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Addition-Cyclization of Lauroyl Isothiocyanate with Hydrazine Derivatives as a Source of 1,2,4-Triazoles

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Abstract: Lauroyl isothiocyanate contain a long chain hydrocarbon part**.** The introduction of hydrocarbon moiety to the synthesized 1,2,4-triazole derevatives augments the antimicrobial action appreciably. The lipophilic property of the hydrocarbon moiety, favours the permeation of the compounds through lipoid barriers in the fungal cell membrane. Lauroyl isothiocyanate (**1**) reacts additively with hydrazine hydrate, phenyl hydrazine, 2-pyridyl hydrazine, benzoyl hydrazine, ethoxycarbonyl hydrazine, as well as thiosemicarbazides. Simultaneous or subsequent cyclization of the resulting 1: 1 adducts in acidic medium yields substituted 1,2,4-triazoles. The aliphatic part of lauroyl isothiocyanate also is affecting the reactivity of its carbonyl group. It is observed from all reactions mentioned that the nucleophilic attack proceeds at either carbonyl group or isothiocyanate function.

Key words: Lauroyl Isothiocyanate · 1,2,4-Triazoles · Hydrazine Derivatives

INTRODUCTION

1,2,4-Triazole derivative [4], is exhibit anti-inflammatory [1], antiviral [2], analgesic [3], antimicrobial, anticonvulsant [5] and antidepressant activities [6]. A series of 1,2,4-triazoles [7] have been patented and extensively employed in agriculture. The previous investigations on the utilization of aroyl isothiocyanates [8-12] afforded many different sizes heterocyclic rings. In the present work, the prototype hydrazine itself, some of its simple congeners and lauroyl isothiocyanate were used as a source of 1,2,4-triazoles bearing long chain hydrocarbon moiety aiming to enhance their biological activities.

MATERIAL AND METHODS

General: Melting points were determined in open capillary tubes on a Gallenkemp melting point apparatus and are uncorrected. The elemental analyses were carried out at the Micro Analytical Unit, Faculty of Science, Cairo University by using Perkin-Elemer 2400 CHN elemental analyser. The IR spectra were recorded on Perkin– Elmer Spectrum RXIFT-IR systems as KBr discs. The 1H NMR spectra were measured on Varian Gemini 300 MHz instrument with chemical shift (λ) expressed in ppm downfield from TMS as internal standard, in DMSO-d6. Mass spectra were recorded on Shimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC was carried out to monitor the progress of all reactions and homogeneity of the synthesized compounds. TLC was determined using TLC aluminum sheets silica gel F254 (Merck) lauroyl isothiocyanate (1): To a solution of lauroyl chloride (3 mmole), in dry acetonitrile (30 mL), solid ammonium thiocyanate (4.5 mmole) was added. The reaction mixture was stirred for half an hour at room temperature [13,14]. The precipitated ammonium chloride was filtered off to give a clear yellow solution of isothiocyanate 1.

Reaction of Isothiocyanate 1 with the Hydrazine Derivatives

General Procedure: To a solution of isothiocyanate **1** (3 mmole), hydrazine hydrate, phenylhydrazine, 2-pyridyl hydrazine, benzoyl hydrazine, ethyl hydrazine carboxylate, semicarbazidehydrochloride, or thiosemicarbazide, in acetonitrile (50 mL) was added. A few drops of triethylamine were added in the case of the reaction with semicarbazidehydhydrochloride The mixture was refluxed for 2–3 hours (TLC) and cooled to room temperature, or was stirred at room temperature or 1 hr. in case of formation of compounds **4a** or **4b**. The precipitated solid was filtered off, washed with water and recrystallised from the suitable solvents.

