Synthesis and Characterization of Some New Derivatives of 2,4-Dihydro-4-benzyl-5- (pyridyl)-3*H*-1,2,4-triazole-3-thione

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Summary: A series of new disulphides, methylthio, triazolium salt, benzylthio, ylthio acetamide and ylthio acetic acid derivatives of 2,4-dihydro-4-benzyl-5- (pyridyl)-3*H*-1,2,4-triazole-3-thione have been synthesized. Their IR, ^{1}H-NMR, MS spectral data and elemental analysis have established structures of new compounds

Introduction

It is well established that various derivatives of 1,2,4-triazole exhibit interesting pharmacological properties like antitubercular [1,2], bacteriostatic [3,4], hypoglycemic [5], diuretic [6] and antifungal [7,8] activities. These observations prompted us to synthesis some new derivatives of 2,5-disubstituted-1,2,4-triazole for antibacterial and antifungal studies.

The reactions leading to the formation of different derivatives of substituted 1,2,4-triazoles are outlined in Scheme 1.

Results and Discussion

The starting compounds 2,4-disubstituted 1,2,4-triazole-3-thiones **1 (a-c)** were synthesized on the basis of already reported procedure [9]. Three new disulphides **2 (a-c)** which bearing two 1,2,4-triazole rings, were prepared by the reaction of triazole with sodium nitrate. In the IR spectra of compounds **2 (a-c)** absence of the absorption at 1255-1290 ($\nu_{C=S}$) and above 3100 cm^{-1} (ν_{NH}) indicated the absence of thione group. In ^{1}H-NMR spectra absence of an exchangeable proton is a strong evidence of the expected reaction. In the mass spectra of compound **(2c)** the molecular ion peaks were at m/z 534. Elimination of phenyl radical from molecular ion yielded a cation at m/z 457 (4.1%). The elemental analysis data of compounds **2 (a-b)** showed good agreement between the calculated and found % C, H, N and S values.

Reaction of compounds **1 (a-c)** with methyl iodide in the alkaline medium in ethanol afforded 4,5-disubstituted-2,4-dihydro-3-methylthio-3*H*-1,2,4-triazole **3 (a-c)**. In the IR spectra of compound **3 (a-c)** absence of signals in the region 2550-2590, 1260-1285 and above 3100 cm^{-1} established the absence of SH, C=S and NH, respectively. This was supported by the ^{1}H-NMR data, which included a 3H singlet in the region 2.62-2.98 ppm assigned to S-CH_3. In the mass spectra of compound **(3a)**, the molecular ion peak appeared at m/z 282 as base peak. Elemental analysis data of the other compounds of this series showed a good agreement of the calculated and found % C, H, N and S values.

Three triazolium iodides **4 (a-c)** were obtained from the respective 1,2,4-triazole-3-thiones **1 (a-c)** by the reaction of their alkaline solution in acetone with methyl iodide in a 1:2 ratio. The ^{1}H-NMR spectra of each of these compounds exhibited two sharp characteristic signals each integrating for three protons at 2.77-2.94 ppm and 3.41-3.68 ppm, attributable to S-CH_3 and N-CH_3 , respectively.

Compounds **5 (a-c)** were obtained according to reported method [10]. The nucleophilic substitution reaction of esters **5 (a-c)** with (D) α-methylbenzyl amine carried out in dry ethanol and potassium carbonate, as a result three new N-substituted-[2,4-dihydro-4- Benzyl-5-(pyridyl)-3*H*-1,2,4-triazol-3-ylthio] acetamides **6 (a-c)** were obtained. The IR spectra of compounds **6 (a-c)** exhibited the characteristic absorption for the secondary amide in the region of 3300-3400 cm^{-1}.

(4,5-Disubstituted-2,4-dihydro-3*H*-1,2,4-triazol-3-ylthio) acetic acids **7 (a-c)** synthesized by two different methods, Alkaline hydrolysis of the esters **5 (a-c)** (method A) and direct reaction of

