α-Bromoacetate as a Mild and Safe Brominating Agent in the Light-Driven Vicinal Dibromination of Unactivated Alkene and Alkynes

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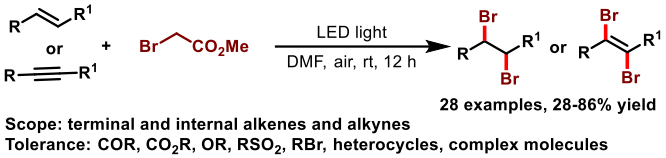
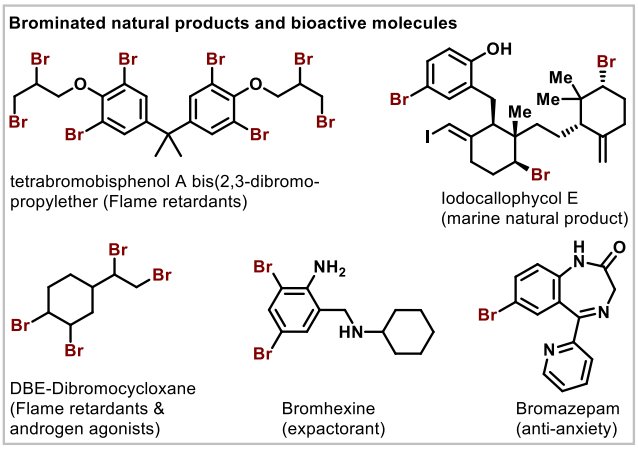
Supporting Information Placeholder

ABSTRACT: Light-induced vicinal dibromination of unactivated alkenes and alkyne has been demonstrated by using methyl α-bromoacetate as a mild brominating agent. Near-visible light (370 nm) light-emitting diode (LED) mediates this simple dibromination reaction under mild conditions with the inexpensive and non-toxic α-bromoacetate. The reaction proceeds well with both terminal and internal alkenes and alkynes, and those contained in natural products and *N*/*O*-heterocycles, indicating its versatility in synthesizing dibrominated organic compounds.

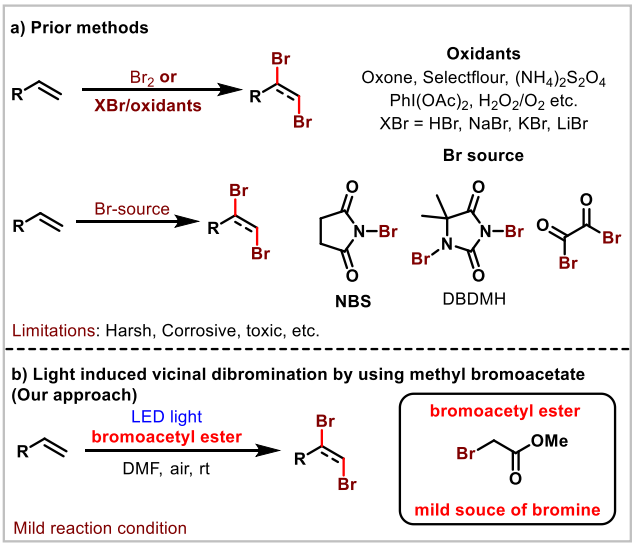


Halogenated compounds are used widely and routinely in organic synthesis due to their convenient accessibility and excellent reactivity. In particular, brominated organic compounds are of particular significance due to their inimitable role in many pharmaceuticals,[1] agrochemicals,[2] and flame-retardants,[3] (Scheme 1) in addition to servings versatile synthetic intermediates in the organic reactions, such as S_N2 reactions, cross-coupling, radical reactions and organometallic chemistry.[4] Despite these attractive features, the preparation of brominated compounds still mainly relies on the use of highly reactive, toxic, hazardous and corrosive elemental Br_2 in stoichiometric amounts under harsh conditions (Scheme 2a).[4c,5] A number of other reagents, such as Oxone, Selectfluor, $(NH_4)_2S_2O_4$, $PhI(OAc)_2$, H_2O_2/O_2, have been implemented in order to use HBr, NaBr, KBr and LiBr as brominating sources through *in situ* oxidation of Br^- to Br^+.[6] Additionally, Morandi[6e] and Hilt[6d] have recently employed electrochemical oxidation approach to use dibromoethane and nBu$_4$NBr as the halogen source to dihalogenate alkenes. However, these methods also predominantly use stoichiometric amounts of the strongly oxidizing reagents to generate the bromonium cation (Br^+) and often require high temperatures that lead to the formation of unwanted by-products.

