A Convenient Synthesis of *N*-Substituted Formamidines by Desulfurization of the Corresponding Thioureas

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Synopsis. *N,N'*-Di- and *N,N,N'*-trisubstituted thioureas were easily desulfurized by Raney nickel to yield the corresponding formamidines, while *N*-monosubstituted thioureas gave *N,N'*-disubstituted formamidines.

Amidines are important compounds for the syntheses of heterocycles as well as their pharmaceutical chemistries owing to their biological activities.[1] Although amidines are generally prepared by the condensation of nitriles and amines, or the substitution of imidates with amines, the syntheses of formamidines require special methods, such as the treatment of amines with chloroimines or imidates,[1] and the treatment of isonitriles and amines with Co(I) catalysis.[2]

The desulfurization of carbon–sulfur bonds using Raney nickel is known as a convenient method for the syntheses of various organic compounds.[3] However, the desulfurization of thioureas with Raney nickel has scarcely been reported and consistent results can not be found. For example, unsubstituted thiourea afforded formamidine hydrochloride in the presence of ammonium chloride[4] or as a mixture of methane, ammonia, and methylamine[5]; *N*-benzylthiourea gave a mixture of methane, ammonia, and toluene[6]; and *N*-(*o*-tolyl)thiourea gave *o*-toluidine.[7] Although Ashworth reported that *N,N'*-diarylthioureas afforded the corresponding formamidines, he did not describe in detail such matters as yeilds and the activities of Raney nickel. Furthermore, in the case of *N*-(*p*-chlorophenyl)thiourea, he obtained only an unidentified basic liquid.[8]

In this paper, we wish to describe the convenient synthesis of many types of substituted formamidines by the desulfurization of the corresponding thioureas as well as and the scope and the limitations of the Raney nickel desulfurization of thioureas.

First, the desulfurization of *N*-monosubstituted thioureas was reinvestigated. When *N*-phenylthiourea was treated with Raney nickel in methanol, the ^{1}H NMR spectrum exhibited a new singlet at δ=7.63 which is characteristic of the formyl proton. Actually, when picric acid was added to the reaction mixture prior to purification, *N*-phenylformamidine picrate was successfully isolated in 15% yield after recrystallization. However, the chromatographic purification of the crude reaction product could not afford the expected *N*-phenylformamidine. The isolated products were *N,N'*-diphenylformamidine and formanilide. By the same treatment of some *N*-monosubstituted thioureas, the corresponding *N,N'*-disubstituted formamidines were obtained (Table 1). Yields resulted in one mole of formamidines **2** formed from two mole of thioureas **1**; also, one mole of the formamide derivatives **3** was formed from one mole of thioureas **1**.

Table 1. Desulfurization of *N*-Monosubstituted Thioureas

	R	Yield/%	
		2	**3**
1a	C_6H_5	41	7
1b	p-$CH_3C_6H_4$	60	34
1c	p-$CH_3OC_6H_4$	47	6
1d	$C_6H_5CH_2$	0	27

Since Roberts[9] and McNab[10] noted an amine exchange reaction involving *N*-(*p*-methylphenyl)-*N'*-phenylformamidine with aniline or *p*-toluidine, the exchange reaction proceeded even in the case of *N*-phenylformamidine; volatile ammonia was given off from the system. Therefore, *N,N'*-disubstituted formamidines were secondary products from an amine exchange reaction between the *N*-monosubstituted formamidines and the anilines which were generated by the hydrolysis of *N*-monosubstituted formamidines owing to air moisture during the work-up. Actually, when **1a** was treated with Raney nickel in the presence of methylamine hydrochloride and diethylamine, *N*-methyl-*N'*-phenyl- and *N,N*-diethyl-*N'*-phenylformamidine were obtained in 46 and 41% yields, respectively. These facts support the idea that amine exchange reaction occurs between an unsubstituted amino group and the secondary mediated amine. Moreover, it was suggested that the desulfurization of unsubstituted thiourea might afford *N,N'*-disubstituted formamidine in the presence of amines. Actually, by the desulfurization of thiourea in the presence of *p*-toluidine, *N,N'*-bis(*p*-methylphenyl)formamidine was isolated. However, its yield was low (9%) since there was almost no separation between the desired formamidine and *p*-toluidine.

