Synthetic Reactions by Complex Catalysts. XVII. Copper-Catalyzed Reaction of Azide with Thiol

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Copper(I) salts effectively catalyze the reaction of azide (I) with thiol (II), producing sulfenylamide (III), primary amine (IV), and disulfide (V). The products depend primarily upon the nature of thiol. In the cases of alkanethiol and aralkanethiol, III, IV, and V are produced and III is the main product, while, in the case of aromatic thiol, IV and V are the products. Mechanistic studies have shown that III is first formed which further reacts with thiol to produce IV and V.

This paper describes a new reaction of azide with thiol by the aid of a copper compound catalyst. The exploration of this reaction was suggested by our previous findings of the specific catalyst activity of copper compounds for the insertion reactions of isocyanide[1] and carbene[2] into the N–H bond of amine, the O–H bond of alcohol, and the S–H bond of thiol. Isocyanide and carbene are characterized by the presence of lone pair electrons in carbon atom. The decomposition of azide with the evolution of nitrogen produces an unstable species of nitrene which also bears lone pair electrons in nitrogen and may be taken as an analog of carbene.

The present study has disclosed that copper(I) salts effectively catalyze the reaction of azide (I) with thiol (II). The products are sulfenylamide (III), primary amine (IV) and disulfide (V). Mechanistic studies have revealed that III is first formed which further reacts with thiol to produce IV and V.

$$\underset{\text{I}}{\text{RN}_3} + \underset{\text{II}}{\text{R'SH}} \xrightarrow[\text{salt}]{\text{Cu}^{\text{I}}} \underset{\text{III}}{\text{RNHSR'}} + \underset{\text{IV}}{\text{RNH}_2} + \underset{\text{V}}{\text{R'SSR'}} \qquad (1)$$

Ia, R = CH_2CO_2Bu-*t*
b, R = CO_2Bu-*t*

IIa, R′ = *t*-Bu
b, R′ = $PhCH_2$
c, R′ = Ph

IIIa, R = CH_2CO_2Bu-*t*; R′ = *t*-Bu
b, R = CO_2Bu-*t*; R′ = $PhCH_2$
c, R = CO_2Bu-*t*; R′ = *t*-Bu
d, R = CH_2CO_2Bu-*t*; R′ = Ph
e, R = CO_2Bu-*t*; R′ = Ph

IVa, R = CH_2CO_2Bu-*t*
b, R = CO_2Bu-*t*

Va, R′ = *t*-Bu
b, R′ = $PhCH_2$
c, R′ = Ph

The primary product of III may be regarded as being a product of the insertion of nitrene (RN:) into the S–H bond of thiol. The results of the present study are interestingly compared with Takebayashi's study in which the decomposition of phenyl azide proceeded very rapidly in benzenethiol to produce aniline and diphenyl disulfide in high yields.[3] A mechanism of radical reaction of an intermediate nitrene was proposed for the phenyl azide–benzenethiol reaction. In addition, the thermal and photolytic decompositions of azide in hydrogen-containing solvents often produce primary amine (IV in eq 1), for which a radical mechanism of hydrogen abstraction of nitrene has been assumed.[3,4] In the present study, the copper-catalyzed reaction of azide with thiol, however, was suggested to be a nonradical process.

Results and Discussion

In the present study, the azide reagents are *t*-butyl azidoacetate (Ia) and azidoformate (Ib), and the thiol reagents are 2-methyl-2-propanethiol (IIa), α-toluenethiol (IIb), and benzenethiol (IIc). The reaction in the presence of cuprous chloride or oxide is illustrated in Table I. Without copper catalyst, two azides, Ia and Ib, did not react with IIa even at 80°. They were recovered unchanged almost quantitatively. In the presence of copper catalyst, however, the azide–thiol reactions proceeded smoothly at room temperature. The products depend primarily upon the nature of thiol. In the cases of alkanethiol and aralkanethiol, III, IV and V are produced and III is the main product. In the case of aromatic thiol, IV and V are the products.

