A simple and green procedure for the synthesis of symmetrical N,N' -disubstituted thioureas on the surface of alumina under microwave irradiation

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Dedicated to Professor (Mrs.) Asima Chatterjee on the occasion of her 85th birthday

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Abstract

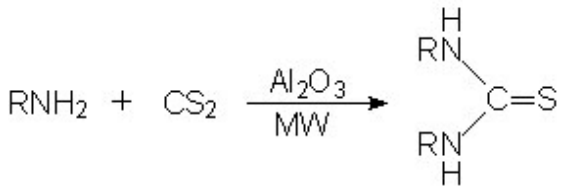
A variety of symmetrical N,N'-disubstituted thioureas have been prepared by a simple reaction of amines and carbon disulfide on the surface of alumina under solvent-free microwave irradiation.

Keywords: Thiourea, amine, carbon disulfide, microwave, alumina

Introduction

The development of simple and eco-friendly synthetic procedures constitutes an important goal in organic synthesis. Many organic solvents, particularly chlorinated hydrocarbons that are used in large quantities in organic reactions are potential threat to human health and environment. Thus, redesign of chemical reactions under solvent-free condition gets a renewed interest. The use of inorganic solid supports such as clay, zeolite, alumina, silica gel for the generation of small organic molecules under solvent-free condition has gained immense popularity because of its ease of set-up, mild conditions, increased yields of products, cost efficiency and environment friendliness compared to their homogeneous counterparts.[1]

As a part of our program to develop green synthetic procedures through surface-mediated solid phase reaction initiated a decade ago,[2] we report here an efficient synthesis of symmetrical N,N'-disubstituted thioureas by a simple reaction of carbon disulfide and amine on the surface of alumina under microwave irradiation (Scheme 1).



Scheme 1

Thiourea derivatives are of much importance being used as neutral receptors for various aninons,[3a] natural product mimics and synthetic intermediates to amidines or guanidines.[3] Although there are several methods[4] for the preparation of disubstituted thioureas including condensation of amine hydrochlorides with potassium thiocyanate[4a] the most direct approach involves interaction of carbon disulfide with primary amines.[4b] However, this reaction is often associated with several byproducts depending on the reaction conditions employed.[4b] A recent procedure[4c] using a heterogeneous catalyst, MCM-TBD shows much improvement. However, this reaction needs to be run in an antoclave at 90°C for 15 h and the catalyst MCM-TBD is not commercially available and is prepared through a series of operations requiring 60 h.[4c]

Results and Discussion

The present experimental procedure is very simple. An amine was added dropwise to the surface of alumina impregnated with carbon disulfide under stirring. The mixture was then irradiated by microwave in a domestic microwave oven for a few minutes. The product was isolated by extraction of the reaction mixture with hot methanol. The alumina after being washed with methanol once more and dried under vacuum at 180°C was recycled for subsequent reactions.

A variety of amines react with carbon disulfide to form the symmetrical *N,N'*-disubstituted thioureas by this procedure. The results are summarized in Table 1. As evident from the results aliphatic as well as aromatic primary amines undergo very facile reaction whereas secondary amines except the cyclic one (entry 12) are resistant to this reaction. The 1,2-diamine (entry 6) produces a cyclic thiourea in high yield.

In general, the reactions are very clean and fast. The products were isolated very pure by simple extraction with hot methanol followed by recrystallization from the same medium. Without microwave irradiation the reaction proceeds only marginally (10-15%).

To conclude, the present solvent-free reaction of carbon disulfide and amines on the surface of alumina under microwave irradiation provides a very simple and efficient procedure for the synthesis of symmetrical *N,N'*-disubstituted thioureas. It provides significant improvements over existing procedures with regard to reaction time, yield, cost efficiency (recycling of alumina) and eco-friendliness.

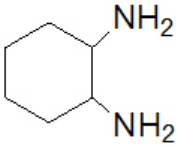
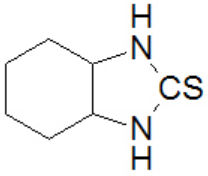
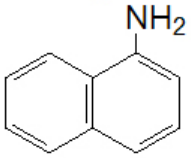
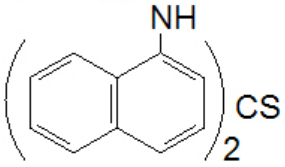
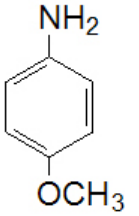
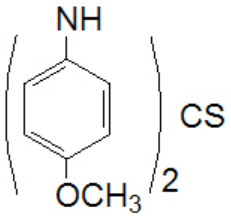
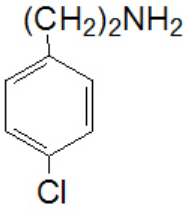
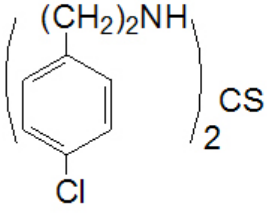
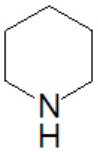
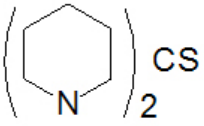
Experimental Section

