ADDITIONS OF ELECTROPHILIC RADICALS TO ELECTRON RICH ALKENES BY THE ATOM TRANSFER METHOD. SURMOUNTING POTENTIALLY REVERSIBLE RADICAL ATOM TRANSFER REACTIONS BY IRREVERSIBLE IONIC REACTIONS

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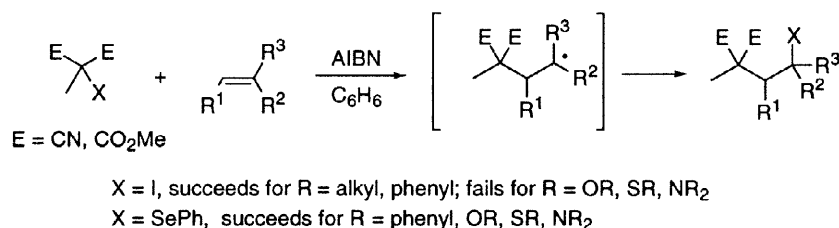
Abstract: Conditions have been developed for the atom transfer radical addition reaction of bromoesters to enol ethers. The putative intermediate haloethers are allowed to ionize and the resulting cations are trapped by addition or elimination reactions. © 1998 Elsevier Science Ltd. All rights reserved.
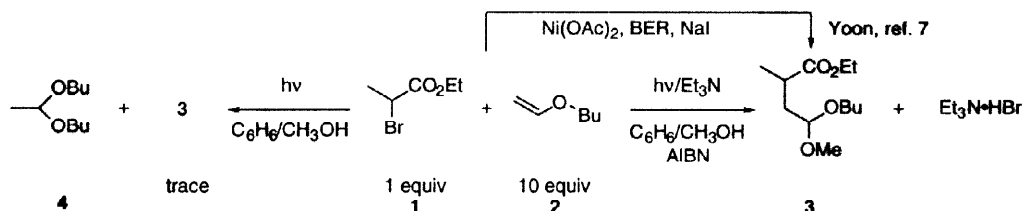
During the mid-to-late 1980's, the atom transfer radical addition (ATRA) reaction emerged from a long period of obscurity to take a position as an important component in modern synthetic radical chemistry.[1] Since then, the scope of radical atom and group transfer reactions has continued to increase, and atom transfer radical polymerization (ATRP) has become a major tool in modern polymer chemistry.[2] In many atom transfer addition reactions, an exothermic radical addition step is followed by an exothermic atom transfer step. Reactions with nearly thermoneutral atom transfer steps can be conducted by using metal catalysis or more simply by using iodine as the halogen (because even thermoneutral iodine transfers are reasonably rapid).[3]

We have extensively studied the atom transfer addition reactions of halomalonates, halomalonitriles, and related compounds (Eq 1).[4] These reactions are now reasonably well understood and have significant preparative value. In studying the scope of these reactions, we learned that iodomalonates and malononitriles are highly reactive towards many types of alkyl- and aryl-substituted alkenes. However, despite a number of attempts, we were never able to develop a useful procedure for addition of these radical precursors to electron rich alkenes like enol ethers, enol thioethers, or enamines.[5] This failure puzzled us since the radical addition step of the proposed chains should clearly be rapid, and the atom transfer step—while nearly thermoneutral of even endothermic—should be facilitated due to the weak C–I bond and to a favorable polar effect. Indeed, the analysis is supported by the fact that related group transfer addition reactions (X = SePh or xanthate) work well.[6] We now report that the analogous halogen atom transfer addition reactions succeed provided that an equivalent amount of a mild base is added to the reaction mixture. This simple expedient significantly extends the scope of this class of ATRA reaction.

Eq 1

E = CN, CO₂Me

X = I, succeeds for R = alkyl, phenyl; fails for R = OR, SR, NR₂
X = SePh, succeeds for R = phenyl, OR, SR, NR₂

The impetus to revisit this line of experimentation came from a recent paper by Yoon and coworkers (Eq 2).[7] They reported that addition of ethyl 2-bromopropionate **1** and related halides to butyl vinyl ether **2** occurred smoothly in methanol in the presence of Ni(OAc)₂, "borohydride exchange resin" (BER) and NaI to provide the adducts **3** as acetals. The role of BER was not rationalized, and excess BER was used even though the transformation is not a reduction. This lead us to speculate that BER simply functioned as a base to neutralize the equivalent of HBr (or HI) that is generated in the formation of **3**. This speculation was strongly supported by observations of Ryu and coworkers reported shortly thereafter.[8] They found that addition of base was essential in atom transfer carbonylations that are presumed to involve acyl iodides and that provide lactones or esters as isolated products.