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***N*-(hydrazinecarbonothioyl) Dodecanamide (2):** (53% yield); colorless crystals; m.p. 95-97°C (ethanol); IR: 3223, 3150 (NH), 2955, 2920, 2850 (alkyl-H), 1688, (C=O), 1185 (C=S); ^{1}H NMR (DMSOd_6) λ: 0.97-0.85 (m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.18-1.24 (m, 16H, CH_3 $(CH_2)_8$ CH_2CH_2C=O), 1.52-1.54 (m, 2H, CH_3 $(CH_2)_8$ CH_2CH_2C=O), 2.38 -2.41 (m, 2H, $CH_3(CH_2)_8$ CH_2CH_2C=O), 7.2 (br. s, 2H, NH_2 exchangeable); 10.6, 13.1 (br. s, 2NH exchangeable); MS *m/z* (%): 273 (M^+., 14.5), 270 (44.9), 255 (21.7), 227 (10.1), 226 (33.3), 115 (47.8), 71 (43.5), 55 (100); Anal. Calcd for $C_{13}H_{27}N_3OS$ (273.44); C, 57.10; H, 9.95; N, 15.37. Found: C, 56.88; H, 9.90 ; N, 15.11 %.

1-(5-Thioxo-3-Undecyl-1H-1,2,4-triazol-4(5H)-yl) Dodecan-1-one (3): (18 % yield); colorless crystals; m.p. 132-134°C (DMF); IR: 3227 (NH), 2919, 2851 (alkyl-H), 1688, (C=O), 1595, (C=N), 1179 (C=S); ^{1}H NMR (DMSOd_6) λ: 0.84-0.86 ((m, 6H, alkyl-H), 1.19-1.25 (m, 36H, alkyl-H), 1.50-152 (m, 2H, alkyl-H), 2.06-2.22 (m, 2H, alkyl-H), 9.43 (br. s, 1NH exchangeable); MS *m/z* (%): 437 (M^+., 4.6), 309 (8.1), 254 (2.3), 183 (34.5), 156 (2.0), 115 (19.5), 99 (6.9), 98 (12.2) 57 (100); Anal. Calcd for $C_{25}H_{47}N_3OS$ (437.73); C, 68.60; H, 10.82; N, 9.60. Found: C,68.34; H, 10.76 ; N, 9.54 %.

***N*-(2-phenylhydrazinecarbonothioyl)dodecanamide (4a)** (73% yield); colorless crystals; m.p. 73-75°C (light petroleum 40-60°C); IR: 3292 (NH), 2955, 2919, 2849 (alkyl-H), 1662, (C=O), 1149 (C=S); *m/z* (%): 349 (M^+., 12.3), 331 (24.5), 316 (7.4), 247 (65.6), 246 (39.9), 194 (16.0), 151 (2.5), 118 (23.9), 105 (8.0), 96 (15.3), 92 (100); Anal. Calcd for $C_{19}H_{31}N_3OS$ (349.53); C, 65.29; H, 8.94; N, 12.02. Found: C, 64.92; H, 9.05 ; N, 11.86 %.

***N*-(2-(Pyridin-2-yl) Hydrazinecarbonothioyl) Dodecanamide (4b):** (77% yield); colorless crystals; m.p. 117-120°C (light petroleum 80-100°C); IR: 3179 (NH), 2918, 2850 (alkyl-H), 1702, (C=O), 1217 (C=S);; *m/z* (%): 350 (M^+., 18.9), 317 (56.8), 247 (32.4), 191 (21.6), 161 (24.3), 152 (32.4), 148 (21.6), 105 (40.5), 102 (37.8), 92 (48), 59 (100); Anal. Calcd for $C_{18}H_{30}N_4OS$ (350.52); C, 61.68; H, 8.63; N, 15.98. Found: C, 61.44 ; H, 8.65; N, 15.78 %.

1-Phenyl-3-(2-Phenylhydrazinyl)-5-Undecyl-1H-1,2,4-Triazole (6a): (53 % yield); colorless crystals; m.p. 105-106°C (light petroleum 60-80°C); IR: 3197 (NH), 3080 (aryl-H.), 2952,2923, 2851 (alkyl-H), 1597, (C=N), 750, 689; ^{1}H NMR (DMSOd_6) λ 0.83-0.87 ((m, 3H, CH_3 $(CH_2)_8$ CH_2CH_2), 1.19-1.25 (m, 16H, $CH_3(CH_2)_8$ CH_2CH_2), 1.45-1.53 (m, 2H, $CH_3(CH_2)_8$ CH_2CH_2), 2.11-2.20 (m, 2H, CH_3 $(CH_2)_8$ CH_2CH_2), 6.65-6.72 (m, 6H, Ar-H), 7.08-7.16 (m, 4H, Ar-H) 7.26, 9.5, (br. s, 2NH exchangeable);: MS *m/z* (%): 405 (M^+., 0.0), 390 (22.2), 389 (72.8), 286 (27.8), 146 (61.1), 119 (72.2), 90 (44.4), 76 (33.3) 60 (100); Anal. Calcd for $C_{25}H_{35}N_5$ (405.58); C, 74.03; H, 8.70; N, 17.27. Found: C,73.89; H, 8.66; N, 16.97 %.