Next, the desulfurizations of various *N,N'*-di- or *N,N,N'*-trisubstituted thioureas were investigated. In these series, the corresponding formamidines were respectively obtained without amine exchange reactions. The results are shown in Table 2. *N,N'*-Disubstituted formamidines were obtained in better yields than that for *N,N,N'*-trisubstituted. When the desulfurization of cyclic *N,N,N'*-trisubstituted thioureas was carried out in the same manner, the corresponding cyclic formamidines were obtained (Table 3).

Consequently, although *N,N'*-di- or *N,N,N'*-trisubstituted thioureas gave the corresponding formamidines by desulfurization with Raney nickel, *N*-monosubstituted thioureas afforded *N,N'*-disubstituted formamidines via an amine exchange reaction on account of the instability of the primary *N*-monosubstituted formamidines.

Table 2. Desulfurization of Di- or Trisubstituted Thioureas

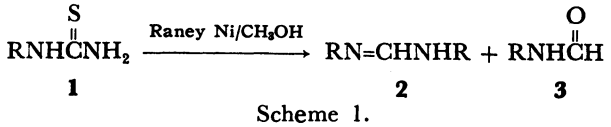
	R^1	R^2	R^3	Yield/%	Product	Mp[Bp](°C)
5a	C_6H_5	H	C_6H_5	85	**2a**	136[a]
5b	p-$CH_3C_6H_4$	H	C_6H_5	50	**6b**	88—89[b]
5c	C_6H_5	H	CH_3	47	**6c**	85—87[c]
5d	p-$CH_3C_6H_4$	H	CH_3	23	**6d**	135—139[d]
5e	$C_6H_5CH_2$	H	$C_6H_5CH_2$	75	**6e**	136—137[e]
5f	C_6H_5	C_2H_5	C_2H_5	27	**6f**	[99—110/5 mmHg †][f]
5g	C_6H_5	C_6H_5	CH_3	27	**6g**	156—159[d]
5h	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	23	**6h**	118—119[d]

a) 137—138°C (reported[8]). b) 86°C (reported[12]). c) 88—89°C (reported[13]). d) Of picrate. e) 135°C (reported[14]). f) 143—144°/15 mmHg† (reported[15]).
† 1 mmHg=133.322 Pa.

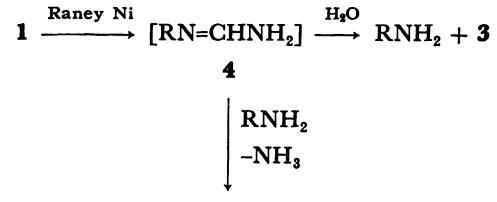
Table 3. Desulfurization of 3,4,5,6-Tetrahydropyrimidine-2(1*H*)-thiones

	R^1	R^2	Product	Yield/%	Mp[a](°C)
7a	C_6H_5	H	**8a**	77	141—142
7b	C_6H_5	CH_3	**8b**	45	157—158
7c	p-$CH_3OC_6H_4$	CH_3	**8c**	65	148—149
7d	m-ClC_6H_4	CH_3	**8d**	28	149—150

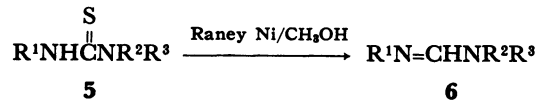
a) Of picrate.



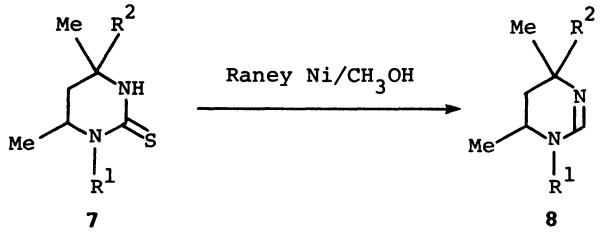
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

Experimantal

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a Jasco IRA-1 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Hitachi R-24 and JEOL-100 spectrometer, respectively, using tetramethylsilane as an internal standard.

Preparation of Active Raney Nickel. Sodium hydroxide pellets (2.0 g) were added to nickel-aluminum alloy (Wako Pure Chemical Industries Ltd., 50%, 1.6 g) in distilled water (20 mL) with vigorous stirring at room temperature. After 15 min, the reaction mixture was immersed in an oil bath (bath temperature 70°C) for 20 min, and then the alkaline solution was decanted. The nickel was washed four times by suspension in distilled water and underwent decantation. The washing procedure was repeated four times with methanol.

