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Microwave-Assisted Nickel-Catalyzed Rapid Reductive Coupling of Ethyl 3-iodopropionate to Adipic Acid

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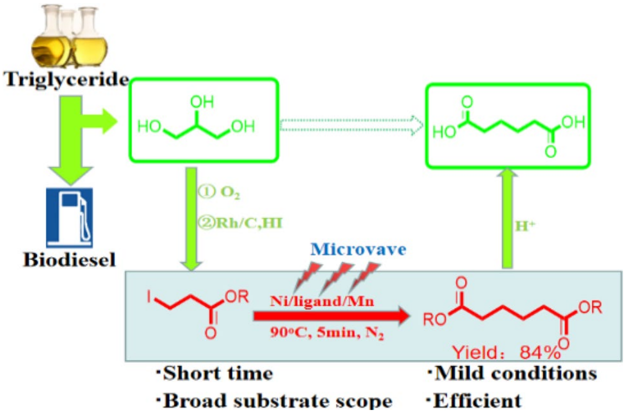
Abstract

3-iodopropionic acid (3-IPA) can be efficiently synthesized from the glycerol derivative glyceric acid (GA), which is a potential biomaterial-based platform molecule. In this report, ethyl 3-iodopropionate was rapidly dimerized to diethyl adipate in a microwave reactor using $NiCl_2{\cdot}6H_2O$ as a catalyst, co-catalyzed by Mn and the 1, 10-Phenanthroline monohydrate ligand. Under the optimum reaction conditions, diethyl adipate can be obtained with 84% yield at 90 °C in just 5 min. Diethyl adipate was hydrolyzed to obtain the adipic acid (AA) in 89% yield with an acid catalyst. AA is an important chemical and a monomer for producing a wide range of high-performance polymeric substances. This rapid coupling method is also applicable to other alkyl halides.

Graphic Abstract



Keywords Nickel catalyst · Wurtz coupling · Microwave-assisted · Adipic acid

1 Introduction

As an important chemical, adipic acid can be used to produce nylon 6–6, polyurethanes, synthetic resins, thickeners, and engineering plastics. It also plays an important role in organic synthesis, medicine, lubricant manufacturing, and it can be directly used as food additives and flavoring agents, etc. [1–6]. Its output ranks second among all dicarboxylic acids, and it still maintains an annual growth rate of 3% [7–9].

Linfeng Zhang and Jing Zheng authors are contribute equally to this work.

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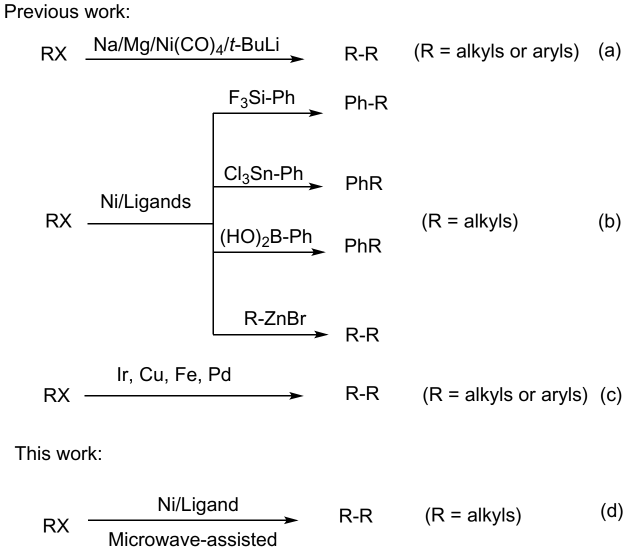
At present, the production of adipic acid mainly relies on petroleum. The traditional method is to hydrogenate benzene to obtain cyclohexane, which is then oxidized to a mixture of cyclohexanol and cyclohexanone (KA oil), and oxidation of KA oil by concentrated nitric acid provides adipic acid (AA) [10, 11]. Companies such as BASF of Germany and DuPont of the USA have successfully developed a new process to produce AA from butadiene. For example, BASF uses pyridine as a promoter and $Co_2(Co)_8$ as a catalyst in the reaction where the butadiene (from the cracked petroleum component) reacts with carbon monoxide and methanol under high temperature and high pressure to produce dimethyl adipate in two steps [12]. Then a lot of water and acidic ion exchange resin were used to get purified adipic acid with up to 72% yield. With the depletion of the non-renewable fossil fuel resources and concerns about the environmental problems during its usage, the use of sustainable biomass resources to produce adipic acid is the research area of current interest. For example, Wang and co-workers reported that ReO_x/ZrO_2 efficiently catalysed the deoxydehydration of D-glucaric acid-1,4-lactone, offering adipic acid ester with two steps in 82% yield [2]. In 2019, Wang also demonstrated the synthesis of adipic acid from 2,5-furandicarboxylic acid, originated from cellulose-based 5-hydroxymethylfurfural, using a platinum catalyst under hydrogen in water [13]. Recently, Tomishige and co-workers reported that the 2-methoxycyclohexanone (2-MCO) can be selectively converted to adipic acid catalyzed by $H_3PW_{12}O_{40}$ [14].

