

A CONVENIENT METHOD FOR THE PREPARATION OF N,N'-DISUBSTITUTED THIOUREAS
USING 2-CHLOROPYRIDINIUM SALT, SODIUM TRITHIOCARBONATE AND AMINES

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N,N'-Disubstituted thioureas were prepared in high yields by treating 2-chloropyridinium salt with sodium trithiocarbonate and subsequently adding amines.

The thiourea derivatives are prepared by the reactions of thiophosgene with amines¹⁾, CS₂ with amines²⁾, isothiocyanates with amines³⁾, and substituted guanidines with H₂S⁴⁾. Each of these method, however, suffers disadvantages in that the thiophosgene possesses poisonous properties¹⁾, severe reaction conditions are required²⁾ and the thiourea derivatives are obtained in poor yields²⁾.

In this communication, we report a convenient method for the preparation of N,N'-disubstituted thioureas by the reactions of 2-chloropyridinium salt [1], Na₂CS₃ [2]⁵⁾, easily prepared from Na₂S and CS₂, and amines. A typical procedure is described for the preparation of N,N'-dibenzylthiourea;

A solution of [1] (306 mg, 1.2 mmol) and [2] (77 mg, 0.5 mmol) in CH₂Cl₂ (5 ml) was stirred at room temperature for 0.5 hr. and, followed by adding benzylamine (235 mg, 2.2 mmol), it was then stirred at reflux for 3 hr. The reaction mixture was filtered, and after removal of the solvent, the residue was separated by silica gel column chromatography using ether as an eluent to afford N,N'-dibenzylthiourea and 1-methyl-2-pyridinethione [4] in quantitative yields. The results of the reactions with amines and diamines are shown in the Table.

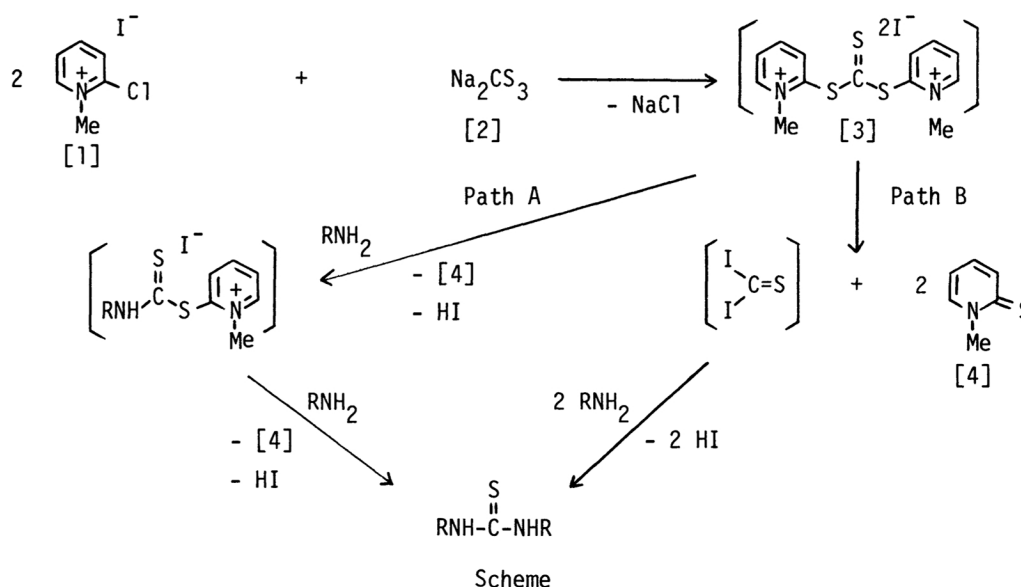


Table The results of the reaction with various amines^{a)}

Run	Amine	Solvent	Temp. (°C)	Time (hr)	RNH(C=S)NHR	Yields(%) ^{b)} 1-methyl-2-pyridinethione
1	n-propylamine	CH ₂ Cl ₂	reflux	5	84	89
2	isopropylamine	CH ₂ Cl ₂	reflux	8	70	94
3	n-butylamine	CH ₂ Cl ₂	reflux	5	98	90
4	isobutylamine	CHCl ₃	50	3	100	93
5	t-butylamine	DMSO	50	3	85	79
6	benzylamine	CH ₂ Cl ₂	reflux	3	100	94
7	aniline	DMSO	30	0.5	91	78
8	4-chloroaniline	DMSO	40	0.5	90	— ^{c)}
9	o-toluidine	DMSO	40	4	94	— ^{c)}
10	p-toluidine	CH ₂ Cl ₂	reflux	5	80	61
11	2-methoxyaniline	DMSO	40	1	92	93
12	4-methoxyaniline	DMSO	40	1 min.	100	— ^{c)}
13	2,6-dimethylaniline	DMSO	40	3 min.	62	— ^{c)}
14	ethylenediamine	DMSO	40	0.5	88	88
15	o-phenylenediamine	DMSO	40	1	85	95

a) 2-chloropyridinium salt [1] : 1.2 mmol, Na₂CS₃ : 0.5 mmol, Amine : 2.2 mmol, Solvent : 5 ml. b) Isolated yields. c) Not determined.

The reaction with anilines having electron-donating substituents and aliphatic primary amines gave N,N'-disubstituted thioureas in high yields in CH₂Cl₂ or CHCl₃. In the reactions with primary amines having such steric hindrances as t-butylamine, o-toluidine and 2,6-dimethylaniline, the corresponding thioureas were obtained in high yields in DMSO. On the other hand, the solution of [1] and [2] in DMSO treated with diamines to afford cyclic thioureas in good yields. However, in the reactions with secondary amines such as dicyclohexylamine and piperidine, and with weakly basic amines such as p-nitroaniline, tetra- and pentachloroaniline, only [4] was formed but the corresponding thioureas were not obtained. A possible mechanism is shown in path A of the scheme. First, [1] reacts with [2] to afford a reactive intermediate [3]⁶⁾ easily, and then an amine attacks a carbon atom on thiocarbonyl group of [3] giving N,N'-disubstituted thiourea and [4]. Existence of the other path was also suggested because the reaction of [1] with [2] in CH₂Cl₂ at reflux for 1 hr gave [4] in 28 % yields besides the quantitative formation of NaCl. Consequently, both path A and B would be considered as possible path of formation of N,N'-disubstituted thioureas.

References

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