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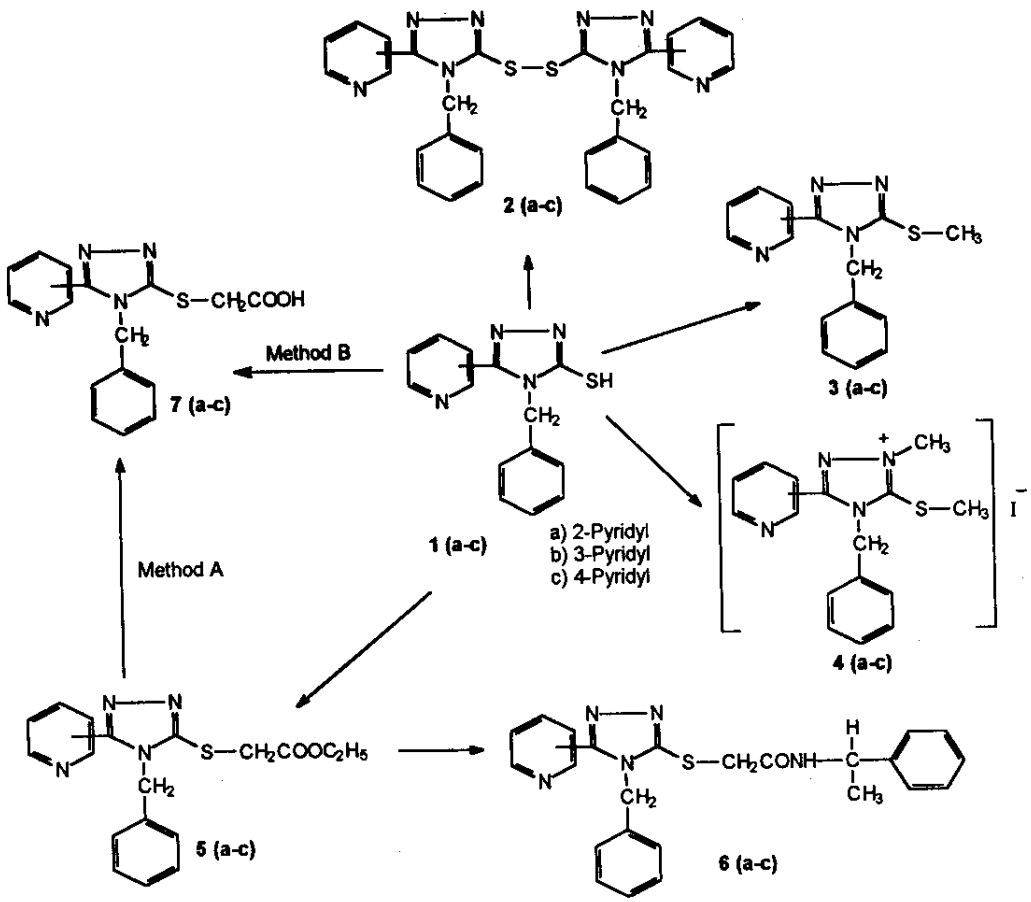


Scheme 1

triazoles **1 (a-c)** with chloroacetic acid (method B). The infra-red spectra of these compounds exhibited characteristic absorption of a carboxylic acid group; C=O stretching at 1715-1728 cm^{-1} which is shifted slightly towards higher frequency as compared to the carbonyl group of esters **5 (a-c)**. The bonded OH vibration also appeared at 2500-2507 cm^{-1}. In the ^{1}H-NMR spectra of each of these compounds, absence of the protons due to ethoxy group, indicated that hydrolysis had occurred completely. Further evidence for the formation of the carboxylic acid group was obtained from presence of a broad singlet (exchangeable) in the region 13.4-14.2 ppm. In the mass spectra of compounds **7 (a-b)** the molecular ion peaks appeared at m/z 326 (36 and 100%). Additional evidence for characterization of compound **(7c)** was obtained from elemental analysis.