2-(2-(1-(Pyridin-2-yl)-5-Undecyl-1H-1,2,4-Triazol-3-yl) Hydrazinyl) Pyridine (6b): (% 83 yield); colorless crystals; m.p. 128-130°C (light petroleum 60-80°C); IR: 3186 (NH), 3057 (aryl-H.), 2918, 2849 (alkyl-H), 1643, 1621 (C=N); ^{1}H NMR (DMSOd_6) λ: 0.79-0.85 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2$), 1.23-147 (m, 16H, $CH_3(CH_2)_8CH_2CH_2$), 1.52-1.64 (m, 2H, $CH_3(CH_2)_8CH_2CH_2$), 2.06-2.28 (m, 2H, $CH_3(CH_2)_8CH_2CH_2$), 6.97-8.74 (m, 5H, Ar-H), 8.69-8.74 (m, 3H, Ar-H) 9.8, 10.24, (br. s, 2NH exchangeable); MS *m/z* (%): 407 (M^+., 0.0), 352 (18.8), 288 (25.0), 207 (21.9), 175 (25.0), 148 (31.3), 134 (65.6), 119 (21.9), 118 (25.0), 109 (9.4) 57 (100); Anal. Calcd for $C_{23}H_{33}N_7$ (407.56); C, 67.78; H, 8.16; N, 24.06. Found: C, 67.55; H, 7.87 ; N, 23.77 %.

N-(2-Benzoylhydrazinecarbonothioyl) Dodecanamide (7a): (87% yield); colorless crystals; m.p. 110-112°C (light petroleum 60-80°C); IR: 3174 (NH), 3028 (aryl-H.), 2919, 2848 (alkyl-H), 1698, 1641 (C=O), 1173 (C=S); 753, 669; ^{1}H NMR (DMSOd_6) λ: 0.84-0.86 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.20-1.27 (m, 16H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.57-1.59 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 2.47-2.50 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 7.48 - 7.89 (m, 5H, ArH), 10.9, 11.4, 12.2 (br. s, 3NH exchangeable); MS *m/z* (%): 377 (M^+., 3.2), 344 (6.4), 343 (4.9), 183 (7.6), 195 (3.5), 179 (3.5), 135 (2.7), 105 (100); Anal. Calcd for $C_{20}H_{31}N_3O_2S$ (377.54); C, 63.63; H, 8.28; N, 11.13. Found: C, 63.22; H, 8.43 ; N 10.98 %.

Ethyl 2-(Dodecanoylcarbamothioyl) Hydrazinecarboxylate (7b): (83% yield); colorless crystals; m.p. 72-74°C (light petroleum 80-100°C); IR: 3208 (NH), 2923, 2851 (alkyl-H), 1740, 1700 (C=O), 1186 (C=S); ^{1}H NMR (DMSOd_6) λ: 0.83-0.87 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.16-1.24 (m, 16H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.49-1.51 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 2.10-2.17, (t, 3H, J = 7.1 Hz, CH_3CH_2O) 2.36-2.41 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 4.08 (q, 2H, J = 6.9 Hz, CH_3CH_2O), 9.6, 11.41, 11.62 (br. s, 3NH exchangeable); MS *m/z* (%): 345 (M^+., 3.7), 327 (1.2), 257 (11.4), 242 (2.9), 183 (19.2), 155 (1.4), 104 (100); Anal. Calcd for $C_{16}H_{31}N_3O_3S$ (345.50); C, 55.62; H, 9.04; N, 12.16. Found: C, 55.76; H, 8.75; N, 11.83 %.

