Atom-transfer Radical Addition of α-Iodo Esters to 1-Alkynyl Sulfides

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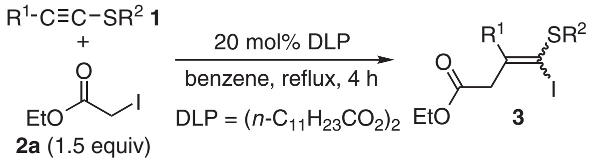
Atom-transfer radical addition of α-iodo esters to 1-alkynyl sulfides is described. The products, 2-alkoxycarbonylmethyl-1-iodo-1-alkenyl sulfides, can be converted into γ-keto esters.

1-Alkynyl sulfides can be good precursors to synthesize various organosulfur compounds.[1] For example, Diels–Alder reactions of 1-alkynyl sulfides with conjugated dienes giving cyclic alkenyl sulfides have been reported.[1c] On the other hand, there are few reports of radical reactions using 1-alkynyl sulfides as substrates,[2] although radical addition would be a powerful method to prepare synthetically useful vinyl sulfides. Here we report atom-transfer radical addition of α-iodo esters to 1-alkynyl sulfides.

Treatment of butyl 1-octynyl sulfide (**1a**) with ethyl iodoacetate (**2a**) in the presence of a catalytic amount of dilauroyl peroxide (DLP) in boiling benzene afforded the corresponding adduct **3aa** in 71% yield (Table 1, Entry 1).[3,4] Although the stereoisomeric ratio was close to 1:1, the reaction proceeded with perfect regioselectivity. Alkynyl sulfides bearing a base-sensitive siloxy moiety or an acid-sensitive THP moiety underwent the radical addition without affecting the protective groups (Entries 2 and 3). Replacement of the butylsulfanyl group of **1a** by methylsulfanyl or phenylsulfanyl group did not affect the reactivity (Entries 4 and 5). A secondary alkyl-substituted alkynyl sulfide **1f** was also applicable to the reaction, albeit the stereoselectivity was still low (Entry 6). Unfortunately, an aryl-substituted alkynyl sulfide, butyl phenylethynyl sulfide (**1g**), was not suitable for the reaction because of the formation of a mixture of regio- and stereoisomers.

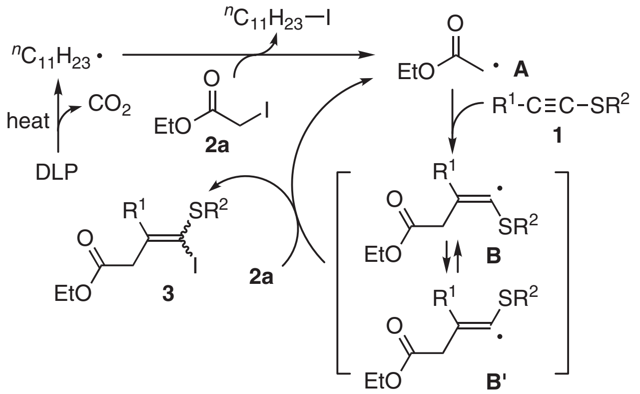
The reaction would proceed in a manner similar to standard atom-transfer radical reactions (Scheme 1).[5] Undecyl radical, thermally generated from DLP with release of CO_2, would abstract iodine from **2a** to provide carbon-centered radical **A**.[6] Because carbonylmethyl radicals are electron-deficient, radical **A** would react smoothly with 1-alkynyl sulfide **1**, an electron-rich alkyne, to furnish the vinyl radical **B**. At this stage, the new carbon–carbon bond is formed regioselectively at the β-position of the sulfur atom, at which higher electron-density resides due to the resonance effect of the sulfur atom. The E/Z isomerization between vinyl radicals **B** and **B′** is fast. In addition, the sizes of R^1 and the ethoxycarbonylmethyl group are comparable. Hence, both stereoisomers would react with **2a**. Iodine-transfer from **2a** to the vinyl radicals would afford product **3** and regenerate radical **A** to complete the radical chain.

Table 1. Atom-transfer radical addition of ethyl iodoacetate **2a** to 1-alkynyl sulfides **1**



Entry	1	R^1	R^2	3	Yield/%[a] [E/Z or Z/E]
1	**1a**	n-C_6H_{13}	n-Bu	**3aa**	71 [56/44]
2	**1b**	t-$BuMe_2SiO(CH_2)_3$	n-Bu	**3ba**	60[b] [54/46]
3	**1c**	$THPO(CH_2)_3$	n-Bu	**3ca**	55[b] [56/44]
4	**1d**	n-$C_{10}H_{21}$	Me	**3da**	82 [57/43]
5	**1e**	n-C_6H_{13}	Ph	**3ea**	72 [52/48]
6	**1f**	i-Pr	n-$C_{12}H_{25}$	**3fa**	53[b] [54/46]

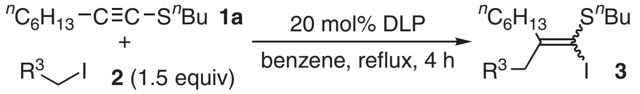
[a]Isolated yields. [b]Compounds **1** (30–40%) were recovered.



Scheme 1.