Desulfurization of Thioureas; Typical Procedures. The mixture of thiourea (2 mmol) and the activated Raney nickel (prepared from 1.6 g nickel-aluminum alloy) in methanol (20 mL) was warmed at 50°C for 1 h and then refluxed for 2 h. After removing the catalyst by filtration, the filtrate was diluted with water and extracted with dichloromethane. It was then dried over anhydrous magnesium sulfate. After evaporating the solvent, the crude product was chromatographed on silica gel with a mixture of hexane-acetone-diethylamine (13:6:1) or benzene-ethyl acetate (3:1). Picrate was prepared as follows. To a solution of formamidine (2 mmol) in ethanol (5 mL), the solution of picric acid (2 mmol) in ethanol was added. After standing for 15 h, the resulting precipitate was recrystallized from ethanol.

Desulfurization of *N*-Phenylthiourea in the Presence of Amines. To a mixture of *N*-phenylthiourea (**1a**, 2 mmol) and methylamine hydrochloride or diethylamine (10 mmol), Raney nickel (0.8 g) was added in a sealed tube and then warmed at 50°C for 1 h and at 80°C for 2 h. The following procedure is the same as that described above.

***N*-Phenylformamidine (4).** ^1H NMR ($CDCl_3$) δ=3.81 (s, 2H, NH_2), 6.6—7.3 (m, 5H, Ar), 7.63 (s, 1H, =CH). Picrate: Mp 198—200°C. (lit,[11] 191°C). Found: C, 44.49; H, 3.18; N, 20.02%. Calcd for $C_{13}H_{11}N_5O_7$: C, 44.70; H, 3.17; N, 20.05%.

***N,N'*-Diphenylformamidine (2a).** Mp 136°C (lit,[8] 137—138°C). ·IR($CHCl_3$) 1640, 3380 cm^{-1}. ^1H NMR ($CDCl_3$) δ=6.9—7.5 (m, 10H, Ar), 8.20 (s, 1H, =CH), 9.4 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) δ=119.1 (d), 123.2 (d), 129.3 (d), 145.3 (s), 149.7 (d).

***N,N'*-Bis(*p*-methylphenyl)formamidine (2b).** Mp 140—141 °C (lit,[10] 139—140 °C). IR ($CHCl_3$) 1680, 3400 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.30 (s, 6H, CH_3), 6.9—7.2 (m, 8H, Ar), 8.14 (s, 1H,=CH), 9.1 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ=20.7 (q), 119.0 (d), 129.8 (d), 132.6 (s), 142.9 (s), 149.6 (d).

***N,N'*-Bis(*p*-methoxyphenyl)formamidine (2c).** Mp 112—113 °C. IR (KBr) 1670, 3150 cm^{-1}. ^1H NMR ($CDCl_3$) δ=3.77 (s, 6H, CH_3), 6.4—7.4 (m, 8H, Ar), 8.02 (s, 1H, =CH), 8.9 (br s, 1H, NH). Found: C, 70.36; H, 6.33; N, 10.95%. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.92%.

***N*-(*p*-Methylphenyl)-*N'*-phenylformamidine (6b).** ^1H NMR ($CDCl_3$) δ=2.27 (s, 3H, $ArCH_3$), 6.7—7.4 (m, 9H, Ar), 8.4 (br s, 1H, NH), 8.08 (s, 1H, =CH).

***N*-Methyl-*N'*-phenylformamidine (6c).** ^1H NMR ($CDCl_3$) δ=2.95 (s, 3H, CH_3), 5.5 (br s, 1H, NH), 6.7—7.4 (m, 5H, Ar), 7.47 (s, 1H, =CH).

***N*-Methyl-*N'*-(*p*-methylphenyl)formamidine (6d).** IR (KBr) 1640, 3300 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.30 (s, 3H, Ar-CH_3), 2.94 (s, 3H, CH_3), 5.0 (br s, 1H, NH), 6.6—7.4 (m, 4H, Ar), 7.62 (s, 1H, =CH). Picrate: found: C, 47.64; H, 3.94; N, 18.61%. Calcd for $C_{15}H_{15}N_5O_7$: C, 47.74; H, 4.00; N, 18.56%.

