Received: 23 March 2019 | Revised: 14 May 2019 | Accepted: 21 May 2019

DOI: 10.1002/jccs.201900111

ARTICLE

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

# Multicomponent reaction of amine, carbon disulfide, and fluoronitrobenzene via nucleophilic attack on the fluorinated carbon for the synthesis of nitrophenyl methylcarbamodithioates

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In this paper, multicomponent reaction of amine, carbon disulfide and fluoronitrobenzene is reported for the synthesis of nitrophenyl methylcarbamodithioate derivatives. The method is based on the nucleophilic attack of the activated methylcarbamodithioate salt to fluoronitrobenzene. Several starting materials are tested and successfully produced the corresponding nitrophenyl methylcarbamodithioate. A possible mechanism for the reaction is suggested.

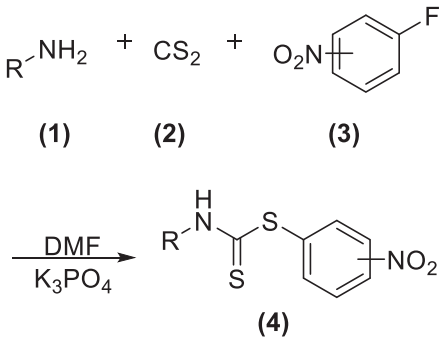
**KEYWORDS**

amine-$CS_2$ reaction, aromatic nucleophilic substitution, multicomponent reaction, nitrophenyl methylcarbamodithioate

## 1 | INTRODUCTION

Nucleophilic substitution reactions on benzene have been of high interest among researchers. Several reviews and books have focused on this class of reactions.[1–3] Due to this interest, several efforts have been focused on this strategy for the synthesis of a diversity of organic compounds.[4,5] This reaction has been used for the synthesis of fluorinated aromatic compounds[6,7] or a number of complex natural products such as martinellic acid[8] and (±)-coerulescine and (±)-horsfiline.[9] Among different substrates, which are used as a target for the nucleophilic attack on the aromatic ring, fluoronitrobenzene is extensively used because of its ability to undergo this reaction.[10] Nucleophilic substitution reaction of fluoronitrobenzene with 4-methoxyaniline in ionic liquids[11] and aromatic amines[12] has been used for the synthesis of more complex organic compounds.

Multicomponent reactions, containing amine and carbon disulfide, have attracted interests as a powerful tool for organic synthesis with high efficiency, high atom economy, short reaction time, and simple reaction setup.[13–15] This strategy has been used for the synthesis of several organic compounds using catalytic or multicomponent reactions. Gold-catalyzed functionalization reactions,[15] and multicomponent reactions[16] based on amine and $CS_2$ are of examples of this approach in the organic synthesis. This method is used for the synthesis of complex compounds, including dialkylaminocarbothioyl thioureas,[17] naphthoquinon-1,3-dithioles,[18] 2-thioxo-1, 3-thiazolanes,[19] 4-oxo-2-thioxo-1,3-thiazinanes,[20] 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one,[21] and stable ionic liquids.[22] Regarding the applicability of nucleophilic substitution reactions on benzene on the one hand, and multicomponent reactions based on amine and carbon disulfide on the other hand; in this article, we develop a novel method based on multicomponent reactions of amine and carbon disulfide including




**SCHEME 1** Synthesis of 4-nitrophenyl methylcarbamodithioate by multicomponent reaction of amines, carbon disulfide, and fluoronitrobenzene

fluoronitrobenzene for the synthesis of 4-nitrophenyl methylcarbamodithioate derivatives (Scheme 1).

## 2 | RESULTS AND DISCUSSION

The desired 4-nitrophenyl carbamodithioate derivatives were synthesized in a one-pot process by the reaction of amines, carbon disulfide, and fluoronitrobenzene under basic conditions. For finding the optimal reaction conditions, the reaction of pipyridine, $CS_2$, and fluoronitrobenzene in different solvents by using various bases was selected as the model reaction. The results of the optimization reactions are presented in Table 1. It can be observed that the desired product is obtained in the highest yield in dimethylformamide (DMF) as a solvent in the presence of $K_3PO_4$ base at 0°C. Performing the reaction in other solvents gave the product, but in lower isolated yields. In addition, lower products have been collected, when the reaction is performed in the presence of other bases.

