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Cyclopropanation

Hypoiodite-Mediated Cyclopropanation of Alkenes

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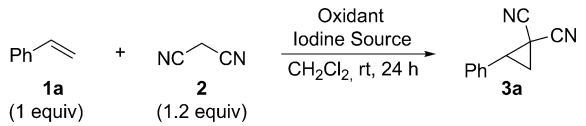
Abstract: An efficient, transition metal-free procedure for the cyclopropanation of alkenes using malononitrile and the LiI-*t*BuOCl combination under mild reaction conditions is described. The reaction mechanism most likely involves *t*BuOI generated in situ from LiI and *t*BuOCl. The utility of this new methodology has been demonstrated by the synthesis of a potential HIV-1 RT inhibitor.

Cyclopropanation of alkenes is an important chemical transformation that leads to a cyclic system commonly found in natural products, bioactive molecules, and intermediates of medicinal compounds.[1] Among the known procedures of cyclopropanation, particularly important methods are based on the use of organoiodine(III) compounds,[2,3] such as iodonium ylides,[3a–c] alkynyl-,[3d,e] and alkenyliodonium salts.[3f] In several procedures, iodonium ylides generated in situ from a β-dicarbonyl compound or malononitrile and a hypervalent iodine reagent (iodosylbenzene[3g,h] or (diacetoxyiodo)benzene[3k–l]), have been utilized as primary carbenoid sources. Most of these organoiodine(III)-mediated cyclopropanations are performed at elevated temperature or require environmentally unsafe transition-metal salts or complexes as catalysts.

Herein we report the first hypoiodite-mediated cyclopropanation of alkenes with malononitrile. This reaction is promoted by *tert*-butyl hypoiodite, which is generated in situ from the LiI-*t*BuOCl combination at room temperature. Recently, the reactions using hypoiodite as active iodine species have attracted significant attention.[4,5] In particular, Minakata and co-workers reported the use of *t*BuOI generated in situ from the NaI-*t*BuOCl combination for the aziridination of alkenes,[5a,b] the cyclization of alkenes with aldoximes[5c] and amides,[5d,f] and the oxidative dimerization of aromatic amines.[5g,h] Several other research groups reported reactions using catalytic amounts of hypoiodite species generated in situ from iodine source as a precatalyst.[6] Very recently, our group has reported metal-free catalytic reactions using hypoiodite species generated in situ from iodine sources and common oxidants.[7]

In the initial study we investigated the cyclopropanation of styrene **1a** (1 equiv) with malononitrile (1.2 equiv) screening several oxidants in the presence of iodine sources under a variety of reaction conditions in dichloromethane (see Table 1; for additional details see Table S1 in the Supporting Information). In the absence of an iodine source, the reaction of styrene with malononitrile **2** and *t*BuOCl failed to produce the desired product **3a** (Table 1, entry 1), while addition of iodide salts resulted in the formation of **3a**. Of the iodide salts examined, LiI was found to be optimal for this reaction (entries 2–6). *t*BuOCl was the most effective oxidant in this reaction (entries 7–11). Decreasing the amounts of LiI and *t*BuOCl from 2 to 1.5 equivalents did not affect the yield of the desired product **3a** (entries 3 and 7); however, lower amounts of LiI, *t*BuOCl and also

Table 1. Optimization of cyclopropanation of styrene.[a]



Entry	*t* [h]	Oxidant [(equiv)]	Iodine source [(equiv)]	**3a** [%][b]
1	24	*t*BuOCl (2)	none	(0)
2	24	*t*BuOCl (2)	NaI (2)	(65)
3	24	*t*BuOCl (2)	LiI (2)	86 (86)
4	24	*t*BuOCl (2)	KI (2)	(<1)
5	24	*t*BuOCl (2)	TBAI (2)	(22)
6	24	*t*BuOCl (2)	I_2 (2)	(0)
7	24	*t*BuOCl (1.5)	LiI (1.5)	86 (85)
8	24	TBHP (1.5)	LiI (1.5)	(9)
9	24	H_2O_2 (1.5)	LiI (1.5)	(15)
10	24	*m*CPBA (1.5)	LiI (1.5)	(25)
11	24	oxone (1.5)	LiI (1.5)	(4)
12	24	*t*BuOCl (1.2)	LiI (1.2)	76 (78)
13	12	*t*BuOCl (1.2)	LiI (1.2)	(57)
14	12	*t*BuOCl (1.5)	LiI (0.5)	(7)

