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Hypervalent iodine-mediated regioselective cyclization of acetylenic malonates: facile synthesis of 1-diiodomethylene indane and cyclopentane derivatives†

Chen Zheng and Renhua Fan*

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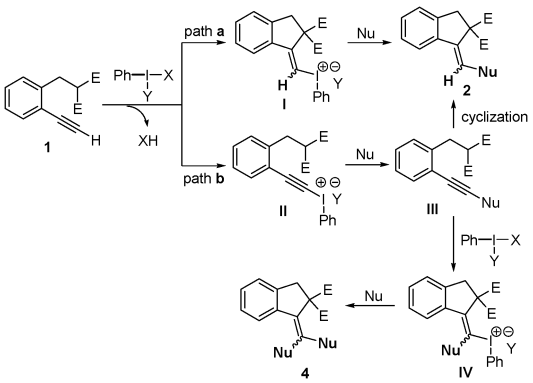
A facile synthesis of potentially useful 1-diiodomethylene indanes and cyclopentanes from the regioselective cyclization of acetylenic malonates with the combination of iodosobenzene with tetrabutylammonium iodide in 2,2,2-trifluoroethanol is reported.

In the last few decades, hypervalent iodine compounds have found broad application in organic synthesis because of their versatility, ready availability, and environmentally friendly nature.[1] As the result of their enhanced electrophilic properties, the reactions of hypervalent iodine compounds with alkynes have been widely investigated.[1,2] Nonterminal alkynes are usually oxidized to the corresponding carbonyl derivatives.[3] The reaction of terminal alkynes gives rise to two potentially useful products: alkynyl- and alkenyl-iodonium salts.[4] Both of them are highly reactive to various nucleophiles.[5,6] On the other hand, the groups of Taguchi,[7] Liang,[8] Barluenga,[9] and Wirth[10] reported the iodine-induced electrophilic cyclizations of acetylenic malonates or β-ketoesters to afford iodo-substituted indene or cyclopentene derivatives with the aid of a base or a Lewis acid. The elegance of these tactics leads us to examine the electrophilic cyclization of acetylenic malonates in the presence of a hypervalent iodine compound.[11]

As shown in Scheme 1, the reaction might proceed in two pathways. In path a, alkenyl-iodonium salt **I** generated from the iodine(III)-induced *5-exo*-carbocyclization will be ready to undergo the nucleophilic attack to provide product **2**. In path b, the ligand exchange of the hypervalent iodine compound with the terminal alkyne group will provide an alkynyl-iodonium salt **II**, and this intermediate will react with the nucleophile to form a Nu-substituted alkyne **III**. Besides the direct cyclization to access product **2**, intermediate **III** might undergo an iodine(III)-induced *5-exo*-carbocyclization followed by the second nucleophilic substitution to afford product **4**.‡

To test our hypothesis, we selected diethyl 2-(2-ethynylbenzyl)-malonate **1a** as the model substrate for reaction condition screening. First, we examined a variety of hypervalent iodine compounds, such as PhI(OH)OTs (HTIB), PhI(OH)OPO(OPh)$_2$, PhI(OAc)$_2$ (DIB), PhI(OCOCF$_3$)$_2$ (BTI), and PhIO. Complicated reactions were observed, and no desired cyclization products were isolated from the reactions. The analysis of the isolated compounds indicated that compound **1a** was oxidized to some unidentified carbonyl compounds. Some of our recent efforts have been addressed in the oxidative cyclizations with the combination of iodosobenzene with tetrabutylammonium iodide (PhIO/Bu$_4$NI), and the *in situ* generated PhI(ONBu$_4$)I was proposed to be the reactive iodine(III) species.[12] Hence, this combination was employed to induce the cyclization of substrate **1a**. The reaction using 2 equiv. of PhIO and 2 equiv. of Bu$_4$NI in dichloromethane gave rise to an iodo-substituted *5-exo*-carbocyclization product **2a** in 46% yield (Table 1, entry 1). The stereochemistry of compound **2a** was determined by the NOE spectrum. Interestingly, in the solvent screening experiments (Table 1, entries 2–10), we found that the formation of compound **2a** was not observed when 2,2,2-trifluoroethanol was used as the solvent. Instead, a diiodo-substituted *5-exo*-carbocyclization product **4a** was isolated in 59% yield. The best ratio of substrate, PhIO, and Bu$_4$NI for the formation of compound **4a** was 1 : 3 : 3, with which the yield increased to 83% (Table 1, entry 12). The reaction proceeded sluggishly at 0 °C, and the higher temperature shortened the reaction time from 24 h to 10 h with a slightly lower yield.