**TABLE 1** Optimization of the reaction conditions

| No. | Solvent | Temperature (°C) | Base | Isolated yield (%) |
|---|---|---|---|---|
| 1 | DMF[a] | 0 | TEA[b] | 21 |
| 2 | DMF | 0 | $K_2CO_3$ | 62 |
| 3 | DMF | 0 | DABCO[c] | 36 |
| 4 | DMF | 0 | KOH | 49 |
| 5 | DMF | 0 | NaOH | 41 |
| 6 | DMF | 0 | $K_2CO_3$ | 85 |
| 7 | DMF | 25 | $K_2CO_3$ | 45 |
| 8 | DMF | 60 | $K_2CO_3$ | 37 |
| 9 | EtOH | 0 | $K_2CO_3$ | 27 |
| 10 | Toluene | 0 | $K_2CO_3$ | 34 |
| 11 | $H_2O$ | 0 | $K_2CO_3$ | 10 |
| 12 | $CH_2Cl_2$ | 0 | $K_2CO_3$ | 41 |

[a]Dimethylformamide.
[b]Trimethylamine.
[c](1,4-diazabicyclo[2.2.2]octane).

Having the optimized reaction conditions, the generality of the method is studied for the synthesis of nitrophenyl methylcarbamodithioate. For this purpose, fluoronitrobenzene derivatives, in which the nitro group is placed in different positions, were used. In addition, various amine derivatives were applied for the synthesis of the desired products. As can be seen in Table 2, all the starting materials have led to the desired products in high isolated yields.

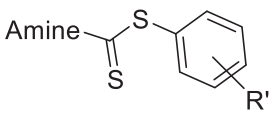
A possible mechanism was proposed for the synthesis of nitrophenyl methylcarbamodithioate derivatives based on previously reported mechanisms. The use of amines and carbon disulfide is an appropriate way for the synthesis of nitrogen-containing and sulfur-containing compounds. The mechanism of this reaction is well reviewed in the literature.[13,23] In addition, nucleophilic substitution on aromatic rings, bearing electron-withdrawing substituents, is previously well studied.[24,25] The suggested mechanism is presented in Scheme 2. In the first step, amine (1) is activated by the base. The activated amine reacts with carbon disulfide (2) to form the corresponding methylcarbamodithioate (5). The prepared methylcarbamodithioate reacts with fluoronitrobenzene (3) and forms 6-fluoro-nitro-6-([methylcarbamothioyl]thio) cyclohexa-2,4-dien-1-ide (6), leading to the corresponding nitrophenyl carbamodithioate (4).

## 3 | EXPERIMENTAL

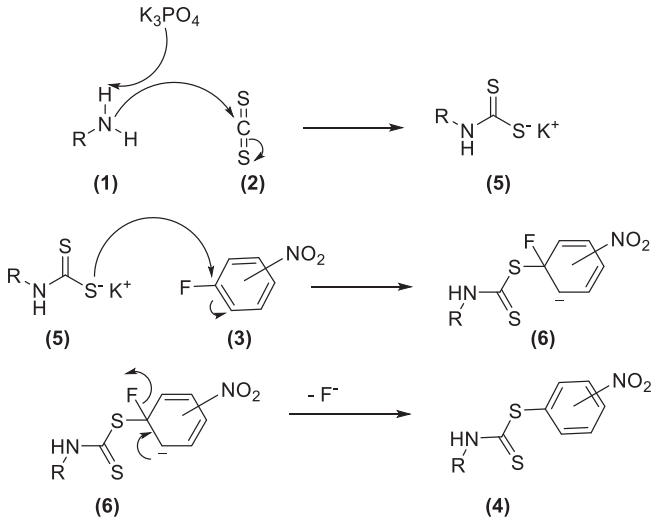
### 3.1 | General

All the chemicals were purchased from Sigma and Merck, and were used as received without any further purifications. Thin

