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Microwave-assisted atom transfer radical addition of polychlorinated compounds to olefins without addition of metal catalysts

Shin Kamijo †, Shoko Matsumura, Masayuki Inoue *

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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ABSTRACT

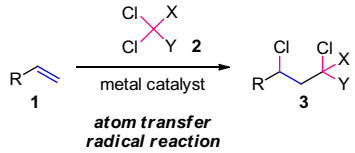
A new operationally simple and robust protocol for the metal-free atom transfer radical reaction (ATRA) has been developed. Polychlorinated compounds were effectively reacted with unactivated terminal olefins to generate 1,3-dichlorinated adducts under microwave irradiation in the presence of silicon carbide (SiC) as a heating element. The present microwave-assisted ATRA proceeds under essentially neutral conditions; thus, polar functionalities are well tolerated. In addition, an oxygen or a nitrogen unit was introduced to the internal side of the carbon chain via nucleophilic cyclization of the 1,3-dichlorinated adducts, and single-step formation of the six-membered carbocycle was realized through cyclization of the intermediate radical. The present methodology provides an expeditious way to prepare synthetically useful molecules from simple and unactivated terminal olefins.

Atom transfer radical addition (ATRA) to olefins enables formation of two contiguous sp^3-carbon centers in a single step (Scheme 1).[1,2] In situ generated radical species in ATRA exhibit both high reactivity and chemoselectivity toward unactivated non-polarized C–C π-bonds without reacting with a wide array of polar functionalities. Since its anion counterparts such as the Michael reaction[3] generally require carbonyl-attached double bonds with full protection of acidic functional groups, ATRA can be more suitable for construction of highly oxygenated molecules with multiple sp^3-carbon centers.[4,5]

We have been particularly interested in ATRA of polychlorinated compounds (**2**: Cl_2CXY), because the resultant bis-substituted product **3** can be converted into various oxygenated structures in a few steps.[6] In addition to radical initiators or photo irradiation, Cu-, Ru-catalyst,[2,7] or photocatalyst[8] have been employed for high-yielding addition of radical species to C–C π-bonds. Here, we report new metal-free, microwave-assisted bis-functionalizations of unactivated terminal olefins **1** with polychlorinated compounds **2**. The present protocol is robust and operationally simple to provide synthetically versatile 1,3-dichloro compounds **3** in high yields.

At the outset of our investigation, the reaction between trichloroacetate **2a**[9,10] and unactivated terminal olefin **1a** was examined to optimize the reaction conditions of metal-free ATRA (Table 1). When a chlorobenzene solution[11] of **2a** was heated to 130 °C using an oil bath, clean recovery of the starting olefin **1a** was observed (entry 1). On the other hand, microwave irradiation realized application of higher temperature (200 °C) to the same mixture,[12] and successfully promoted the regioselective addition (entry 2). However, the expected adduct **3aa** was obtained only in 29% yield. We then employed silicon carbide (SiC) as a heating element to accelerate the reaction, because SiC is known to absorb microwave energy and effectively transfer the generated thermal energy to the solution.[13,14] The reaction in the presence of SiC indeed completed within 1 h, and the yield of the regioselective adduct **3aa** was increased to 88% (entry 3). The present microwave-assisted ATRA necessitated no special precaution against moisture or air, and produced **3aa** (71% yield, entry 4) even in the presence of the radical inhibitor galvinoxyl (0.1 equiv). Indifference of the protocol to the potentially inhibitive contaminants demonstrated its robustness and practicality.

Scheme 2 illustrates the proposed mechanism for regioselective formation of **3aa**. Upon microwave irradiation in the presence of



Scheme 1. Metal-catalyzed atom transfer radical addition (ATRA) of polychlorinated compounds with olefins.

* Corresponding author. Tel.: +81 3 5841 1354; fax: +81 3 5841 0568.
E-mail address: inoue@mol.f.u-tokyo.ac.jp (M. Inoue).
† Present address: Graduate School of Science and Engineering, Yamaguchi University, Yoshida, Yamaguchi 753-8511, Japan.

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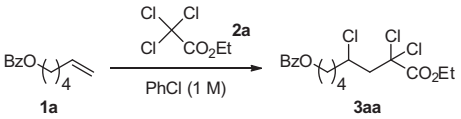
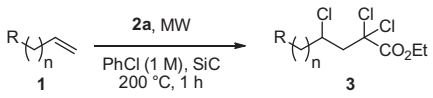
Table 1
Optimization of reaction conditions for ATRA between trichloroacetate **2a** and olefin **1a**[a]



Entry	Temperature (°C)	Heating element	Time (h)	Yield[b] (%)
1[c]	130	None	24	0[d]
2[e]	200	None	1	29[f]
3[e]	200	SiC	1	88[g]
4[e,h]	200	SiC	1	71

[a] Conditions: olefin **1a**, CCl_3CO_2Et **2a** (5 equiv), PhCl (1 M), silicon carbide (SiC) (200 mg/mmol of **1a**) as a heating element.
[b] Yield was calculated based on NMR analysis of the crude mixture unless otherwise noted.
[c] Oil bath was used.
[d] Olefin **1a** was recovered in 93% yield.
[e] Microwave irradiation was employed.
[f] Olefin **1a** was recovered in 69% yield.
[g] Isolated yield.
[h] The reaction was conducted in the presence of galvinoxyl (0.1 equiv).

