Tetrahedron Letters 53 (2012) 4368–4371

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 27 April 2012
Revised 1 June 2012
Accepted 6 June 2012
Available online 12 June 2012

Keywords:
Microwave
Atom transfer radical addition
Cyclization
Olefin
Polychlorinated compounds

ABSTRACT

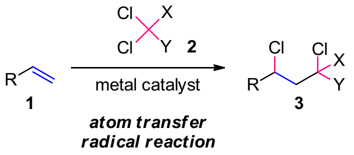
A new operationally simple and robust protocol for the metal-free atom transfer radical reaction (ATRA) has been developed. Polychlorinated compounds were effectively reacted with unactivated terminal olefins to generate 1,3-dichlorinated adducts under microwave irradiation in the presence of silicon 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.

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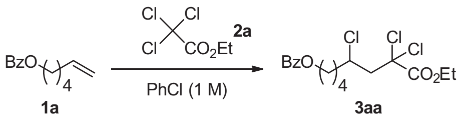
http://dx.doi.org/10.1016/j.tetlet.2012.06.027

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.

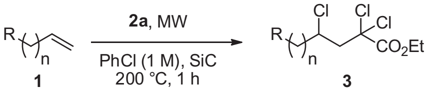
[f] Olefin **1a** was recovered in 69% yield.

[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.

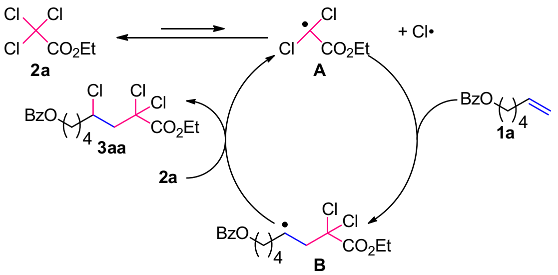
[c] The reaction was conducted at 170 °C.

[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).

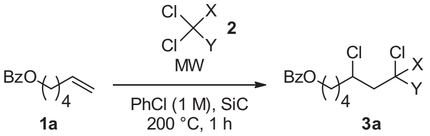


Scheme 2. Proposed mechanism for the present ATRA under microwave irradiation.

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-

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.

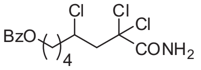
[b] Isolated yield.

[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′**.



3ae'

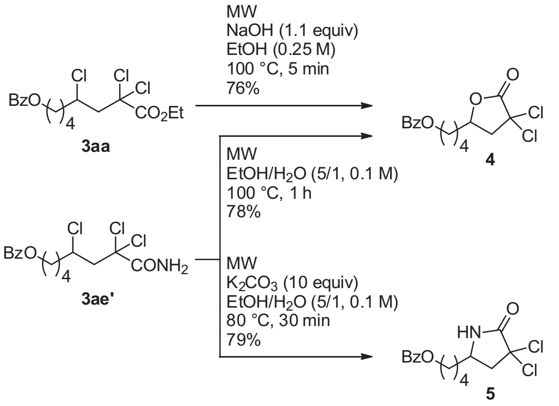
[g] The reaction was conducted in toluene instead of PhCl.

tate **2b** and dichloropropanoate **2c** did not proceed, and the starting olefin **1a** was quantitatively recovered (entries 2 and 3). These negative results were expected, considering that the dichlorinated product **3aa** is inert under the reaction conditions (entry 1). Nevertheless, efficiency in homolytic cleavage of the C–Cl bond of **2** was confirmed to correlate with the number of radical-stabilizing chloro group attached at the latent carbon radical center. In fact, both the trichloro derivatives **2d** and **2f**[18] participated in the present ATRA (entries 4–6). While adduct **3ad** was produced from phenyl trichloroacetate **2d** in high yield (entry 4), the acid chloride adduct tentatively formed from trichloroacetyl chloride **2f** was converted into ethyl ester **3aa** (64% yield) and amide **3ae**′ (61% yield) upon treating with EtOH/Et_3N and NH_3/Et_3N, respectively, in the same flask. ATRA of trichloroacetonitrile **2f** also proceeded to form the corresponding adduct **3af** in 79% yield. Dichlorinated compounds underwent microwave-assisted ATRA, when the chloro group was substituted by another radical stabilizing carbonyl or nitrile group (entries 8 and 9). Dichloromalonate **2e**[19] and dichloromalononitrile **2h**,[6,20,21] were converted into **3ag** in 64% yield and **3ah** in 78% yield, respectively.

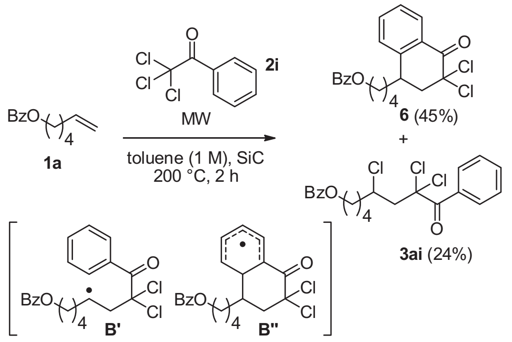
The newly formed C–Cl bonds of adducts **3aa** and **3ae**′ were converted into C–O or C–N bonds via a single intramolecular reaction (Scheme 3). Treatment of ester **3aa** with 1.1 equiv of NaOH in EtOH resulted in formation of lactone **4** without touching the benzoate moiety.[22] The same lactone **5** was obtained in good yield simply by heating amide **3ae**′ in aqueous EtOH.[23] On the other hand, formation of the C–N bond was accomplished by treating amide **3ae**′ under basic conditions (K_2CO_3 in EtOH/H_2O) to produce lactam **5** in good yield. Therefore, by taking advantage of the reactivity of the C–Cl bond and the carbonyl moiety, the synthetically useful oxygen and nitrogen units were successfully installed.

Finally, one-step formation of the six-membered ring from the terminal olefin was realized, when trichloroacetophenone **2i** was used (Scheme 4). Microwave-assisted ATRA of **2i** to olefin **1a** afforded the dihydronapthalenone derivative **6** as a major product along (45% yield) with ATRA adduct **3ai** (24% yield).[24] In this reaction, cyclization of the secondary radical of **B**′ to the phenyl ring was faster than the Cl-transfer, resulting in formation of the fused bicycle **6** through **B**″. The present tandem radical reaction is potentially useful for construction of various functionalized carboskeletons, which are not readily available via other methods.[25]

In conclusion, we developed a new operationally simple and robust protocol for chemo- and regioselective ATRA of polychlorinated compounds **2** to unactivated olefins **1**. The present microwave-assisted ATRA proceeds without a metal catalyst under essentially neutral conditions; thus, various polar functionalities such as benzoyloxy, benzyloxymethyloxy, siloxy, hydroxy, tosylamide, and chloro groups are well tolerated. Polychlorinated esters, acid chloride, and cyanides can be utilized as the starting halides **2**, and their reactivity as a radical precursor is successfully controlled by the number of radical-stabilizing functional groups (Cl, C=O or CN) attached at the latent carbon radical center. In addition, an oxygen or a nitrogen unit is introduced to the internal side of the carbon chain via the intramolecular reaction of the adducts, and formation of the two C–C bonds is realized through the tandem radical reaction. The present methodology provides an expeditious way to prepare various synthetically useful molecules from simple and unactivated terminal olefins.



Scheme 3. Functional group manipulations for installation of oxygen and nitrogen units.



Scheme 4. The reaction between trichloroacetophenone **2i** and olefin **1a**.

Acknowledgments

This research was financially supported by the Funding Program for Next Generation World-Leading Researchers (JSPS) to M.I.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.027.

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