TABLE I

REACTION OF AZIDE WITH THIOL[a]

$$\underset{\text{I}}{\text{RN}_3} \xrightarrow{\substack{\text{R'SH}\\ \text{II}}} \underset{\text{III}}{\text{RNHSR'}} \xrightarrow{\text{R'SH}} \underset{\text{IV}}{\text{RNH}_2} + \underset{\text{V}}{\text{R'SSR'}}$$

N_3R, 10 mmol	R′SH, 45∼69 mmol	Catalyst, 1 mmol	Product, % III[b]	IV[b]	V[b]
$N_3CH_2CO_2Bu$-*t* (Ia)	*t*-BuSH (IIa)	Cu_2O	64	30	31
$N_3CH_2CO_2Bu$-*t* (Ia)	*t*-BuSH (IIa)		0	0	0
N_3CO_2Bu-*t* (Ib)	$PhCH_2SH$ (IIb)	CuCl	60	30	35
N_3CO_2Bu-*t* (Ib)	*t*-BuSH (IIa)	CuCl	77	20	16
N_3CO_2Bu-*t* (Ib)	*t*-BuSH (IIa)		0	0	0
$N_3CH_2CO_2Bu$-*t* (Ia)	PhSH (IIc)	Cu_2O	0	99	102[c]
N_3CO_2Bu-*t* (Ib)	PhSH (IIc)	CuCl	0	99	107[c]

[a] Reactions were carried out at room temperature for 4∼10 hr under nitrogen atmosphere. [b] Product yields are based upon the amount of azide. [c] The production of diphenyl disulfide over 100% may be ascribed to the oxidation of thiol by oxygen in the reaction system.

In the reaction of Ia and IIa, two experimental findings support the mechanism in which IIIa is first formed; IIIa further reacts with the second molecule of IIa to produce IVa and Va.

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[2] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and T. Shimizu, *Tetrahedron Lett.*, 1273 (1967); *J. Org. Chem.*, **33**, 544 (1968).

[3] M. Takebayashi and T. Shingaki, *Kogyo Kagaku Zasshi*, **64**, 469 (1961).

[4] (a) O. C. Dermer and M. T. Edmison, *J. Amer. Chem. Soc.*, **77**, 70 (1955); (b) J. F. Heacock and M. T. Edmison, *ibid.*, **82**, 3462 (1960); (c) J. E. Leffler and Y. Tsuno, *J. Org. Chem.*, **28**, 902 (1963); (d) W. Lwowski and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.*, **87**, 1947 (1965); (e) L. Horner and G. Bauer, *Tetrahedron Lett.*, 3573 (1966); (f) W. Lwowski, *Agnew. Chem.*, **79**, 922 (1967).

TABLE II

REACTION[a] OF t-BuSNHCH$_2$CO$_2$Bu-t (IIIa) WITH t-BuSH (IIa)

$$\underset{\text{IIIa}}{t\text{-BuSNHCH}_2\text{CO}_2\text{Bu-}t} + \underset{\text{IIa}}{t\text{-BuSH}} \longrightarrow \underset{\text{IVa}}{\text{NH}_2\text{CH}_2\text{CO}_2\text{Bu-}t} + \underset{\text{Va}}{t\text{-BuSSBu-}t}$$

Catalyst	Time, hr	IIIa, %	IVa, %	Va, %
No catalyst	22	100	0	0
CuCl (1 mmol)	6	40	60	61.5
CuCl (1 mmol) p-BQ[b] (4 mol%)	6	38	62	61

[a] Reaction conditions: IIIa (1 mmol) and IIa (4.4 mmol) at 80° under nitrogen atmosphere. [b] p-BQ = p-benzoquinone.

$$\underset{\text{Ia}}{\text{N}_3\text{CH}_2\text{CO}_2\text{Bu-}t} + \underset{\text{IIa}}{t\text{-BuSH}} \xrightarrow{\text{Cu}^+\text{ catalyst}} \underset{\text{IIIa}}{t\text{-BuSNHCH}_2\text{CO}_2\text{Bu-}t}$$

$$\text{IIIa} + \text{IIa} \xrightarrow{\text{Cu}^+\text{ catalyst}} \underset{\text{IVa}}{\text{NH}_2\text{CH}_2\text{CO}_2\text{Bu-}t} + \underset{\text{Va}}{t\text{-BuSSBu-}t} \qquad (2)$$

In the first experiment, IIIa was subjected to the reaction with IIa. The IIa–IIIa reaction in the presence of cuprous chloride proceeded to produce IVa and Va (Table II). No other product was detected in the reaction mixture. It is important to note that the IIa–IIIa reaction also requires a copper catalyst. Without catalyst, IIIa was recovered quantitatively from the heat-treated mixture of IIa and IIIa. Furthermore, the copper-catalyzed reaction of IIIa with IIa was not affected by the addition of p-benzoquinone as a radical scavenger.