***N,N'*-Dibenzylformamidine (6e).** IR ($CHCl_3$) 1630, 3280 cm^{-1}. ^1H NMR ($CDCl_3$) δ=4.29 (s, 4H, Ar-CH_2), 6.7—7.8 (m, 10H, Ar), 7.98 (s, 1H, =CH).

***N,N,*-Diethyl-*N'*-phenylformamidine (6f).** IR ($CDCl_3$) 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.17 (t, 6H, J=7 Hz, CH_2CH_3), 3.30 (q, 4H, 4H, J=7 Hz, CH_2CH_3), 6.7—7.3 (m, 5H, Ar), 7.37 (s, 1H, =CH).

***N*-Methyl-*N,N'*-diphenylformamidine (6g).** IR ($CHCl_3$) 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=3.41 (s, 3H, CH_3), 6.8—7.5 (m, 10H, Ar), 8.00 (s, 1H, =CH). Picrate: Found: C, 54.44; H, 3.86; N, 15.94%. Calcd for $C_{20}H_{17}N_5O_7$: C, 54.67; H, 3.90; N, 15.94%.

***N,N*-Dibenzyl-*N'*-methylformamidine (6h).** IR ($CHCl_3$) 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ=3.16 (s, 3H, CH_3), 4.29 (s, 4H, CH_2Ar), 6.8—7.5 (m, 10H, Ar), 7.61 (s, 1H, =CH). Picrate: Found: C, 56.52; H, 4.52; N, 14.98%. Calcd for $C_{22}H_{21}N_5O_7$: C, 56.56; H, 4.49; N, 14.99%.

1,4,5,6-Tetrahydro-4,6-dimethyl-1-phenylpyrimidine (8a). IR ($CHCl_3$) 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.03 (d, 3H, J=6.0 Hz, 6-CH_3), 1.26 (d, 3H, J=6.0 Hz, 4-CH_3), 1.4—2.3 (m, 2H, 5-CH_2), 3.1—4.1 (m, 2H, 4,6-CH), 7.0—7.6 (m, 6H, Ar and =CH). Picrate: Found: C, 51.70; H, 4.53; N, 16.52%. Calcd for $C_{18}H_{19}N_5O_7$: C, 51.79; H, 4.58; N, 16.77%.

1,4,5,6-Tetrahydro-4,4,6-trimethyl-1-phenylpyrimidine (8b). IR ($CHCl_3$) 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.06 (d, 3H, J=5.4 Hz, 6-CH_3), 1.21 (s, 3H, 4-CH_3), 1.27 (s, 3H, 4-CH_3), 1.4—2.2 (m, 2H, 5-CH_2), 3.6—4.2 (m, 1H, 6-CH), 6.9—7.6 (m, 6H, Ar and =CH). Picrate: Found: C, 52.77; H, 4.84; N, 16.21%. Calcd for $C_{19}H_{21}N_5O_7$: C, 52.89; H, 4.92; N, 16.24%.

1,4,5,6-Tetrahydro-1-(*p*-methoxyphenyl)-4,4,6-trimethylpyrimidine (8c). IR ($CHCl_3$) 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.02 (d, 3H, J=6.6 Hz, 6-CH_3), 1.21 (s, 3H, 4-CH_3), 1.23 (s, 3H, 4-CH_3), 1.4—2.2 (m, 2H, 5-CH_2), 3.3—3.9 (m, 1H, 6-CH), 3.75 (s, 3H, OCH_3), 6.7—7.0 (m, 4H, Ar), 7.03 (s, 1H, =CH). Picrate: Found: C, 52.00; H, 5.05; N, 15.13%. Calcd for $C_{20}H_{23}N_5O_8$: 52.05; H, 5.02; N, 15.17%.

1-(*m*-Chlorophenyl)-1,4,5,6-tetrahydro-4,4,6-trimethylpyrimidine (8d). IR ($CHCl_3$) 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.08 (d, 3H, J=6.0 Hz, 6-CH_3), 1.20 (s, 3H, 4-CH_3), 1.27 (s, 3H, 4-CH_3), 1.4—2.2 (m, 2H, 5-CH_2), 3.6—4.2 (m, 1H, 6-CH), 6.8—7.6 (m, 5H, Ar and =CH). Picrate: Found: C, 49.16; H, 4.33; N, 14.88%. Calcd for $C_{19}H_{20}ClN_5O_7$: C, 48.98; H, 4.32; N, 15.03%.

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