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Synthesis and mass spectral study of thiourea and thiocarbamiate derivatives from phthalimidoacyl isothiocyanates

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Abstract : Phthalimidoacyl isothiocyanates **(1a,b)** reacted with aromatic amines or alcohols to give thiourea derivatives **(4a-g)** or thiocarbamic acid ester derivatives **(5a,b)** respectively. The electron impact ionization mass spectra of the synthesized compounds were studied. The MS peaks obtained correspond very well with their fragmentation patterns.

Keywords : Thiourea derivatives; Thiocarbamate derivatives; Mass spectroscopy.

INTRODUCTION

Thiourea and its related molecules are important as structural components and as intermediates in agricultural and pharmaceutical chemistry[1]. Literature also states that the antiviral[2] and antibacterial[3] activities of thiourea derivatives are due to the presence of the –NH-C(S)-NH- function in the molecule and the changes in this activity depend on the nature of its substituents. Moreover, these compounds have attracted considerable attention for their potential use as binding units for artificial receptors in supramolecular chemistry[4]. Furthermore, in the field of advanced material chemistry, thioureas can serve as a useful scaffold by connecting them to electroluminescent organic dyes[5]. Recently, they have been investigated as H-bonding additives for organocatalytic carbonyl-ene reactions[6].

RESULTS AND DISCUSSION

The reaction of phthalimidoacyl isothiocyanate **(1a,b)**[7], with ammonia solution produced the acid amides **(3a,b)** via the intermediate phthalimidoacyl thiourea derivatives **(2a,b)**. The formation of the compounds **(3a,b)** was confirmed authentically by their synthesis from the corresponding acid chlorides and ammonia solution. The mechanism of formation of **(3a,b)** probably due to loss of HN=C=S molecule, as shown in scheme 1. The structures of compounds **(3a,b)** were proven by their micro-analytical and spectral data. Thus, their IR spectra showed the presence of υ (NH_2) in the region 3438-3413 cm^{-1}, and 3317-3303 cm^{-1}, doublet in the region 1778-1771 cm^{-1} and 1710 cm^{-1} for coupling carbonyl band of cyclic imides and υ (C=O) of amide in the region 1686-1678 cm^{-1}. In the ^{1}HNMR spectrum of **(3a)** the signal due to CH_2 was recorded at 4.18 ppm integrating two proton, a multiplet in the region 7.86-7.94 ppm integrating four aromatic protons, as well as a brood two singlets due to NH protons at 7.30 and 7.73 ppm that were exchangeable with D_2O. ^{13}C NMR of **(3a)** showed six peaks related to

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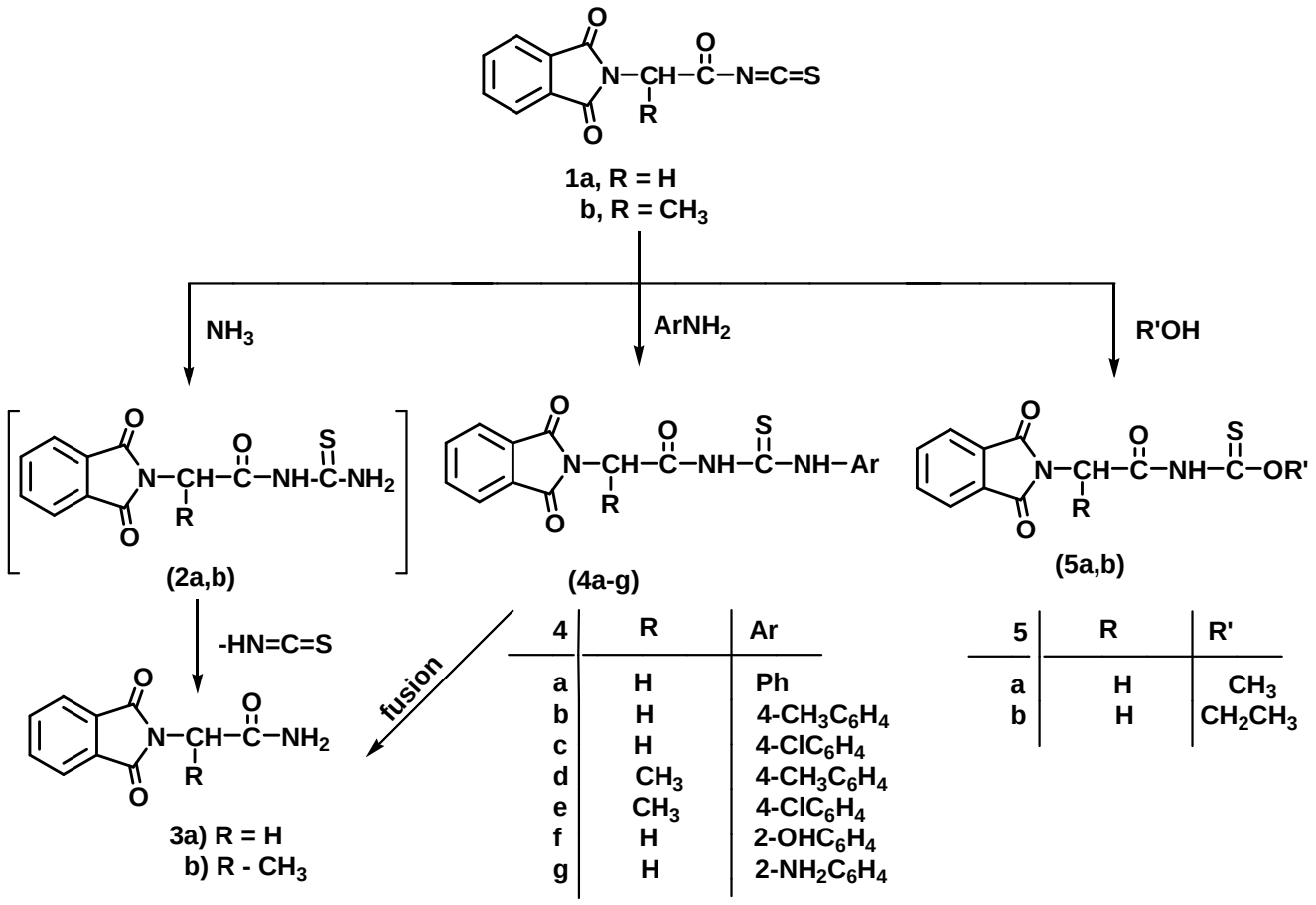