[a] Reaction conditions: styrene **1a** (1 equiv), malononitrile **2** (1.2 equiv), iodine source (0–2 equiv), and oxidant (1.2–2 equiv) in dichloromethane at room temperature. [b] Yields of isolated product **3a** (numbers in parentheses show yields determined from ^{1}H NMR spectra of reaction mixtures).

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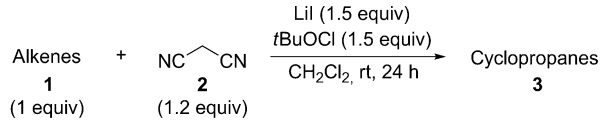
shorter reaction time led to reduced yields of **3a** (entries 12–14).

Using the optimized reaction condition with LiI as the iodide source, we have investigated the conversion of various substituted alkenes **1** to the respective cyclopropane derivatives **3** (Table 2). In general, all styrenes with either electron-donating or electron-withdrawing substituents in the aromatic ring afforded corresponding cyclopropanes **3** in high yields (entries 2–9). In the reactions of α- and β-substituted styrenes, the products were obtained in good yields (entries 10–15). The reactions of α-substituted styrenes (α-methylstyrene and α-phenylstyrene) and aliphatic alkene (1-octene) required 3 equivalents of both LiI and *t*BuOCl in order to obtain products in

Table 2. Cyclopropanation of alkenes with malononitrile under optimized conditions.[a]



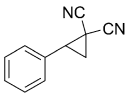
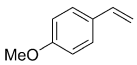
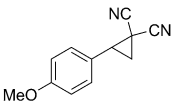
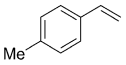
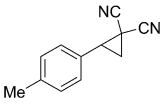
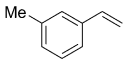
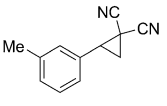
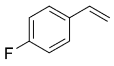
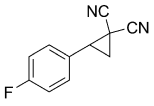
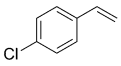
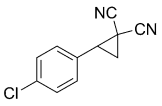
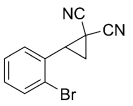
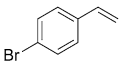
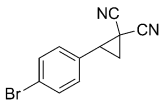
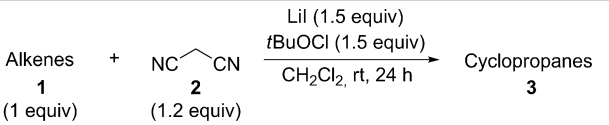
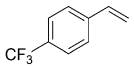
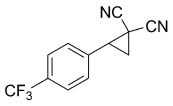
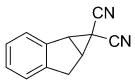
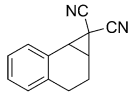
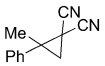
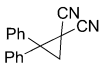
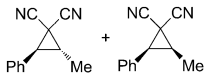
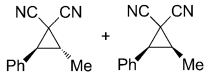
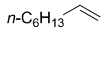
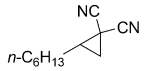
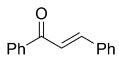
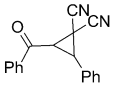
Entry	Alkene **1**	Product **3**	Yield [%][b]
1	 **1a**	 **3a**	86
2	 **1b**	 **3b**	92
3	 **1c**	 **3c**	96
4	 **1d**	 **3d**	74
5	 **1e**	 **3e**	91
6	 **1f**	 **3f**	88
7	 **1g**	 **3g**	77
8	 **1h**	 **3h**	87

Table 2. (Continued)