Few more efforts have been directed towards achieving dibromination of alkenes and alkynes by directly using electrophilic brominating reagents such as *N*-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and oxalyl bromide in the presence of catalysts, such as thiourea, benzoic acid, triphenylphosphine oxide, iodobenzamide and nitroxides.[7] Li and coworkers has recently described a catalyst free protocol for 1,2 dibromination of alkenes by using DBDMH as a bromine source.[8] In 2011, Liu and coworkers reported 1,2-dihalogenation of alkynes with *N*-halosuccinimides.[9] Despite these significant improvements, dihalogenation of alkenes and alkynes with mild reagents, and under mild and neutral conditions is still a major challenge. Herein, we report a simple α-bromoacetate as a convenient and non-toxic reagent for dibromination of alkenes and alkynes under



Scheme 1. Brominated organic compounds and their applications

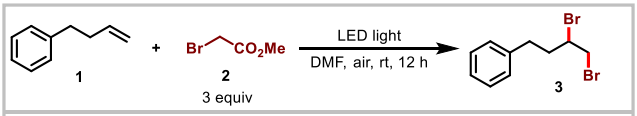


Scheme 2. Methods for the vicinal dibromination of alkenes and alkynes

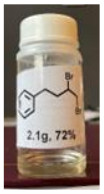
mild and neutral reaction conditions (Scheme 2b). This reaction exploits the near-visible light LED photoredox condition for the homolysis of C-Br bond in α-bromoacetate to generate Br• as the brominating species.

During our studies on photoredox-catalyzed alkene carbobromination phenylbutene **1** with α-bromocarbonyls via a radical addition-radical pairing (RARP) mechanism,[10] we observed that exposure of the reaction to air completely shunned carbobromination and induced selective 1,2-dibromination (Table 1, entry 1). A control experiment in the absence of the photocatalyst (4-CzIPN) showed that the dibromination still proceeded in good yields (entry2). Further experiments at different wavelengths of the LED light suggested that the reaction performed best at 370 nm LED light (77 kcal/mol) (entries 2-4), suggesting that the reaction could potentially occur via the direct photohomolysis of the C-Br bond by the LED light. Variation of the reaction parameters, such as the use of different solvents or equivalents of α-bromoacetate suggested that 3 equiv. of the brominating reagent in DMF at 370 nm wavelength was the optimal condition for dibromination (entries 5-8). α-Bromoacetate could also be replaced with 1 equiv. of α,α-dibromoacetate to effect dibromination in a comparable yield (entry 9). The reaction can be conducted in gram-scale quantity (10 mmol), which afforded the product in 72% (2.1 g) isolated yield (entry 3).

Table 1. Observation of dibromination and further optimization of reaction parameters[a]



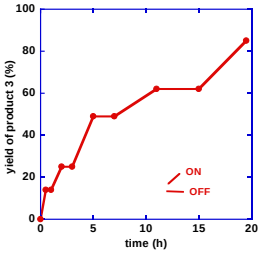
entry	modified conditions	yield of **3** (%)[b]
1	blue LED (440 nm), 2 mol % 4CzIPN	38
2	without 4CzIPN	40
3	370 nm LED	85 (72)
4	390 nm LED	75
5	370 nm LED, 2 equiv of **2**	65
6	370 nm LED, 4 equiv of **2**	82
7	370 nm LED, IPA	15
8	370 nm LED, H_2O, Acetone, THF, CH_3CN, Ethylene glycol, EtOH or MeOH instead of DMF	0
9	370 nm LED, IPA, 1 equiv of $(Br)_2CHCO_2Me$ instead of **2**	80
10	reaction in dark	0
11	370 nm LED, 1 equiv TEMPO	trace



