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A Facile Conversion of Symmetrical to Unsymmetrical Thioureas

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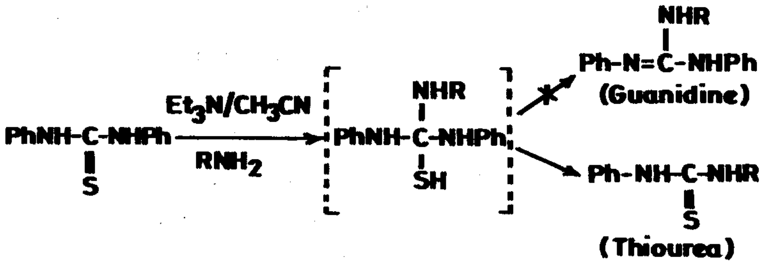
Abstract: **A convenient route for quantitative conversion of symmetrical thioureas into unsymmetrical thioureas is described. The method circumvents the use of toxic isothiocyanates and a case study is reported using 1,3-diphenylthiourea.**

1,3-Disubstituted guanidines have of late been identified to display important agrochemical and pharmaceutical properties.[1] Cyanogen chloride and phosgene the hazardous reagents offer excellent routes to guanidines.[2] It is also known that desulphurisation of thioureas leads to the desired compounds involving the intermediacy of carbodiimides.[3]

In an attempt at the synthesis of 1,3-disubstituted guanidines, we subjected symmetrical 1,3-disubstituted thioureas to reaction with various amines in presence of a tertiary amine. This led however, to the isolation of unsymmetrical thioureas as exclusive products in lieu of the expected guanidines which would result from hydrogen sulphide extrusion as depicted in the scheme 1.



Scheme 1

Notwithstanding the formation of 1,3-disubstituted thioureas, this work however offers an excellent route for the synthesis of a variety of unsymmetrical thioureas which are otherwise obtained only on reaction of amines with toxic isothiocyanates and which generally take longer periods to complete.[4-7] Incidentally, unsymmetrical thioureas are also found to exhibit agrochemical properties[8] and are commercially interesting compounds.[9]

The scope of this work (see table) was extended to cover gaseous amines available as aqueous solutions under phase transfer conditions while the reaction did not proceed with sterically hindered amines. The reactions proceed best in terms of overall yields and reduced reaction times in the presence of a tertiary amine such as triethylamine.

The mechanistic aspects as well as the applicability of this method to include various symmetrical aliphatic and aromatic thioureas are under study.

Thus to sum up this approach furnishes the best possible method to synthesise mixed thioureas exclusively in excellent yields and in shorter times. The choice of solvent is acetonitrile; however, other solvents such as methanol, ethanol, THF or DMF may be used. Triethylamine was used as the tertiary amine in all cases. The identity of each product synthesised was established by comparison with the authentic sample.

EXPERIMENTAL SECTION

All reagents of laboratory grade were obtained and purified prior to use. Melting points are uncorrected. IR Spectra were recorded on a BRUKER FTIR IFS-85 spectrometer. ^{1}H NMR spectra were obtained using GEOL GSX-400 NMR Spectrometer and HITACHI 60 MHz spectrometer. Mass spectra were taken in a SHIMADZU GCMS-QP1000A (70ev) mass spectrometer.

TYPICAL EXPERIMENTAL PROCEDURE

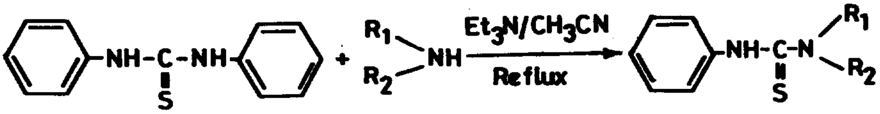
a) Reaction of diphenylthiourea with aliphatic and aromatic amines

A stirred reaction mixture consisting of diphenylthiourea (0.01M, 2.28g) in acetonitrile (15ml), the amine (0.015M) and triethylamine (0.002M, 0.3ml) was heated under gentle reflux. The progress of the reaction was monitored by tlc. The time taken for completion of the reaction varied with the amines used and the reactions were generally over within 3h. The reaction mixture was concentrated in vacuo before dilution with cold water (200ml) containing 2N HCl (10ml) to neutralise free amine present. Subsequent extraction ($CHCl_3$, 4x30 ml), followed by usual workup gave the desired mixed thioureas which upon crystallisation (hexane-chloroform) afforded the pure product in excellent yield (70-92%).

b) **Reaction of diphenylthiourea with gaseous amine available as aqueous solution using phase transfer catalyst**

To a stirred solution of diphenylthiourea (0.01M, 2.28 g) in ethyl acetate (20 ml), the amine (0.03M, 3-fold excess) and triethylamine (0.002M, 0.3 ml) were added successively. A catalytic amount of trimethylbenzylammonium bromide (10 mg) was added to the above reaction mixture which was subsequently stirred under gentle reflux for 3h. The routine workup furnished the pure product as described above in good yields (70-80%).

TABLE : UNSYMMETRICAL THIOUREAS BY THE REACTION OF DIPHENYLTHIOUREA WITH AMINES



Ent. No.	Products		Reaction Time (hrs)	Yield[(a)] (%)	Melting Points(°c)	
	R_1	R_2			Observed	Literature
1	H	Cyclohexyl	1.5	90	150	150-151(10)
2	-	Morpholinyl	1.5	92	138-140	132(11)
3	H	n-Butyl	2.0	80	90-92	91(12)
4	H	Hydroxyethyl	2.5	77	140-142	137-138(13)
5[b]	-	Diethyl	1.5	87	55-57	53-57(14)
6	H	O-Tolyl	2.5	90	140-142	141-142(15)
7	H	Benzyl	2.0	92	162-164	167-168(16)
8	H	Methyl	3.0	70	154-157	154(17)
9	-	Dimethyl	3.0	72	136-138	134-137(18)
10	H	H	2.5	80	154-155	154(19)

a. Yields of pure products

b. Purified by Silica gel column chromotography by eluting with hexane containing 1% ethyl acetate.

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