2-(Dodecanoylcarbamothioyl) Hydrazinecarboxamide (10): (79% yield); colorless crystals; m.p.152-154°C (ethanol); IR: 3317, 3247, 3200 (NH), 2919, 2852 (alkyl-H), 1678 (C=O), 1198 (C=S); ^{1}H NMR (DMSOd_6) λ: 0.83-0.87 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.24-1.30 (m, 16H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.49-1.51 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 2.37-2.39 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 6.35 (br. s, 2H, NH_2 exchangeable), 5.81, 9.34, 11.29 (br. s, 3H, NH exchangeable); MS *m/z* (%): 316 (M^+., 3.9), 273 (5.9), 257 (7.4), 198 (11.8), 183 (20.6), 117 (48.5), 115 (78.4), 57 (100); Anal. Calcd for $C_{14}H_{28}N_4O_2S$ (316.46); C, 53.13; H, 8.92; N, 17.70. Found: C, 52.78; H, 8.66; N, 17.43 %.

3-Undecyl-1H-1,2,4-Triazole-5(4H)-Thione (13): (% 82 yield); colorless crystals; m.p.124-126°C (ethanol); IR: 3246, 3131 (NH), 2920, 2851 (alkyl-H), 1657, 1608 (C=N), 1171 (C=S); ^{1}H NMR (DMSOd_6) λ 0.78-0.86 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2$), 0.91-1.36 (m, 16H, $CH_3(CH_2)_8CH_2CH_2$), 1.48-1.57 (m, 2H, $CH_3(CH_2)_8CH_2CH_2$), 1.98-2.11 (m, 2H, $CH_3(CH_2)_8CH_2CH_2$), 7.23, 13.13, (br. s, 2NH exchangeable); MS *m/z* (%): 255 (M^+., 23.6), 240 (9.6), 222 (14.4), 212 (15.9), 156 (12.0), 129 (25.5), 115 (87.5), 99 (72.4), 67 (26.9), 59 (100); Anal. Calcd for $C_{13}H_{25}N_3S$ (255.42); C, 61.13; H, 9.87; N, 16.45. Found: C, 60.82; H, 9.53; N, 15.98 %.

1-(3-Phenyl-5-Thioxo-1H-1,2,4-Triazol-4(5H)-yl) Dodecan-1-One (8): A solution of compound **4a** (0.01 mol) in glacial acetic acid (30 mL) was added to polyphosphoric acid (20 mL). The reaction mixture was heated at 150–180°C for 1 h, then left to cool at room temperature. The precipitated solid obtained after addition of ice cold water was filtered off and recrystallized from ethanol; 66% yield; colorless crystals; mp 280-282°C; IR: 3159 (NH), 3044 (aryl-H.), 2901, 2781 (alkyl-H), 1693 (C=O), 1562 (C=N), 1245 (C=S), 761, 658; ^{1}H NMR (DMSOd_6) λ: 0.83-0.85 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.22-1.24 (m, 16H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.60 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 2.49-2.51 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 7.51 - 7.93 (d, 5H, ArH), 12.50 (br. s, 1NH exchangeable); MS *m/z* (%): 359 (M^+., 0.0), 260 (40.0), 259 (26.7), 222 (33.1), 144 (40.0), 119 (40.0), 77 (40.0), 55 (100); Anal. Calcd for $C_{20}H_{29}N_3OS$ (359.53); C, 66.81; H, 8.13; N, 11.69. Found: C, 66.43; H, 7.77 ; N, 11.83%.