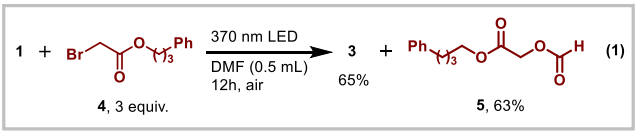
[a]Reactions were conducted at 0.10 mmol scale in 0.5 ml solvent. [b]^{1}H NMR yields using tetrachloroethane as a standard. Isolated yield from a 10 mmol scale reaction in parenthesis.

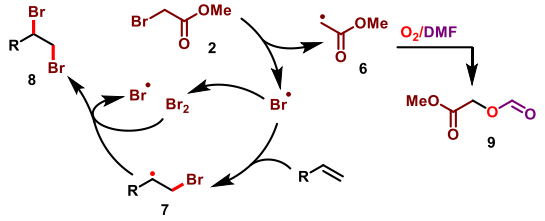
We conducted further experiments to understand the reaction mechanism. The dibromination reaction doesn't proceed in dark (Table 1, entry 10, and Scheme 3) and in the presence of a radical source, such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), (entry 11) indicating that the reaction evokes radical intermediates but doesn't involve chain propagation for dibromination. Most importantly, we were able to isolate and fully characterize a formate product **5** generated upon trapping of the carbon-centered radical with O_2/DMF when a phenylpropyl α-bromoacetate (2 equiv) was used as a brominating source (eq. 1). This observation confirms the direct homolysis of the C-Br bond in α-bromoacetate by the 370 nm LED light.

On the basis of our mechanistic experiments, we propose a plausible reaction mechanism as outlined in Scheme 4. The reaction is initiated by the homolytic cleavage of the C-Br bond in α-bromoacetate under irradiation with the 370 nm LED light, thereby leading to the formation of Br• and the acylmethyl radical (•CH_2CO_2Me). Br• then adds to an alkene generating a *sec*-C• which either recombines with another Br• or abstracts a Br atom from molecular Br_2 formed upon combination of two Br•. The acylmethyl radical is captured by molecular O_2 and DMF to generate 2-(formyloxy)acetate **5**.