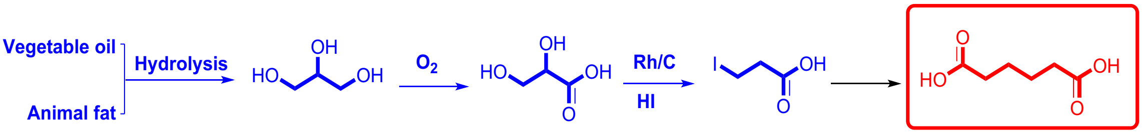
With the expansion of the biodiesel market, the supply of its by-product glycerol has exceeded its demand [15]. Glycerol has been converted to a variety of value-added products, such as glyceric acid [16–19], 1,2-propandiol [20–22], 1,3-propandiol [23–25]. In our previous work, we developed a method to convert glyceric acid to 3-iodopropionic acid (3-IPA) with up to 99.9% yield under the catalysis of hydroiodic acid [26]. 3-IPA is an important platform chemical that can be converted to various value-added products due to the reactivity of the halide group. The present work mainly explores the technology of producing adipic acid through 3-IPA coupling, aiming to establish the process of adipic acid production from glycerol (Scheme 1).

Alkylhalides coupling to form bialkyls in mild condition is of great interest. The classical method is Wurtz coupling mediated by sodium metal (Scheme 2a) [27]. However, the use of the reactive Na metal is a concern and it has limitations for the reaction of secondary alkyl halides. Transition metal-catalyzed cross-coupling of halogen compounds to form carbon–carbon bond is among the most powerful methods in organic synthesis [28, 29]. Fu etc. reported the efficient coupling of unactivated primary and secondary alkyl halides with alkylzincs, arylboronic acids monoorganotin or organosilicon reagents together in the presence of ligands and nickel catalysts (Scheme 2b) [30–33]. Recently, methods mediated by stoichiometric (Ir or Cu) or catalytic (Pd, Fe, or Cu) amount of metals have been developed (Scheme 2c) [34–38], but their scope and functional-group compatibility is limited. Another method of reductive coupling of alkyl halides is to convert part of alkyl halides into organometallic reagents, and then react with the remaining alkyl halides [39]. However, their application in dimer molecular synthesis has some disadvantages, including sensitive to air and water, an often narrow substrate scope and a low reaction rate [40–42]. Therefore, the development of an efficient method for the generation of bialkyls via alkylhalide coupling, particularly in mild conditions, is of great importance in organic synthesis and for practical applications.

Here we further improved the Csp^3–Csp^3 bond formation method [39, 43–45] by using microwave-assisted heating for



Scheme 2 Previous synthesis of bialkyls via alkylhalide coupling



Scheme 1 Proposed reaction path from glycerol to adipic acid

the synthesis of bialkyls from alkylhalides (Scheme 2d). The potential of microwave-assisted heating has been well explored in organic synthesis as a non-classical approach to enhance yields in significantly short reaction time [46–48]. To the best of our knowledge, alkyl halides coupling catalyzed by nickel compounds with microwave irradiation via Csp^3–Csp^3 cross-coupling has not been described yet in literature. Herein, by using microwave irradiation and nickel-based catalysts, 84% yield of diethyl adipate can be obtained in 5 min from ethyl 3-iodopropanoate. And the functional group tolerance with this method is confirmed to be good. The reaction mechanism was also deduced based on Weix's proposal [49] and some control experiments.