**TABLE 2** Generality and scope of the method




| No. | Amine | *R′* | Isolated yield (%) |
|---|---|---|---|
| **4a** | Pipyridine | 3-$NO_2$ | 80 |
| **4b** | 2-methoxy aniline | 4-$NO_2$ | 72 |
| **4c** | 3-methoxypropan-1-amine | 4-$NO_2$ | 85 |
| **4d** | 2-methoxyethan-1-amine | 4-$NO_2$ | 90 |
| **4e** | 1-(2-methoxyphenyl)piperazine | 4-$NO_2$ | 85 |
| **4f** | Phenyl piperazine | 2-$NO_2$ | 75 |
| **4g** | 4-methylphenyl piperazine | 2-$NO_2$ | 75 |
| **4h** | Benzyl piperazine | 2-$NO_2$ | 73 |




**SCHEME 2** Suggested mechanism for the synthesis of nitrophenyl methylcarbamodithioate derivatives

layer chromatography (TLC) was carried out on silica gel 254 analytical sheets obtained from Fluka. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker FT- 500 spectrometers using tetramethyl silane (TMS) as internal standard in pure deuterated solvents. Chemical shiftsare given in the δ scale in parts per million (ppm) and singlet (s), doublet (d), triplet (t), multiplet (m) and doublets of doublet (dd) are recorded. The copies of 1HNMR and 13CNMR spectra are presented in appendix S1. The Infrared (IR) spectra were obtained on a Nicolet Magna FT-IR 550 spectrophotometer (potassium bromide disks). Purification of all products was conducted by recrystallization from ethanol.

## 3.2 | General procedure for the synthesis of 4-nitrophenyl carbamodithioate derivatives

Amine derivative (2 mmol) and $K_3PO_4$ (2 mmol) were dissolved in DMF (5 mL) and then carbon disulfide (3 mmol) was added. The reaction mixture was placed in an ice bath and stirred for 2 hr. Then, fluoronitrobenzene (2 mmol) was added to the reaction mixture and stirred for 12 hr. After the reaction completion, monitored by TLC, the precipitate was filtered and was recrystallized from ethanol and dried at reduced pressure.

## 3.3 | Spectral data

### 3.3.1 | 4-Nitrophenyl piperidine-1-carbodithioate (4a)

White solid; yield: 80%, mp = 205–207°C. IR (KBr): 3,060 ($C–H_{aromatic}$), 1,639 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 1.58–1.61 (m, 2H, $CH_2$), 2.79 (m, 4H, $2CH_2$), 4.22 (m,4H, $2CH_2$), 7.66 (d, $J$ = 8.0 Hz, 2H, $H_{2',6'}$), and 8.17 (d, $J$ = 8.0 Hz, 2H, $H_{3',5'}$) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 23.4, 25.1, 25.8, 51.0, 52.8, 123.3, 123.4, 130.2, 130.3, 145.4, 146.5, and 192.4 ppm; MS (70 eV): $m/z$ = 282 (M+).

### 3.3.2 | 4-Nitrophenyl (2-methoxyphenyl) carbamodithioate (4b)

White solid; yield: 72%, mp =226–230°C. IR (KBr): 3,060 ($C–H_{aromatic}$), 1,629 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 6.86 (t, $J$ = 7.5 Hz, 1H, H5′), 6.96 (d, $J$ = 8.0 Hz, 1H, H3′), 7.11 (d, $J$ = 7.5 Hz, 1H, H6′), 7.21 (t, $J$ = 8.0 Hz, 1H, H4′), 7.62 (d, $J$ = 8.0 Hz, 2H, H2,6), 8.17 (d, $J$ = 8.0 Hz, 2H, H3,5), and 10.15 (s, 1H, NH) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 55.2, 110.6, 110.8, 120.1, 120.4, 123.4, 123.5, 126.4, 127.8, 129.9, 130.0, 146.2, 146.4, 157.2, and 194.7 ppm; MS (70 eV): $m/z$ = 320 (M+).