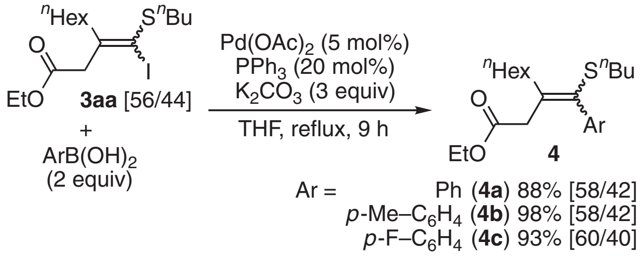
Next, we examined the scope of alkyl halides (Table 2). Benzyl iodoacetate (**2b**) and *tert*-butyl iodoacetate (**2c**) also added to **1a** to give the corresponding adducts, **3ab** and **3ac** in good yields (Entries 1 and 2). Iodoacetonitrile (**2d**) also underwent the addition reaction (Entry 3). However, radical addition of α-iodoacetophenone (**2e**), *N*,*N*-diethyliodoacetamide (**2f**), or diethyl bromomalonate (**2g**) to **1a** resulted in failure, suffering from giving a complex mixture (for the reaction with **2e**) or no conversion (for the reactions with **2f** or **2g**).

Table 2. Atom-transfer radical addition of α-iodo esters and nitrile **2b**–**2d** to butyl 1-octynyl sulfide (**1a**)

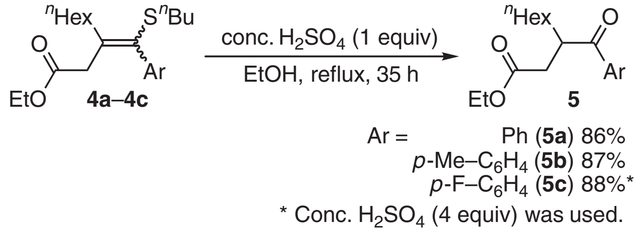


Entry	2	R^3	3	Yield/%[a] [E/Z or Z/E]
1	**2b**	CO_2Bn	**3ab**	84 [55/45]
2	**2c**	CO_2t-Bu	**3ac**	74 [55/45]
3	**2d**	CN	**3ad**	74 [54/46]

[a]Isolated yields.



Scheme 2.



Scheme 3.

We then attempted transformation of 1-iodo-1-alkenyl sulfides **3** to exploit the utility of **3** in organic synthesis. The Suzuki–Miyaura cross-coupling reaction[7] of **3aa** with phenyl-, *p*-methylphenyl-, or *p*-fluorophenylboronic acid in the presence of a palladium catalyst afforded the corresponding arylated product, 1-aryl-1-alkenyl sulfide **4** in excellent yield (Scheme 2).

Finally, we investigated hydrolysis of the resulting 1-aryl-1-alkenyl sulfides **4** under acidic conditions. Several conventional conditions[8] failed to hydrolyze **4**. Instead, treatment of **4** with concentrated sulfuric acid in boiling ethanol provided the corresponding γ-keto esters **5a**–**5c** in high yields (Scheme 3).

In conclusion, we have achieved atom-transfer radical addition of α-iodo esters to 1-alkynyl sulfides. The products could be converted into γ-keto esters easily.[9]

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References and Notes

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3 Typical experimental procedure: Under argon, a mixture of butyl 1-octynyl sulfide (**1a**, 0.099 g, 0.50 mmol) and benzyl iodoacetate (**2b**, 0.21 g, 0.75 mmol) was heated in boiling benzene (1 mL) in the presence of DLP (0.040 g, 0.10 mmol) for 4 h. After the reaction mixture was cooled to ambient temperature, the solvent was removed in vacuo. Purification by silica gel column chromatography (hexane/ethyl acetate = 40/1) afforded **3ab** in 84% yield (0.20 g, 0.42 mmol, stereoisomeric ratio = 55/45). Benzyl 3-[(butylsulfanyl)iodomethylidene]-nonanoate (**3ab**): IR (neat): 2927, 2856, 1738, 1456, 1150, 696 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.86–0.95 (m, 6H), 1.22–1.35 (m, 6H), 1.35–1.45 (m, 4H), 1.45–1.57 (m, 2H), 2.37 (t, $J = 8.0$ Hz, 0.55×2H), 2.56 (t, $J = 8.0$ Hz, 0.45×2H), 2.69 (t, $J = 7.5$ Hz, 0.55×2H), 2.72 (t, $J = 7.5$ Hz, 0.45×2H), 3.46 (s, 0.45×2H), 3.63 (s, 0.55×2H), 5.14 (s, 0.55×2H), 5.16 (s, 0.45×2H), 7.31–7.41 (m, 5H); ^{13}C NMR (CDCl$_3$): δ 13.88 (two signals overlapped), 14.27 (two signals overlapped), 21.97, 22.00, 22.75, 22.76, 27.19, 28.27, 29.24, 29.26, 31.06, 31.13, 31.74, 31.76, 35.81, 37.67, 38.12, 39.27, 43.56, 48.41, 66.82, 66.88, 95.31, 96.35, 128.32 (two signals overlapped), 128.38, 128.42, 128.70, 128.72, 135.88, 135.93, 147.78, 148.62, 169.64, 169.82; Found: C, 53.42; H, 6.70%. Calcd for $C_{21}H_{31}IO_2S$: C, 53.16; H, 6.59%.

4 The use of AIBN [2,2′-azobis(isobutyronitrile)] instead of DLP decreased the yield of **3aa** drastically because the initiation step, iodine-abstraction from **2a** by 1-cyano-1-methylethyl radical, did not work efficiently.

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6 None of the undecylated alkenyl sulfides were observed.

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