2 Experimental Section

2.1 Materials

All chemicals and materials, ethyl 3-iodopropionate (98%, Aladdin), Mn (> 98%, Aladdin), $NiCl_2 \cdot 6H_2O$ (98%, Innochem), 1, 10-phenanthroline monohydrate (≥ 99.0%, Innochem), H_2SO_4 (≥ 98%, Xilong Scientific), DMSO (≥ 98%, Xilong Scientific), $CDCl_3$ (99.9%, Innochem) and n-dodecane (≥ 99.0%, Aladdin), were commercially available and directly used without further treatment.

2.2 Catalytic Reaction and Product Analysis

A flame-dried 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with $NiCl_2 \cdot 6H_2O$ (2.38 mg, 0.01 mmol), 1, 10-phenanthroline monohydrate (**a**) (1.98 mg, 0.01 mmol) and Mn (55 mg, 1 mmol). N_2 was used to displace the air, followed by the addition of substrate ethyl 3-iodopropionate (1 mmol) and DMSO (2 mL). The reaction mixture was stirred in a microwave reactor (100 W) at 90 °C for 5 min. The cooled and filtered product was tested by GC/MS (Agilent 6890-5973 N) and GC (Agilent 6890 N, HP-plot Q capillary column FI detector).

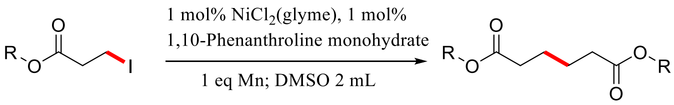
^1H NMR (Bruker Ascend 400 M) spectra were recorded at 400 MHz NMR spectrometer using $CDCl_3$ as solvent, Diethyl adipate and free radicals were detected by LC–MS (SCIEX, UPLC-X500RQTOF). After the reaction, a certain amount of n-dodecane was added to the product as the internal standard, which was detected in GC. The conversion rate and yield were calculated based on the peak area ratio of n-dodecane and diethyl adipate.

3 Results and Discussions

First, we attempted to dimerize 3-IPA using $NiCl_2$(glyme) catalyst, and 1,10-phenanthroline monohydrate as the ligand, together with 1 equivalent of Mn powder at 40 °C in DMSO solvent for 24 h [50]. The yield of adipic acid (AA) was only 9% (Table 1, entry 1). The yield of the product did not improve much when increasing the temperature to 90 °C (Table 1, entry 2). We speculated that the carboxyl group may hinder the reaction, so ethyl 3-iodopropionate was then used as the substrate. Fortunately, the product (diethyl adipate) yield increased to 45% at 40 °C (Table 1, entry 3). Neither raising the temperature nor prolonging the reaction time could further improve the yield dramatically, and the side product was ethyl propionate probably by direct reduction (Fig. S1) (Table 1, entries 4–5). The structure of the coupling product diethyl adipate was characterized and confirmed via ^1H NMR analysis as well as high-resolution mass spectrometry (HRMS) as shown in the supporting information (Figs. S2 and S3).

To further improve the reaction efficiency, microwave radiation was used to facilitate the reaction. First, the optimal reaction temperature and reaction time were explored, and it was found that 90 °C and 5 min could provide the best result (see supporting information in Table S1). With the same reaction reagents as in Table 1, entry 5, 78% yield of the product can be obtained in 5 min under microwave radiation, which is a big advancement compared to the traditional method. Then, several different nickel-based catalysts [30, 32, 33] were tested (Table 2, entries 1–5). It was found that $NiCl_2 \cdot 6H_2O$ provided the best result. Besides, $NiCl_2 \cdot 6H_2O$ is the cheapest among all the Ni catalyst tested. Next, several different ligands (b-d) were screened. The replacement of 1, 10-phenanthroline monohydrate (**a**) with other ligands (**b-d**) did not increase the yield (Table 2, entries 6–8). And, the yield was found to be very low without any ligand (Table 2,

