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Synthesis of New Unsymmetrical 1,3-Disubstituted-thioureas

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The biological actions of thioureas and their derivatives are well known. They contain the —N=C=S group characteristic of well-known compounds exhibiting toxicity to fungi.[1,2] Recently various thiourea derivatives have been screened for antibacterial and antifungal activities.[3] Significant acaricidal,[4] herbicidal[5] and antiviral[6] activities have also been reported for these compounds. Further these compounds have been found useful in several chemical and biological applications.[7] Of many synthetic methods used for substituted thioureas,[8] the direct reaction of isothiocyanates with amines is the most common.

In continuation of the work to synthesize substituted thioureas[9] having potential biological activity, the author has synthesized seventeen unreported substituted thioureas (**3**) by reacting aromatic and aliphatic amines (**1**) with different isothiocyanates (**2**). The compounds thus synthesized are recorded in Table I.

$$\underset{(1)}{R\,NH_2} + \underset{(2)}{R'-N=C=S} \rightarrow \underset{(3)}{R-NH-\overset{\overset{S}{\|}}{C}-NH-R'}$$

EXPERIMENTAL

All melting points were determined in open capillary tubes and are uncorrected.

All aryl and alkyl isothiocyanates were prepared by known literature methods.

1-(3-Pyrazolyl)-3-phenyl-thiourea

A mixture of 3-aminopyrazole (0.01 M) and phenyl isothiocyanate (0.01 M) was refluxed in absolute ethanol (15 ml) on a water-bath for half an hour. Excess of ethanol was evaporated by distillation. On cooling the residue, a crystalline precipitate was obtained. It was filtered, washed with little ether and dilute ethanol, dried and recrystallized.

Compounds 1～9 were prepared by adapting this method and are listed in Table I along with their relevant data.

1-(4-Fluorophenyl)-3-phenyl-thiourea

To a freshly distilled solution of 4-fluoroaniline (0.01 M) in minimum quantity of absolute ethanol was added a solution of phenyl isothiocyanate (0.01 M) in minimum quantity of absolute ethanol. The reaction mixture was gently heated on a water-bath for ten

TABLE I. 1,3-DISUBSTITUTED-THIOUREAS (**3**)[a]

Compound	R	R′	mp (°C)	Yield (%)	Molecular formula	S[b] (%)	
						Found	Calcd.
1.	3-Pyrazolyl	Phenyl	179	86	$C_{10}H_{10}N_4S$	14.56	14.67
2.	3-Pyrazolyl	4-Methoxyphenyl	199	100	$C_{11}H_{12}N_4OS$	13.06	12.90
3.	3-Pyrazolyl	4-Chlorophenyl	180	88	$C_{10}H_9ClN_4S$	12.61	12.70
4.	3-Pyrazolyl	4-Bromophenyl	188	79	$C_{10}H_9BrN_4S$	10.87	10.77
5.	3-Pyrazolyl	1-Naphthyl	180[c]	68	$C_{14}H_{12}N_4S$	12.14	11.94
6.	2-Pyridyl	Phenyl	167	98	$C_{12}H_{11}N_3S$	14.20	13.97
7.	2-Pyridyl	4-Methoxyphenyl	184	91	$C_{13}H_{13}N_3OS$	12.56	12.35
8.	2-Pyridyl	4-Chlorophenyl	217	90	$C_{12}H_{10}ClN_3S$	12.46	12.14
9.	2-Pyridyl	4-Bromophenyl	192	83	$C_{12}H_{10}BrN_3S$	10.47	10.39
10.	4-Fluorophenyl	Phenyl	168	99	$C_{13}H_{11}FN_2S$	13.09	13.01
11.	4-Fluorophenyl	4-Methoxyphenyl	163	89	$C_{14}H_{13}FN_2OS$	11.52	11.59
12.	4-Fluorophenyl	4-Bromophenyl	159	96	$C_{13}H_{10}BrFN_2S$	10.16	9.84
13.	4-Fluorophenyl	Cyclohexyl	145	97	$C_{13}H_{17}FN_2S$	12.40	12.69
14.	2-Bromophenyl	4-Methoxyphenyl	165	90	$C_{14}H_{13}BrN_2OS$	9.36	9.49
15.	2-Bromophenyl	4-Bromophenyl	169	87	$C_{13}H_{10}Br_2N_2S$	8.38	8.29
16.	Cyclohexyl	4-Methoxyphenyl	134	100	$C_{14}H_{20}N_2OS$	12.45	12.12
17.	Cyclohexyl	4-Bromophenyl	170	84	$C_{13}H_{17}BrN_2S$	9.97	10.22

[a] Compounds 1～5, 7～9, 11, 12, 14, 15 were recrystallized from dioxane and 6, 10, 13, 16, 17 from ethanol.

[b] All the compounds also gave satisfactory C, H, and N analyses.

[c] Decomposes.

minutes and stirred well with a glass rod when a crystalline precipitate was obtained. It was separated, washed with little ether and dilute ethanol, dried and recrystallized.

Compounds 10~17 were prepared by using this method and are presented in Table I along with their relevant data.

Biological activity

Compounds 1~9 have been screened for their nematicidal, acaricidal, insecticidal and herbicidal activity. Surprisingly none of them showed any activity. Fungicidal and antiviral activity of the rest of the compounds are in progress. The results will be communicated in another paper.

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