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Transition metal-free dimerization of alkynes using hypervalent iodine reagents

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ABSTRACT

conditions.

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Introduction

The 1,3-diyne moiety is an important structural motif, that is frequently found in many biologically active compounds or natural products¹ as well as functional materials.² Since the seminal report by Glaser describing the Cu-mediated oxidative homocoupling of terminal alkynes almost 150 years ago,³ a lot of efforts have been made in the development of different and complementary strategies to facilitate the coupling of alkynes.^{4–7} Most commonly, such (homo)-coupling reactions are facilitated by transition metals like Cu or Pd, either in a catalytic or in a stoichiometric fashion.^{4,5}

Our group has recently reported the modestly enantioselective organocatalytic α -cyanation of ketoesters **2** using the cyano benziodoxole **1** as an electrophilic cyanide-transfer reagent.⁸ In attempts to use reagent **1** to carry out the cyanation of pheny-lacetylene **4**, we realized that under neither of the tested conditions any of the targeted nitrile **5** can be obtained. Surprisingly however, in some cases we observed small quantities of the homocoupling product **7**. This came as a surprise as, to the best of our knowledge, the oxidative dimerization of acetylene derivatives like **4** facilitated by hypervalent iodine reagents has so far only been reported very sparingly.⁶ In this early example the coupling could be carried out by the addition of alkynyl-copper reagents to preform alkynyl-phenyl iodonium salts.⁶ However, apart from this Letter, the use of commonly employed alkynyl-based iodonium salts as electrophilic alkyne transfer reagents⁹ was, as far as we

* Corresponding author. E-mail address: mario.waser@jku.at (M. Waser). know, not yet described for the synthesis of 1,3-diynes like compound $7.^9$ Based on these facts, we now carried out a detailed investigation of this interesting transformation.

Results and discussion

This communication describes the use of hypervalent iodine reagents to facilitate the homo-coupling of

terminal alkynes. A variety of different aliphatic and aromatic alkynes were successfully dimerized when

using acetoxy-benziodoxole as the activating agent under operationally simple transition metal-free

In our initial experiments we only observed the formation of **7** in a few cases. After the first evaluation of the reaction parameters we soon realized that this coupling only occurred when minor quantities of acetoxy-benziodoxole **6** were present (originating from the synthesis of **1**),¹⁰ but not when pure cyanide **1** was used (Scheme 1).







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Based on this first hint, we tested a series of different commonly employed hypervalent iodine reagents under different conditions to evaluate the best-suited system for the formation of 7 (Table 1). Initial attempts with reagent **6** revealed that *n*-BuLi and LiHMDS are the only strong bases that allow for the formation of 7 (see entries 1-4). Fortunately, in these two cases diyne 7 was obtained in high yields of up to 90% (entries 1 and 2) when performing the reaction in THF (starting from -40 °C for the addition of the base and then stirring at room temperature for 2 h). Attempts to use only half an equivalent of iodine-reagent 6 resulted in less than 50% yield after 2 h (entry 5). However, a prolonged reaction time of 40 h gave 70% of product 7. This indicates that a mechanism where half of the starting alkyne **4** will add to the iodonium reagent first, giving an electrophilic alkyne-transfer reagent which is then attacked by the remaining alkyne (which should be present as the Li-acetvlide) is possible. However, it is not clear why the reaction is that much slower when using only 0.5 equiv of 6. Using only 0.5 equiv of *n*-BuLi also resulted in less than 50% yield under the standard conditions (entry 6). Unfortunately, we were not able to use catalytic amounts of 6 in combination with an alternative stoichiometric oxidant (entry 7). We next tested a variety of other easily available hypervalent iodine reagents (entries 8-13) under the optimum reaction conditions. Among those, only Dess-Martin periodinane 9 and derivative 12 allowed for some product formation, whereas acyclic derivatives **10** and **11** gave no product at all.

Having identified suitable conditions for the high-yielding homocoupling of **4**, we employed other terminal alkynes in this reaction. It was found that a variety of different aryl alkynes were well tolerated under these conditions (giving products **13–17** shown in Scheme 2). In addition, aliphatic alkynes can also be dimerized with this method. Hereby it is fair to mention that especially the presence of NH-carbamate groups resulted in a reduced yield (see compound **24**). Nevertheless, a variety of different terminal alkynes could be successfully coupled.