### 3.3.3 | 4-Nitrophenyl (3-methoxypropyl) carbamodithioate (4c)

White solid; yield: 85%, mp =203–206°C. IR (KBr): 3,426 (N-H), 3,055 ($C–H_{aromatic}$), 1,607 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 1.80 (t, $J$ = 6.5, 2H, $CH_2$), 3.22 (m, 2H, S-$CH_2$), 3.61(t, $J$ = 6.5 Hz, 2H, O-$CH_2$), 3.99 (s, 3H, O-$CH_3$), 7.63 (d, $J$ = 8.0 Hz, 2H, $H_{2,6}$), 8.17 (d, $J$ = 8.0 Hz, 2H, $H_{3,5}$), and 10.07 (s, 1H, $NH_{Thioamide}$) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 27.5, 44.5, 57.8, 69.3, 123.4, 123.5, 130.0, 130.1, 146.2, 146.5, and 194.7 ppm; MS (70 eV): $m/z$ = 286 (M+).

### 3.3.4 | 4-Nitrophenyl (2-methoxyethyl) carbamodithioate (4d)

White solid; yield: 85%, mp =198–200°C. IR (KBr): 3,026 ($C–H_{aromatic}$), 1,610 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 3.52 (t, $J$ = 5.5, 2H, S-$CH_2$), 3.74 (t, $J$ = 5.5 Hz, 2H, O-$CH_2$), 3.99 (s, 3H, O-$CH_3$), 7.63 (d, $J$ = 8.0 Hz, 2H, $H_{2,6}$), 8.17 (d, $J$ = 8.0 Hz, 2H, $H_{3,5}$), and 9.71 (s, 1H, $NH_{Thioamide}$) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 46.8, 57.8, 57.9, 68.8, 123.4, 123.5, 130.0, 130.1, 146.2, 146.5, and 195.3 ppm; MS (70 eV): $m/z$ = 272 (M+).

### 3.3.5 | 4-Nitrophenyl 4-(2-methoxyphenyl) piperazine-1-carbodithioate (4e)

White solid; yield: 85%, mp = 210–215°C. IR (KBr): 3,053 ($C–H_{aromatic}$), 1,610 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 3.87 (s, 3H, O-$CH_3$), 4.10 (m, 4H, N–$CH_{2\text{-piperazine}}$), 4.51 (m, 4H, N–$CH_{2\text{-piperazine}}$), 6.93 (d, $J$ = 7.0 Hz, 1H, $H_{3'}$), 7.03 (d, $J$ = 7.5 Hz, 1H, $H_{6'}$), 7.43 (t, $J$ = 7.5 Hz, 1H, $H_{5'}$), 7.57 (t, $J$ = 7.0 Hz, 2H, $H_{4'}$), 7.86 (d, $J$ = 7.5 Hz, 2H, $H_{2,6}$), and 8.01 (d, $J$ = 7.5 Hz, 2H, $H_{3,5}$) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 50.2, 51.9,

55.4, 111.4, 118.5, 121.1, 123.8, 124.9, 125.0, 128.5, 133.0, 133.4, 140.0, 152.2, and 195.9 ppm; MS (70 eV): *m/z* = 389 (M+).

### 3.3.6 | 2-Nitrophenyl 4-phenylpiperazine-1-carbodithioate (4f)

White solid; yield: 75%, mp =203–205°C. IR (KBr): 3,062 ($C–H_{aromatic}$), 1,610 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 4.09 (m, 4H, $N–CH_{2\text{-piperazine}}$), 4.46 (m, 4H, $N–CH_{2\text{-piperazine}}$), 6.84–6.99 (m, 5H, Ph), 7.43 (t, $J$ = 7.5 Hz, 1H, $H_5$), 7.57 (t, $J$ = 7.0 Hz, 2H, $H_4$), 7.85 (d, $J$ = 7.5 Hz, 2H, $H_6$), and 8.01 (d, $J$ = 7.5 Hz, 2H, $H_3$) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 49.9, 52.9, 115.7, 115.9, 118.4, 120.5, 128.9, 133.0, 133.4, 141.1, 141.5, 147.7, and 195.2 ppm; MS (70 eV): *m/z* = 359 (M+).

