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# A novel approach to the synthesis of aryldithiocarbamic acid esters with arylamines and $CS_2$ in aqueous media

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**ABSTRACT**

*An efficient, novel and highly simple procedure for the direct synthesis of aryl dithiocarbamates from the one-pot reaction of amines, carbon disulfide, and alkyl halides, without the use of any catalyst and aqueous condition at room temperature.*

**Keywords:** Dithiocarbamate, amines, carbon disulfide, alkyl halides, sodium hydroxide

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## INTRODUCTION

Organic dithiocarbamates have attracted a great deal of importance due to their interesting chemistry and wide utility[1-7]. Dithiocarbamates have a wide range of uses and applications and are produced in great quantities throughout the world. Dithiocarbamate acid ester **(1)** is a common class of organic molecules. They exhibit valuable biological effects, including antibacterial activity, antifungal activity, antioxidant activity [8]inhibition of cardiac hypertrophy [9]etc. Dithiocarbamic acid ester represents a new kind of compound with a novel structure, significant anticancer activity and very low toxicity. It is the analogue of carbamate in which both oxygen atoms are replaced by sulfur atoms (figure 1).

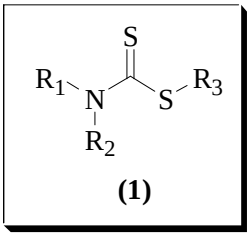



**Figure 1: General formula of the dithiocarbamate**

Dithiocarbamates have received considerable attention due to their numerous biological activities [10] and their pivotal role in agriculture [11] and as linkers in solid phase organic synthesis [12] They are also used in the rubber industry as vulcanization accelerators [13] and in controlled radical polymerization techniques [14] Because they have a strong metal binding capacity, they can also act as inhibitors of enzymes and have a profound effect on biological systems. Dithiocarbamates are also widely used in medicinal chemistry and have found application in the treatment of cancer [15](figure 2) and have been tested in clinical trials for various indications including HIV [16-19] Furthermore; dithiocarbamates are versatile classes of ligands with the ability to stabilize transition metals in a wide range of oxidation states [20] the ability to chelate heavy metals [21-22]to function as NO scavengers [23] radical chain transfer agents in the reversible addition fragmentation chain transfer (RAFT) polymerizations [24]for the protection of amino groups in peptide synthesis [25]as radical precursors [26]and recently in the synthesis of ionic liquids [27].

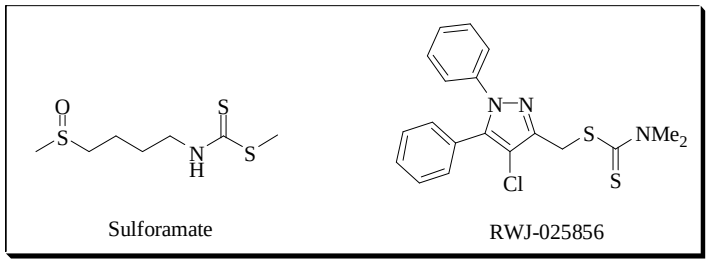


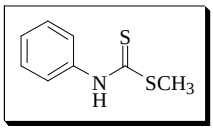

**Figure 2: Structures of dithiocarbamates with anticancer activity**

A number of methodologies have been developed; the standard preparation of carbamates/dithiocarbamates generally involves the use of toxic and highly reactive phosgene/thiophosgene and its derivatives [28], thereby posing environmental and safety problems. As a result, considerable effort has been made to develop a phosgene/thiophosgene free route [29] for the preparation of carbamates and thiocarbamates. However, many of these methods suffer from limitations, such as long reaction times, use of expensive and strongly basic reagents, use of volatile solvents, tedious work-up, and low yields [30].