Experimental

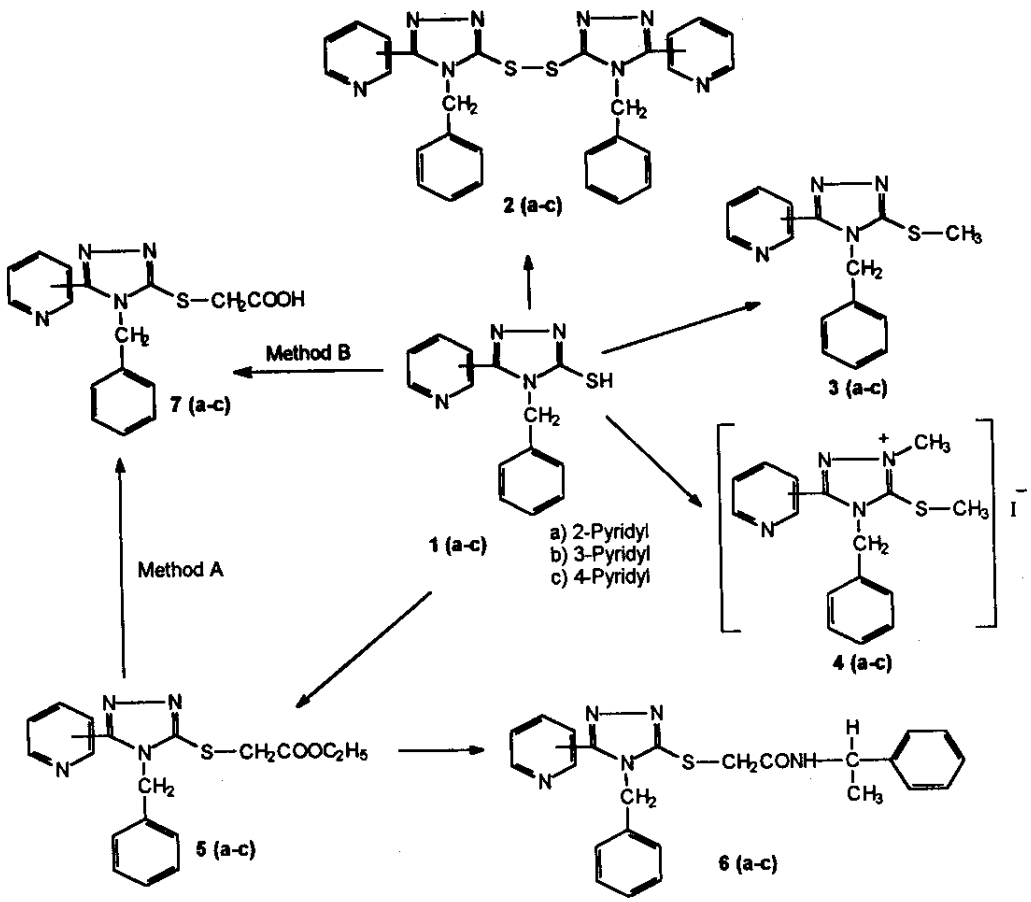
Melting points were determined using a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elemer 1320 spectrophotometer using KBr disc. ^{1}H-NMR spectra were recorded on a Bruker 250 and 80 MHz instrument using TMS as internal standard. The EIMS recorded on MAT-112-s-machine.

Bis-[(4,5-disubstituted)-1,2,4-triazole-3-yl]disulphides 2 (a-c)

The disulphides **2 (a-c)** were prepared by following reported method [11] which involved the reaction of sodium nitrite in acetic acid 4,5-disubstituted-1,2,4-triazole.

General procedure

A solution of 4-benzyl-5-(pyridyl)-3*H*-1,2,4-triazole-3-thiones **1 (a-c)** (200 mg, 75 mmol) and sodium nitrite (0.26 g, 0.97 mmoles) in acetic acid (5 ml) was kept at room temperature for 3h. The reaction mixture was then poured into water (10 ml), extracted with ethyl acetate (2x15 ml). The organic



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4,5-Disubstituted-3-mercaptomethyl-1,2,4-triazolium iodide 4 (a-c)

General procedure

To a mixture of 4,5-disubstituted-1,2,4-triazole **1(a-c)** (1 mmole) in 10 ml acetone containing potassium hydroxide (1 mmole) was added methyl iodide (2 mmole). The mixture was kept at room temperature with stirring over night and then filtered. The solvent was removed *in vacuo*. After removal of the solvent, ether was added to furnish a crystalline solid in each case. The solid was filtered and washed with ether trice.

4-Benzyl-5-(2-pyridyl)-3-mercaptomethyl-1,2,4-triazolium iodide (**4a**): Reaction time required 3 h, m.p. = 108-110°C, yield = 86.9%. IR (ν_{max}, KBr, Cm^{-1}): 3015, 2973, 1620, 1520, 1062. ^{1}H-NMR (D_2O, 250 MHz) δ: 2.77 (3H, s, S-CH_3), 3.68 (3H, s, N-CH_3), 5.46 (2H, s, N-CH_2), 7.05-7.36 (5H, m, Ar-H), 7.87-7.89 (1H, dd, J=2.2, 6.9 Hz, H-5"), 7.91-7.93 (1H, ddd, J=0.8, 2.3, 7.5 Hz, H-3"), 8.21-824. (1H, dd, J=3.1, 7.9 Hz, H-4"), 8.84-8.86 (1H, ddd, J=0.9, 2.4, 8.1 Hz, H-6"). **Elemental analysis found** (Calc.)%: C: 45.34 (45.28), H: 4.04 (4.01), N: 13.17 (13.21), S: 7.64 (7.55).