Scheme 1

carbon atoms, including signal at 40.13 ppm for CH_2, signals in the rang 123.65 - 134.65 ppm for aromatic carbon atoms and two signal at 167.77 and 168.17 ppm corresponding to carbon atoms of C=O groups. Further proof for the assigned structures of compounds **(3a,b)** were gained from their MS which revealed their molecular ion peaks.

Treatment of isothiocyanates **(1a,b)** with aromatic amines, namely aniline, *p*-toluidine, and *p*-chloroaniline produced the corresponding thiourea derivatives **(4a-e)** in good yields. The formation of compounds **(4a-e)** is based on nucleophilic addition of amino group to isothiocyanate carbon atom. On the other hand, heating compounds **(4a-e)** above their melting points afforded amides **(3a)** and **(3b)** respectively. The structures of compounds **(4a-e)** were elucidated by their micro-analytical and spectral data. The IR spectral data of compounds **(4a-e)** showed the presence of absorption bands correlated with υ (NH), doublet for coupling carbonyl band of cyclic imides, υ (C=O) of amide and, υ (C=S) of thiourea. Their ^{1}HNMR spectra displayed signal due to alkyl protons, aromatic protons, as well as a brood NH protons in the downfield region that were exchangeable with D_2O. Further support for the assigned structures of compounds **(4a-e)** were got from their MS which revealed their molecular ion peaks excepting compounds **(4b)** and **(4c)**. The MS peaks obtained for **(4b)** and **(4c)** correspond very well with their fragmentation pattern.

Similarly, the reaction of phthalimidoacetyl isothiocyanate **(1a)** with the *o*-aminophenol, *o*-phenylenediamine or primary alcohols, like methanol and ethanol in acetonitrile furnished thiourea derivatives **(4f,g)**. and thiocarbamate derivatives **(5a,b)** respectively. The structures of compounds **(4f,g)** and **(5a,b)** were established by their micro-analytical and spectral data

MASS SPECTROSCOPY

TABLE 1 list the m/z (relative abundance %) values of the principal fragments of the synthesized com-

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pounds. The MS of compounds **(3a,b)** showed their molecular ions and peaks corresponding to fragmentation pattern. The main fragmentation pathway of compound **(3a)** is summarized in scheme 2. The detection of both complementary fragments of the cleavage and rearrangement processes is attributed to their comparable ionization potentials. From the study of the mass spectra of compound **(3a)**, it was found that the molecular ion had fragmented via two main routes. Route a) involves loss of water to give phthalimidonitrile ion m/z 186, which loss CN to give an ion m/z 160. Route b), the predominant one, which, involves loss of HNCO to give N-methyl phthalimide ion as a base peak m/z 161, which underwent further fragmentation as shown in scheme 2.

