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Mechanochemical transformation of tetraaryl[3]cumulenes to benzofulvenes via electrophilic iodocyclization†

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We demonstrate solvent-free mechanochemical iodocyclization of tetraaryl[3]cumulenes using *N*-iodosuccinimides as the first example of the molecular transformation of cumulenes based on mechanochemistry. This mechanochemical reaction provides the corresponding benzofulvenes in good yields, overcoming the limitation of conventional methods using organic solvents.

Molecular transformation based on mechanochemistry has drawn considerable attention in organic synthesis owing to some advantages such as shorter reaction time and reduction or elimination of solvent use.[1] Therefore, many efforts have been devoted to developing mechanochemical synthesis including oxidation,[2] reduction,[3] condensation,[4] metalation,[5] and transition metal-catalysed cross-coupling reactions.[6] In addition, the mechanochemistry-based synthetic methods overcome the solubility issues in organic synthesis and enable the molecular transformation of insoluble organic compounds under milling conditions.[7]

Cumulenes, which have cumulative C–C double bonds, are recognized as an important class of sp-hybridized carbons that have unique structural properties and reactivities leading to a wide variety of hydrocarbon structures through dimerization,[8] trimerization,[9] intermolecular cycloaddition,[10] and related cyclization reactions.[11] Although the mechanochemical synthesis of odd-numbered tetraaryl[*n*]cumulenes has been reported,[12] the molecular transformation of cumulenes based on mechanochemistry remains unexplored.

Recently, we reported the iodocyclization reactions of tetraaryl[3]cumulenes affording benzofulvene and tetraaryl[5] cumulene affording fulvene scaffolds in solution, respectively.[13] For example, the electrophilic iodocyclization reaction of tetraaryl[3]cumulenes **1** using *N*-iodosuccinimide (NIS) proceeded smoothly via an iodonium intermediate in nitromethane at ambient temperature and gave the corresponding benzofulvenes **2** in good-to-high yields (Scheme 1a).[13a] We also reported that the other common organic solvents were found to be ineffective for this reaction. Due to the potential applications of benzofulvene as a versatile building block for functional materials,[14] it is important to develop environmentally friendly synthetic methods. Here we demonstrate the solvent-free iodocyclization reaction of tetraaryl[3]cumulenes **1** leading to benzofulvenes **2** under milling conditions (Scheme 1b).

Initially, we aimed to optimize the reaction conditions for the iodocyclization reaction of tetraaryl[3]cumulenes **1** using tetraphenyl[3]cumulene (**1a**) as a model substrate. The results are summarized in Table 1.

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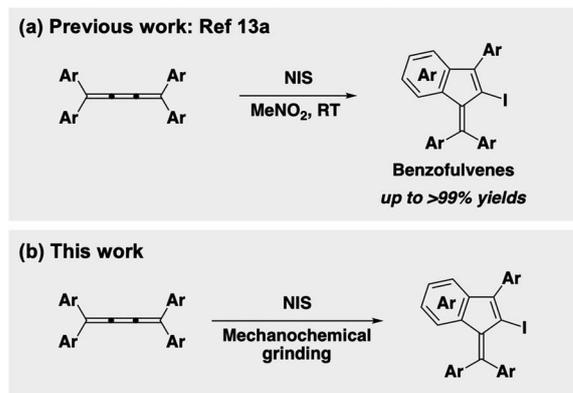
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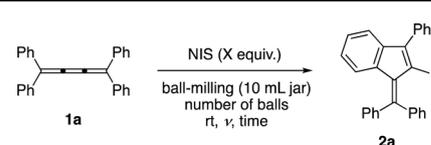

Scheme 1 Construction of a benzofulvene scaffold by the iodocyclization reactions of tetraaryl[3]cumulenes.

Table 1 Optimization of reaction conditions[a]

Entry	Number of balls	ν (Hz)	Time (min)	X (equiv.)	Yield[b] (%)
1	2 (15 mm)[c]	25	30	1.2	41
2	2 (15 mm)[c]	25	30	1.2	22
3	1 (15 mm)[c]	25	30	1.2	19
4	3 (15 mm)[c]	25	30	1.2	21
5	4 (15 mm)[c]	25	30	1.2	12
6	6 (15 mm)[c]	25	30	1.2	14
7	2 (15 mm)[c]	25	30	1.2	14
8	2 (15 mm)[c]	20	30	1.2	35
9	2 (15 mm)[c]	30	30	1.2	37
10	2 (15 mm)[c]	25	60	1.2	32
11	2 (15 mm)[c]	25	90	1.2	25
12	2 (15 mm)[c]	25	30	2.2	71
13	2 (15 mm)[c]	25	30	3.3	62
14[d]	2 (15 mm)[c]	25	30	2.2	63
16[e]	2 (10 mm)[c]	25	30	2.2	53