Entry	Alkene **1**	Product **3**	Yield [%][b]
9	 **1i**	 **3i**	83
10	 **1j**	 **3j**	78
11	 **1k**	 **3k**	79
12	 **1l**	 **3l**	57 (74)[c]
13	 **1m**	 **3m**	22 (71)[c]
14	 **1n**	 **3n+3o**	74 (93:7)[d]
15	 **1o**	 **3n+3o**	78 (92:8)[d]
16	 **1p**	 **3p**	23 (50)[c]
17	 **1q**	 **3q**	18 (17)[c]

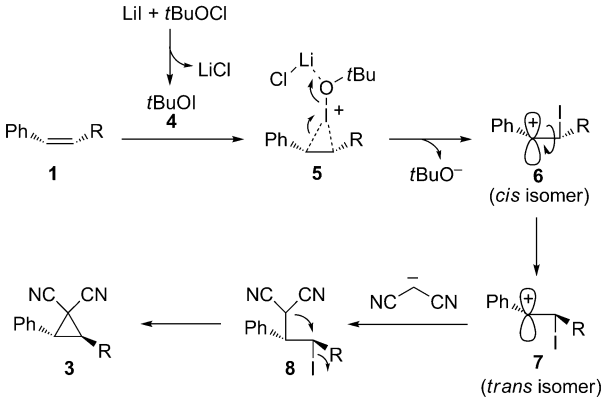
[a] Reactions of alkenes **1** (1 equiv), malononitrile **2** (1.2 equiv), LiI (1.5 equiv) and *t*BuOCl (1.5 equiv) were performed in CH_2Cl_2 at room temperature for 24 h. [b] Yields of isolated products **3**. [c] Numbers in parentheses show yields of products when 3 equiv of LiI and *t*BuOCl were used. [d] The product ratio was determined by ^{1}H NMR spectroscopy.

good yields (entries 12, 13, 16). It is noteworthy that the reactions of *cis*- and *trans*-β-styrenes under these conditions gave the *trans*-cyclopropane **3n** as major product in good yield, and *cis*-cyclopropane **3o** was detected only as a minor product (entries 14, 15). The reaction of α,β-unsaturated ketone **1q** afforded corresponding cyclopropanes in low yields, and these yields were not improved upon using 3 equivalents of both LiI and *t*BuOCl (entries 17). Our procedure was more efficient compared to the previously reported methods of cyclopropanation of alkenes with malononitrile using hypervalent iodine reagents.[3i,l] Moreover, the previously reported reactions of α- or β-methylstyrenes did not give any products of cyclopropanation, while our method afforded these products in good yields. The structure of dicyanocyclopropane **3k** (Table 2, entry 11) was established by a single crystal X-ray analysis (see Supporting Information for details).

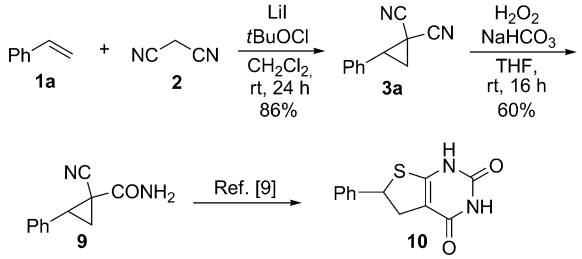
In order to gain additional information on the mechanism of this reaction, we have performed several control experiments (see the Supporting Information for details). Most likely, this reaction involves *t*BuOI as active species generated from LiI and *t*BuOCl. The intermediacy of *t*BuOI was examined by generating it in situ by different methods using either NaI-*t*BuOCl[5] or I_2-*t*BuOK[8] in place of LiI-*t*BuOCl. In both cases, the cyclopropane **3a** was isolated in about 50% yield, which suggests that in situ generated *tert*-butoxy hypoiodite species, *t*BuOI **4** are the active species in this reaction. However, the yields of **3a** using our optimized condition compared to the other *t*BuOI generation methods were much better. We have found that the presence of LiCl, which is produced from LiI-*t*BuOCl, is important for this reaction. When LiCl was used as the additive in NaI-*t*BuOCl and I_2-*t*BuOK conditions, cyclopropane **3a** was obtained in 74% and 73% yields, respectively. As expected, the addition of NaCl instead of LiCl was not effective under NaI-*t*BuOCl or I_2-*t*BuOK conditions. This result suggests that LiCl may act as a Lewis acid facilitating the formation of *t*BuOI or the LiCl-*t*BuOI complex in this reaction. During our mechanistic studies, we observed isomerization of *cis*-β-styrene to *trans*-β-styrene when the combinations of LiI-*t*BuOCl and I_2-*t*BuOK were used in the absence of malononitrile **2**.