General Procedures. The melting points were determined on a glass dish with an electrical bath (Reichert, Austria) and are uncorrected. IR spectra were taken as KBr pellets. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in $CDCl_3$ and d_6-DMSO solutions. Alumina (acidic, Brockmann grade 1 for column chromatography purchased from SRL, India) was activated by heating at 180^{o}C for 4 h under vacuum (0.05 mg of Hg) before use. The amines are all commercial materials and were distilled prior to use for reaction.

General procedure for condensation of amine and carbon disulfide. Representative procedure for the synthesis of *N,N'*--di-*n*-butyl thiourea (entry 2)

N-Butylamine (10 mmol, 730 mg) was added very slowly (dropwise) to carbon disulfide adsorbed on the surface of alumina (3g) in a round bottom flask fitted with a moisture guard tube under stirring (this addition is exothermic and thus for gram scale reaction a cooling bath should be used to keep the reaction under control). The flask containing the solid mass was then placed in a domestic microwave oven and irradiated by microwave (10% power, 120W) for 2 min (monitored by TLC). After being cooled, the reaction

Table1. Synthesis of *N, N'* – disubstituted thiourea under microwave irradiation

Entry	Amine	Product	Time (m)	Yield (%)[a]
1	$CH_3CH_2NH_2$	$(CH_3CH_2NH)_2CS$	5	66
2	$CH_3(CH_2)_3NH_2$	$[CH_3(CH_2)_3NH]_2CS$	2	89
3	$(CH_3)_2CHNH_2$	$[(CH_3)_2CHNH]_2CS$	3	87
4	*c* - $C_6H_{11}NH_2$	$(c\text{-}C_6H_{11}NH)_2CS$	2	92
5	$PhCH_2NH_2$	$(PhCH_2NH)_2CS$	8	86
6			3	91
7	$PhNH_2$	$(PhNH)_2CS$	15	74
8			20	62
9			15	89
10			5	89
11	(R)-PhCHNH$_2$ CH$_3$	[(R)-PhCHNH]$_2$CS CH$_3$	8	93
12			15	55

[a]Yields refer to those of pure isolated products characterized by spectral (IR, ^{1}H and ^{13}C NMR).

mixture was extracted (shaken) with hot methanol and filtered while hot. A few drops of water was added to the hot methanol solution and it was then left undisturbed. The product, *N,N'*-dibutyl thiourea crystallizes out from the medium and was collected by filtration. The crystals were dried under vacuum to provide the pure product (1.67 g, 89%), m.p. 61°C (lit[5] 61-62°C); IR 3219, 2960, 1566, 1519, 1245, 1078 cm^{-1}; ^1H NMR δ 5.89 (broad, 2H), 3.42 (broad m, 4H), 1.64-1.54 (m, 4H), 1.45-1.33 (m, 4H), 0.95 (t, *J* = 7.29 Hz, 6H); ^{13}C NMR δ 181.7, 44.5 (2C), 31.4 (2C), 20.5 (2C), 14.1 (2C).

This procedure is followed for all the reactions listed in Table 1. All the products are known compounds and were identified by m.p. and spectroscopic data (IR, ^1H and ^{13}C NMR) which are in good agreement with the reported values. These data are provided below in order of their entries in Table 1 as ready reference.

***N,N'*-Diethylthiourea (entry 1).** White crystal; m.p. 78°C (lit.[4e] 78°C); IR 3232, 3091, 2972, 1568, 1519, 1448, 1249 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:2)] δ 6.31 (s, 2H), 2.52-2.48 (m, 4H), 0.21 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR δ 181.1, 36.6 (2C), 12.9 (2C).

***N,N'*-Diisopropylthiourea (entry 3).** White crystal; m.p. 140°C (lit.[6] 142°C); IR 3288, 3220, 2970, 1562, 1517, 1460, 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.69 (s, 2H), 4.23-4.20 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 12H); ^{13}C NMR δ 179.7, 46.4 (2C), 23.0 (4C).