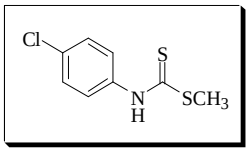
## MATERIALS AND METHODS

All reactions were performed using oven-dried glassware; organic solutions were concentrated under reduced pressure using Buchi rotary evaporator. All other reagents and solvents were obtained from commercial suppliers and were used without further purification. Reactions and chromatographic fractions were monitored by thin layer chromatography. TLC Silica gel-60 $F_{254}$, Merck was used for TLC and silica gel (100-200 mesh, SRL, India) was used for column chromatography.

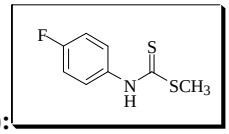
**General experimental procedure for preparation of dithiocarbamates:**
To a stirring solution of aniline (1.0 eq) and DMSO (20 ml) in 250 ml round bottomed flask, 20 N NaOH (1.2 eq) solution was added drop wise, and followed by addition of $CS_2$ (2.5 eq), the stirring was continued for 1 hour at room temperature. Then the reaction mixture was cooled to 0 ºC. To this alkyl halide (2.0 eq) was added drop wise and the stirring was continued for 1 hour at 0 ºC. The completion of the reaction was monitored by TLC, then the reaction mixture was poured into stirring ice cold water, solid was obtained was filtered and dried under vaccum and the solid compound was purified by column and confirmed by spectral data.



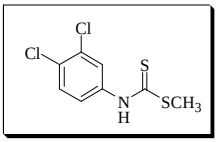
**Phenyl-dithiocarbamic acid methyl ester (1a):**
mp: 87-88 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.66 (s, 1H, NH), 7.60 (br s, 2H), 7.41-7.37 (m, 2H), 7.25-7.22 (m, 1H), 2.57 (s, 3H); Mass (ESI): 184.0 $[M+H]^+$.

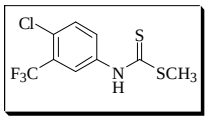


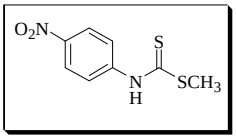
**(4-Chloro-phenyl)-dithiocarbamic acid methyl ester (1b):**
mp: 108-109 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.74 (s, 1H, NH), 7.68 (br s, 2H), 7.46-7.7.44 (m, 2H), 2.58 (s, 3H); Mass (ESI): 217.5 $[M+H]^+$.

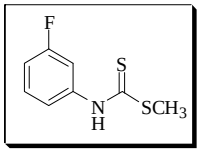


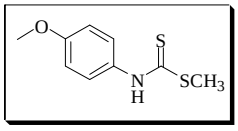
**(4-Fluoro-phenyl)-dithiocarbamic acid methyl ester (1c):**
mp: 108-109 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.64 (s, 1H, NH), 7.61 (br s, 2H), 7.25-7.20 (m, 2H), 2.57 (s, 3H); Mass (ESI): 202.2 $[M+H]^+$.

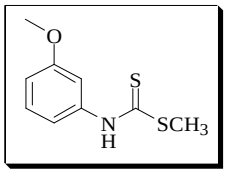
**(3, 4-Dichloro-phenyl)-dithiocarbamic acid methyl ester (1d):** 
mp: 132-133 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.84 (s, 1H, NH), 8.10 (s, 1H), 7.69-7.64 (m, 2H), 2.59 (s, 3H); Mass (ESI): 250.1 $[M-H]^+$.

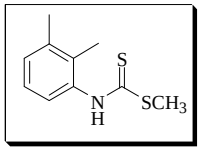
**(4-Chloro-3-trifluoromethyl-phenyl)-dithiocarbamic acid methyl ester (1e)** 
mp: 141-142 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.96 (s, 1H, NH), 8.32 (s, 1H), 8.06-8.04 (m, 1H), 7.76-7.74 (m, 1H), 2.61 (s, 3H); Mass (ESI): 284.1 $[M-H]^+$.