4-Benzyl-5-(3-pyridyl)-3-mercaptomethyl-1,2,4-triazolium iodide (**4b**): Reaction time required 4 h, m.p. = 225-227°C, yield = 68.3%. IR (ν_{max}, KBr,cm^{-1}): 3010, 2975, 1630, 1522, 1062. ^{1}H-NMR (D_2O, 250 MHz) δ: 2.94 (3H, s, S-CH_3), 3.41 (3H, s, N-CH_3), 5.32 (2H, s, N-CH_2), 7.01-7.24 (5H, m, Ar-H), 7.52-7.54 (1H, dd, J=0.6, 7.5 Hz, H-5"), 7.72-7.75 (1H, dd, J=2.9, 7.6 Hz, H-4"), 8.12-8.14 (1H, dd, J=2.7, 8.1 Hz, H-6"), 8.75-8.79 (1H, dd, 4.1, 7.5 Hz, H-2") **Elemental analysis found** (Calc.) % : C: 45.32 (45.28), H: 4.01 (4.01), N: 13.23 (13.21), S: 7.49 (7.55).

4-Benzyl-5-(4-pyridyl)-3-mercaptomethyl-1,2,4-triazolium iodide (4c)

Reaction time required 3 h, m.p. = 118-120°C, yield = 95.2%. **IR (ν_{max}, KBr,cm^{-1}):** 3005, 2945, 1635, 1598, 1520, 1063. **^{1}H-NMR (D_2O, 250 MHz)** δ**:** 2.81 (3H, s, S-CH_3), 3.47 (3H, s, N-CH_3), 5.57 (2H, s, N-CH_2), 7.03-7.27 (5H, m, Ar-H), 7.41-7.46 (2H, dd, J=2.4, 7.5 Hz, H-3".5"), 8.47-8.51 (2H, dd, 2.5, 7.5 Hz, H-2"). **MS, *m/z* (%):** 424 (1.3, M^+), 300 (11.1), 299 (18.3), 297 (100), 284 (14.7), 237 (7.6), 221 (6.4), 207 (15.2), 147 (9.6), 119 (13.4), 104 (4.9), 91 (16.5).

N-Substituted[4-benzyl-5-(pyridyl)-1,2,4-triazole-3-ylthio)acetamides 6 (a-c)

General procedure

Each of the esters **5 (a-c)** (0.408 mmole) was dissolved in dry ethanol (10 ml). K_2CO_3 (1 g) was added to the solution. (D)(+)α-Methylbenzyl amine (0.408 mmoles) was separately dissolved in dry ethanol (5 ml) and added to the above solution. The reaction mixture was then subjected to refluxe. TLC monitored the completion of the reaction. After the reaction was over, reaction mixture was filtered while hot. In each case, rotary evaporation of solvent furnished a crude solid, which was subjected to column chromatography. The product thus obtained was recrystallized from ethanol.

N-[(D)(+)α-1-Methylbenzyl)-[4-benzyl-5-(2-pyridyl)-3H-1,2,4-triazole-3-ylthio]-actamide (6a)

Reaction time required 5 h, m.p. = 228-230°C, yield = 66.6%, IR (ν_{max}, KBr, Cm^{-1}): 3400-3300, 3025, 2984, 1675, 1532, 1050. ^{1}H-NMR (DMSO, 250 MHz) δ : 2.48-2.50 (3H, d, J=1.2 Hz, CH_3), 3.4-3.7 (1H, q, J=7.9, 10.1, 13.9 Hz, C-H), 3.75 (2H, s, S-CH_2), 5.31 (2H, s, Ar-CH_2), 6.98-7.01 (4H, d, J=3.7, Hz, H-2', 2"), 7.25-7.28 (2H, dd, J=0.7, 3.7 Hz, H-4', 4"), 7.31-7.33 (4H, dd, J=0.8, 3.6 Hz, H-3', 3"), 7.50-7.52 (1H, dd, J=2.1, 7.3 Hz, H-5'"), 7.91-7.95 (1H, dd, J=2.1, 7.2 Hz, H-3'"), 7.96-8.15 (1H, dd, J=1.4, 7.2 Hz, H-4'"), 8.58-8.62 (1H, dd, J=1.2, 11.8 Hz, H-6'"), 9.9 (1H, s, D_2O exchanged, NH). **Elemental analysis found** (Calc.) % : C: 67.01 (67.13), H: 5.30 (5.36), N: 16.25 (16.32), S: 7.42 (7.46).

