Radical Carbonylation of Alkynes in the Presence of Thiols

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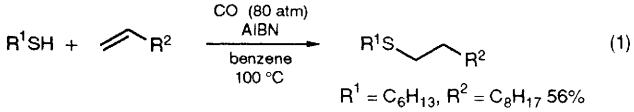
Treatment of alkynes with thiols under an atmosphere of carbon monoxide initiated by azobis(isobutyronitrile) (AIBN) gives β-alkylthio-α,β-unsaturated aldehydes.

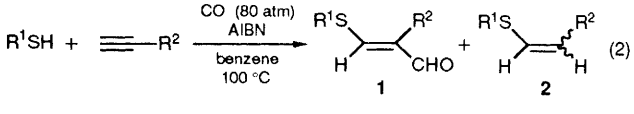
Carbonylation reactions of alkynes and alkenes have attracted significant attention in organic synthesis.[1] Although metal-catalysed carbonylation reactions are well known, we have been interested in radical-mediated carbonylation reactions. Alkyl radicals generated by the addition of phenylthio radical to alkenes are known to be effectively trapped by molecular oxygen,[2] we envisioned that such radicals could also be trapped by carbon monoxide to give the carbonylation products. Foster *et al.*[3] and Sauer[4] previously carried out radical reactions of ethylene and acetylene with thiols under high pressure of carbon monoxide [3000 atm (1 atm = 101.33 kPa)] to obtain the corresponding carbonylation products in very low yields (11–18%). However, recently Ryu *et al.* reported that alkyl radicals generated by the of alkyl halides with tin hydride were effectively trapped by carbon monoxide at relatively low pressure (65–80 atm).[5] Thus, we reexamined the radical reactions of alkynes and alkenes with thiols to find the conditions that afford the carbonylation products in higher yields under lower pressure of carbon monoxide.

Initially, we carried out the reaction of alkenes with thiols under 80 atm of carbon monoxide, but no carbonylation products were obtained [eqn. (1)]. The exclusive formation of the alkyl sulfides seems to indicate that hydrogen abstraction of alkyl radicals generated by the addition of alkylthio radical to the alkene is much faster than the reaction with carbon monoxide. However, we found that radical reactions of alkynes with thiols in the presence of carbon monoxide under similar conditions gave the corresponding carbonylation products in good yields [eqn. (2)]. Herein we report the preliminary results of this study.



(1)

$R^1 = C_6H_{13}$, $R^2 = C_8H_{17}$ 56%

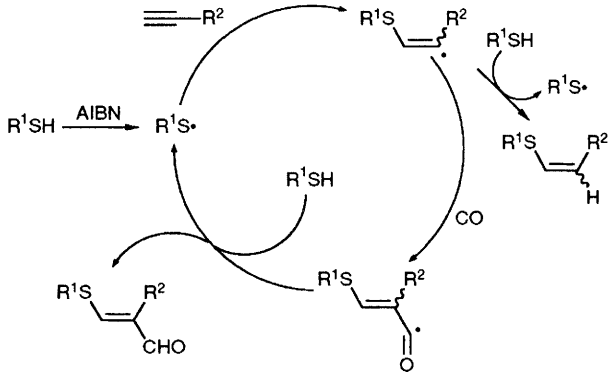


(2)

Table 1 Radical carbonylation of alkynes in the presence of thiol

Thiol R^1	Alkyne R^2	Yield (%)[a] 1	2
C_6H_{13}	C_8H_{17}	70	9
c-C_6H_{11}	C_8H_{17}	68	7
Bu^t	C_8H_{17}	60	0
Ph	C_8H_{17}	39	28
EtO_2CCH_2	C_8H_{17}	69	15
C_6H_{13}	Ph	41	0
Bu^t	Ph[b]	60	0
C_6H_{13}	CH_2CH_2OAc	54	10

[a] Isolated yields. [b] Benzoylperoxide was used as radical initiator.

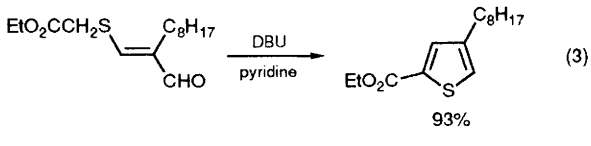


Scheme 1

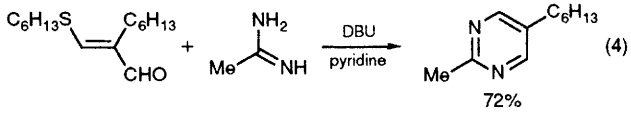
The reactions of alkynes with thiols and carbon monoxide were carried out as follows: A solution of alkyne (0.5 mmol), thiol (1.2–1.5 equiv.), and azobis(isobutyronitrile) (AIBN) (0.4 equiv.) in benzene (50 ml) was placed in an autoclave. Carbon monoxide gas was introduced (80 atm) and the mixture was heated at 100°C for 10 h. Evaporation of the solvent followed by flash chromatography afforded the carbonylation products **1** together with alkenyl sulfides **2**[6] (Table 1). Various thiols including hexyl mercaptan, cyclohexyl mercaptan, *tert*-butyl mercaptan, and ethyl thioglycolate were effective, but the use of thiophenol resulted in low selectivity of the carbonylation product **1** over the alkenyl sulfides **2**.

It is noteworthy that the carbonylation products **1** were obtained as a single stereoisomer. The stereochemistry of **1** (R^1 = c-C_6H_{11}, R^2 = C_8H_{17}) was determined by ^1H NMR spectroscopy. Since the NOE (nuclear Overhauser effect) was observed between the aldehyde proton and the vinyl proton, the stereochemistry of the carbonylation product was determined as *E*.

We propose the following radical chain mechanism (Scheme 1). The alkylthio radical adds to the alkyne to give the β-alkylthio alkenyl radical. The reaction of this radical with carbon monoxide followed by hydrogen abstraction from the thiol gives the carbonylation product and regenerates the alkylthio radical. The alkenyl radical intermediate seems to be a mixture of *E* and *Z* isomers because isomerization of such radicals is known to be very fast.[7] Alkenyl sulfides **2** obtained as byproducts were a mixture of *E* and *Z* isomers. However, only the *E* isomer of the carbonylation product **1** was obtained in the present reaction. Probably there is an equilibration



(3)



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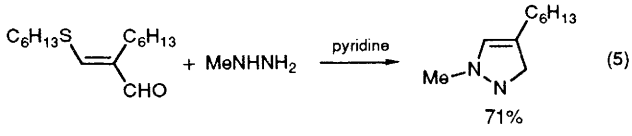

(5)

between the *E* and the *Z* isomers of **1** in the presence of alkylthiol or alkylthio radicals, and the more stable *E*-**1** was obtained as a thermodynamic product.

2-Alkyl-3-alkylthiopropenals obtained by the present reaction are useful intermediates in the synthesis of heterocyclic compounds. For example, 2-octyl-3-(ethoxycarbonylmethylthio)propenal, which was prepared from dec-1-yne and ethyl thioglycolate, cyclized intramolecularly with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine to give 2,4-disubstituted thiophene in high yield [eqn. (3)].[8] 2-Alkyl-3-alkylthiopropenals can also be converted into 2,5-disubstituted pyrimidines[9] or 1,4-disubstituted pyrazoles[9] by the reaction with acetamidine or methylhydrazine, respectively [eqns. (4) and (5)].

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