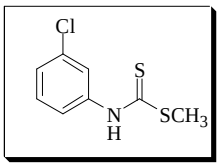
**(4-Nitro-phenyl)-dithiocarbamic acid methyl ester (1f):** 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 12.03 (s, 1H, NH), 8.76 (s, 1H), 8.12-8.06 (m, 2H), 7.70-7.66 (m, 1H), 2.62 (s, 3H); Mass (ESI): 227.2 $[M-H]^+$.

**(3-Fluoro-phenyl)-dithiocarbamic acid methyl ester (1g):** 
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.64 (s, 1H, NH), 7.61 (br s, 2H), 7.25-7.21 (m, 2H), 2.57 (s, 3H); Mass (ESI): 200.2 $[M-H]^+$.

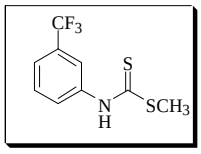
**(4-Methoxy-phenyl)-dithiocarbamic acid methyl ester (1h):** 
mp: 101-102 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.50 (br s, 1H, NH), 7.53 (br s, 2H), 6.95-6.93 (d, $J$ = 8.40 Hz, 2H), 3.76 (s, 3H), 2.55-2.49 (m, 3H); Mass (ESI): 214.1 $[M+H]^+$.

**(3-Methoxy-phenyl)-dithiocarbamic acid methyl ester (1i):** 
mp: 120-122 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.65 (s, 1H, NH), 7.34 (s, 1H), 7.29 (t, $J$ = 8.0 Hz, 1H), 7.22-7.18 (m, 1H), 6.82 (d, $J$ = 7.56 Hz, 1H), 3.77 (s, 3H), 2.56 (s, 3H); Mass (ESI): 214.0 $[M+H]^+$.

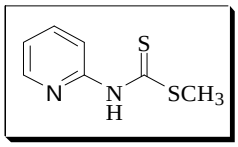
**(2,3-Dimethyl-phenyl)-dithiocarbamic acid ethyl ester (1j):** 
$^1$H NMR (400 MHz, $CDCl_3$): δ 8.85 (br s, 1H, NH), 7.3-7.12 (m, 3H), 3.3 (q, $J$ = 8.0 Hz, 2H), 2.38 (s, 3H), 2.18 (s, 3H), 1.3 (t, $J$ = 3.6 Hz, 3H); Mass (ESI): 226.0 $[M+H]^+$.



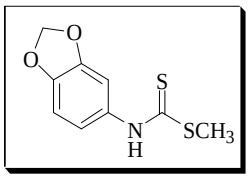
**(3-Chloro-phenyl)-dithiocarbamic acid methyl ester (1k):**
mp: 91-93 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.77 (s, 1H, NH), 7.85 (s, 1H), 7.58 (d, *J* = 7.88 Hz, 1H), 7.41 (t, *J* = 8.04 Hz, 1H), 7.28 (d, *J* = 7.56 Hz, 1H); Mass (ESI): 217.5 [M+H]$^+$.



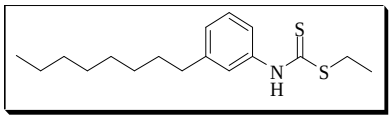
**(3-Trifluoromethyl-phenyl)-dithiocarbamic acid methyl ester (1l):**
mp: 71-72 ºC; Mass (ESI): 252 [M+H]$^+$.



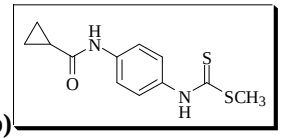
**Pyridin-2-yl-dithiocarbamic acid methyl ester (1m):**
mp: 88-89 ºC; Mass (ESI): 185.1 [M+H]$^+$.



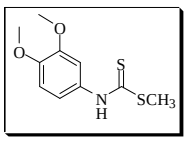
**Benzo[1,3]dioxol-5-yl-dithiocarbamic acid methyl ester (1n):**
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.51 (s, 1H, NH), 6.96-6.91 (m, 3H), 6.05 (s, 2H), 2.50 (s, 3H); Mass (ESI): 228.0 [M+H]$^+$.