Table 1 Effect of temperature and reaction time on the reaction

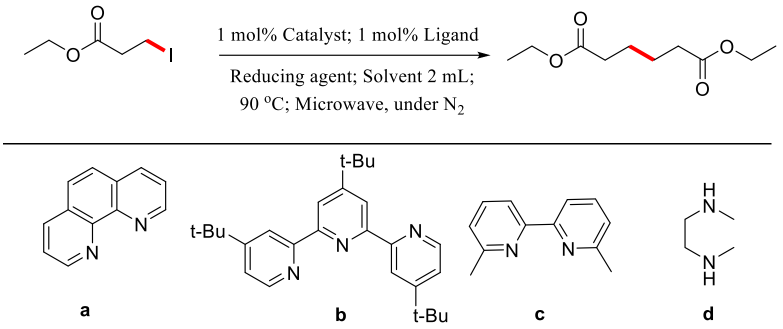


Entry	T (°C) (Oil bath)	Reaction time(H)	Conv. (%)	Yield (%)[a]
1 (R = H)	40	24	40	9
2 (R = H)	90	24	46	10
3 (R = Et)	40	24	> 99	45
4 (R = Et)	90	24	> 99	53
5 (R = Et)	90	36	> 99	54

All the reactions were performed on a 1 mmol scale

[a] Yields were determined by GC with n-dodecane as an internal standard

Table 2 Screening of optimal reaction conditions



Entry	Catalyst	Ligand	Solvent	Reducing agent (eq)	Conv. (%)	Yield (%)[a]
1	$NiCl_2(glyme)$	**a**	DMSO	Mn (1)	> 99	78
2	$NiBr_2(glyme)$	**a**	DMSO	Mn (1)	> 99	75
3	NiO	**a**	DMSO	Mn (1)	24	19
4	$Ni(Ac)_2\cdot 4H_2O$	**a**	DMSO	Mn (1)	40	13
5	$\mathbf{NiCl_2\cdot 6H_2O}$	**a**	**DMSO**	**Mn (1)**	**> 99**	**84**
6	$NiCl_2\cdot 6H_2O$	**b**	DMSO	Mn (1)	> 99	68
7	$NiCl_2\cdot 6H_2O$	**c**	DMSO	Mn (1)	88	57
8	$NiCl_2\cdot 6H_2O$	**d**	DMSO	Mn (1)	83	49
9	$NiCl_2\cdot 6H_2O$	-	DMSO	Mn (1)	66	20
10	$NiCl_2\cdot 6H_2O$	**a**	DMF	Mn (1)	> 99	71
11	$NiCl_2\cdot 6H_2O$	**a**	DMI	Mn (1)	91	52
12	$NiCl_2\cdot 6H_2O$	**a**	DMAC	Mn (1)	> 99	69
13	$NiCl_2\cdot 6H_2O$	**a**	DMSO	Mn (2)	> 99	86
14	$NiCl_2\cdot 6H_2O$	**a**	DMSO	Mn (0.5)	87	71
15	$NiCl_2\cdot 6H_2O$	**a**	DMSO	Fe (1)	12	N.D
16	$NiCl_2\cdot 6H_2O$	**a**	DMSO	Zn (1)	23	11
17[b]	$NiCl_2\cdot 6H_2O$	**a**	DMSO	Mn (1)	> 99	82
18[c]	$NiCl_2\cdot 6H_2O$	**a**	DMSO	Mn (1)	> 99	79

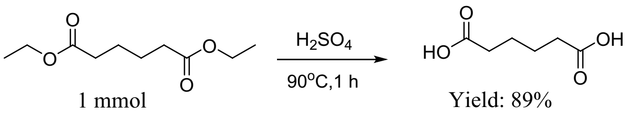
All the reactions were performed on a 1 mmol scale with microwave irradiation in 5 min

[a] Yields were tested by GC with n-dodecane as an internal standard

[b] Added an equivalent NaI

[c] ethyl 3-iodopropionate 1.04 g (4.56 mmol)

entry 9). Different solvents were also studied for a better result. Solvent has a big effect on the result, and DMSO was found to be the best solvent (Table 2, Entry 5). Other solvents such as DMF, DMI and DMAC all gave worse results (Table 2, entries 10–12). Then, different types and amounts of reducing agents were inspected. Increasing the manganese powder amount from 1 equiv. to 2 equiv. increased the yield from 84% to 86%. Reducing the amount of manganese powder to 0.5 equivalent led to the lower yield of only 71% (Table 2, entries 5 and 13–14). In order to compare with other types of reductants [37, 45], equivalent amount of zinc powder or iron powder was used to replace manganese powder, and the reaction yield dropped sharply to 11% or even no product (Table 2, entries 15–16). NaI was reported to be helpful in such reactions [50], however, the reaction yield has no significant change with 1 equiv. NaI addition (Table 2, entry 17). Thus, the best result was obtained with $NiCl_2\cdot 6H_2O$ as catalyst, 1,10-phenanthroline monohydrate as ligand, 1 equivalent Mn as reducing reagent, and 84% yield of