It was found that the molecular ions of compounds **(4a-e)** fragmented further and involved two main routes, except compounds **(4a)** and **(4b)**. Fragmentation pattern of compound **(4c)** is illustrated as representative example (scheme 3). Unfortunately, the MS of compound **(4c)** did not show the molecular ion peak; however, the obtained MS peaks correspond very well with its fragmentation pattern. Thus, route a) showed N-pthalimidoacetamide ion at m/z 204 and *p*-chlorophenyl isothiocyanate ion at m/z 169/171. Route b) gave the height recorded ion at m/z 314/316 by loss of HNCS, which split into two ions at m/z 188 and m/z 126/128, the former ion loss CO molecule to give the base peak at m/z 160.

The fragmentations process of compounds **(4a,b)** is based mainly on one route that involved the formation of a common ion at m/z 188 that loss CO molecule to give an ion m/z 160 and ions corresponded mono-substituted thiouredo moiety at m/z 151 and 165 respectively. On other hand, the MS of both compounds **(4f)** and **(4g)** didn't reveal the molecular ion peaks, instead they are subjected to the same fragmentation process since they give ion m/z 278 and ion m/z 277 respectively via loss of H_2S molecule followed by HNCO. The obtained ions further underwent fragmen-

TABLE 1 : EI mass spectra (70 eV) of compounds (3-5) m/z (relative intensity, %).

No.	M^+	ions
3a	$[C_{10}H_8N_2O_3]^{\cdot+}$	186 (0.5), 161 (100), 160 (89), 147 (1), 133 (10.6), 132 (6.6), 118 (1.3), 117 (3.7),
	204 (1.14)	104 (14), 90 (1.4), 76 (9.7). 50 (2.2).
3b	$[C_{11}H_{10}N_2O_3]^{\cdot+}$	202 (0.4),175 (18), 174 (100), 147 (22), 146 (3.8), 133 (2.9), 132 (2.4), 104 (10.8),
	218 (0.8)	76 (24.5), 50 (24.6).
4a	$[C_{17}H_{13}N_3O_3S]^{\cdot+}$	188 (3.9), 160 (26.8), 151 (4.2)146 (4.5), 135 (100), 133 (2.2) 132 (2.4), 118 (1.1),
	339 (2.2)	104 (5.8), 93 (15.9), 91 (3.3), 77 (60), 76 (8.8), 50 (13.5).
4b	$[C_{18}H_{15}N_3O_3S]^{\cdot+}$	188 (16.4), 165 (1.1), 149 (43.2),146 (15), 133 (2.7), 132 (1.9), 118 (1.7), 107 (80),
	353 (0.0)	106 (100), 105 (3.7), 91 (25.3), 79 (8.4), 78 (12.8), 64 (2.3), 50 (10.1).
4c	$[C_{17}H_{12}ClN_3O_3S]^{\cdot+}$	316 (0.5), 314 (1.5), 204 (0.7), 188 (3.9), 187 (0.5), 185 (0.5), 171 (12.7), 169 (32.3),161 (86.5),
	373 (0.0)	160 (100), 133 (10), 129 (1.9), 128 (1.5), 127 (5.5), 126 (1), 125 (1.4), 104 (22), 76 (26.9)
4d	$[C_{19}H_{17}N_3O_3S]^{\cdot+}$	220 (14), 202 (6.5), 193 (12), 174 (100), 165 (4.6), 149 (35.3), 147 (21), 133 (5.8),
	367 (13.4)	132 (16), 106 (22), 105 (5) 104 (17), 91(30), 76 (26.9), 50 (25).
4e	$[C_{18}H_{14}ClN_3O_3S]^{\cdot+}$	215 (2.1), 213 (5.2), 202 (7.9), 187 (1.1), 185 (1.2), 174 (100), 171 (7.6), 169 (22),
	389 (3.3)	146 (2.8), 133 (4), 132 387 (6.6) (15.3), 104 (14), 76 (27), 50 (25).
4f	$[C_{17}H_{13}N_3O_4S]^{\cdot+}$	278 (3), 188 (22.2), 160 (100),146 (9.8), 133 (7), 132 (3.9), 118 (1.4), 104 (17.9),
	355 (0.0)	90 (2.2), 76 (15.7), 64 (10.4)
4g	$[C_{17}H_{14}N_4O_3S]^{\cdot+}$	277 (3.4), 188 (2.6), 162 (10.4), 160 (100), 150 (62.5), 133 (11.8), 132 (8), 118 (7.8),
	354 (0.0)	105 (10.8), 104 (17.8), 77 (10.8), 76 (12).
5a	$[C_{12}H_{10}N_2O_4S]^{\cdot+}$	219 (11.9), 188 (14.7), 160 (100), 146 (1.2), 133 (4.2), 132 (22.4), 118 (1.2), 104 (11),
	278 (2.4)	90 (2.2), 76 (4.9), 59 (1.7), 50 (10.2).
5b	$[C_{13}H_{12}N_2O_4S]^{\cdot+}$	233 (10.5), 188 (3.5), 160 (100), 146 (2.5), 133 (3.5), 132 (5.6), 118 (3.7), 104 (11.3),
	292 (3.0)	90 (1), 76 (11.3), 50 (6.2).