In the second series of experiments, the change of the amounts of three products during the course of reaction of Ia with excess IIa was examined (Figure 1). The amount of IIIa increased in the first 2 hr, then it remained unchanged in the subsequent 2 hr, and finally it began to decrease when Ia was consumed. The productions of IVa and Va continued to increase during the whole period of reaction. At a reaction time of 4 hr, Ia was consumed almost completely and the combined yield of IIIa and IVa became about 100% on the basis of Ia. After 4 hr, the decrease of IIIa corresponded to the increase of IVa. These findings support the mechanism of consecutive reactions; *i.e.*, IVa and Va are produced from the primary product of IIIa. In addition, the time-conversion curve of the Ia–IIa reaction with cuprous oxide catalyst was not affected by the addition of 4 mol % of p-benzoquinone.

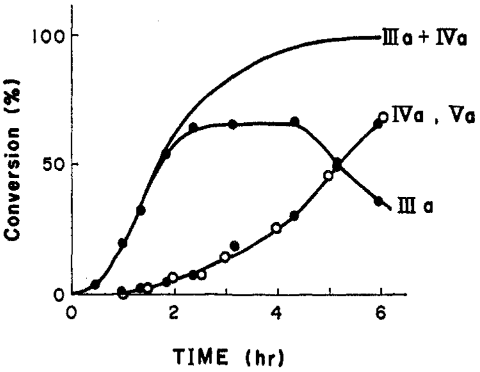

Figure 1.—Time conversion of the reaction of N$_3$CH$_2$COOBu-t (Ia) with t-BuSH (IIa) by Cu$_2$O catalyst at 80°: IIIa, t-BuSNHCH$_2$CO$_2$Bu-t (●); IVa, NH$_2$CH$_2$CO$_2$Bu-t (●); Va, t-BuSSBu-t (○).

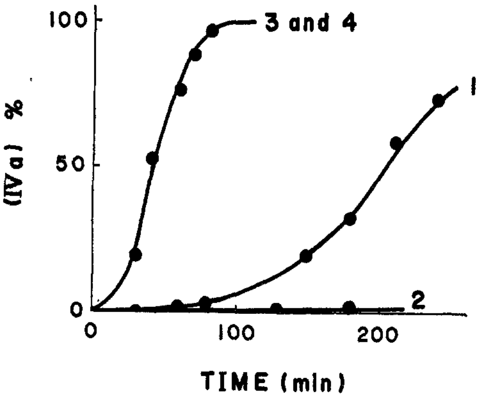

Figure 2.—Time conversion of the reactions of t-butyl azidoacetate (Ia) with benzenethiol (IIc) [reaction conditions: t-butyl azidoacetate (7 mmol), benzenethiol (39 mmol); at 80° under N$_2$]: 1, no catalyst; 2, p-benzoquinone (11.8 mol%); 3, Cu$_2$O (1 mmol); 4, Cu$_2$O (1 mmol)-p-benzoquinone (20.0 mol %).

The copper-catalyzed reaction of azide with aromatic thiol is also important especially from the mechanistic point of view. The Ia–IIc and Ib–IIc reactions took place to produce the corresponding primary amine (IV) and disulfide (V) (Table I). The corresponding benzenesulfenylamides (III) were not detected in the reaction mixtures. In addition, the reaction of azide with aromatic thiol occurred without any added catalyst. In the presence of copper compound, however, the reaction proceeds at much faster rates. The time-conversion curves of the Ia–IIc reaction under varying conditions are shown in Figure 2. The extent of reaction was monitored by the glpc analysis of IVa. Heating of a mixture of Ia and IIc at 80° under nitrogen atmosphere without any added catalyst caused the reaction between the two components to produce IVa and Vc (curve 1). This agrees with a report of Takebayashi.[3] Addition of p-benzoquinone suppressed the reaction (curve 2). As to the inhibition by p-benzoquinone, the reaction of p-benzoquinone with thiol is known.[5] Therefore, p-benzoquinone might have been consumed by the reaction with thiol. In the experiment of Figure 2, however, the amount of p-benzoquinone is as high as 11.8 mol % of thiol; the suppression of the reaction may be ascribed to the scavenging by the remaining p-benzoquinone. Reference experiments have shown that smaller amounts of p-benzoquinone, *e.g.*, 5 mol %, do not inhibit the azide–thiol reaction.

Addition of a small amount of cuprous oxide caused the Ia–IIc reaction at a much higher rate (curve 3). Here, it is important that the time-conversion curve of the copper-catalyzed reaction is not affected even by 20 mol % of p-benzoquinone. These findings may be taken to suggest a nonradical mechanism of the copper-catalyzed reaction.