N-[(D)(+)α-1-Methylbenzyl)-[4-benzyl-5-(3-pyridyl)-3H-1,2,4-triazole-3-ylthio]-actamide (6b)

Reaction time required 9 h, m.p. = 225-227°C, yield = 43.7%, IR (ν_{max}, KBr, cm^{-1}): 3400-3300, 3020, 2981, 1680, 1530, 1055. ^{1}H-NMR (DMSO, 250 MHz) δ : 2.49-2.50 (3H, d, J=0.9 Hz, CH_3), 3.3-3.6 (1H, q, J=8.2, 10.0, 13.8 Hz, C-H), 3.73 (2H, s, S-CH_2), 5.29 (2H, s, Ar-CH_2), 6.95-6.97 (4H, d, J=3.6, Hz, H-2', 2"), 7.24-7.27 (2H, dd, J=0.45, 3.6 Hz, H-4', 4"), 7.29-7.32 (4H, dd, J=0.65, 3.5 Hz, H-3', 3"), 7.48-7.51 (1H, dd, J=1.1, 3.7 Hz, H-5'"), 7.93-7.95 (1H, dd, J=2.1, 7.4 Hz, H-4'"), 7.97-8.05 (1H, dd, J=0.7, 1.1 Hz, H-6'"), 8.66-8.71 (1H, dd, J=1.2, 11.8 Hz, H-2'"), 9.8 (1H, s, D_2O exchanged, NH). MS, m/z (%) : 429 (1.3, M^+), 428 (51.0), 365 (28.6), 345 (31.7), 251 (29.5), 105 (14.7), 104 (22.2), 91 (100).

N-[(D)(+)α-1-Methylbenzyl)-[4-benzyl-5-(4-pyridyl)-3*H*-1,2,4-triazole-3-ylthio]- actamide (**6c**) : Reaction time required 7 h, m.p. = 148-150°C, yield = 83.6%, IR (ν_{max}, KBr, cm^{-1}) : 3400-3300, 3015, 2980, 1683, 1550, 1045. ^{1}H-NMR (DMSO, 250 MHz) δ : 2.52-2.54 (3H, d, J=1.1 Hz, CH_3), 3.2-3.5 (1H, q, J=7.2, 10.4, 13.1 Hz, C-H), 3.75 (2H, s, S-CH_2), 5.34 (2H, s, Ar-CH_2), 7.01-7.08 (4H, d, J=3.8, Hz, H-2', 2"), 7.26-7.29 (2H, dd, J=0.7, 3.4 Hz, H-4', 4"), 7.31-7.35 (4H, dd, J=0.6, 3.6 Hz, H-3', 3"), 7.39-7.52 (2H, dd, J=08, 8.2 Hz, H-3'", 5'"), 7.95-8.05 (2H, dd, J=0.7, 8.4 Hz, H-2'", 6'"), 10.1 (1H, s, D_2O exchanged, NH). **Elemental analysis found** (Calc.) %: C: 67.12 (67.13), H: 5.39 (5.36), N: 16.28 (16.32), S: 7.50 (7.46).

(4,5-Disubstituted-1,2,4-triazol-3-ylthio)acetic acid 7 (a-c)

General procedure

Method A

Each of the six esters **5 (a-c)** (1 mmole) was dissolved in 5% aqueous solution of sodium hydroxide (10 ml) and refluxed for 3 h. After this period of time, the reaction mixture was cooled and extracted with ethyl acetate (2x10 ml). The aqueous layer was then separated and acidified with dil. hydrochloric acid (pH ≅4) to yield a precipitate. The crude solid was filtered, washed thoroughly with cold water and recrystallized from ethanol.