***N,N'*-Dicyclohexylthiourea (entry 4).** White crystal; m.p. 181°C (lit.[4f] 182.5°C); IR 3304, 3140, 2939, 1504, 1439, 1019 cm^{-1}; ^1H NMR [d_6-DMSO] δ 7.82 (s, 2H), 3.30 (m, 2H), 1.87-1.49 (m, 8H), 1.29-1.05 (m, 12H); ^{13}C NMR δ 139.2, 50.2 (2C), 33.3 (2C), 31.2 (2C), 26.1 (2C), 25.4 (2C), 24.6 (2C).

***N,N'*-Dibenzylthiourea (entry 5).** White crystal; m.p. 148°C (lit.[4d] 148°C); IR 3290, 3028, 2945, 1585, 1556, 1454, 1286 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:3)] δ 7.26 (s, 2H), 6.79-6.65 (m, 10H), 4.12 (s, 4H); ^{13}C NMR δ 181.0, 136.8 (2C), 126.2 (4C), 125.3 (4C), 124.6 (2C), 45.2 (2C).

Octahydrobenzoimidazole-2-thione (entry 6). Yellowish crystal; m.p. 150-153°C (lit.[7] 151-160°C); IR 3215, 2935, 2864, 1510, 1452, 1353, 1101 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:1)] δ 7.35 (s, 2H), 2.58 (m, 1H), 2.25 (m, 1H), 1.19-0.49 (m, 8H); ^{13}C NMR δ 186.7, 64.1, 55.3, 28.9, 26.8, 23.7, 19.9.

***N,N'*-Diphenylthiourea (entry 7).** White crystal; m.p. 153°C (lit.[4d] 153-154°C); IR 3205, 3120, 3035, 1598, 1556, 1450, 1344 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:1)] δ 7.79 (s, 2H), 5.85-5.75 (m, 4H), 5.59-5.47 (m, 4H), 5.44-5.35 (m, 2H); ^{13}C NMR δ 178.9, 138.4 (2C), 127.2 (4C), 123.4 (2C), 120.3 (4C).

***N,N'*-Dinaphthylthiourea (entry 8).** Brownish crystal; m.p. 198°C (lit.[4d] 198°C); IR 3338, 3161, 2968, 1624, 1595, 1527, 1276 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:1)] δ 8.50 (s, 2H), 6.92-5.47 (m, 14H); ^{13}C NMR δ 181.1, 142.5, 134.3, 132.2, 128.5, 126.3, 126.2, 126.0, 125.0, 124.8, 124.3, 123.9, 123.8, 123.7, 123.6, 121.9, 121.4, 121.2, 120.4, 114.1, 106.1.

***N,N'*-Di-(*p*-methoxyphenyl)thiourea (entry 9).** Brownish crystal; m.p. 180°C (lit.[4g] 180°C); IR 3219, 3022, 2960, 1610, 1548, 1510, 1467, 1245, 1033 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:1)] δ 7.26 (s, 2H), 5.37-5.34 (m, 4H), 4.91-4.87 (m, 4H), 1.78 (s, 6H); ^{13}C NMR δ 185.9, 162.3 (2C), 137.4 (2C), 131.7 (4C), 119.0 (4C), 60.6 (2C).

***N,N'*-Di-(*p*-chlorophenethyl)thiourea (entry 10).** White crystal; m.p. 119°C, (lit.[8] 119-120°C); IR 3261, 3220, 3058, 2933, 1895, 1596, 1560, 1488, 1097 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:1)] δ 6.62-6.44 (m, 8H), 3.03-3.02 (m, 4H), 2.18 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR δ 188.1, 143.5 (2C), 136.7 (2C), 135.7 (4C), 133.7 (4C), 50.2 (2C), 39.9 (2C).

***N,N'*-Di-(*R)*-1-phenylethyl)thiourea (entry 11).** White crystal; m.p. 199°c, (lit.[9] 200°C); IR 3205, 3120, 3008, 1598, 1548, 1494, 1344 cm^{-1}; ^1H NMR [$CDCl_3$ + d_6-DMSO (1:2)] δ 7.70 (s, 2H), 7.31-7.20 (m, 10H), 5.43 (m, 2H), 1.41 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR δ 181.7, 145.1 (2), 129.1 (4C), 127.5 (2C), 126.9 (4C), 53.1 (2C), 23.3 (2C).

***N,N'*-Bispentamethylenethiourea (entry 12).** Yellowish crystal; m.p. 59°C, (lit.[10] 59-60°C); IR 2933, 2852, 1583, 1461, 1409, 1218 cm^{-1}; ^1H NMR [$CDCl_3$] δ 4.37 (t, *J* = 5.4 Hz, 4H), 3.31 (t, *J* = 4.8 Hz, 4H), 1.94-1.65 (m, 12H); ^{13}C NMR δ 208.9, 52.4 (2C), 45.6 (2C), 26.6 (2C), 24.9 (2C), 23.3 (2C).

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