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Synthesis of 3-(substitutedthiocarbamide)-aniline derivatives from di-tert-butyl dicarbonate (BoC) protected 3-chloroaniline

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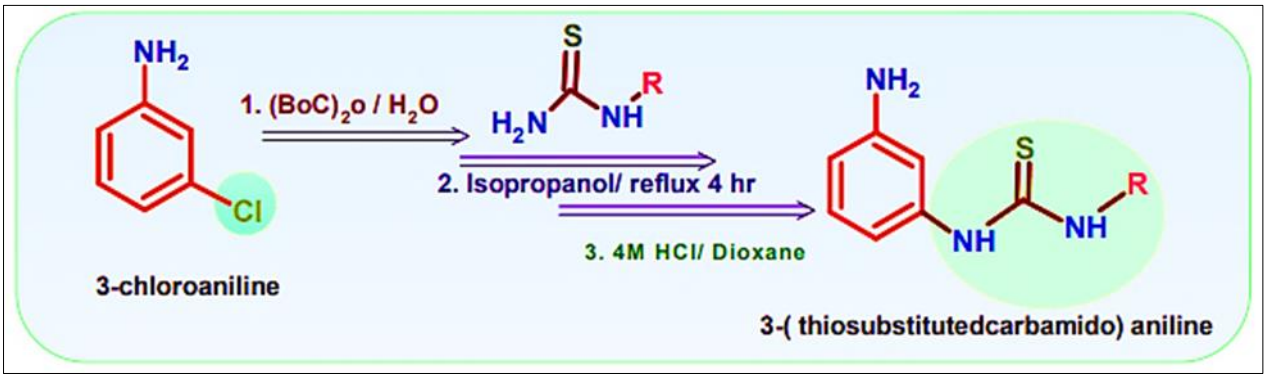
Abstract

Synthesis of substituted thiocarbamide derivatives is important in the fields of medicinal, agricultural, chemical, and pharmaceutical. Thiocarbamides are commonly utilized as starting materials for several organic synthetic processes and have been studied in search for easy and effective methods of chemical synthesis. In the existing research work, 3-chloroaniline was protected by a di-tert-butyl dicarbonate (BoC) protecting agent. Substituted thiocarbamide derivatives were synthesized using condensation of various substituted thioureas with amino group-protected 3-chloroaniline. The structures of all compounds of 3(substitutedthiocarbamido)-aniline were characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR, LCMS and CHNS elemental analysis.

Keywords: 3-chloroaniline; Di-tert-butyldicarbonate; Thiocarbamide derivatives; Protecting agent

Graphical Abstract



1. Introduction

Thiourea, often known as thiocarbamide, is a chemical compound having the formula $SC(NH_2)_2$ with a molecular weight of 76.12 g/mol [1,5]. The class of chemicals known as substituted thiocarbamide has the generic formula (R_1R_2N) (R_3R_4N) CS [6,8]. Thiocarbamides are soluble in organic solvents that are polar protic and aprotic, such as acetone and dimethyl sulfoxide. It is also soluble in water, but insoluble in non-polar solvents. Because of the difference in electronegativity between sulfur and nitrogen, the chemical properties of thiourea change significantly. Thiocarbamides show higher acidity and are stronger hydrogen bond donors [9, 12]. Being able to be involved with bonding with hydrogen, which is able to be further adjusted by proper nitrogen atom substitution, is critical for a wide range of uses

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for this class of organic molecules [13, 15]. Thiocarbamide compounds serve as building blocks in the synthetic process of heterocyclic compounds [16, 19]. As a result of its propensity to undergo structural changes, the thiourea moiety has primarily been synthesized [20, 22]. Thiocarbamide is an ideal precursor for the synthesis of numerous novel compounds due to its reactive primary amine groups [23, 26]. The importance of thiocarbamide derivatives in medicine is widely recognized, and research into simple and efficient techniques for the synthesis of molecules with heterocyclic rings has opened up a new dimension, allowing for the development of synthetic routes with the potential for use in the creation of medications [27, 31].

2. Material and Method

2.1. General

All chemicals are used of analytical grade. The melting points were determined on an open capillary tube and are uncorrected. Progress of the reaction was using thin-layer chromatography (TLC) in petroleum ether: ethyl acetate (4.5: 0.5) solvent system. IR spectra were recorded using FTIR Perkin Elmer (400 MHz) Spectrophotometer KBr disc.^{1}H NMR spectra were recorded using Brucker Avance (500 MHz) NMR Spectrometer instrument using $CDCl_3$ solvent and TMS as an internal standard, LCMS spectra were recorded by Waters Corporation (Alliance II-2795) micro mass spectrometer and CHNS analysis were done by Thermo Scientific (Flash 2000) elemental analyzer.