Eq 2

Ni(OAc)₂, BER, NaI → Yoon, ref. 7

$$\text{OBu} \quad + \quad 3 \quad \xrightarrow[\text{C}_6\text{H}_6/\text{CH}_3\text{OH}]{hv} \quad \overset{\text{CO}_2\text{Et}}{\underset{\text{Br}}{\diagup}} \quad + \quad \overset{O}{\searrow}\text{Bu} \quad \xrightarrow[\substack{\text{C}_6\text{H}_6/\text{CH}_3\text{OH} \\ \text{AIBN}}]{hv/\text{Et}_3\text{N}} \quad \overset{\text{CO}_2\text{Et}}{\underset{\text{OMe}}{\diagdown \text{OBu}}} \quad + \quad \text{Et}_3\text{N}\cdot\text{HBr}$$

| | 4 | | trace | 1 equiv **1** | 10 equiv **2** | | **3** |

We initially conducted two reactions of **1** (limiting reagent) and **2** (10 equiv) in benzene containing methanol (5 equiv) and hexabutylditin (10 mol%). Both reaction mixtures were subjected to UV irradiation with a standard Hanovia lamp for 4 h (Eq 2). In the mixture resulting from the reaction conducted in the absence of triethylamine, we detected a small amount of the desired product **3**, but the major new (non-volatile[9]) product after workup was acetaldehyde dibutyl acetal **4**. In contrast, during irradiation a precipitate (Et₃N•HBr) appeared in the reaction conducted in the presence of Et₃N (1.2 equiv). After workup, this reaction provided mixed acetal **3** as a clean crude product (~1/1 mixture of diasteromers, purified yield not determined). In optimizing reaction conditions, we quickly learned that the ditin could simply be replaced by AIBN (10%); a preparative experiment with AIBN provided **3** in 97% crude yield and 95% yield after purification by short column chromatography. That the reaction occurs without any tin additive greatly facilitates purification. Within the limits of detection, the product was exclusively the mixed acetal **3**; neither the dimethyl nor the dibutyl acetals were evident.[10]

Using butyl vinyl ether as a constant component, a series of reactions was run by varying the radical precursors and the alcohol trap. These reactions were all conducted on 0.8 mmol scale, and the isolated yields of purified products are listed in Table 1.[11] The results show that other simple alcohols (entries 1 and 2) can be used in place of methanol and that an assortment of simple radical precursors can be used (entries 3-5). Only in the case of the rather unreactive tertiary radical[3b] (entry 5) did the yield dip noticeably (to 70%). Omission of the alcohol from the reaction mixture resulted in formation of the corresponding enol ether product (entry 6), while addition of diethylamine in place of the alcohol yielded the known aldehyde (entry 7)[12] after treatment of the crude reaction mixture with dilute HCl.

Table 1. Radical Addition of α-Bromo Esters to Vinyl Ether.

entry	substrate	alcohol	product	yield(%)
1	EtO-C(=O)-CH₂-Br	PhCH₂OH	EtO-C(=O)-CH₂-CH(OBn)-O-Bu	91
2	EtO-C(=O)-CH₂-Br	cyclohexanol	EtO-C(=O)-CH₂-CH(OC₆H₁₁)-O-Bu	89
3	EtO₂C-CHBr-CO₂Et	MeOH	EtO₂C-CH(CO₂Et)-CH(OMe)-O	94
4	EtO₂C-C(CH₃)Br-CO₂Et	MeOH	EtO₂C-C(CO₂Et)-CH(OMe)-O	99
5	EtO-C(=O)-CBr(CH₃)₂	MeOH	EtO-C(=O)-C(CH₃)₂-CH(OMe)-O	70
6	EtO-C(=O)-CHBr-Me	–	EtO-C(=O)-C(Me)=CH-O	91 (E:Z = 1:1)
7	EtO-C(=O)-CHBr-Me	Et₂NH	EtO-C(=O)-CH(Me)-CH₂-CHO	81[a]

a. The aldehyde was obtained after treatment of the reaction mixture with 0.5 N aq HCl solution

Brief trials to develop a few extensions met with mixed success. Attempts to form C–C bonds by adding reagents like enol silyl ethers have not yet been successful, although the possibilities have certainly not been exhausted. On the other hand, when α-haloacids were used in this reaction (in the absence of alcohol), δ-alkoxy-δ-lactones were formed, as shown by the examples in Eq 3. These products have a number of uses in organic synthesis.[13]