Table 1

Identification of the best-suited iodine reagent and conditions for the dimerization of ${\bf 4}$



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	Entry	[I]-reagent	Base	Yield ^a (%)
	1	6 (1.1 equiv)	LiHMDS (1.1 equiv)	84
	2	6 (1.1 equiv)	n-BuLi (1.1 equiv)	90
	3	6 (1.1 equiv)	t-BuOK (1.1 equiv)	n.r.
	4	6 (1.1 equiv)	NaH (1.1 equiv)	n.r.
	5	6 (0.5 equiv)	n-BuLi (1.1 equiv)	<50 ^b (70) ^c
	6	6 (1.1 equiv)	n-BuLi (0.5 equiv)	<50 ^b
	7	6 (0.1 equiv) ^d	n-BuLi (1.1 equiv)	<10 ^b
	8	1 (1.1 equiv)	n-BuLi (1.1 equiv)	n.r.
	9	8 (1.1 equiv)	n-BuLi (1.1 equiv)	n.r.
	10	9 (1.1 equiv)	n-BuLi (1.1 equiv)	30
	11	10 (1.1 equiv)	n-BuLi (1.1 equiv)	n.r.
	12	11 (1.1 equiv)	n-BuLi (1.1 equiv)	n.r.
	13	12 (1.1 equiv)	n-BuLi (1.1 equiv)	18

The bold entry highlights the most active system identified in the screening. ^a Isolated yields.

^b NMR yield.

^c After 40 h reaction time.

^d Using additional stoichiometric oxidants like, e.g., Oxone, NaIO₄ or Ca(ClO)₂.



Scheme 2. Application scope for the homocoupling of different alkynes in the presence of benziodoxole reagent 6.



Scheme 3. Control experiment using preformed alkynebenziodoxole 25.

Finally, we were interested to obtain more insight into a possible mechanism of this reaction. As already noted during the optimization of the reaction conditions, a possible path could be the formation of the electrophilic alkyne-transfer reagent **25** first, which is then reacting with a Li-acetylide (e.g., **Li-4**). We thus carried out control experiments where we used preformed literature-known alkynebenziodoxole **25**¹² under the optimized conditions and reacted it with **Li-4** (Scheme 3). Full conversion was observed within 2 h giving dimer **7** in 90% yield, which strongly supports that the herein reported reaction actually proceeds via the formation of compound **25** as the key-intermediate. This mechanism also opens the door for future applications directed toward the formation of dissymmetrically substituted divnes.

Conclusion

The use of hypervalent iodine reagents allows for the efficient transition metal-free dimerization of a variety of terminal alkynes. Key to success in this transformation is the use of acetoxy-benzio-doxole **6** as the activating agent, which clearly outperformed other hypervalent iodine species. Based on control experiments that were carried out using preformed hypervalent iodine-based alkyne-transfer reagents we propose a mechanism where one equivalent of the alkyne adds to benziodoxole **6** to give an electrophilic alkynebenziodoxole derivative **25** first, which then reacts with the Li-acetylide of the second equivalent of the alkyne. This strategy should thus also provide a future option to obtain dissymmetric 1,3-diynes.

Experimental section

General procedure for the dimerization of terminal alkynes

A 1.6 M solution of *n*-BuLi in hexanes (1.1 equiv) was added to a solution of the corresponding terminal alkyne (1.0 equiv) in THF (5 mL per mmol) at -40 °C. After stirring for 30 min, acetoxy-ben-

ziodoxole **6** (1.1 equiv) was added in one portion. The mixture was kept at $-40 \,^{\circ}$ C for 10 min and then allowed to reach room temperature while stirring for 2 h. Then, the reaction mixture was quenched with a saturated solution of NaHCO₃ and extracted three times with dichloromethane. After the evaporation of the solvent, the crude product was purified by column chromatography (silica gel; heptanes/EtOAc) to afford the alkyne dimer **7**, as well as **13**–**24**, in the reported yields.

1,4-Diphenylbuta-1,3-diyne (7)

This is obtained as a white solid in 90% yield (0.2 mmol scale). Analytical data are in full accordance with literature:¹¹ ¹H NMR (300 MHz, CDCl₃, 298 K): δ /ppm = 7.56–7.52 (m, 4H), 7.39–7.33 (m, 6H); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ /ppm = 132.5, 129.2, 128.5, 121.8, 81.6, 73.9; MS (ESI): *m*/*z* calcd for C₁₄H₁₀: 203.08 [M+H]⁺; found: 203.08.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03. 007.

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