4**. ^bBased on GC analysis of the crude reaction mixture.

ketone derivatives **4** were found as byproduct in this new reaction. Initial studies addressed the influence that the amount of acid has over the reaction outcome. As depicted, no appreciable influence over the product distribution was noticed for R¹ = Ph, and only a slight increase in the combined yield was observed. However, for R¹ = *n*-Bu, higher selectivity in the synthesis of **3a** is possible. Interestingly, this selectivity was greatly increased when 2 equiv of HBF₄ were added. Consequently, **1b** and addition of 2 equiv of the acid were routinely employed to further investigate other features of this uncommon iodo-benzannulation sequence. Some important results are summarized in Table 1.

Entries 1 and 2 show both aryl-**2a** and alkyl-substituted terminal alkynes **2b** can be selectively cross-coupled with **1b** to give compounds **3a** and **3b**, respectively. These reactions gave the desired iodinated compounds in satisfactory isolated yield and, interestingly, proceeded in a regioselective manner.⁷ Internal alkynes were also tested (see entries 4 and 5) and reacted according to a similar trend, opening a convenient entry to a selective and direct elaboration of 1,2,3-trisubstituted naphthalenes. For the case of internal alkynes,

(2) To this aim, not only organometallic transformations but also thermally and photochemically driven reactions have been reported. For illustrative examples, see: (a) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2003**, *68*, 1938. (b) Takahashi, T.; Li, Y.; Stepnicka, P.; Kitamura, M.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 576. (c) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Am. Chem. Soc.* **2001**, *123*, 9178. (d) Bowles, D. M.; Anthony, J. E. *Org. Lett.* **2000**, *2*, 85. (e) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (f) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (g) de Frutos, Ó; Echavarren, A. M. *Tetrahedron Lett.* **1997**, *38*, 7941. (h) Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154. (i) Bradford, C.; Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1995**, *36*, 4189.

(3) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028.

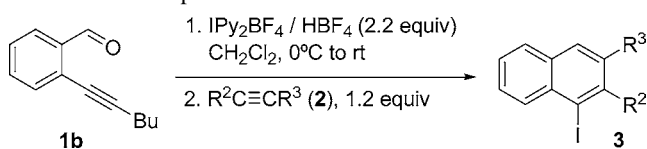
(4) For a recent synthetic application of this commercially available reagent, see: Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.

(5) The structures for compounds **3** and **4** are based on their spectroscopic and analytical data. For the case of **3d** and **3e**, 2D-NMR experiments (HMBC) confirmed the depicted structures (see Supporting Information). For compounds **4**, satisfactory comparison with already published data was possible for some compounds (see characterization data in ref 1b).

(6) See for instance: Barluenga, J.; Campos, P. J.; González, J. M.; Suárez, J. L.; Asensio, G. *J. Org. Chem.* **1991**, *56*, 2234.

(7) No evidences for the formation of other regioisomers of compound **3** were obtained from GC analysis of crude reaction mixtures.

Table 1. Iodonaphthalene Derivatives **3**

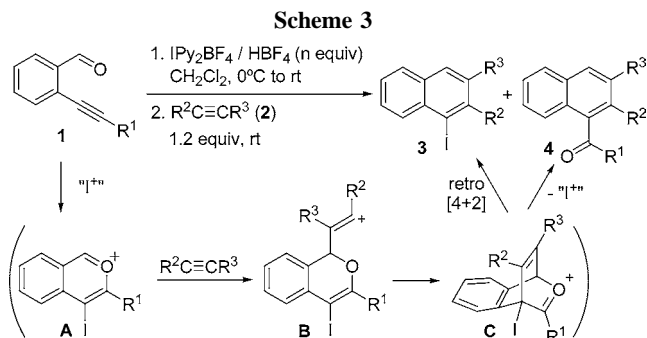


entry	product	R ²	R ³	<i>t</i> (h)	yield (%) ^a
1^b	3a	Ph	H	1	68
2^b	3b	<i>n</i> -Pr	H	1	60
3^b	3c	4-MeO-C ₆ H ₄	H	0.5	42
4^b	3d	Ph	Me	0.5	65
5^b	3e	Ph	CO ₂ Et	3	42

^a Isolated yield for compounds **3**, referenced to **1b** (1 mmol scale). ^b In all cases the crude reaction mixture contained variable amounts of the corresponding ketone **4** (see Scheme 1). Entry (GC ratio **3**:**4**) from crude reaction mixture: 1 (10:1), 2 (8:1), 3 (2.5:1), 4 (15:1), 5 (17:1).

the transformation is more prone toward the formation of compounds of type **3**, as proved by higher values for the ratio **3**:**4** in crude reaction mixtures. Thus, though pure **3e** was obtained in only moderate yield in a yet unoptimized process, no significant amounts of the related naphthyl ketones were isolable after chromatographic purification of the crude reaction mixture.