[a] Conditions: **1a** (0.3 mmol) and NIS (X equiv.) in a stainless-steel ball-milling jar (10 mL). [b] The yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] The values in parentheses are the diameters of balls. [d] ZrO$_2$ jar and balls were used instead of stainless-steel jar and balls. [e] 5 mL stainless-steel jar was used instead of 10 mL stainless-steel jar.

Table 2 Scope and limitation of mechanochemical iodocyclization of tetraaryl[3]cumulenes **1** [a]
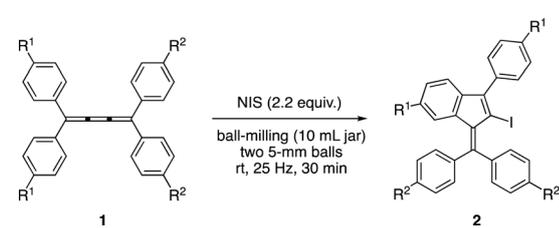
Entry	Substrate	R^1	R^2	Product	Yield[b] (%)
1	**1a**	H	H	**2a**	69
2	**1b**	Me	Me	**2b**	91
3	**1c**	OMe	OMe	**2c**	14
4	**1d**	F	F	**2d**	0
5	**1e**	Cl	Cl	**2e**	Trace
6	**1f**	OMe	H	**2f**	61
7	**1g**	OMe	Me	**2g**	90
8	**1h**	OMe	Cl	**2h**	82

[a] Conditions: **1** (0.3 mmol) and NIS (0.66 mmol) in a stainless-steel ball-milling jar (10 mL) equipped with two stainless-steel balls of 15 mm diameter. [b] Isolated yields.

When 0.3 mmol of **1a** and 1.2 equiv. of NIS were placed in a 10 mL stainless-steel jar equipped with two stainless-steel balls of 15 mm diameter and agitated at 25 Hz in a vibratory ball-mill for 30 minutes, the objective benzofulvene **2a** was obtained in 41% yield (entry 1). The use of iodine instead of NIS as the iodonium cation source decreased the yield of **2a** (entry 2). The other combinations of the number of balls and their diameter also resulted in lower yields (entry 1 vs. entries 3–7). The reactions at the milling frequencies of 20 or 30 Hz led to low yields (entries 8 and 9). The longer reaction time slightly decreased the yields of **2a** (entries 10 and 11). Notably, increasing the amount of NIS improved the reaction and the benzofulvene **2a** was obtained in up to 71% yields (entries 12 and 13). The use of a ZrO$_2$ jar and balls resulted in lower yield than the use of a stainless-steel jar and balls (entry 14). We also conducted the reaction in a 5 mL jar equipped with two stainless-steel balls of 10 mm diameter. However, the use of a 5 mL jar was ineffective for this reaction (entry 15). Because the use of 2.2 equiv. of NIS led to the highest yield, we found that the reaction using 2.2 equiv. of NIS in a 10 mL stainless-steel jar equipped with two stainless-steel balls of 15 mm diameter at a milling frequency of 25 Hz for 30 minutes provides the optimum conditions for this reaction (entry 12).

Next, we investigated the substrate scope using various tetraaryl[3]cumulenes **1** under the optimized reaction conditions (Table 2).

The reaction using tetrakis(p-methylphenyl)[3]cumulene (**1b**) proceeded smoothly under milling conditions; the corresponding benzofulvene **2b** was obtained in 91% yield. On the other hand, mechanochemical iodocyclization of **1c** gave the benzofulvene **2c** in low yield owing to the formation of unidentified oligomer products under milling conditions. Similar unidentified oligomer formation was observed in the absence of NIS under milling conditions. Because the formation of oligomer products was observed after the mechanochemical reaction of **1c** even in the absence of NIS, we consider that the oligomerization of **1c** preferentially occurs rather than intermolecular reaction under milling conditions. Halogen substituents such as F (**1d**) and Cl (**1e**) at aryl rings were ineffective for electrophilic iodocyclization owing to the unfavorable nucleophilic attack of the electron-deficient aryl ring on iodonium intermediates. It was found that the regioselective iodocyclization of unsymmetrical tetraaryl[3]cumulenes **1f–h** occurred from the electron-rich aromatic ring to the iodonium cation, affording the corresponding benzofulvenes **2f–h** as the sole product in good yield, respectively. The structures of **2f** and **2g** were determined by ^{1}H NMR according to our previous report.[13a] The structure of **2h** was determined by NMR spectroscopy, HRMS, and single-crystal crystallographic analysis. X-ray analysis of **2h** unequivocally revealed that the iodocyclization occurred at the p-methoxyphenyl ring, resulting in the formation of a methoxy-substituted benzofulvene scaffold (Fig. S1†).