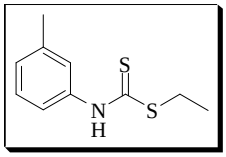
**(3-Octyl-phenyl)-dithiocarbamic acid ethyl ester (1o):**
$^1$H NMR (400 MHz, $CDCl_3$): δ 8.82 (br s, 1H, NH), 7.40-7.15 (m, 4H), 3.30 (q, *J* = 1.2 Hz, 2H), 2.61 (t, *J* = 8.80 Hz, 3H), 1.69-0.89 (m, 17H); Mass (ESI): 310.0 [M+H]$^+$.



**[4-(Cyclopropanecarbonyl-amino)-phenyl]-dithiocarbamic acid methyl ester (1p)**
$^1$H NMR (200 MHz, DMSO-$d_6$): δ 11.56 (br s, 1H, NH), 10.27 (br s, 1H, NH), 7.61-7.56 (m, 4H), 2.55 (s, 3H), 1.79-1.70 (m, 1H) 0.81-0.78 (m, 4H); Mass (GC-LC/MS): 219.0 [M$^+$-$SCH_3$].



**(3, 4-Dimethoxy-phenyl)-dithiocarbamic acid methyl ester (1q):**
Mass (ESI): 244.0 [M+H]$^+$.

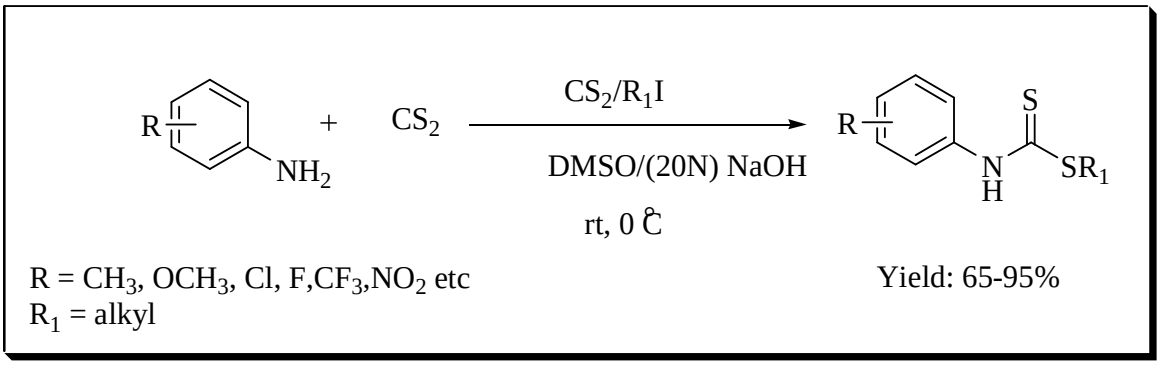


**m-Tolyl-dithiocarbamic acid ethyl ester (1r):**
mp: 62-63 ºC; Mass (ESI): 212.3 [M+H]$^+$.

## RESULTS AND DISCUSSION

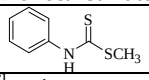
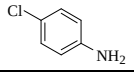
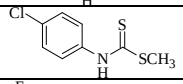
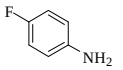
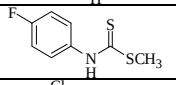
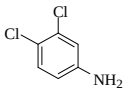
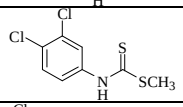
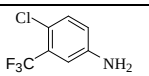
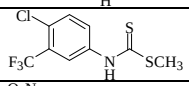
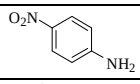
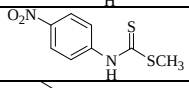
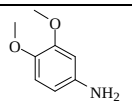
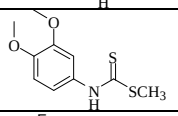
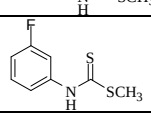
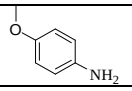
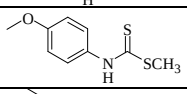
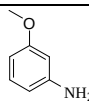
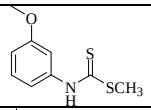
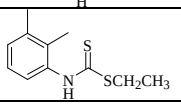
In continuation of our earlier work [31-33], we came across the synthesis of dithiocarbamates and in the present communication we are particularly interested in the synthesis of aryl dithiocarbamates via a method suitable for large scale preparations as well as not requiring to toxic starting materials.