A mechanistic proposal accounting for the observed products is outlined in Scheme 3. An initial attack of the

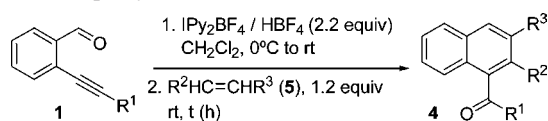


iodonium ion to the alkyne moiety⁸ assisted by the neighboring carbonyl functionality leads to the reactive benzo[*c*]pyriliium cation **A**. As earlier proposed for the AuCl₃-catalyzed synthesis of naphthyl ketone derivatives,⁹ stepwise cycloaddition of the alkyne onto the pyriliium system¹⁰ would render intermediate **C** that determines the regioselectivity of the process. From there, loss of iodonium ion affords the minor reaction product **4**, in a formally catalytic process. Competitive retro [4 + 2] cycloaddition gives access to the

(8) (a) Barluenga, J.; Rodríguez, M. A.; Campos, P. *J. Org. Chem.* **1990**, *55*, 3104. (b) Barluenga, J.; Llorente, I.; Alvarez-García, L. J.; González, J. M.; Campos, P. J.; Díaz, M. R.; García-Granda, S. *J. Am. Chem. Soc.* **1997**, *119*, 6933. (c) See also ref 3.

(9) For related intermediate species triggered by gold salts instead of iodonium ions, see ref 1b.

(10) For the chemistry of this class of compounds, see: Kuznetsov, E.; Shcherbakova, I. V.; Balaban, A. T. *Adv. Heterocycl. Chem.* **1990**, *50*, 157.

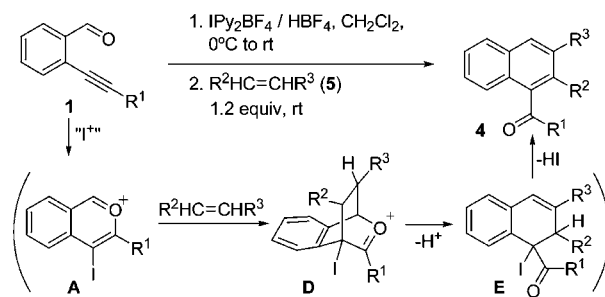
Table 2. Naphthyl Ketone Derivatives **4**

entry	alkene	product	R ¹	R ²	R ³	t (h)	yield (%) ^a
1	5a	4a	Ph	Ph	H	1	78
2	5a	4b	<i>n</i> -Bu	Ph	H	2	70
3	5b	4e	Ph	<i>n</i> -Bu	H	2	73
4	5c	4f	Ph	Ph	Me	1	65
5	5d	4g	Ph	Ph	CO ₂ Me	19	74
6	5e	4h	Ph	-CH ₂ CH ₂ CH ₂ CH ₂ -		2	70

^a Isolated yield for compounds **4**, referenced to **1** (1 mmol scale).

major component **3**. To support this mechanism, the quenching of the reaction mixture with 1-octanol was investigated. Interestingly, besides the desired naphthalene compounds, significant amounts of octylpentanoate were found also to be present in the crude reaction mixture, providing an additional evidence for the participation of **C** in the formation of idonaphthalenes **3**. Furthermore, differences between C–Au and C–I bonds might account for a distinctive reaction manifold, as observed for these approaches to the construction of substituted naphthalene rings.

We attempted to expand the scope of this iodonium-triggered chemistry to allow for a synthetic entry to compounds **4**. In this regard, we decided to explore the related process using alkenes instead of alkynes in cyclization reactions with compounds **1**. Our preliminary results are summarized in Table 2. A fast process takes place, resulting in an efficient preparation of the target naphthyl ketone, as sole reaction product. This new reaction offers a nice selectivity for the assayed alkenes **5**. With respect to R¹ in **1**, both aliphatic and aromatic substituents gave satisfactory results (entries 1 and 2). Both aliphatic- and aromatic-substituted terminal alkenes are adequate components for this benzannulation chemistry, though a longer reaction time (2 h) was required for the former to raise a similar yield of the corresponding **4**. Disubstituted alkenes (entries 4 and 5) offer an interesting alternative to prepare 2,3-disubstituted 1-naphthyl ketones in a very simple process, both in terms of the chemicals and simplicity of the operational protocol. Cyclic alkenes also

Scheme 4

enter in this approach to access ketones **4** (see entry 6). This is a remarkable feature, because the resulting compound **4h** cannot be easily targeted from alternative approaches based on simple alkynes.

In terms of a plausible mechanistic interpretation for this reaction and based on the previous observations for the parent alkyne transformation, a related intermediate **D** can be assumed. Loss of a proton would produce compound **E**, and elimination of HI with concomitant aromatization easily furnish **4** (Scheme 4).

In summary, new metal-free protocols for the synthesis of different types of substituted naphthalenes have been presented. The combination of **1**, iodonium ions, and either alkynes **2** or the convenient alkenes **5** drives complex reaction sequences in a predictable manner and with attractiveness for preparative purposes. In this synthetic scenario, the advantage offered by a sole triggering element such as iodine is unique. It suggests further developments, specially offering valuable alternatives to transition-metal-mediated transformations.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3** and **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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