Eq 3
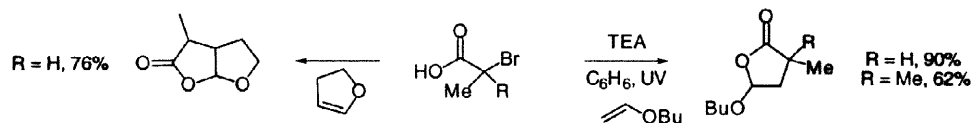
A suggested mechanism for these transformations is shown in Scheme 1. Radicals **5** bearing one (or two) electron withdrawing groups should add readily to enol ethers to provide **6**. According to the radical stabilization energies (RSE) of Rüchardt,[14] product radical **6** (RSE = –5.9 kcal/mol) is more stable than starting radical **5** (RSE = –2.9 kcal/mol). This implies that the bromine atom transfer reaction between the radical **6** and **7** is endothermic. Nonetheless, we suggest that it can occur at a reasonable rate due to a favorable polar effect (see **TS**) to provide **8**. Intermediate α-bromoether **8** is presumably unstable under the reaction conditions and ionizes to oxonium ion **9**. In the absence of base, HBr is formed, and this then initiates acid catalyzed acetal and enol ether exchange. In the presence of base, the HBr is neutralized and the bromoether **8** is smoothly converted to either an enol ether **10** or a mixed acetal **11**, depending on the conditions. This drives the radical reaction forward by removing **8** as a potential bromine donor from the medium. The sequence of bromine transfer followed by ionization amounts to an inner sphere electron transfer. At this point, we have no experimental evidence for the intermediacy of the α-bromoether **8**, so we cannot rule out an alternative outer sphere electron transfer process where **6** and **7** react directly to product oxonium ion **9**.[15] However, we can confidently rule out an ionic mechanism based on bromonium ions and related species; such addition reactions would provide the other regioisomer.

Scheme 1
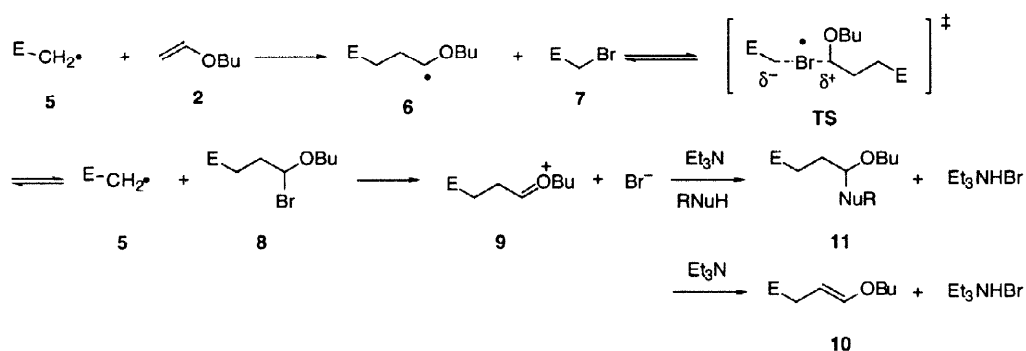
The results in this paper are important for several reasons. The reported transformations have clear preparative value; an assortment of different products have already been prepared and there is potential to extend the work with different radical precursors, acceptors, and nucleophiles. This is also a new method for sequencing a radical reaction prior to an ionic one.[1d] The procedure is attractive because no tin is needed and because iodides are not required; bromides are sufficiently reactive. Finally, perhaps most important are the broader implications for halogen atom transfer chemistry. As this field has developed, it has been concluded that halogen transfer reactions that provide product halides capable of ready ionization will probably not be useful. However, our work, Yoon's[7] and Ryu's[8] taken together begin to suggest that this conclusion is premature. Useful reactions can be developed when the product halides are allowed to ionize and when the resulting cations are trapped in a productive fashion that does not interfere with the radical chain.

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9. We presume that other volatile acetal exchange products may also have been produced.

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11. **Representative Experiment:** A solution of ethyl bromopropionate (0.14 g, 0,77 mmol), butyl vinyl ether (0.77 g, 7.7 mmol), methanol (0.12 g, 3.8 mmol), and triethylamine (0.09 g, 0.90 mmol) in dry benzene (3.0 mL) was irradiated with a UV lamp. Triethylamine HBr salt was observed in the reaction mixture after stirring for 4 hr. The reaction mixture was filtered, and the salt was washed with diethyl ether. The combined filtrate was concentrated and the residue was purified by silica gel column chromatography (hexanes: EtOAc = 8:1) to afford 0.17 g (0.73 mmol, 95%) of the compound 4 as a clear oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.14 (d, J = 7.1 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.34 (m, 2 H), 1.49 (m, 2 H), 1.60 (m, 1 H), 2.00 (m, 1 H), 2.52 (m, 1 H), 3.27 (s, 3 H), 3.37 (m, 1 H), 3.53 (m, 1 H), 4.09 (q, J = 7. 1 Hz, 2 H), 4.42 (t, J = 5.9 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.9, 14.2, 17.6, 19.4, 31.9, 35.7, 36.8, 52.7, 60.2, 65.8, 102.1, 176.3; IR (neat, cm^{-1}) 2876, 1735, 1464, 1377, 1179, 1120, 1074; HRMS (EI) m/z calcd for C$_{12}$H$_{24}$O$_4$ (M$^+$ − OCH$_3$) 201.1491, found 201.1495; LRMS (EI) m/z 201 (45), 187 (31), 159 (40), 117 (37), 99 (92), 71 (59), 61 (100).

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