For the Ia–IIc reaction, a mechanism involving the sulfenylamide as an intermediate product (IIId) is also suggested. Unlike the reaction with aliphatic thiol, the sulfenylamide (IIId) was not detected in the reaction mixtures both in noncatalyzed and copper-

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(5) M. Schubert, *J. Amer. Chem. Soc.*, **69**, 712 (1947).

$$\underset{\text{Ia}}{N_3CH_2CO_2Bu\text{-}t} + \underset{\text{IIc}}{PhSH} \xrightarrow{Cu^+\ \text{catalyst}} \underset{\text{IIId}}{[t\text{-}BuO_2C\text{-}CH_2NHPh]} \xrightarrow{\text{IIc}}$$

$$\underset{\text{IVa}}{NH_2CH_2CO_2Bu\text{-}t} + \underset{\text{Vc}}{PhSSPh} \qquad (3)$$

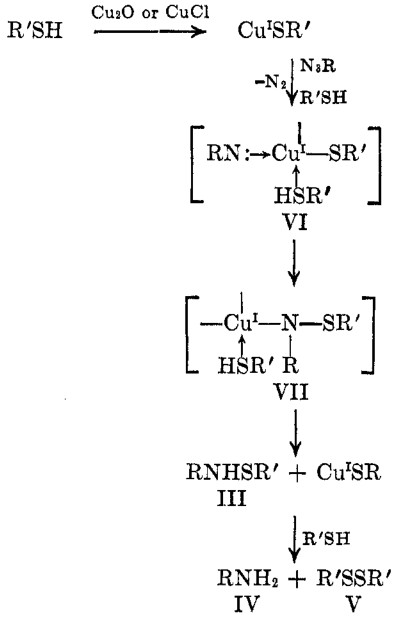
catalyzed reactions. A reference experiment, however, showed that the reaction of N,N-diethylbenzenesulfenylamide with benzenethiol proceeded quickly even at 0° to afford diethylamine and diphenyl disulfide (eq 4). This reaction did not require any added catalyst.

$$Et_2N\text{-}SPh + PhSH \longrightarrow Et_2NH + PhSSPh \qquad (4)$$

The reaction of sulfenylamide and thiol has been reported also by Mukaiyama, *et al.*[6]

As the real species of catalyst, cuprous mercaptide may be postulated, because the reaction mixtures with cuprous oxide and with cuprous chloride as the catalyst always contained the corresponding cuprous mercaptide. The insertion of nitrene to the copper(I)–sulfur bond constitutes an essential step for the formation of the sulfenylamide intermediate. A tentative mechanistic scheme is given as follows (Scheme I). Nitrene from azide is coordinated with cuprous mercaptide, and the insertion probably takes place in the ligand sphere of a mixed ligand complex (VI). After the insertion, the hydrogen transfer from thiol to cuprous sulfenylamide in VII produces III and cuprous mercaptide.

SCHEME I



Experimental Section

Reaction of 2-Methyl-2-propanethiol (IIa) with *t*-Butyl Azidoacetate (Ia).—To a stirred mixture of IIa (44 mmol) and cuprous oxide (1 mmol), Ia (10 mmol) was added dropwise during 30 min at room temperature under nitrogen atmosphere. Stirring was then continued for additional 10 hr at 80°. After the insoluble part was removed by filtration, the filtrate was distilled *in vacuo* to give a distillate (1.9 g) boiling at 90∼94° (5 mm). The distillate was then analyzed by glpc. The products were N-*t*-butoxycarbonylmethyl-2-methyl-2-propanesulfenylamide (IIIa; 64%), *t*-butyl ester of glycine (IVa; 30%), and di-*t*-butyl disulfide (Va; 31%). IIIa was identified by ir and nmr spectra and elemental analysis: ir of IIIa (neat) 3360 (s), 1740 (vs) and 1250–1100 cm^{-1} (vs); nmr ($CDCl_3$) τ 6.38 (2 H, s, $-CH_2-$), 8.51 (9 H, s, $-OC_4H_9$-*t*), 8.79 (9 H, s, $-S-C_4H_9$-*t*).

Anal. Calcd for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.38. Found: C, 54.26; H, 9.93; N, 6.10.

IVa was identified by ir and nmr spectra: ir of IVa (neat) (3360 (s), 1730 (vs), 1370 (s), 1240 (s) and 1150 cm^{-1} (s); nmr ($CDCl_3$) τ 6.70 (2 H, s, $-CH_2-$), 7.98 (2 H, broad, $-NH_2$), and 8.55 (9 H, s, $-OC_4H_9$-*t*).

