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COMMUNICATIONS

Cyclization of Carbonyl Groups onto Alkynes upon Reaction with IPy_2BF_4 and Their Trapping with Nucleophiles: A Versatile Trigger for Assembling Oxygen Heterocycles

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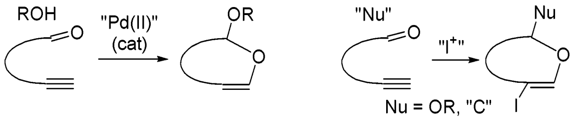
Electrophilic addition reactions of polarized reagents across unsaturated functionalities are of relevance to prepare difunctional compounds.[1] To this regard, different sources of halonium ions are useful reagents.[2] However, these intermediates have been scantly reported for carbon−carbon bond-forming reactions,[3] a bonus routinely credited to metal-mediated transformations.[4] Recently, an interesting Pd(II)-catalyzed cyclization has been described for the conversion of acetylenic aldehydes to alkenyl ethers.[5] Herein, a new, metal-free entry into related heterocycles is presented. Overall, smooth access to a wide set of iodinated adducts is achieved upon reaction of bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4)[6] with those unsaturated carbonyl precursors and, remarkably, with an unprecedented set of nucleophiles. Alcohols, as well as different C-nucleophiles, behave as efficient partners in this new reaction of alkynes triggered by iodonium ions (eq 1).

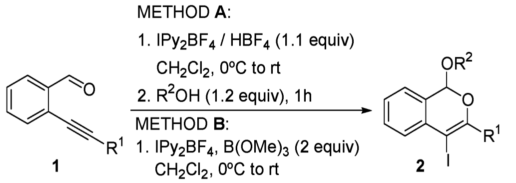


(1)

The cyclization of acetylenic aldehydes **1** by reaction with IPy_2BF_4 and different alcohols was initially investigated. The reaction uses the standard activation of the iodinating agent by addition of HBF_4, that liberates a more reactive form of the iodonium reagent.[7] Sequential treatment of the iodinating mixture with several *ortho*-(alkynyl)benzaldehydes **1**, and then with alcohols, nicely afforded compounds **2**. These results are summarized in Scheme 1 (method **A**). Thus, not only linear and branched R^2 side chains have been used, but also the labile propargyl alcohol has been an effective nucleophile. The R^1 moiety can also be modified, the reaction being found to work well for R^1 = aryl, alkyl, and alkenyl. The yields of compounds **2** were much dependent on the reaction scale (see entries 1,2 and 5,6); nevertheless, the values for conversion based on the NMR analysis of crude reaction mixtures were essentially comparable.[8] Alternatively, this iodine-addition, ring-closing, nucleophilic trapping sequence can also be carried out by reacting a mixture of the iodinating agent and $B(OMe)_3$ with **1** (Scheme 1, method B). Thus, a single reagent such as $B(OMe)_3$ acts both as Lewis acid and as the source of the methoxy group to furnish compounds **2**. Furthermore, in this event, compounds **2** were prepared in good yield in a 1 mmol scale process.

Using this approach, the enolizable ketone **3** gave **4** in moderate yield, most probably because of partial decomposition under acid media (eq 2).[9] In this case, the cyclization follows the more common 5-exo-dig cyclization mode,[10] furnishing a five-member ring, rather than the 6-endo cyclization noticed for aldehydes **1**.[11]

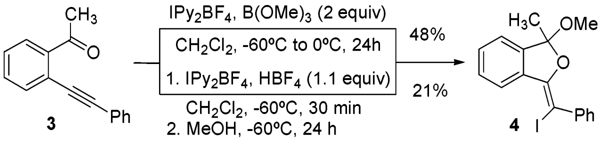
Scheme 1 [a]



Entry	**1** R^1	R^2OH	**2**[a] (Method **A**: %)	**2**[a] (Method **B**: %)
1	**1a** Ph	CH_3OH	**2a** (63)	**2a** (88)[d]
2	**1a** Ph	CH_3OH	**2a** (84)[b]	
3	**1a** Ph	$(CH_3)_2CHOH$	**2b** (61)	
4	**1a** Ph	$HC{\equiv}CCH_2OH$	**2c** (57)[c]	
5	**1b** Bu	CH_3OH	**2d** (58)	**2d** (82)
6	**1b** Bu	CH_3OH	**2d** (87)[b]	
7	**1c** 1-Cyclohexenyl	CH_3OH	**2e** (62)	**2e** (79)[e]

[a] (a) Isolated yield for compound **2**, referred to **1** (1 mmol scale). (b) 5 mmol of the corresponding starting material **1** was used. (c) Reaction time 4 h, after R^2OH addition. (d) Using 0.5 mmol $(OMe)_3$, 85% yield in 2 h. (e) Reaction time 3 h.