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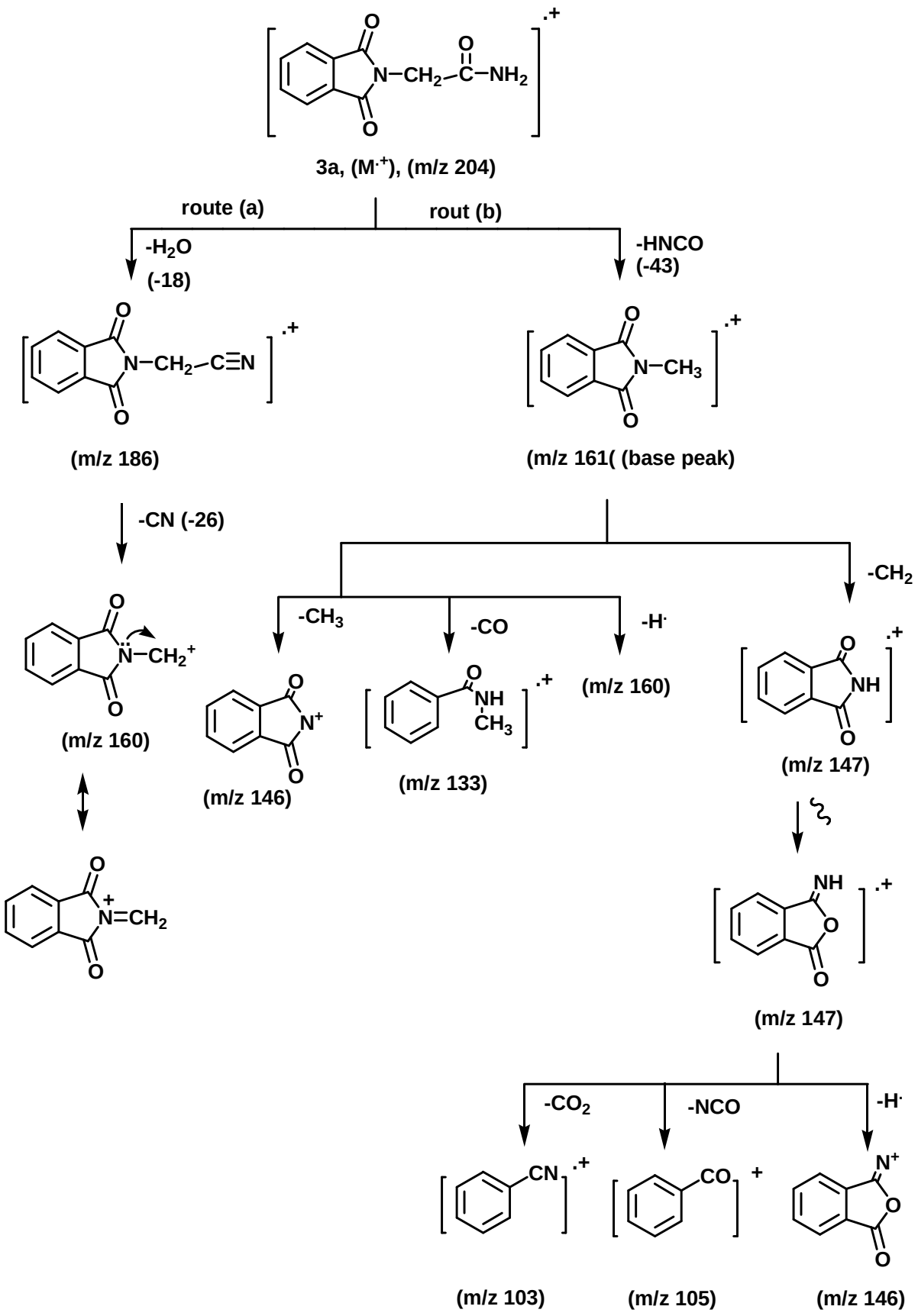