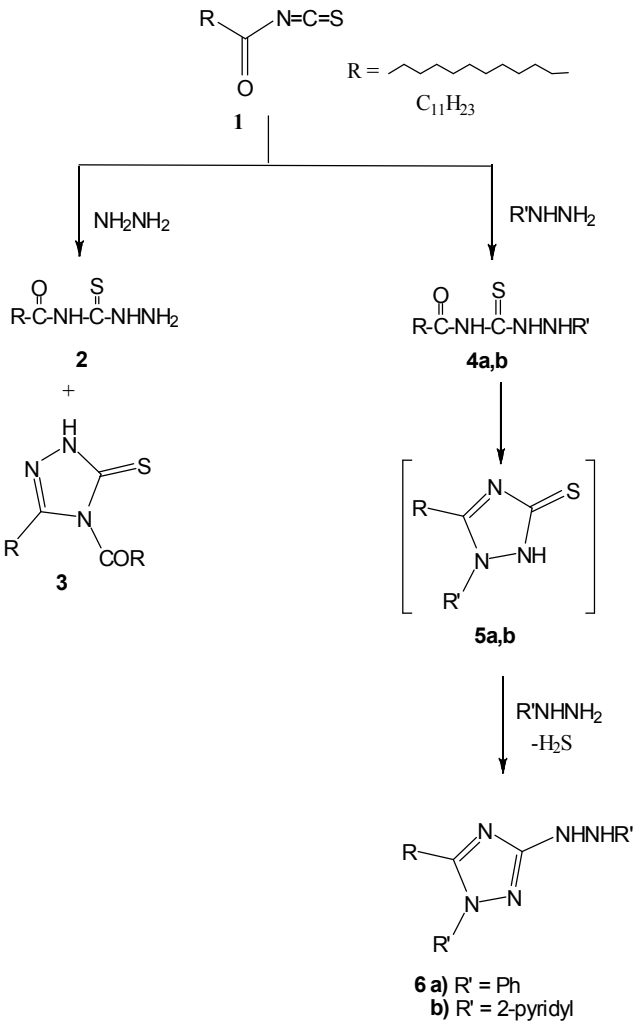
Formation of Compounds 9 or 11: A suspension of **7b** or **10** (0.5 g) in ethanol (30 mL), 3M hydrochloric acid (5 mL) was refluxed for 2 h. The solution was vacuum-evaporated to a small volume. A solution of sodium carbonate (0.1 N) was added until effervescence ceased. The colorless precipitate obtained was filtered off and recrystallised from benzene to give **9** or **11**.

4-Dodecanoyl-5-Thioxo-1,2,4-Triazolidin-3-One (9): (73% yield); colorless crystals; m.p. 171–173°C; IR: 3250, 3120 (NH), 2923, 2851 (alkyl-H), 1186 (C=S); ^{1}H NMR (DMSOd_6) λ: 0.83-8.86 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.24 (m, 16H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.57-1.59 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 2.47-2.52 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 13.13 (br. s, 2H, NH exchangeable); MS *m/z* (%): 299 (M^+., 19.4), 298 (16.1), 202 (9.7), 191 (67.7), 187 (45.2), 122 (45.2), 77 (100.0), 73 (64.5); Anal. Calcd for $C_{14}H_{25}N_3O_2S$ (299.43); C, 56.16; H, 8.42; N, 14.03. Found: C, 55.87; H, 8.11; N, 13.74 %.

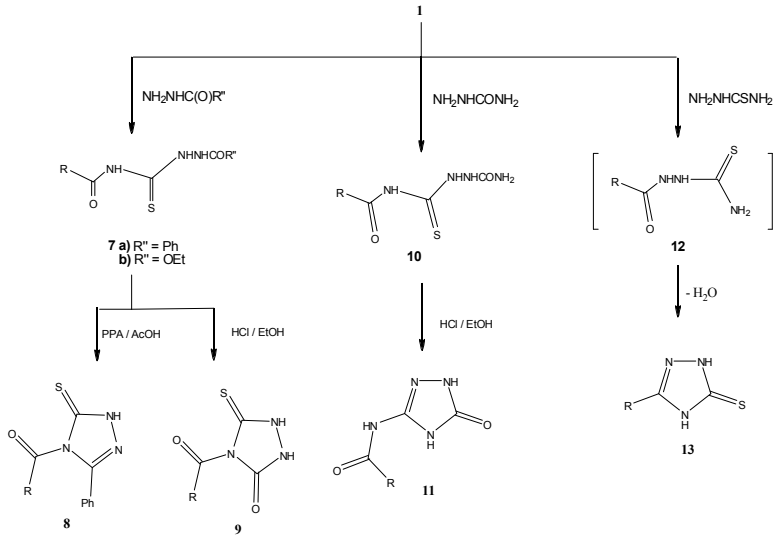
N-(5-oxo-4,5-Dihydro-1H-1,2,4-Triazol-3-yl) Dodecanamide (11): (% 76 yield); colorless crystals; m.p. 126-128°C (toluene); IR: 3179 (NH), 2923, 2848 (alkyl-H), 1666 (C=O); ^{1}H NMR (DMSOd_6) λ: 0.83-0.86 ((m, 3H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.19-1.26 (m, 16H, $CH_3(CH_2)_8CH_2CH_2C$=O), 1.50-1.55 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 2.42-2.46 (m, 2H, $CH_3(CH_2)_8CH_2CH_2C$=O), 7.06, 8.21, 12.11 (br. s, 3H, NH exchangeable); MS *m/z* (%): 282 (M^+., 0.2), 254 (2.1), 239 (4.8), 224 (0.7), 211 (1.2), 155 (2.3), 127 (4.4), 99 (100); Anal. Calcd for $C_{14}H_{26}N_4O_2$ (282.38); C, 59.55; H, 9.28; N, 19.84. Found: C, 59.65; H, 8.89; N, 19.69 %.