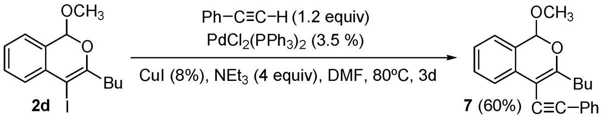
A distinctive feature of this novel approach to cyclize ω-alkynyl-carbonyl derivatives is the introduction of carbon-based nucleophiles **5** in the reaction sequence. Interesting results were obtained using silyl-masked C-nucleophiles,[12] providing a straight and useful access to more elaborated heterocycles **6** (Table 1).[13] Overall, these reactions offer nice examples of unprecedented Mukaiyama-like cross-coupling[14] and Hosomi−Sakurai allylation[15] reactions triggered by an unconventional Lewis acid, such as the result of the addition of an iodonium ion to an alkyne. Moreover, electron-rich arenes can be used as the nucleophile, resulting in a novel arylation reaction of an aldehyde in acid media.



(2)

Besides its novelty, another intrinsic feature of this reaction deals with the incorporation of iodine. This element could modulate the biological profile of a bioactive compound,[16] and its chemistry adds synthetic interest.

We have found that compound **2d** can be nicely cross-coupled with phenylacetylene (eq 3).[17]



(3)

A mechanistic proposal accounting for the observed products is outlined in eq 4. One can assume the initial attack of the iodonium ion to the alkyne moiety[18] assisted by the neighboring carbonyl

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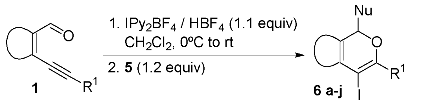
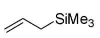
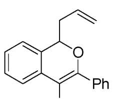
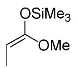
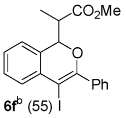
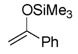
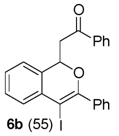
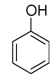
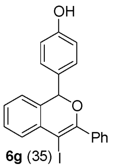
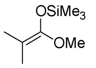
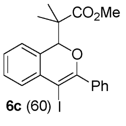
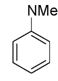
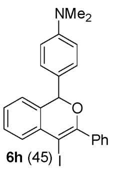
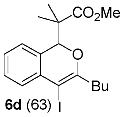
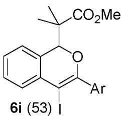
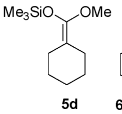
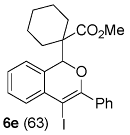
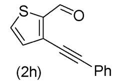
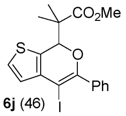
Table 1. Cyclization with IPy_2BF_4 and Trapping with C-Nucleophiles

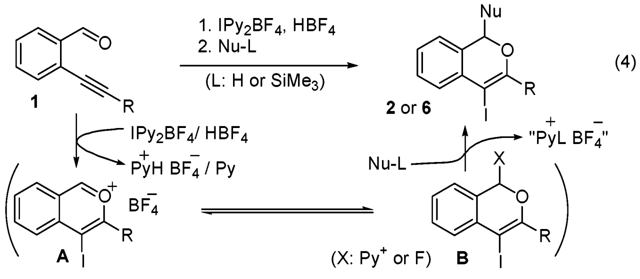


1 → **6 a-j**

R^1 (h)	**5** ($NuSiMe_3$) (NuH)	**6**^{a} (%)	R^1 (h)	**5** ($NuSiMe_3$) (NuH)	**6**^{a} (%)
Ph (1h)	 **5a**	 **6a** (42)	Ph (1h)	 **5e**^{b}	 **6f**^{b} (55)
Ph (1h)	 **5b**	 **6b** (55)	Ph (16h)	 **5f**	 **6g** (35)
Ph (1h)	 **5c**	 **6c** (60)	Ph (1.5h)	 **5g**	 **6h** (45)
Bu (1h)	**5c**	 **6d** (63)	Ar (5h) Ar = 4-$NO_2C_6H_4$	**5c**	 **6i** (53)
Ph (2h)	 **5d**	 **6e** (63)	 (2h)	**5c**	 **6j** (46)

^{a} Isolated yield for compounds **6**, referred to **1** (reactions using 1 mmol of **1**). ^{b} 1:1 mixture of diastereoisomers by ^1H NMR of the crude reaction mixture.

functionality to furnish the reactive species **A**.[19] This intermediate could equilibrate with **B** by incorporation of nucleophilic species already present in the reaction media.[20] Subsequent addition of the external nucleophile would give rise to the observed compounds.[21]



(4)

Overall, new metal-free protocols for consecutive C−O and C−C bond making have been executed; as a consequence, new three-component sequences have been established.[22] The iodonium approach offers some advantages, such as conceptually a broad compatibility with the nucleophile, and also those related to the incorporation of iodine. Its rich chemistry adds interest to this clean process and highlights its role as an electrophilic promoter beyond that of a proton. Further studies in this area are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **4**, **6**, and **7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) A more sluggish reaction takes place in the absence of added acid. Thus, for **2a**, the reaction of **1a** and MeOH took up to 7 h, to be completed in an extension similar to that reported in Table 1 (58%, for 1 mmol scale).

(8) Analysis of crude reaction mixtures by NMR showed quantitative conversion of **1** to **2**, that is formed as a single regioisomer.

(9) The cyclization of ketones was not reported for the related palladium-catalyzed cyclization, see ref 5a, in this manuscript. Compound **4** features a distinctive deshielded signal at 8.9 ppm in the ^1H NMR.

(10) See, for instance: (a) Yamamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 582. (b) Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318. (c) Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1269. (d) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976. (e) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc, Chem. Commun.* **1994**, 493.

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