Scheme 2

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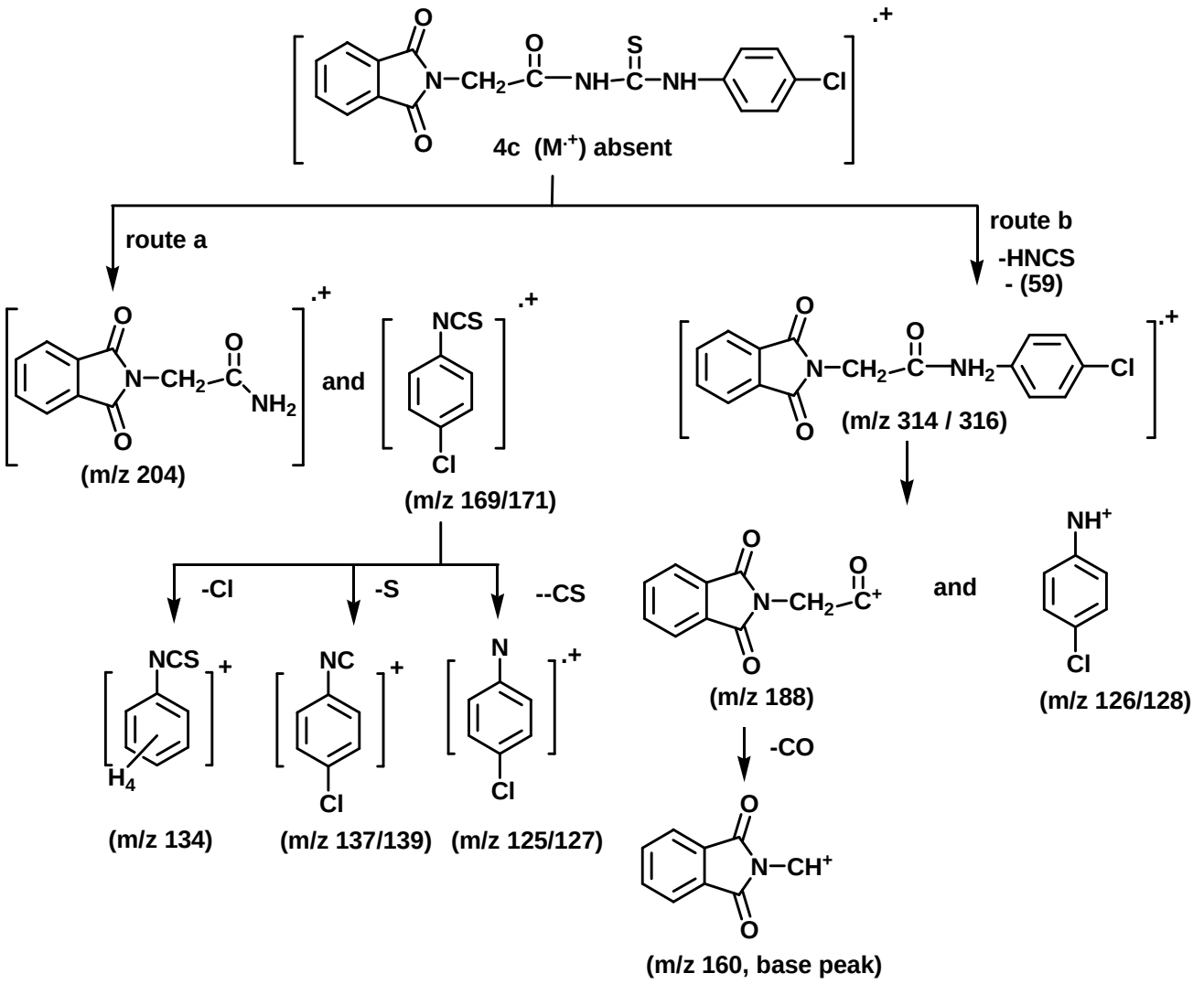

Scheme 3

tation to give ion m/z 188 that upon loss of CO molecule produced the ion m/z 160 as a base peak. As shown in TABLE 1, compounds **(5a)** and **(5b)** show relatively small molecular ions that loss HNCS to give ion m/z 219 and ion m/z 233 respectively. Both the ions m/z 219 and m/z 233 fragmented into ion m/z 160 as a base peak and an ion ROCO at m/z 59 and m/z 73 respectively, the second route came from loss of an ion OR to obtain the common ion m/z 188 that further loss CO to give the base peak at m/z 160 (scheme 4)

EXPERIMENTAL

General

All melting points of the reaction products were determined in open capillary tubes on a Gallenkemp melting point apparatus and are uncorrected. The elemental analysis was carried out by using Perkin-Elemer 2400 CHN elemental analyzer. The infrared spectra recorded on Perkin-Elemer Modle 297 Infra-red spectrometer and Pye Unicam SP1200 spectrophotometer using KBr wafer technique. The ^{1}HNMR and ^{13}CNMR were measured on Oxford NMR 300-Varian Gemini 2000 NMR spectrometer, JEOL JNM-EX 270 FTNMR spectrometer and Varian Gemini 200 MHz, Brucher AC-200 MHz with chemical shift (δ) expressed in ppm downfield from TMS as internal standard, in DMSO-d6. Mass spectra were determined with KRATOS Model MS 25 mass spectrometer (Magnetic Sector) and HP Model MS-5988 at 70 eV. TLC carried out the monitoring of the progress of all reactions and homogeneity of the synthesized compounds. TLC was