### 3.3.7 | 2-Nitrophenyl 4-(*p*-tolyl)piperazine-1-carbodithioate (4g)

White solid; yield: 75%, mp =236–240°C. IR (KBr): 3,037 ($C–H_{aromatic}$), 1,608 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 2.27 (s, 3H, $CH_3$), 4.07 (m, 4H, $N–CH_{2\text{-piperazine}}$), 4.46 (m, 4H, $N–CH_{2\text{-piperazine}}$), 6.81 (d, $J$ = 8.0 Hz, 2H, $H_{3',5'}$), 7.09 (d, $J$ = 8.0 Hz, 2H, $H_{2',6'}$), 7.43 (t, $J$ = 7.5 Hz, 1H, $H_5$), 7.56 (t, $J$ = 7.0 Hz, 2H, $H_4$), 7.85 (d, $J$ = 7.5 Hz, 2H, $H_6$), and 8.01 (d, $J$ = 7.5 Hz, 2H, $H_3$). ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 20.4, 49.4, 52.1, 116.8, 125.1, 128.6, 129.8, 130.3, 133.0, 133.4, 148.1, and 196.3 ppm; MS (70 eV): *m/z* = 373 (M+).

### 3.3.8 | 2-Nitrophenyl 4-benzylpiperazine-1-carbodithioate (4h)

Purple solid; yield: 65%, mp =225–232°C. IR (KBr): 3,035 ($C–H_{aromatic}$), 1,606 (C=S) $cm^{-1}$; $^1H$ NMR (DMSO-d6, 500 MHz): $\delta$ = 4.09 (m, 4H, $N–CH_{2\text{-piperazine}}$), 4.45–4.52 (m, 4H, $N–CH_{2\text{-piperazine}}$), 4.92 (s, 2H, $CH_2$), 7.23–7.30 (m, 5H, Ph), 7.43 (t, $J$ = 7.5 Hz, 1H, $H_5$), 7.56 (t, $J$ = 7.0 Hz, 2H, $H_4$), 7.85 (d, $J$ = 7.5 Hz, 2H, $H_6$), and 8.01 (d, $J$ = 7.5 Hz, 2H, $H_3$) ppm; $^{13}C$ NMR (DMSO-d6, 125 MHz): $\delta$ = 42.5, 48.7, 52.1, 116.3, 120.6, 125.0, 128.6, 129.3, 133.0, 133.1, 133.4, 150.2, and 196.1 ppm; MS (70 eV): *m/z* = 373 (M+).

## 4 | CONCLUSIONS

In this article, a novel method is reported for the synthesis of nitrophenyl methylcarbamodithioate derivatives, based on the multicomponent reaction of amine, carbon disulfide, and fluoronitrobenzene. Nitrophenyl methylcarbamodithioate derivatives were synthesized by the nucleophilic substitution reaction between the activated methylcarbamodithioate salt and fluoronitrobenzene. The activated methylcarbamodithioate salt is prepared by the reaction of amine with carbon disulfide in the presence of $K_3PO_4$ as a base. Several starting materials were tested and the corresponding nitrophenyl methylcarbamodithioate was successfully produced, which proved the generality of the method.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Bahadorikhalili S, Mohammadi S, Asadi M, Barazandeh M, Mahdavi M. Multicomponent reaction of amine, carbon disulfide, and fluoronitrobenzene via nucleophilic attack on the fluorinated carbon for the synthesis of nitrophenyl methylcarbamodithioates. *J Chin Chem Soc*. 2019; 1–5. https://doi.org/10.1002/jccs.201900111