Recently, Ito and co-workers have developed a high-temperature ball-milling technique for the palladium-catalysed Suzuki–Miyaura cross-coupling reaction of insoluble aryl halides with aryl boronic acids.[7b] Their accomplishments encouraged us to demonstrate the iodocyclization reaction of tetraaryl[3]cumulenes under high-temperature milling conditions. In this study, we demonstrated the iodocyclization
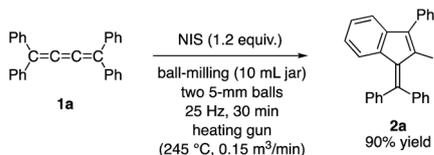
Scheme 2 Mechanochemical iodocyclization reaction of **1a** at high temperature.
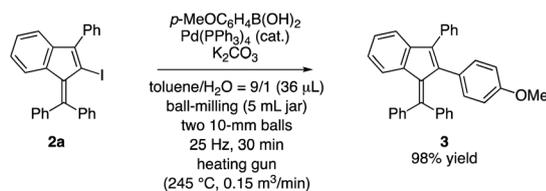
Scheme 3 Mechanochemical Suzuki–Miyaura cross-coupling reaction of benzofulvene **2a** with *p*-methoxyphenylboronic acid at high temperature.

reactions of **1a** and **1e** using a temperature-controllable heating gun with a preset temperature of 245 °C under milling conditions. After heating for 30 minutes, the internal temperature reached 144 °C, which was confirmed with an infrared radiation thermometer. Notably, the reaction of **1a** proceeded smoothly even in the presence of 1.2 equiv. of NIS and provided the benzofulvene **2a** in 90% yield (Scheme 2). Unfortunately, the high-temperature ball-milling technique did not improve the iodocyclization of tetrakis(*p*-chlorophenyl)[3]cumulene (**1e**) and the reaction afforded a trace amount of complex mixture.

We previously reported the utility of 1-(diphenylmethylene)-3-phenyl-2-iodo-1*H*-indene (**2a**) as a coupling partner in the common transition metal-catalysed cross-coupling reactions in solution, leading to tetrafunctionalized benzofulvenes.[13a] From the viewpoint of green chemistry, we conducted the mechanochemical Suzuki–Miyaura cross-coupling reaction of **2a** with *p*-methoxyphenylboronic acid under liquid-assisted griding (LAG) conditions. The reaction proceeded smoothly at high temperature conditions and provided the corresponding tetraarylated benzofulvene **3** in 98% yield (Scheme 3).

Conclusions

In conclusion, we have demonstrated the solvent-free mechanochemical iodocyclization of seven tetraaryl[3]cumulenes. Although the reactions of **1d** and **1e** having four electron deficient aryl rings did not proceed owing to their low nucleophilicities, the reactions of other tetraaryl[3]cumulenes gave the corresponding benzofulvenes **2** in up to 91% yield even under milling conditions. This environmentally friendly approach enabled the molecular transformation of tetraaryl[3]cumulenes to benzofulvenes without using nitromethane, which has explosive properties. The high-temperature ball-milling technique was also found to promote the iodocyclization reaction of **1a**, providing benzofulvene **2a** in 90% yield even in the presence of 1.2 equiv. of NIS. In addition, the LAG mechanochemical

Suzuki–Miyaura cross-coupling reaction of **2a** provided the highly functionalized benzofulvene scaffold in 98% yield.

Author contributions

Fumitoshi Yagishita: conceptualization, methodology, writing – original draft; Shoma Mukai: investigation; Sota Abe: investigation; Shoko Ueta: investigation; Yasushi Yoshida: investigation; Yukihiro Arakawa: investigation; Keiji Minagawa: writing – review & editing; Yasushi Imada: supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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