(4-Benzyl-5-(2-pyridyl)-1,2,4-triazol-3-ylthio)acetic acid (7a)

Reaction time required 3 h, m.p. = 188-189°C, yield = 81.4%, **IR (ν_{max}, KBr, cm^{-1}):** 3400, 3040, 2955, 2500, 1728, 1580, 1190. **^{1}H-NMR (DMSO-d^6, 250 MHz) δ :** 4.08 (2H, s, S-CH_2), 5.84 (2H, s, Ar-CH_2), 7.11-7.30 (5H, m, Ar-H), 7.32-7.47 (1H, m, H-5"), 7.48-7.52 (1H, ddd, J=1.1, 2.6, 3.4 Hz, H-3"), 7.94-8.01 (1H, ddd, J=1.8, 7.9, 9.65 Hz, H-4"), 8.12-8.6 (1H, ddd, J=1.6, 4.6, 7.9 Hz, H-6"), 14.2 (1H, bs, D_2O exchanged, OH). **MS, m/z (%) :** 326 (36.0, M^+), 282 (8.1), 268 (28.1), 235 (22.2), 191 (11.4), 178 (12.8), 104 (14.6), 91 (100). **Elemental analysis found (Calc.) %:** C: 58.87 (58.90), H: 4.31 (4.29), N: 17.25 (17.18).

4-Benzyl-5-(3-pyridyl)-1,2,4-triazol-3-ylthio)acetic acid (7b)

Reaction time required 3 h, m.p. = 203-205°C, yield = 75.3%, **IR (ν_{max}, KBr, cm^{-1}):** 3400, 3040, 2980, 2950, 2515, 1715, 1580, 1195. **^{1}H-NMR (DMSO-d^6, 250 MHz) δ :** 4.10 (2H, s, S-CH_2), 5.32 (2H, s, Ar-CH_2), 6.97-7.01 (2H, dd, J=1.9, 7.8 Hz, Ar-H), 7.27-7.36 (3H, m, Ar-H), 7.49-7.54 (1H, dd, J=1.4, 7.8 Hz, H-5"), 7.95-7.99 (1H, dd, J=3.2, 7.9 Hz, H-4"), 8.67-8.69 (1H, d, J=1.6, Hz, H-6"), 8.72-8.73 (1H, dd, J=1.7, 4.8 Hz, H-2"), 13.8 (1H, bs, D_2O exchanged, OH). **MS, m/z (%) :** 326 (100, M^+), 282 (4.1), 268 (12.7), 235 (3.9), 191 (6.7), 178 (2.3), 104 (1.5), 91 (42.3). **Elemental analysis Found (Calc.) %:** C: 58.84 (58.90), H: 4.32 (4.29), N: 17.19 (17.18).

(4-Benzyl-5-(4-pyridyl)-1,2,4-triazol-3-ylthio)acetic acid (7c)

Reaction time required 3 h, m.p. = 220-222°C, yield = 87.6%, **IR (ν_{max}, KBr, cm^{-1}) :** 3390, 3030, 2985, 2950, 1715, 1580, 1192. **^{1}H-NMR (DMSO-d^6, 250 MHz) δ :** 4.12 (2H, s, S-CH_2), 5.30 (2H, s, Ar-CH_2), 6.99-7.10 (2H, dd, J=2.3, 7.9 Hz, Ar-H), 7.29-7.34 (3H, m, Ar-H), 7.47-7.53 (2H, dd, J=4.9, 7.9 Hz, H-3", 5"), 8.37-8.39 (2H, dd, J=4.7, 7.8 Hz, H-2", 6"), 13.4 (1H, bs, D_2O exchanged, OH). **Elemental analysis found (Calc.) %:** C: 58.86 (58.90), H: 4.32 (4.29), N: 17.22 (17.18).

Method-B

Compound **1 (a-c)** (5 mmol; 1.34 g) was dissolved in 10 ml 1.6 N aq. Sodium hydroxide solution and mixed with chloroacetic acid (5 mmol; 0.47 g, dissolved in 10 ml water). The mixture was refluxed for 2.0-2.5 h. after the reflux time was over, the reaction mixture was cooled, filtered and acidified with 1N HCl to pH 3-4. The reaction mixture was then cooled in an ice bath, which resulted in precipitation of the crude product. This was filtered and recrystallized from ethanol-water. The IR, ^{1}H-NMR and elemental analysis of these compounds were in good agreement with **7 (a-c)**.

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