RESULTS AND DISCUSSION

Refluxing an equimolar amounts of hydrazine hydrate and lauroyl isothiocyanate (1) in acetonitrile produced a mixture of 1,2,4-triazole derivatives 3 and an open chain compound 2.The formation of compound 3 may understood from cyclocondensation of compound 2 with another molecule of isothiocyanate 1 during reflux. Similar reaction of 1 with phenyl hydrazine and/or 2-pyridyl hydrazine in acetonitrile afforded exclusively 1,2,4-triazole derivatives 6a and/or 6b in one-pot reaction. The formation of compounds 6a,b can be visualized on the basis of cyclocondensation of phenyl hydrazine or 2-pyridyl hydrazine with isothiocyanate 1 to give the non isolable 1,2,4-triazole derivatives 5a,b. A second molecule of hydrazine derivative attacks the thioxo group to produce compounds 6a,b. However, treatment of 1 with phenyl hydrazine or 2-pyridyl hydrazine at room temperature afforded thiosemicarbazide derivatives 4a,b.



Scheme 1



Scheme 2

The structures of compounds 2-4 and 6 were elucidated from their microanalytical and spectral data. Thus, their IR spectral data showed absorption correlated with υ(NH) and υ(C=O), except for compounds 6a,b, in addition to υ(C=N) for compounds 3,6. Their 1H NMR spectra displayed signals corresponding very well with their structures. The MS spectra of compounds 2-4 and 6 revealed their molecular ions peaks, or important peaks which are in accordance with their proposed structures (see Experimental).

The reaction of isothiocyanate 1 with benzoylhydrazine or ethoxycarbonylhydrazine gave good yields of linear 1: 1 adducts 7a,b as shown in Scheme 2. Heating compound 7a with polyphosphouric acid (PPA) affected ring closure with elimination of a molecule of water to give 1,2,4-triazole derivative 8. On the other hand compound 7b yields 1,2,4-triazole derivative 9 upon heating with a catalytic amount of hydrochloric acid in ethanol. The structures of compounds 7-9 were elucidated from their microanalytical and spectral data. Thus, their IR spectral data showed absorption correlated with υ(NH) and υ(C=O). Their 1H NMR spectra displayed signals corresponding very well with their structures. The MS spectra of compounds 7-9 revealed their molecular ions peaks, as well as some important peaks which are in according to their proposed structures (see Experimental).

A further aspect of reactivity of isothiocyanate 1 was exemplified by its reaction with semicarbazidehydrochloride to give an adduct 10. Boiling compound 10 in ethanolic / HCl solution was accompanied by release of H_2S gas to produce 1,2,4-triazole derivative 11 as shown in Scheme 2. However, treatment of 1 with thiosemicarbazide furnished 1,2,4-triazole derivative 13 in one-pot reaction. The formation of 13 is visualized to proceed through isothiocyanato group displacement of 1 to give an intermediate 12 (not isolated) that underwent cyclocondensation to give 1,2,4-triazole derivative 13. The spectroscopic data correspond very well with their structures see Experimental [8-12].

CONCLUSION

The aliphatic part of lauroyl isothiocyanate is affecting the reactivity of its carbonyl group. It is observed from all reactions mentioned that the nucleophilic attach proceeds at either carbonyl group or isothiocyanate function.

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