Scheme 3 Hydrolysis of diethyl adipate

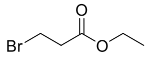
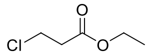
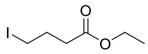
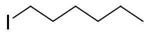
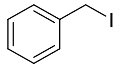
diethyl adipate can be obtained from 3-iodopropanic acid at 90 °C for 5 min as shown in Table 2 entry 5. The gram-level reaction was carried out with 1 mol% catalyst, and the yield barely decreased (Table 2, entry 18). It shows that this method has potential industrial applications. And microwave assisted cross-coupling is a good way to obtain diethyl adipate from 3-iodopropanic acid in a short time.

Here we further demonstrated that AA can be obtained in 89% yield from diethyl adipate at 90 °C for 1 h with H_2SO_4 (0.048 mol/L) (Scheme 3). This opens up a new pathway for the conversion of glycerol to adipic acid.

To test the applicability of this method, other halide substituted substrates were also used for the coupling reactions. As shown in Table 3, the method showed good generality, and a variety of synthetically valuable functional groups were found to be compatible with this transformation. First, the reactivity of different halogenated hydrocarbons was tested. It was found that ethyl 3-bromopropionate and ethyl 3-chloropropionate can also be dimerized to give corresponding dimer products, but the results were poor (Table 3, entries 1 and 3). The results were greatly improved by simply adding 1 equivalent of NaI [50] to the reaction. The yield of diethyl adipate from ethyl 3-bromopropionate increased from 46% to 81% and the yield of diethyl adipate from ethyl 3-chloropropionate climbed from 11% to 79% after NaI addition (Table 3, entries 2 and 4). This could be due to the substitution effect of I^- as a better leaving group. Analog of ethyl 3-iodopropionate with longer carbon chains were also used for the coupling reactions (Table 3, entries 5 and 6). It was also found that the reactivity of long-chain hydrocarbons was very low when NaI was not added, but can be significantly improved after NaI addition, which was also true for the long chain iodoalkanes (Table 3, entries 7 and 8). For aryl halide, dimeric products with very good yield can be obtained and NaI addition can also improve the yield (Table 3, entries 9 and 10). Therefore, the application scope of this reaction was greatly improved by NaI addition.

Table 3 Scope of the reductive coupling of alkyl halide

$$2R\text{-}X \xrightarrow[\text{DMSO 2 mL; 90°C; 5 min; Microwave; Under } N_2]{\text{1 mol\% } NiCl_2 \cdot 6H_2O\text{; 1 mol\% } \mathbf{a}\text{; 1 eq Mn}} R\text{-}R$$

Entry	Substrate	Additive (eq)	conv. (%)	Yield (%)^a
1		–	75	46
2		NaI (1)	> 99	81
3		–	25	11
4		NaI (1)	94	79
5		–	26	14
6		NaI (1)	95	77
7		–	29	11^c
8		NaI (1)	89	71^c
9		–	95	78
10		NaI (1)	> 99	85

All reactions were performed on a 1 mmol scale with microwave irradiation in 5 min

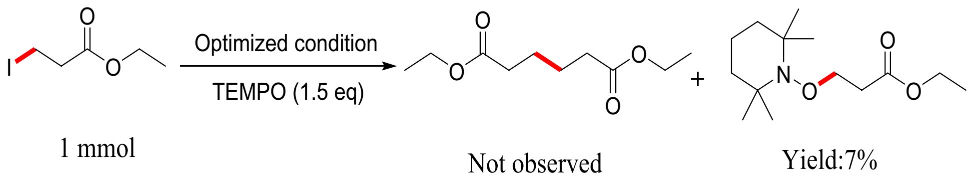
^{a}Yields were tested by GC with n-dodecane as an internal standard