Reaction of α-Toluenethiol (IIb) with *t*-Butyl Azidoformate (Ib).—The reaction was carried out by a similar procedure. The products were N-*t*-butoxycarbonyl-α-toluenesulfenylamide (IIIb; 60%), *t*-butyl urethan (IVb; 30%), and dibenzyl disulfide (Vb; 35%). IIIb was identified by ir and nmr spectra and elemental analysis: ir of IIIb (Nujol) 3440 (w), 1720 (vs), 1360 (vs), 760 (vs), and 690 cm^{-1} (s); nmr ($CDCl_3$) τ 2.72 (5 H, s, $-C_6H_5$), 6.40 (2 H, s, $-CH_2-$) and 8.55 (9 H, s, $-OC_4H_9$-*t*).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.56; H, 6.94; N, 5.67.

IVb and Vb were identified by comparison of ir and nmr spectra with those of the corresponding authentic samples.

Reaction of 2-Methyl-2-propanethiol (IIa) with *t*-Butyl Azidformate (Ib).—To a stirred mixture of IIa (55 mmol) and cuprous chloride (1 mmol), Ib (10 mmol) was added dropwise during 30 min at room temperature under nitrogen atmosphere. Stirring was then continued for additional 10 hr at room temperature. Then the insoluble part was removed from the reaction mixture by filtration and the filtrate was concentrated and analyzed by glpc. The products were N-*t*-butoxycarbonyl-2-methyl-2-propanesulfenylamide (IIIc; 77%), *t*-butylurethan (IVb; 20%), and di-*t*-butyl disulfide (Va; 16%). IVb and Va were identified by comparison of the glpc retention times and ir spectra with those of the corresponding authentic samples. IIIc was isolated by preparative glpc, white crystalline, mp 95–96°, whose structure was determined by ir and nmr spectra and elemental analysis: ir of IIIc (KBr, tablet) 3320 (s), 1715 (vs), 1450 (s), 1360 (s), 1245 (s), 940 (vw) and 840 cm^{-1} (s); nmr ($CDCl_3$) τ 4.5 (1 H, broad, $-NH-$), 8.50 (9 H, s, $-OC_4H_9$-*t*), 8.75 (9 H, s, $-S-C_4H_9$-*t*).

Anal. Calcd for $C_9H_{19}NO_2S$: C, 52.65; H, 9.33; N, 6.82. Found: C, 52.38; H, 9.62; N, 6.74.

Reaction of 2-Methyl-2-propanethiol (IIa) with *t*-Butyl Azidoacetate (Ia) (Figure 1).—A mixture of IIa (44 mmol), Ia (8 mmol), and cuprous oxide (1 mmol) was heated at 80° under nitrogen atmosphere. The amounts of IIIa, IVa and Va at several times of reaction were determined by glpc.

Reaction of Benzenethiol (IIc) with *t*-Butyl Azidoacetate (Ia) (Figure 2).—Curve 1 reaction: a mixture of IIc (39 mmol) and Ia (7 mmol) was heated at 80° under nitrogen atmosphere without any added catalyst. Curve 2 reaction: *p*-benzoquinone (11.8 mol %) was added at the beginning of curve 1 reaction. Curve 3 reaction: a mixture of IIc (39 mmol), Ia (7 mmol), and cuprous oxide (1 mmol) was heated at 80°. Curve 4 reaction: *p*-benzoquinone (20.0 mol %) was added at the beginning of curve 3 reaction.

Reaction of N,N-Diethylbenzenesulfenylamide[7] with Benzenethiol.—N,N-Diethylbenzenesulfenylamide (4.9 mmol) was added dropwise to benzenethiol (40 mmol) cooled with ice bath under nitrogen atmosphere without any added catalyst. The reaction immediately occurred, and ceased in 5 min. Then the insoluble part was separated from the reaction mixture by filtration. Diphenyl disulfide (94%) was obtained from the insoluble part. The filtrate was analyzed by glpc. The product was diethylamine (85%). Any other product was not detected from the reaction mixture. Diethylamine was identified by comparison of the glpc retention time and ir spectra with those of the authentic sample.

Registry No.—Ia, 6367-36-8; Ib, 1070-19-5; IIa, 75-66-1; IIb, 100-53-8; IIc, 108-98-5; IIIa, 25297-00-1; IIIb, 25297-01-2; IIIc, 25297-02-3; IVa, 6456-74-2; Va, 110-06-5.

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(6) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968).

(7) H. Lecher and F. Holschneider, *Ber.*, **57**, 757 (1924).