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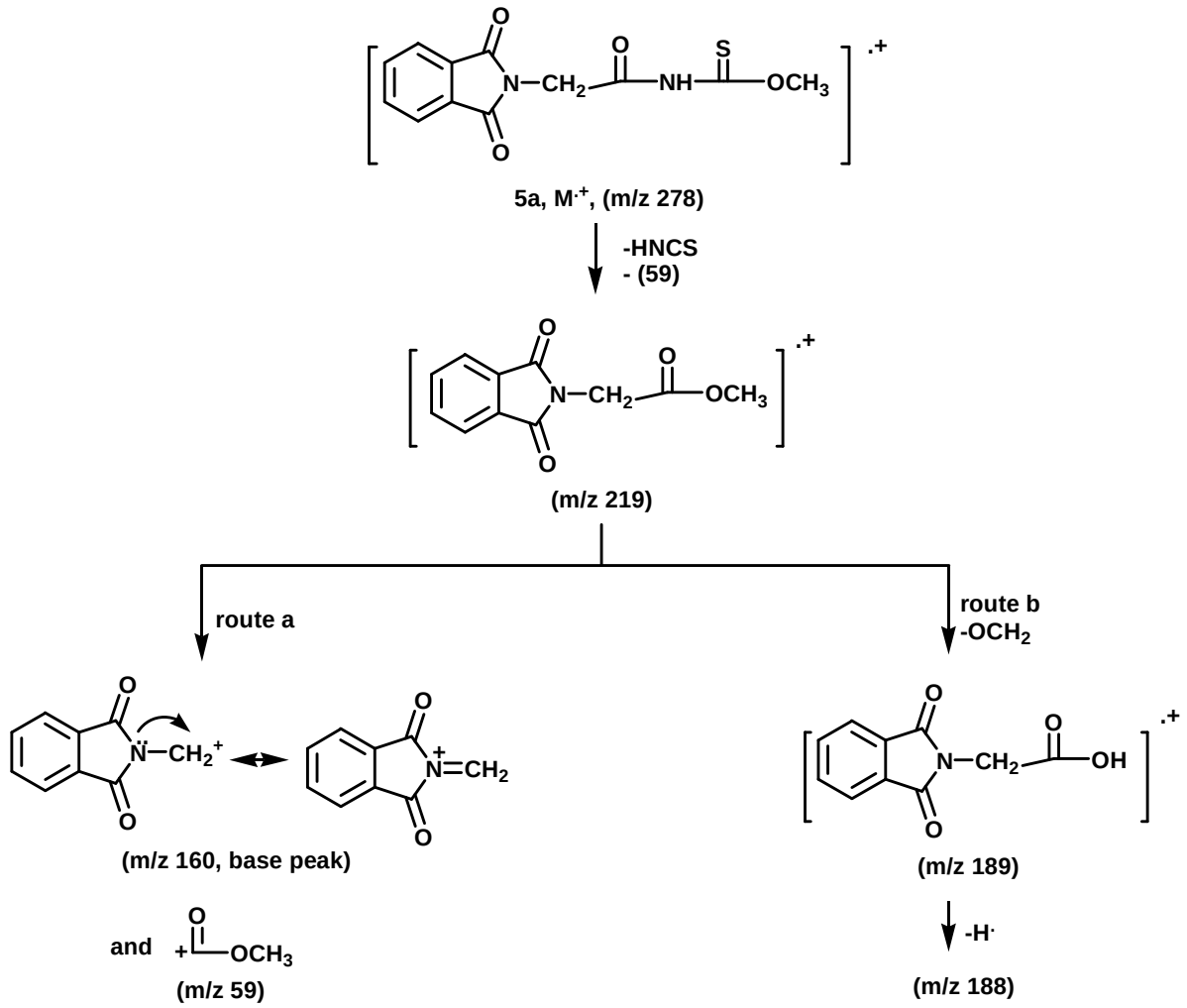

Scheme 4

determined using TLC aluminum sheets silica gel F_{254} (Merck).

Synthesis of phthalimidoacyl isothiocyanates (1a,b)

To a solution of phthalimidoacetyl chloride or 2-phthalimidopropionyl chloride (3 mmole), in dry acetonitrile (30 mL) or dry acetone (30 mL), solid ammonium thiocyanate (3 mmole) was added. The reaction mixture was stirred for half an hour at room temperature[8,9]. The precipitated ammonium chloride was filtered off to give a clear solution of isothiocyanate derivatives **(1a,b)**.

Reaction of isothiocyanate (1a,b) with the different nucleophiles

General procedure

To a solution of isothiocyanate **(la)** or **(1b)** (3 mmole), in dry acetonitrile (50 mL) an equimolar amount of ammonia solution, aniline, *p*-toludine, *p*-chloroaniline, *o*-aminophenol, *o*-phenylenediamine, methanol, or ethanol was added. The reaction mixture was refluxed for 2-3 hours (TLC), cooled to room temperature. The precipitated solid was sucked, washed with ethanol and recrystallized from a suitable solvent to give the corresponding compounds.