2.2. Protection of amino group of 3-chloroaniline using di-tert-butyldicarbonate (BoC): The amino group in (**1**) 3-chloroaniline (5 mmol) was first protected by using di-tert-butyldicarbonate (5 mmol). This reaction mixture was magnetically stirred for about 4 hrs. in water media to yield (**2**) BoC-protected 3-chloroaniline.

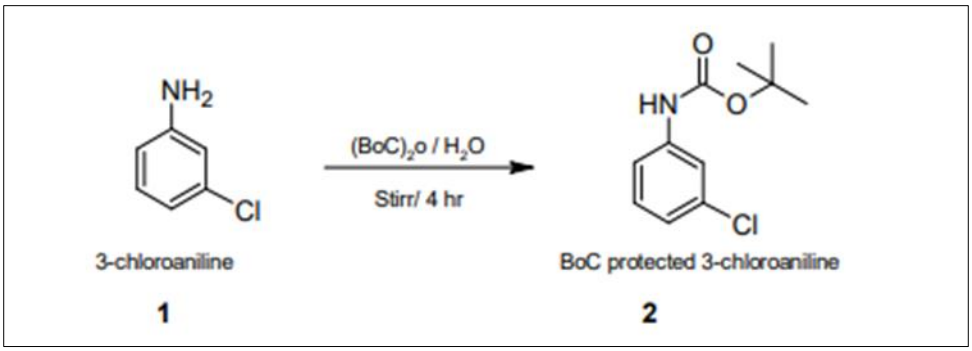

Figure 1 Protection of amini group in 3-chloraaniline

Spectral data of BoC-protected 3-chloroaniline compound: (2)

tert-butyl (3-chlorophenyl) carbamate (IUPAC Name), White solid,

M.F. $C_{11}H_{14}ClNO_2$, M.P.: 70-72 ^{0}C,

I.R. (KBr pellets, ν in cm^{-1}): (N-$H_{stret.}$) 3414.32, (C-H) 2934.62, (C=O) 1690.57, (C=C) 1616.68, 1540.31, (C-N) 1482.32, (C-Cl) 1283.32, (C-O) 1158.42, (Ar C-H_{bend}) 852.19, 772.99, (N-H_{bend}) 620.94

^{1}H-NMR (500MHz, $CDCl_3$, δ in ppm): 1.50 (s, 9H, -CCH_3), 6.77 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 6.98 (dt, 1H, Ar-H), 7.15 (d, 1H, Ar-H), 7.51 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 28.29 (3CH_3), 77.03 ($CDCl_3$), 81.02 (CCH_3), 116.40, 118.52, 123.02, 129.90, 134.74, 139.57 (Ar-C), 152.42 (C=S)

CHNS Analysis: C, H, N % calc. 57.03, 6.15, 6.06. found 58.03, 6.20, 6.15

Mass: m/z (M^{+}) 228.05, M.W. 227.69

2.2. Synthesis of BoC protected 3-(substitutedthiocarbamide)-aniline derivatives

(**2**) BoC-protected 3-chloroaniline (5 mmol) reflux about 5 hrs. with (**a-e**) substituted thiourea compounds (5 mmol) in the presence of organic solvent isopropanol gives (**2a-e**) amino group protected 3-sustitutedthiocarbamido aniline derivative.

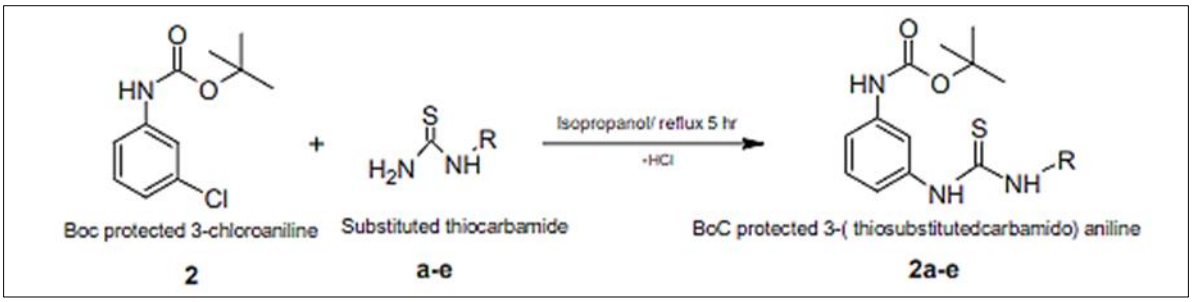

Figure 2 Synthesis of BoCprotected 3-(thiosustitutedcarbamido)aniline compound

2.4. Synthesis of BoC deprotected 3-(substitutedthiocarbamide) aniline derivatives

Finally, (**3a-e**) white solid of 3-sustitutedthiocarbamido aniline synthesis was finished by deprotection of the amino group, stirring it with 4M HCl in methanol for about 2 hr. Then pour in ice water under vigorous stirring. Products were collected by filtration, washed with cold water and dried. Further recrystallized using ethyl alcohol for further characterization of compounds.