Table 2
Bis-functionalization of various terminal olefins **1** with trichloroacetate **2a** via ATRA[a]



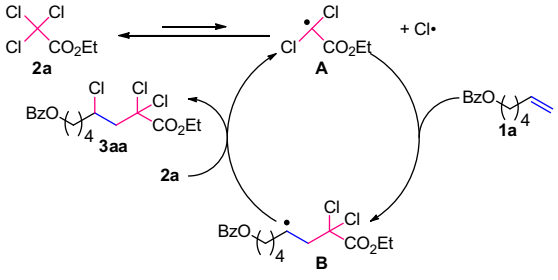
Entry	Compound	R	*n*	Yield[b] (%)
1	**1a**	OBz	4	88 (**3aa**)
2[c]	**1b**	OBOM	4	55 (**3ba**)[d]
3	**1c**	OTBDPS	4	79 (**3ca**)
4	**1d**	OH	4	54 (**3da**)
5[c]	**1e**	NHTs	4	55 (**3ea**)[e]
6	**1f**	Cl	4	68 (**3fa**)
7	**1g**	Ph	2	98 (**3ga**)

[a] Conditions: olefin **1**, trichloroacetate **2a** (5 equiv), PhCl (1 M), SiC (200 mg/mmol of **1**) as a heating element, heated at 200 °C by microwave irradiation for 1 h unless otherwise noted.
[b] Isolated yield.
[c] The reaction was conducted at 170 °C.
[d] Olefin **1b** was recovered in 17% yield.
[e] Olefin **1e** was recovered in 27% yield.

SiC, **2a** is in equilibrium with minute amounts of **A** and the Cl radical (Cl·) due to the relatively weak C–Cl bond of **2a** (66.7 kcal/mol).[15] The generated radical **A** is both highly electron-deficient and stable, because the two carbon-attached chloro groups and one carbonyl group have σ-withdrawal effects, and the lone-pair of a chloro group as well as the π-bond of a carbonyl group generally stabilize the adjacent carbon radical.[16] Radical **A** then adds to the electron-rich unactivated C–C π-bond from the less hindered side, leading to formation of the more electron-rich and less-stabilized secondary radical **B**. Halogen transfer from **2a** to **B** in turn affords adduct **3aa** and regenerates the stable radical **A**. This cycle produces **A** continuously,[17] while Cl· is formed slowly from the homolytic cleavage of **2a**. Accordingly, the higher concentration of **A** permits its exclusive addition to the olefin in the presence of Cl·. Moreover, ATRA of the product **3aa** is inhibited: its C–Cl bond is only activated by one chloro group and one carbonyl group, thus, the radical formation from **3aa** is disfavored in comparison to **2a**.[13] These physicochemical characteristics of the molecules in Scheme 2 should contribute to high-yielding formation of **3aa**.

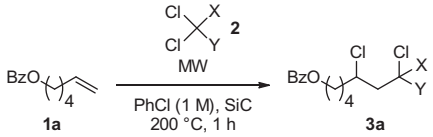
Next, we demonstrated the functional group compatibility of microwave-assisted ATRA (Table 2). Terminal olefins **1** having various functionalities on the side chain were successfully reacted with **2a** under the optimized conditions. Similar to benzoyl protected **1a** (entry 1), the reactions of benzyloxymethyl- (**1b**) and TBDPS-protected alcohols (**1c**) both proceeded smoothly to provide adducts **3ba** in 55% yield and **3ca** in 79% yield, respectively (entries 2 and 3). Furthermore, it was found that the alcohol protective group was not necessary for the present transformation. Alcohol **1d** was efficiently converted into the corresponding adduct **3da** in 54% yield (entry 4). The nitrogen functionality (**1e**) and chloride moiety (**1f**) were retained under the reaction conditions to produce adducts **3ea** in 55% yield and **3fa** in 68% yield, respectively (entries 5 and 6). When the non-functionalized substrate **1g** was used, adduct **3ga** was formed in excellent yield (entry 7).

We then explored the applicability of a series of polychlorinated compounds **2** for radical-based bis-functionalization of olefin **1a** under the optimized conditions (Table 3). In contrast to the excellent reactivity of trichloroacetate **2a** (entry 1), ATRA of dichloroace-



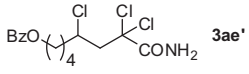
Scheme 2. Proposed mechanism for the present ATRA under microwave irradiation.

Table 3
Applicability of polychlorinated compounds **2** for olefin bis-functionalization via ATRA[a]



Entry	Compound	X	Y	Yield[b] (%)
1	**2a**	Cl	CO_2Et	88 (**3aa**)
2	**2b**	H	CO_2Me	0 (**3ab**)[c]
3	**2c**	Me	CO_2Me	0 (**3ac**)[c]
4	**2d**	Cl	CO_2Ph	87 (**3ad**)
5[d,e]	**2e**	Cl	COCl	64 (**3aa**)
6[d,f]	**2e**	Cl	COCl	61 (**3ae′**)
7[d]	**2f**	Cl	CN	79 (**3af**)
8	**2g**	CO_2Me	CO_2Me	64 (**3ag**)
9[d,g]	**2h**	CN	CN	78 (**3ah**)

[a] Conditions: olefin **1a**, polychlorinated compound **2** (5 equiv), PhCl (1 M), SiC (200 mg/mmol of **1a**) as a heating element, heated at 200 °C by microwave irradiation for 1 h unless otherwise noted.
[b] Isolated yield.
[c] Olefin **1a** was recovered in 99% yield.
[d] The reaction was conducted at 170 °C.
[e] The crude mixture was treated with EtOH (5 equiv) and Et_3N (5 equiv) at rt for 3 h to give ester **3aa**.
[f] The crude mixture was diluted with PhCl and treated with NH_3 gas (excess) and Et_3N (5 equiv) at rt for 2.5 h to give amide **3ae′**.



[g] The reaction was conducted in toluene instead of PhCl.