2-phthalimidoacetamide (3a)

79 % yield; pale yellow crystals; m.p 266-268 °C (ethanol); IR (KBr) ν: 3413, 3317, 1771, 1710, 1678 cm^{-1}; ^{1}HNMR (DMSO- d_6) δ: 4.18 (s, 2H), 7.30 (br. s, 1H, NH), 7.73 (br. s, 1H, NH), 7.86-7.94 (m, 4H), ^{13}C NMR 40.13 (CH_2), ar-C [123.65, 131.88, 134.65], 167.77 (CO), 168.17 (CO); *Anal. Calcd.* For $C_{10}H_8N_2O_3$ (204.18); C, 58.82; H, 3.95; N, 13.72; Found: C, 58.80; H, 3.74; N, 13.70%.

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2-phthalimidopropionamide (3b)

83 % yield; pale yellow crystals; m.p 210-212 °C (ethanol); IR (KBr) ν: 3438, 3303, 1778, 1710, 1686 cm^{-1}; *Anal. Calcd.* For $C_{11}H_{10}N_2O_3$ (218.21); C, 60.55; H, 4.62; N, 12.84; Found: C, 60.52; H, 4.18; N, 12.65%.

1-phthalimidoacety-3-phenyl thiourea (4a)

69 % yield; pale yellow crystals; m.p 209-211 °C (ethanol); IR (KBr) ν: 3485, 3192, 1777, 1712, 1697, 1373 cm^{-1}; ^{1}HNMR (DMSO- d_6) δ: 4.63 (s, 2H), 7.26 (t, *J* = 12 Hz, 1H), 7.40 (t, *J* = 9 Hz, 2H), 7.63 (d, *J* = 9 Hz, 2H), 7.88-7.98 (m, 4H), 11.96 (br. s, 1H, NH), 12.02 (br. s, 1H, NH), ^{13}C NMR 40.53 (CH_2), ar-C [123.54, 124.51, 126.65, 128.78, 131.58, 134.95, 137.86], 167.48 (CO), 168.56 (CO), 178.47 (CS); *Anal. Calcd.* For $C_{17}H_{13}N_3O_3S$ (339.37); C, 60.17; H, 3.86; N, 12.38; Found: C, 59.77; H, 3.82; N, 11.88 %.

1-phthalimidoacety-3-(*p*-toluyl)thiourea (4b)

63 % yield; pale yellow crystals; m.p 213-215 °C (ethanol); IR (KBr) ν: 3469, 3221, 1774, 1718, 1688, 1382 cm^{-1}; ^{1}HNMR (DMSO- d_6) δ: 2.08 (s, 3H), 4.59 (s, 2H), 7.20 (d, *J* = 9 Hz, 2H), 7.57 (d, *J* = 9 Hz, 2H), 7.91-7.96 (m, 4H), 10.73 (br. s, 1H, NH), 12.11 (br. s, 1H, NH), *Anal. Calcd.* For $C_{18}H_{15}N_3O_3S$ (353.39); C, 61.18; H, 4.28; N, 11.89; Found: C, 61.10; H, 4.22; N, 11.37 %.

1-phthalimidoacety-3-(*p*-chlorophenyl)thiourea (4c)

71 % yield; pale yellow crystals; m.p 217-219 °C (ethanol); IR (KBr) ν: 3469, 3257, 1777, 1712, 1694, 1378 cm^{-1}; ^{1}HNMR (DMSO- d_6) δ: 4.64 (s, 2H), 7.51 (d, *J* = 6 Hz, 2H), 7.77 (d, *J* = 6 Hz, 2H), 7.89-8.18 (m, 4H), 11.83 (br. s, 1H, NH), 12.00 (br. s, 1H, NH), ^{13}C NMR 40.53 (CH_2), ar-C [123.56, 126.55, 128.76, 130.60, 131.60, 135.00, 136.88], 167.48 (CO), 168.44 (CO), 178.74 (CS); *Anal. Calcd.* For $C_{17}H_{12}ClN_3O_3S$ (373.81); C, 54.62; H, 3.24; N, 11.24; Found: C, 54.33; H, 3.21; N, 10.89 %.

1-(2-phthalimidopropionyl)-3-(*p*-toluyl)thiourea (4d)

67 % yield; pale yellow crystals; m.p 178-180 °C (toluene); IR (KBr) ν: 3275, 1775, 1703, 1595, 1385 cm^{-1}; *Anal. Calcd.* For $C_{19}H_{17}N_3O_3S$ (367.42); C, 62.11; H, 4.66; N, 11.44; Found: C, 62.17; H, 4.45; N, 11.32 %.