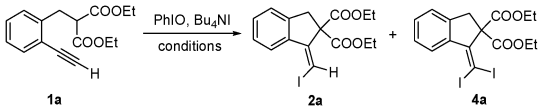
Scheme 1

1,1-Diiodoalkene derivatives are of increasing importance because they are versatile intermediates to undergo various selective bond forming reactions in a sequential manner to construct complex carbon frameworks.[13] Although a wide series

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China. E-mail: rhfan@fudan.edu.cn; Fax: +86-21-6510-2412; Tel: +86-21-6564-2019

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR of new compounds. See DOI: 10.1039/c1cc15529f

Table 1 Evaluation of reaction conditions



1a 2a 4a

Entry	PhIO/equiv.	Bu_4NI/equiv.	Solvent	**2a**[a] (%)	**4a**[a] (%)
1	2	2	CH_2Cl_2	46	n.d.[b]
2	2	2	THF	47	n.d.[b]
3	2	2	$PhCH_3$	32	n.d.[b]
4	2	2	CH_3CN	65	n.d.[b]
5	2	2	DMSO	44	n.d.[b]
6	2	2	EtOAc	31	n.d.[b]
7	2	2	MeOH	36	n.d.[b]
8	2	2	*t*-BuOH	27	n.d.[b]
9	2	2	CF_3CH_2OH	n.d.	59
10	2	2	H_2O	50	n.d.[b]
11	3	2	CF_3CH_2OH	n.d.[b]	49
12	3	3	CF_3CH_2OH	n.d.[b]	83
13	3	4	CF_3CH_2OH	n.d.[b]	35
14	4	3	CF_3CH_2OH	n.d.[b]	25

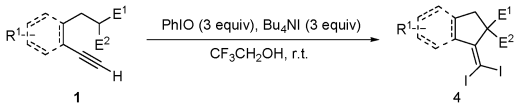
[a] Isolated yield based on substrate **1a**. [b] n.d. = not detected.

of 1,1-diiodoalkenes are easily prepared,[14] only few methods for the regiospecific synthesis of diiodomethylene cyclic compounds are known. The group of Harada reported the preparation of (diiodomethylene)cycloalkanes from the base-mediated cyclization of **1**, ω-diiodo-1-alkynes.[15] The group of Giacomini developed an iododecarboxylation of 4-(carboxyalkylidene)azetidin-2-one to synthesize diiodovinyl-β-lactams.[16] McNelis and co-workers described a ring expansion of 1-iodoethynyl-2-methyl-cyclopentanols with iodine and HTIB to form 2-(diiodomethylidene)-6-methylcyclohexanone.[17]

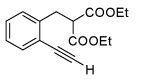
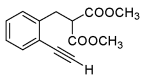
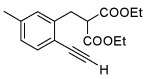
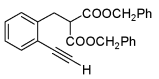
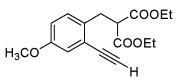
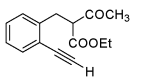
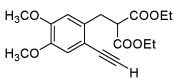
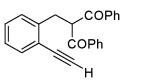
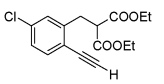
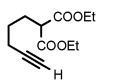
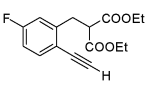
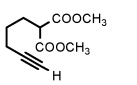
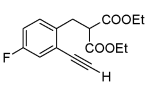
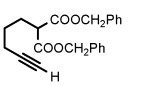
Motivated by the synthetic potential of the possible method, the generality of the present PhIO/Bu_4NI induced cyclization was then investigated under the established conditions (Table 2). 2-(2-Ethynylbenzyl)malonates were effective substrates, and their reactions provided the expected products **4a–4i** in good yields (Table 2, entries 1–9). Additionally, the cyclization was found to tolerate a range of different groups with different electronic demands on the aromatic ring. No corresponding diiodomethylene indane derivative was isolated from the reaction of ethyl 2-(2-ethynylbenzyl)-3-oxobutanoate **1j** or 2-(2-ethynylbenzyl)-1,3-diphenyl-propane-1,3-dione **1k** (Table 2, entries 10 and 11). The reactions of 4-pentynylmalonates afforded diiodomethylene cyclopentanes **4l–4n** in moderate to good yields (Table 2, entries 12–14).

The treatment of compound **1a** with iodine and a base (*t*-BuOK[8] or NaH[10a]) under the reported iodine-induced electrophilic cyclization conditions gave rise to compound **2a** in 39% or 35% yield, respectively. The formation of compound **4a** was not observed. The replacement of PhIO with $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ led to the failure in the formation of compound **4a**. When Bu_4NBr or Bu_4NCl was used instead of Bu_4NI, no corresponding dibromomethylene or dichloromethylene indane derivative was obtained. Under the standard conditions, compound **2a** or 1-methylene indane derivative **5** could not be converted to compound **4a**. The reaction of 2-(2-ethynylbenzylidene)malonate **6** or 2-(2-ethynylphenyl)-malonate **8** afforded the corresponding 2-iodoethynyl compound **7** or **9** in 95% or 75% yield, respectively (Scheme 2).