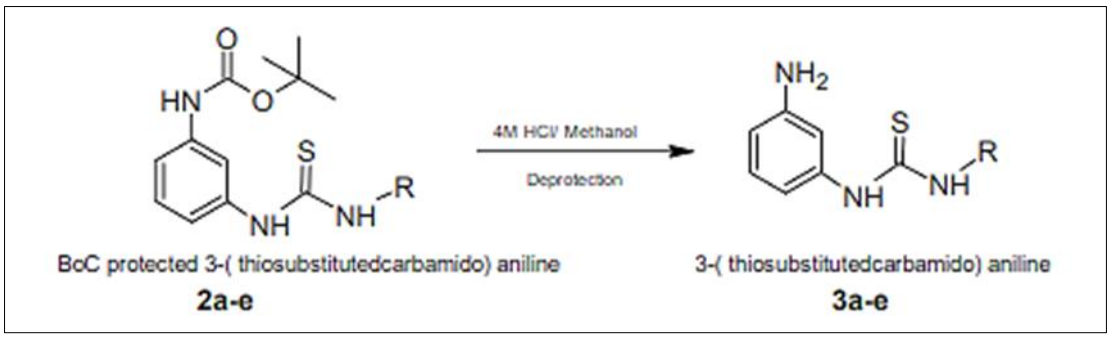

Figure 3 Deprotection of Boc from 3-(thiosustitutedcarbamido) aniline compound

2.3. Spectral data of 3-(substitutedthiocarbamide) aniline derivatives

2.3.1. ***(3a)*** *N-(3-aminophenyl) thiourea (IUPAC Name)*

M.F. $C_7H_9N_3S$, M.P.= 82-84 ^{0}C

I.R. (KBr pellets, ν/cm^{-1}): (N-H_{stret}) 3282, (Ar-H) 2976, (Ar C=C) 1688, (C=S) 1282, (C-N) 1153, (p-Ph) 851

^{1}H NMR (500MHz, $CDCl_3$, δ in ppm): 6.69 (s, 1H, Ar-H), 6.98 (dt, 1H, Ar-H), 7.15 (dt, 2H, Ar-H), 7.51 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 77.04 ($CDCl_3$), 116.41, 118.53, 123.02, 129.90, 134.73, 139.58 (Ar-C), 152.44 (C=S)

CHNS Analysis: C, H, N, S (%) calc. 50.27, 5.42, 25.13, 19.17, found 58.34, 6.16, 6.20, 0.054

Mass: m/z=167.05, M.W.= 167.23

2.3.2. ***(3b)*** *N-(3-aminophenyl)-N'-phenyl thiourea*

M.F. $C_{13}H_{13}N_3S$, M.P.= 72-74 ^{0}C

I.R. (KBr pellets, ν/cm^{-1}): (N-H_{stret}) 3282, (Ar-H) 2979, (Ar C=C)1689, (C=S)1282, (C-N) 1153, (p-Ph) 851

^{1}H NMR (500MHz, $CDCl_3$, δ in ppm): 6.68 (s, 1H, Ar-H), 6.98 (dt, 1H, Ar-H), 7.15 (dt, 2H, Ar-H), 7.25 (d, 1H, Ar-H), 7.51 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 77.04 ($CDCl_3$), 116.38, 118.51, 123.03, 129.90, 134.75, 139.57 (Ar-C), 152.40 (C=S)

CHNS Analysis: C, H, N, S (%) calc. 64.17, 5.39, 17.27, 13.18, found 58.25, 6.07, 6.26, 0.048

Mass: m/z= 243.08, M.W.= 243.33

2.3.3. ***(3c)*** *N-(3-aminophenyl)-N'-(prop-2-en-1-yl) thiourea*

M.F. $C_{10}H_{13}N_3S$, M.P.= 76-78 ^{0}C

I.R. (KBr pellets, ν/cm^{-1}): (N-H_{stret}) 3282, (Ar-H) 2979, (Ar C=C)1688, (C=S)1284, (allyl broad stret.) 1711, (C-N) 1153, (p-Ph) 851

^{1}H NMR (500MHz, $CDCl_3$, δ in ppm): 6.56 (s, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 7.19 (dt, 1H, Ar-H), 7.28 (d, 1H, Ar-H), 7.53 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 77.03 ($CDCl_3$), 116.40, 118.53, 123.02, 129.90, 134.73, 139.58 (Ar-C), 152.44 (C=S)