1-(2-phthalimidopropionyl)-3-(*p*-chlorophenyl)thiourea (4e)

73 % yield; pale yellow crystals; m.p 153-155 °C (toluene); IR (KBr) ν: 3267, 1776, 1702, 1591, 1380 cm^{-1}; ^{1}HNMR (DMSO- d_6) δ: 1.58 (d, J = 7.2 Hz, 3H), 5.05 (q, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.83-7.90 (m, 4H), 11.76 (br. s, 1H, NH), 12.19 (br. s, 1H, NH); *Anal. Calcd.* For $C_{18}H_{14}ClN_3O_3S$ (387.84); C, 55.74; H, 3.64; N, 10.83; Found: C, 55.38; H, 3.71; N, 10.67 %.

1-phthalimidoacetyl-3-(2-hydroxyphenyl)thiourea (4f)

70 % yield; pale yellow crystals; m.p 216-218 °C (ethanol); IR (KBr) ν: br. 3300-2800, 3331, 3028, 1774, 1707, 1380 cm^{-1}; ^{1}HNMR (DMSO- d_6, 300MHz) δ: 4.61 (s, 2H), 7.05-6.82 (m, 3H), 7.97-7.85 (m, 4H), 8.54 (d, *J*=6.0 Hz, 1H), 10.21 (br. s, 1H, NH), 11.89 (br. s, 1H, NH), 12.37 (br. s, 1H, NH); ^{13}C NMR 40.49 (CH_2), ar-C [115.06, 118.33, 122.96, 123.43, 125.73, 126.49, 131.45, 134.81, 148.70], 167.28 (CO), 168.20 (CO), 176.50 (CS); *Anal. Calcd.* for $C_{17}H_{13}N_3O_4S$ (355.37): C 57.46, H 3.69, N 11.82; found C 57.37, H 3. 54, N 11.75 %.

1-phthalimidoacetyl-3-(2-aminophenyl)thiourea (4g)

62 % yield; pale yellow crystals; m.p 219-222 °C (acetic acid); IR (KBr) ν: br. 3460-3360, 3190, 3028, 1780, 1730, 1322 cm^{-1}; ^{1}HNMR (DMSO- d_6, 300MHz) δ: 4.59 (s, 2H), 5.01 (br. s, 1H, NH) 7.35-6.65(m, 4H), 8.00-7.90 (m, 4H),11.39 (br. s, 1H, NH), 11.96 (br. s, 2H, 2NH); ^{13}C NMR 40.49 (CH_2), ar-C [115.83, 115.99, 123.02, 123.42, 127.28, 127.80, 131.43, 134.81, 143.29], 167.26 (CO), 168.00 (CO), 179.39 (CS); *Anal. Calcd.* for $C_{17}H_{14}N_4O_3S$ (354.38): C 57.62, H 3.98, N 15.81; found C 56.91, H 3. 80, N 15.48 %.

O-methyl 2-(N-phthalimido)acetylcarbamothioate (5a)

61 % yield; pale yellow crystals; m.p 197-180 °C (toluene); IR (KBr) ν: br. 3240, 1771, 1703, 1613,

1374 cm^{-1}; ^{1}HNMR (DMSO- d_6, 300MHz) δ: 4.03 (s, 3H), 4.52 (s, 2H) 7.80-7.97 (m, 4H), 12.60 (br. s, 1H, NH); ^{13}C NMR 41.35 (CH_2), 58.35 (CH_3), ar-C [123.53, 131.62, 134.95], 164.77 (CO), 167.49 (CO), 189.59 (CS); *Anal. Calcd.* for $C_{12}H_{10}N_2O_4S$ (278.28): C 51.79, H 3.62, N 10.07; found C 52.48, H 3. 40, N 10.06 %.

O-ethyl 2-(N-phthalimido)acetylcarbamothioate (5b)

64 % yield; pale yellow crystals; m.p 145-147 °C (toluene); IR (KBr) ν: br. 3320, 1776, 1715, 1610, 1372 cm^{-1}; ^{1}HNMR (DMSO- d_6, 300MHz) δ: 1.33 (t, J = 7.1 Hz, 3H), 4.52 (q, J = 6.9 Hz, 2H), 4.53 (s, 2H), 7.82-7.98 (m, 4H), 12.10 (br. s, 1H, NH); ^{13}C NMR 13.50 (CH_3), 41.37 (CH_2), 67.99 (CH_2), ar-C [123.53, 131.63, 134.95], 164.69 (CO), 167.51 (CO), 188.76 (CS); *Anal. Calcd.* for $C_{13}H_{12}N_2O_4S$ (292.31): C 53.42, H 4.14, N 9.58; found C 53.93, H 3.96, N 9.81 %.

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