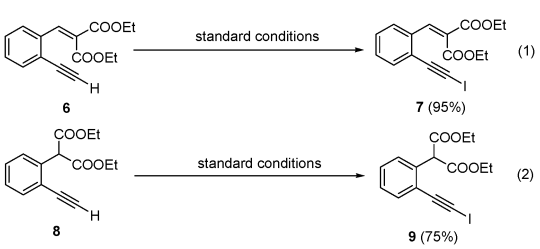
Table 2 PhIO/Bu_4NI mediated electrophilic cyclization



1 4

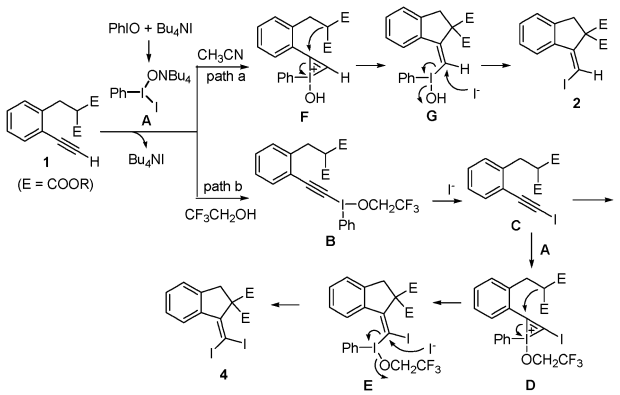
Entry	Substrate	**4**[a] (%)	Entry	Substrate	**4**[a] (%)
1		**4a** (83)	8		**4h** (78)
2		**4b** (86)	9[b]		**4i** (81)
3		**4c** (68)	10		**4j** (0)
4		**4d** (75)	11		**4k** (0)
5		**4e** (74)	12		**4l** (50)
6		**4f** (76)	13		**4m** (52)
7		**4g** (78)	14[b]		**4n** (73)

[a] Isolated yield based on substrate **1**. [b] Reaction at 50 °C.



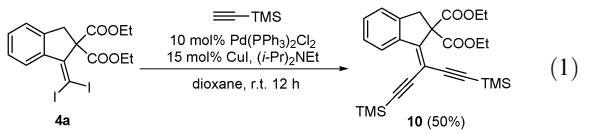
Scheme 2

Although, so far, we cannot be certain of the actual role of CF_3CH_2OH in the formation of compound **4**, a tentative mechanism is depicted in Scheme 3. The reaction of acetylenic malonate **1** with the generated active iodine(III) species **A**[18] will proceed in two different pathways dependent on the reaction solvent. In path b, the reaction in 2,2,2-trifluoroethanol forms an intermediate **B**, which can be attacked by the iodide ion *via* a Michael addition—generation of alkylidene carbene—rearrangement sequence[19] to generate 2-(2-(2-iodoethynyl)benzyl)-malonate **C**. In the presence of another molecule **A**, compound **C** is converted into an intermediate **E** *via* an iodine(III)-mediated electrophilic *5-exo*-carbocyclization. This is followed by the second nucleophilic displacement with the iodide ion to afford diiodomethylene indane derivative **4** accompanied by the reductive elimination of PhI. In path a, iodine(III) compound **A** activates the acetylene group to promote the intramolecular nucleophilic attack of malonate on the triple bond. The annulation yields an intermediate **G**, which is ready to be attacked by the iodide ion to generate product **2**.



Scheme 3 Hypothesized reaction pathway.

Then compound **4a** was subjected to Sonogashira coupling reaction conditions[20] to provide a tetrasubstituted alkene **10** in 50% yield (eqn (1)).



(1)

In conclusion, we have developed an efficient regioselective cyclization of acetylenic malonates with the combination of iodosobenzene with tetrabutylammonium iodide in 2,2,2-trifluoroethanol to afford the synthetically useful 1-diiodomethylene indane and cyclopentane derivatives in moderate to good yields. Current dedication has also been made to extend its scope, to explore its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

Financial support from National Natural Science Foundation of China (21072033) is gratefully acknowledged.

Notes and references

‡ Representative experimental procedure: the mixture of acetylenic malonate (0.2 mmol) with Bu_4NI (221 mg, 0.6 mmol) in CF_3CH_2OH (2 mL) was treated with PhIO (132 mg, 0.6 mmol) at 25 °C, and the reaction mixture was allowed to stir at 25 °C for 24 h. Upon completion by TLC, the reaction was quenched with saturated $Na_2S_2O_3$, and extracted by ethyl acetate (50 mL × 3). The organic layer was dried over anhydrated Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to give the corresponding product **4**.

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