A New Route to Nitriles from Thioamides

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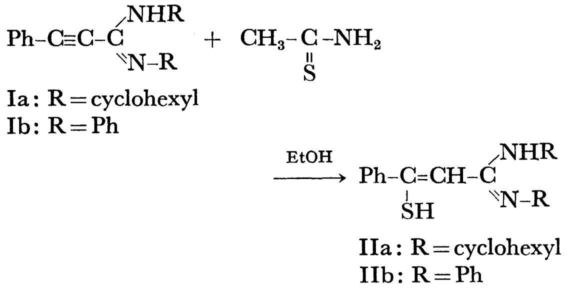
In the preceding paper,[1] we reported that a new cleavage reaction of a carbon-carbon triple bond occurred in the protonated propiolamidine system. In this paper, a new kind of fragmentation reaction is described, involving reactions of phenylpropiolamidines with thioamides, thioureas, and thiosemicarbazides.

The reaction of *N,N′*-dicyclohexylphenylpropiolamidine (Ia) with thioacetamide in boiling ethanol gave *N,N′*-dicyclohexyl-β-mercaptocinnamamidine [IIa; mp 158—159°C. Found: C, 73.43; H, 8.65; N, 8.13; S, 9.39%. Calcd for $C_{21}H_{30}N_2S$: C, 73.64; H, 8.83; N, 8.16; S, 9.36%. NMR (δ in $CDCl_3$): 6.26 (1H, s, =CH–)] in 50% yield, while dimethyl acetylenedicarboxylate and methyl propiolate reacted with thioacetamide to give (1′-iminoethyl)thiodimethyl fumarate and *cis,cis*- and *cis,trans*-dimethyl-β-thiodiacrylic esters, respectively.[2] Subsequently, IIa afforded 5-cyclohexylamino-3-phenylisoxazole (mp 128—129°C)[3] by the reaction with hydroxylamine hydrochloride.

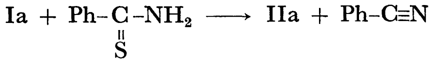


$$\mathrm{Ph{-}C{\equiv}C{-}C}\begin{smallmatrix}\nearrow \mathrm{NHR}\\ \searrow \mathrm{N{-}R}\end{smallmatrix} + \mathrm{CH_3{-}\underset{\underset{S}{\parallel}}{C}{-}NH_2} \xrightarrow{\mathrm{EtOH}} \mathrm{Ph{-}\underset{SH}{\underset{|}{C}}{=}CH{-}C}\begin{smallmatrix}\nearrow \mathrm{NHR}\\ \searrow \mathrm{N{-}R}\end{smallmatrix}$$

Ia: R = cyclohexyl
Ib: R = Ph

IIa: R = cyclohexyl
IIb: R = Ph

A reaction of Ia with thiobenzamide also gave IIa and benzonitrile in 53 and 65% yield, respectively. The reaction provided a convenient synthetic route to nitriles from thioamides under mild, neutral conditions.

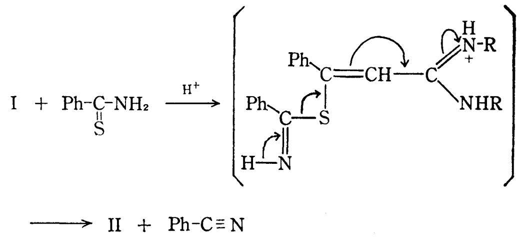


$$\mathrm{Ia} + \mathrm{Ph{-}\underset{\underset{S}{\parallel}}{C}{-}NH_2} \longrightarrow \mathrm{IIa} + \mathrm{Ph{-}C{\equiv}N}$$

Both reactions of Ia with 1-phenylthiourea and with 1,3-diphenylthiourea gave IIa in 32 and 39% yield, respectively, but thiourea and 1,3-di-*n*-butylthiourea failed to react with Ia and the thioureas were predominantly recovered. This shows that the acidity of N–H in thioureas would be a factor influencing the reaction.

N,N′-Diphenylphenylpropiolamidine (Ib) reacted with 4-phenylthiosemicarbazide to afford *N,N′*-diphenyl-β-mercaptocinnamamidine [IIb: mp 162—164°C. Found: C, 76.43; H, 5.28; N, 8.60; S, 9.79%. Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48; S, 9.70%. NMR (δ in $CDCl_3$): 6.47 (1H, s, =CH–)] in 16% yield: IIb was also obtained by reaction of Ib with thioacetamide, but in a poorer yield than IIa. The difference in yield suggests that the basicity of the amidine function plays an important role in the reaction. Addition of hydrogen chloride slightly improved the yield of IIb. Thiosemicarbazide also reacted with Ia to give IIa.

Thiol synthesis using thioamides is common and the cleavage of the C–S bond is usually carried out by alkaline hydrolysis. The facile fission of the C–S bond under such mild conditions as in the above cases may be attributed to the heterolytic fragmentation reaction. Although the proton source is not clear, we assume that the driving force of the fragmentation reaction would be due to the electron withdrawing character of the protonated amidine moiety, as shown in Scheme 1, since a thioamide could act as the proton source. This would also support the view that both the basicity of the amidine nitrogen and the acidity of N–H in the thioureas seem to be the important factors in promoting the reaction.



Scheme 1

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[1] H. Fujita, R. Endo, K. Murayama, and T. Ichii, This Bulletin, **45**, 1581 (1972).

[2] J. W. Lown and J. C. N. Ma, *Can. J. Chem.*, **45**, 953 (1967); Y. Kishida and A. Terada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1351 (1968).

[3] H. Fujita, R. Endo, A. Aoyama, and T. Ichii, This Bulletin, in press.