CHNS Analysis: C, H, N, S (%) calc. 57.94, 6.32, 20.27, 15.47, found 58.39, 5.89, 6.18, 0.051

Mass: m/z=207.08, M.W.= 207.23

2.3.4. ***(3d)*** *N-(3-aminophenyl)-N'-methyl thiourea*

M.F. $C_8H_{11}N_3S$, M.P.= 81-83 ^{0}C

I.R. (KBr pellets, ν/cm^{-1}): (N-H_{stret}) 3382, (Ar-H) 2976, (Ar C=C)1689, (C=S)1243, (C-N) 1153, (p-Ph) 851

^{1}H NMR (500MHz, $CDCl_3$, δ in ppm): 6.86 (s, 1H, Ar-H), 7.01 (d, 1H, Ar-H), 7.15 (dt, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.51 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 77.01 ($CDCl_3$), 116.35, 118.35, 123.01, 129.85, 134.70, 139.75 (Ar-C), 152.40 (C=S)

CHNS Analysis: C, H, N, S (%) calc. 53.01, 6.12, 23.18, 17.69 found 58.38, 6.17, 6.30, 0.051

Mass: m/z= 181.07, M.W.= 181.26

2.3.5. ***(3e)*** *N-(3-aminophenyl)-N'-(4-chlorophenyl) thiourea*

M.F.: $C_{13}H_{12}ClN_3S$, M.P.: 75-77 ^{0}C

I.R. (KBr pellets, ν/cm^{-1}): (N-H_{stret}) 3279, (Ar-H) 2990, (Ar C=C)1688, (C=S)1243, (C-N) 1153, (p-Ph) 851

^{1}H NMR (500MHz, $CDCl_3$, δ in ppm): 6.68 (s, 1H, Ar-H), 6.98 (dt, 1H, Ar-H), 7.15 (dt, 2H, Ar-H), 7.25 (d, 1H, Ar-H), 7.51 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 77.04 ($CDCl_3$), 116.38, 118.52, 123.05, 129.91, 134.74, 139.58 (Ar-C), 152.41 (C=S)

CHNS Analysis: C, H, Cl, N, S (%) calc. 56.21, 4.35, 12.76, 15.13, 11.54, found 58.20, 6.05, 6.20, 0.042

Mass: m/z=277.04, M.W.= 277.77

Table 1 Synthesis of 3-(substitutedthiocarbamide) aniline from substituted thioureas

Entry	Substituted thiourea	Derivative No.	M.P. (^{0}C)	Yield (%)
1	H	3a	82-84 ^{0}C	76%
2	Phenyl	3b	72-74 ^{0}C	72%
3	Allyl	3c	76-78 ^{0}C	70%
4	Me	3d	81-83 ^{0}C	73%
5	p-Cl	3e	75-77 ^{0}C	64%

3. Result and Discussion

Novel compounds of thiocarbamide derivatives were synthesized from aromatic aniline and different substituted thiourea compounds. Spectral characterization shows that the successful formation of resulting target derivatives was completed.

The IR spectra of 3a to 3e derivatives presented the successful formation of derivatives. The presence of N-H stretching frequencies was observed at 3314-3282 cm^{-1} broad absorption bands. The absorption attributed to Ar-H at 2979-2989 cm^{-1}, while absorption bands at 1688-1589 cm^{-1} due to aromatic C=C bond. The absorption bands were observed at 1282-1243 cm^{-1} due to C=S stretching frequency confirmed the formation of thiourea in compounds. The aromatic C-H bending absorption bands at 851-770 cm^{-1} were observed.

Further formation of 3a to 3e derivatives was supported by ^{1}H and ^{13}C NMR spectra. Multiple peaks observed at ^{1}H NMR spectra from 6.69-7.15 ppm were assigned to aromatic protons. Singlet peak ascribed to CSNH observed at 7.51-7.53 ppm indicate formation of thiocarbamide. The 13C NMR spectra at 152.4 ppm supported to C=S formation. The multiple resonance frequency observed at 116.4 to 139.5 ppm were assigned to aromatic carbons in the compounds. 77.04 ppm observed to carbon of CDCl3 solvent.

4. Conclusions

In the present research work, thiocarbamide derivatives were successfully synthesized using an amine group-protected di-tert-butyl dicarbonate (BoC) 3-chloroaniline with substituted thiourea compounds. After that, the deprotection of di-tert-butyl dicarbonate (BoC) from the amine group to gives novel compounds of thiocarbamide derivatives. Spectrometric Characterization using ^{1}H and ^{13}C NMR, IR, LCMS and CHNS analysis has shown the successful formation of novel thiocarbamide derivatives.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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