^{b}Yields were tested by GC with n-decane as an internal standard

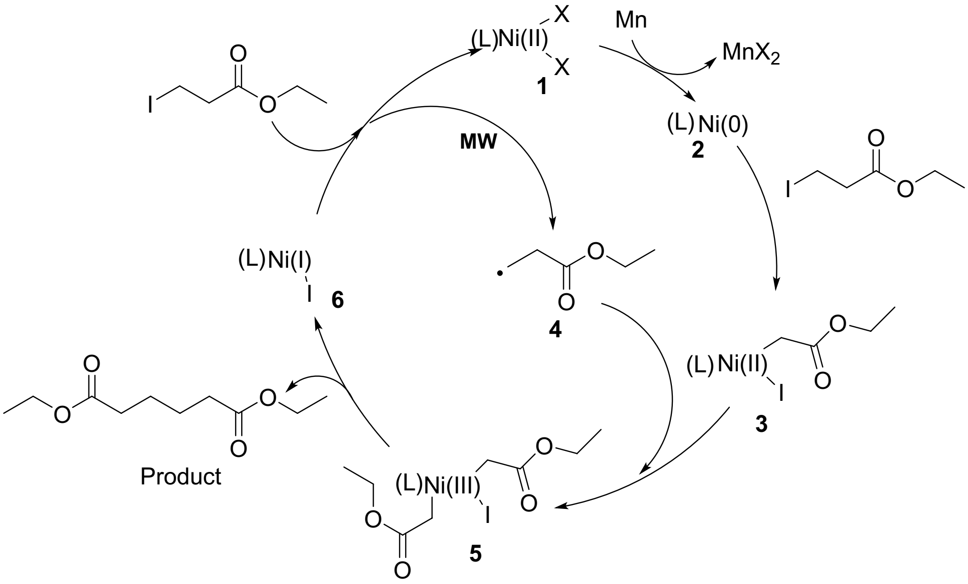
For the reductive coupling reaction, David and Diao et al. proposed a radical-cage-rebound process [51–54], then Hegedus and Weix et al. proposed the free radical chain mechanism [49, 55–59]. To understand our reaction mechanism, some control experiments were carried out. First, no product can be detected without the Ni catalyst, demonstrating the necessity of the Ni catalyst. In addition, when a radical scavenger such as TEMPO (2, 2, 6, 6-tetramethylpiperidinyloxy) was added to the reaction system, the reductive coupling product was not observed, indicating a radical reaction pathway (Scheme 4). NaI could promote the reaction probably by facilitating the radical generation. Besides, the adduct product of TEMPO and alkyl radical was detected by LC–MS (SCIEX, UPLC-X500RQTOF) as showing in supporting information (Fig. S6).

On the basis of above experimental results and the mechanism proposed by Hegedus and Weix, a plausible free radical chain mechanism is depicted in the Scheme 5. First, the nickel precatalyst **1** is reduced by Mn to form active nickel

Scheme 4 Free radical trapping experiment



Scheme 5 Possible sequence of coupling mechanism of halides



(0) intermediate **2**. And then **2** selectively reacts with ethyl 3-iodopropionate to form organic nickel (II) (**3**). Free radical **4** and organic nickel (II) (**3**) combine to generate the organic nickel (III) (**5**), which further produces dimer product diethyl adipate, and generates the organic nickel (II) (**6**), the resulting organic nickel (II) (**6**) rapidly induces the production of free radical **4** from the halogenated substrate by using microwave irradiation, and itself gets oxidized to nickel precatalyst **1** to complete the cycle (Scheme 5).

4 Conclusions

In summary, we developed a rapid and effective nickel-catalyzed coupling of glycerol-derived ethyl 3-iodopropionate under microwave irradiation with a good yield of diethyl adipate product. Compared with the traditional method, the reaction time was greatly shortened (a few minutes vs. several hours). Diethyl adipate was further hydrolyzed under acid conditions to obtain adipic acid with good yield. Our process offers a practical path for the conversion of glycerol to adipic acid. Besides, we found that this method is applicable to most alkyl halides and aryl halides with assistance of NaI, providing a new method to explore the high-value utilization of halide substituted compounds.

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Compliance with Ethical Standards

Conflict of interest The authors declare no competing financial interest.

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