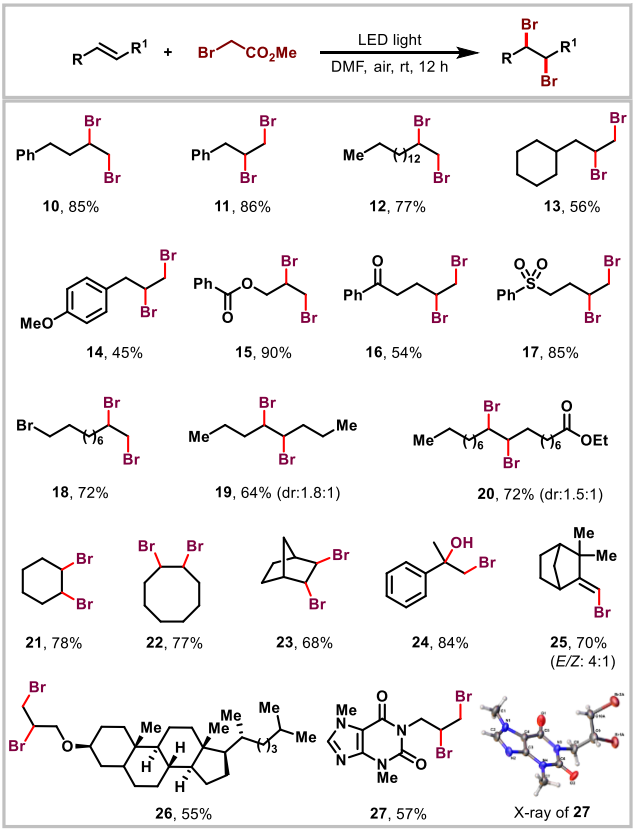
Scheme 3. Light on-off experiments





Scheme 4. Proposed reaction mechanism

Table 2. Substrate scope for dibromination of alkenes

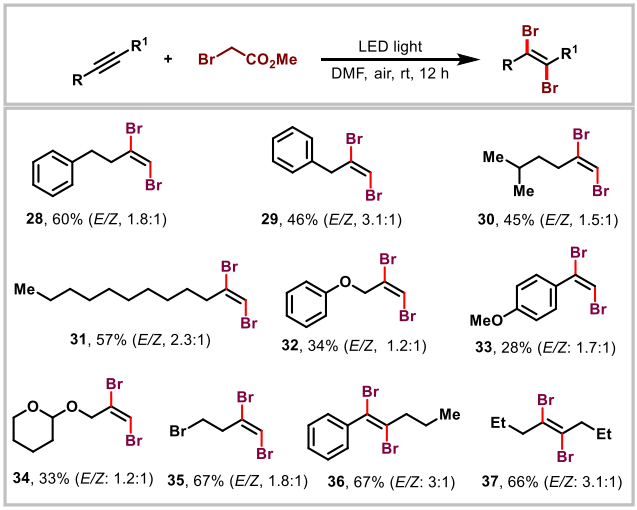


[a]Reactions were run at 0.50 mmol scale in 2.5 mL DMF unless stated otherwise. The percentage numbers are the yields of isolated products.

Having established the optimal reaction conditions and the possible reaction mechanism, we then began to evaluate the generality of the protocol (Table 2). The reaction proceeds well with both unfunctionalized and functionalized unactivated alkenes and tolerates a diverse set of functional groups, such as aryl, ester, ketone, methoxy and sulfonyl, affording the dibrominated products **10**-**20** in good yields. The reaction is also compatible with alkenylalkyl bromides in which the alkene was dibrominated to give a tribromoalkane **18** without affecting the native bromo group. Internal alkenes contained in linear, monocyclic and bicyclic motifs are also readily dibromination in good yields (**21**-**23**). However, reactions with styrenes and sterically congested alkenes generated bromohydrin and vinyl bromide (**24**-**25**) instead of dibrominated products, potentially due to reaction with O_2 or H_2O and dehydrobromination, respectively. To our delight, alkenes studded in complex carbocyclic and heterocyclic natural products, such as the steroid 5d-cholestan-3β-ol and alkaloid theobromine, also proved to be viable substrates for dibromination. (**26**-**27**). The structure of the dibrominated theobromine derivative was also confirmed by a single crystal X-ray crystallography. While the dibromination of acyclic internal alkenes proceeded with low diastereoselectivity, the cyclic dibrominated products were generated as single diastereoisomers.

The reaction condition is also applicable for the dibromination of alkynes as demonstrated in Table 3. A variety of terminal and internal alkynes bearing aryl, alkyl, methoxy, phenoxy and alkoxypyrane were readily dibrominated, affording the desired products (**28**-**37**) with moderate to good yields. The dibrominated products with both the terminal and internal alkynes were generated in moderate ratios of *E*- and *Z*-isomers.

Table 3: Substrate scope for dibromination of alkynes



[a]Reactions were run at 0.50 mmol scale in 2.5 mL DMF unless stated otherwise. The percentage numbers are the yields of isolated products.

In Summary, we developed a simple method for vicinal dibromination of unactivated alkenes and alkyne under irradiation with a 370 nm LED light by using α-bromoacetate as a mild and safe brominating agent. The reaction tolerates sensitive functional groups like esters, ketones and alkyl bromides, and works well with both terminal and internal alkenes and alkynes. α-Bromoacetate could prove to be an excellent brominating agent in bromination chemistry under near-visible light since it is readily available, inexpensive, nontoxic, and stable for handling and transportation. In addition, since this new dibromination protocol enables to generate Br•/Br_2 in small potions sustained over time, there's a low risk for producing unwanted side products in the reaction.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, mechanistic studies, characterization data, and NMR spectra for new products.

X-ray crystallographic data for compound **27** (deposition number 2353921) is available from the Cambridge Crystallographic Data Center.

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