The initial reactions were carried out between simple aniline and various substituted anilines in presence of aq. NaOH, $CS_2$, $CH_3I$ and DMSO. Stirring continued for 1-2 hours at room temperature and then followed by 0 $^0$C (Scheme 1). These reaction conditions are proved to be good synthetic procedure for various dithiocarbamates (Table 1) with 65-95% isolated yield.




**Scheme 1**

**Table 1.0: Synthesis of dithiocarbamates**

| S.No | Aniline | Dithiocarbamate | Yield (%) |
|---|---|---|---|
| 1 |  |  | 90 |
| 2 |  |  | 88 |
| 3 |  |  | 80 |
| 4 |  |  | 76 |
| 5 |  |  | 77 |
| 6 |  |  | 70 |
| 7 |  |  | 85 |
| 8 |  |  | 79 |
| 9 |  |  | 81 |
| 10 |  |  | 80 |
| 11 |  |  | 75 |

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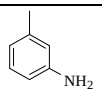
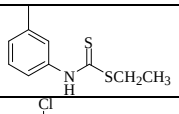
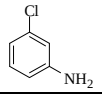
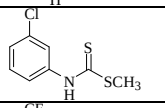
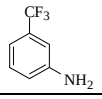
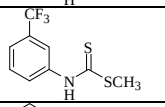
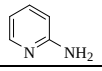
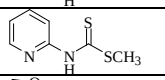
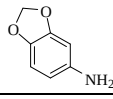
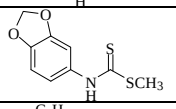
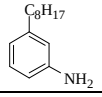
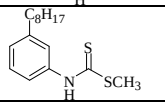
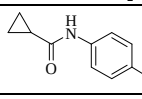
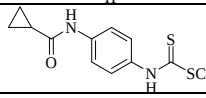
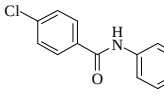
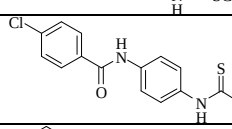
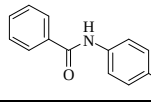
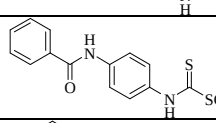
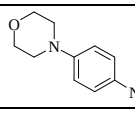
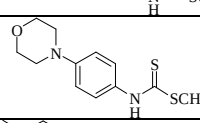
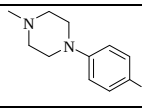
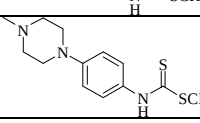
| 12 |  |  | 72 |
| 13 |  |  | 81 |
| 14 |  |  | 72 |
| 15 |  |  | 69 |
| 16 |  |  | 70 |
| 17 |  |  | 78 |
| 18 |  |  | 70 |
| 19 |  |  | 69 |
| 20 |  |  | 65 |
| 21 |  |  | 74 |
| 22 |  |  | 73 |

## CONCLUSION

We have developed a novel procedure for the synthesis of dithiocarbamates having functional groups like methyl, methoxy, nitro, halo and $CF_3$ from commercially available anilines and prepared some various substituted anilines with morpholine, 1-Methyl piperazine, benzamide, cyclopropane carboxylic acid amide, 4-Chloro-benzamide etc. The present method can be used for the synthesis of biological active compounds and their diverse functionalized analogues. This methodology has several advantages including simple reaction conditions, operational, experimental simplicity combined with high functional group tolerance.

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