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A Concise and Convenient Method for the Synthesis of Pure Substituted Thioureas

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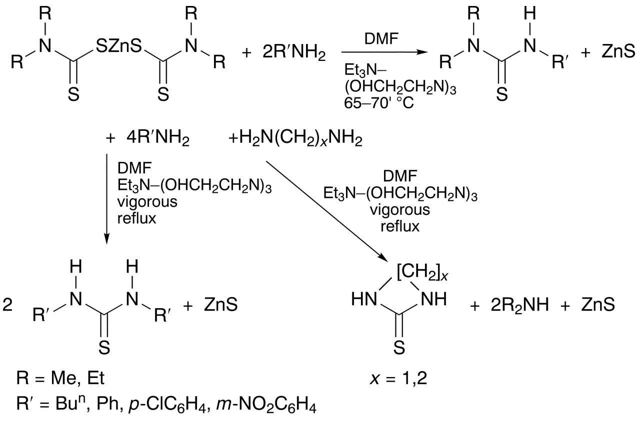
Zinc dialkyldithiocarbamates offer excellent substrates for the pure thioureas required for antifungal and X-ray crystallographic studies.

The synthetic methodology for variously substituted symmetrical[1] and unsymmetrical[2] thioureas and guanidines[3] has been well established in this laboratory and their biological activity is also well known.[4] In pursuit of our interest in the study of the antifungal properties of thioureas, we required the products in a highly pure state. It may be noted that the end products were contaminated with sulfur which is undesirable for antifungal studies since sulfur is well known to function as a fungicide. The removal of sulfur from the product poses problems in the isolation of the pure product. The approach presented herein makes use of dialkyldithiocarbamates, particularly the zinc salt, which as substrates provide a ready access to mixed thiocarbamides. The highlights of the work include easy removal of the by-product zinc sulfide by filtration, trapping of hydrogen sulfide by triethanolamine[5] and excellent yield of the product in a pure form. The method involves the reaction of a zinc salt of dialkyldithiocarbamic acid with primary aliphatic or aromatic amine in the ratio of 1:2 in dimethylformamide at 65–70 °C which led to the trisubstituted unsymmetrical thioureas (Scheme, Table A).

In the above procedure (Scheme), if 4 equivalents of amine nucleophile were used instead of 2, both the dialkyl amine functionalities were displaced to yield 1,3-disubstituted symmetrical thioureas (Scheme, Table B). 1,3-Diaryl symmetrical thioureas containing deactivated arylamines, which are otherwise difficult to synthesise, were obtained in good yields. The reactions of zinc dialkyldithiocarbamate were extended to those with aliphatic diamines to provide cyclic thioureas (Scheme, Table C). Cava and co-workers[18] studied the reactions of tetramethylthiuram disulfide (TMTD) with phenyllithium and showed the products to be a mixture of about equal amounts of the thioamide and the corresponding aryldithiocarbamate formed by competing nucleophilic attack at the thione carbon of the TMTD and the sulfur atom respectively. However, in our reactions the formation of the product is rationalised in terms of the formation of the intermediate isothiocyanate resulting from the nucleophilic attack on the thione carbon of zinc dialkyldithiocarbamate exclusively. To conclude then, this strategy involving the inexpensive zinc salts as ideal substrates for the synthesis of differently substituted thioureas works better than other methods available for this purpose.[23]



Scheme

Table A Synthesis of trisubstituted thioureas using zinc dialkyldithiocarbamates

Entry	Product R	 R′	Reaction time/h	Yield (%)
1	Me	*n*-Butyl	2.0	76
2	Me	Phenyl	2.0	86
3	Me	*o*-Tolyl	2.0	88
4	Me	*m*-$NO_2C_6H_4$	2.5	86
5	Et	Cyclohexyl	1.5	90
6	Et	Phenyl	1.5	82
7	Et	*o*-Tolyl	1.5	79
8	Et	*p*-ClC_6H_4	2.5	75

Table B Synthesis of 1,3-disubstituted symmetrical thioureas using dialkyldithiocarbamates

Entry	Product R	 R′	Reaction time/h	Yield (%)
9	Me	Phenyl	2.0	86
10	Me	*o*-Tolyl	2.0	80
11	Me	Cyclohexyl	2.0	88
12	Me	*n*-Butyl	2.0	78
13	Me	*m*-$NO_2C_6H_4$	3.0	72
14	Me	*o*-ClC_6H_4	2.5	76
15	Et	Phenyl	2.0	84
16	Et	*o*-Tolyl	2.0	82
17	Et	*m*-$NO_2C_6H_4$	3.0	71

Table C Synthesis of cyclic thioureas using zinc dialkyldithiocarbamates

Entry	Product R	 X′	Reaction time/min	Yield (%)
18	Me	2	30	76
19	Me	3	45	70
20	Et	2	45	80
21	Et	3	60	72

Techniques used: ^{1}H NMR and elemental analysis

References: 23

Schemes: 3

Tables A–C: Reaction times, yield, mp and literature references for all thioureas

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