From these control experiments, we propose the hypoiodite-mediated cyclopropanation mechanism outlined in Scheme 1. The active species, *t*BuOI **4**, and LiCl generated in situ from LiI-*t*BuOCl combination, form the LiCl-*t*BuOI complex that reacts with alkene **1** to give the iodonium ion **5**, which is then opened at the benzylic position to give the cationic intermediate **6**. The intermediate **6** rotates to the thermodynamically more stable *trans* isomer **7**, which reacts with malononitrile anion, formed from **2** in the presence of *tert*-butoxy anion. This sequence of events gives β-iodo compound **8**, which upon anionic cyclization affords cyclopropane **3**.

Our new cyclopropanation procedure was applied in the synthesis of potential HIV-1 RT inhibitor. The dicyanocyclopropane **3a** upon partial hydrolysis under mild basic condition afforded the cyanocarboxamide cyclopropane **9** in moderate yield (Scheme 2). This cyclopropane **9** has been used as a precursor for the preparation of the potential HIV-1 RT inhibitor **10** as previously described.[9]



Scheme 1. Proposed mechanism of *t*BuOI-mediated cyclopropanation.



Scheme 2. Synthesis of potential HIV-1 RT inhibitor **10**.

In summary, we have developed a new procedure for the cyclopropanation of alkenes using malononitrile and the LiI-*t*BuOCl combination. The reaction mechanism most likely involves *t*BuOI generated in situ from LiI and *t*BuOCl. The synthetic usefulness of this new procedure was demonstrated by the synthesis of potential HIV-1 RT inhibitor.

Experimental Section

Malononitrile **2** (0.150 mmol), LiI (0.1875 mmol), and *t*BuOCl (0.1875 mmol) were added to a solution of alkene **1** (0.125 mmol) in dichloromethane (1.5 mL). The resulting light-brown suspension was stirred at room temperature for 24 h. After reaction completion, the mixture was washed with 5% aqueous $Na_2S_2O_3$ (5 mL), and the solution was extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. Purification by preparative TLC (hexane/ethyl acetate = 3:1) afforded analytically pure dicyanocyclopropane **3**.

Acknowledgements

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Keywords: cyclopropanation reactions · hypoiodous acid · iodine · oxidation · small ring systems

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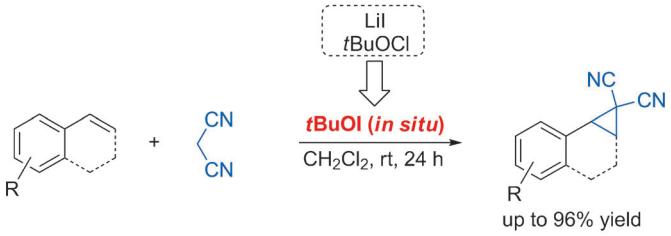

An efficient, transition-metal-free procedure for the cyclopropanation of alkenes using malononitrile and the LiI-*t*BuOCl combination under mild reaction conditions is described. The reaction mechanism most likely involves *t*BuOI generated in situ from LiI and *t*BuOCl. The utility of this new methodology has been demonstrated by the synthesis of a potential HIV-1 RT inhibitor (see scheme).

Cyclopropanation

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Hypoiodite-Mediated Cyclopropanation of Alkenes