A NOVEL ONE-STEP SYNTHESIS OF 3-SUBSTITUTED-5,6-DIHYDROTHIAZOLO[2,3-c]-1,2,4-TRIAZOLES AND -6,7-DIHYDRO-5H-1,2,4-TRIAZOLO[3,4-b][1,3]THIAZINES

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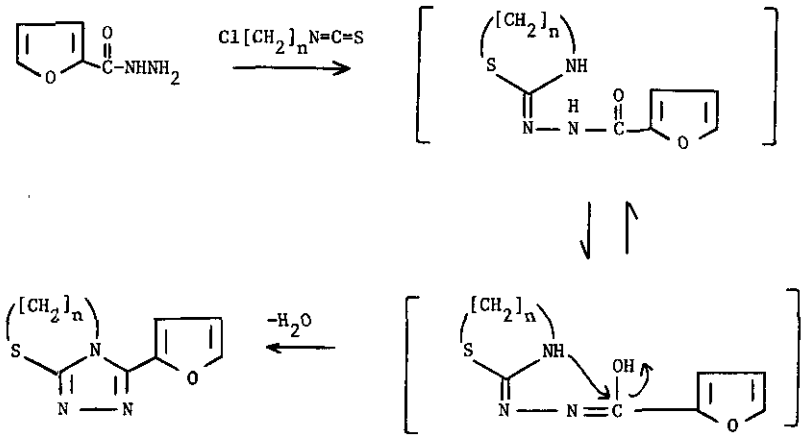
Abstract - 3-Substituted-5,6-dihydrothiazolo[2,3-c]-1,2,4-triazoles and -6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3]-thiazines have been synthesized in one step by reaction of the acid hydrazides with haloalkyl isothiocyanates.

The availability and chemical versatility of haloalkyl isothiocyanates have made them useful starting materials for preparative heterocyclic chemistry. We have recently described a new one-step synthesis of 2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one and 3,4-dihydro-2H,6H-[1,3]-thiazino[2,3-b]quinazolin-6-one by the reaction of methyl anthranilate with chloroalkyl isothiocyanates.[1]

In this communication we report the discovery of a novel general method for the synthesis of 3-substituted-5,6-dihydrothiazolo[2,3-c]-1,2,4-triazoles and -6,7-dihydro-5H-1,2,4-triazolo[3,4-b]-[1,3]thiazines.[2]

Reaction of 2-furoic acid hydrazide with 2-chloroethyl isothiocyanate[3] in refluxing xylene followed by addition of triethylamine gave 3-(2-furanyl)-5,6-dihydrothiazolo[2,3-c]-1,2,4-triazole 1 in 59% yield as white leaflets, m.p. 142-143°C; ir νmax (Nujol): 1620 (C=N) and 1520 cm^{-1} (C=C); ^{1}Hnmr ($CDCl_3$): δ (ppm) 4.15 (t, 2H, CH_2S), 4.50 (t, 2H, CH_2N), 6.55 (q, H, $FurH_4$), 6.95 (d, 1H, $FurH_3$), 7.65 (s, 1H, $FurH_5$); ms (electron impact, 70 eV): m/e 193 (M^+, base). The reaction involves the intermediate formation of a thiazoline and the elimination of water to give 1 via an intramolecular ring closure.

Similarly, we found that the reaction of 2-furoic acid hydrazide with 3-chloropropyl isothiocyanate and triethylamine,[4] yielded 3-(2-furanyl)-6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3]-thiazine 2 (80%), m.p. 211-212°C; ir νmax (Nujol): 1615 (C=N) and 1520 cm^{-1} (C=C); ^{1}Hnmr (DMSO-d_6): δ (ppm) 2.45 (m, 2H, C-CH_2-C), 3.30 (t, 2H, CH_2S), 4.43 (t, 2H, CH_2N), 6.63 (q, 1H, $FurH_4$), 7.25 (d, 1H, $FurH_3$), 7.90 (s, 1H, $FurH_5$); ms (electron impact, 70 eV): m/e 207 (M^+, base).



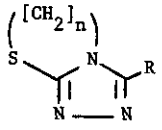
1 n = 2

2 n = 3

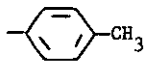
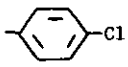
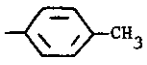
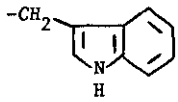
The physical and spectral properties of some representative examples are summarized in Table 1. The reaction is generally effective for a wide range of aliphatic, aromatic and heterocyclic acid hydrazides.

TABLE 1

Physical and Spectral Properties of Selected 3-Substituted-5,6-Dihydrothiazolo[2,3-c]-1,2,4-triazoles and -6,7-Dihydro-5H-1,2,4-triazolo[3,4-b][1,3]thiazines.



R	n	m.p. °C. (Solvent)	Yield, %	Spectral Data
	2	228.5-230 (Ethanol)	55	ir νmax (Nujol): 1600, 1520 cm^{-1}; ^{1}Hnmr (DMSO-d_6 + TFA): 4.15 (t, 2H, CH_2S), 4.70 (t, 2H, CH_2N), 7.80 (q, 4H, ArH); ms: m/e 237.
	2	192-193 (Ethanol)	42	ir νmax (Nujol): 1640, 1585 cm^{-1}; ^{1}Hnmr (DMSO-d_6): 4.15 (t, 2H, CH_2S), 4.55 (t, 2H, CH_2N), 7.52 (t, 1H, ArH), 8.20 (d, 1H, ArH), 8.70 (d, 1H, ArH), 9.00 (s, 1H, ArH); ms: m/e 204.

R	n	m.p. °C. (Solvent)	Yield, %	Spectral Data
	2	225.5-227 (Ethanol)	55	ir νmax (Nujol): 1630, 1615, 1540 cm^{-1}; ^{1}Hnmr (DMSO-d_6): 2.45 (s, 3H, CH_3), 4.15 (t, 2H, CH_2S), 4.73 (t, 2H, CH_2N), 7.60 (q, 4H, ArH); ms: m/e 217.
$-CH_3$	3	154-156 (Xylene)	25	ir νmax (Nujol): 1530 cm^{-1}; ^{1}Hnmr ($CDCl_3$): 2.2-2.6 (m, 2H, CCH_2C), 2.40 (s, 3H, CH_3), 3.20 (t, 2H, CH_2S), 4.00 (t, 2H, CH_2N); ms: m/e 155.
$-CH_2CH_2CH_3$	3	57-58 (EtOAc-Hexane)	67	ir νmax (Nujol): 1525 cm^{-1}; ^{1}Hnmr (DMSO-d_6): 1.10 (t, 3H, $CH_2CH_2\underline{CH_3}$), 1.75 (m, 2H, $CH_2\underline{CH_2}CH_3$); 2.40 (m, 2H, $-SCH_2\underline{CH_2}CH_2N-$), 2.70 (t, 2H, $\underline{CH_2}CH_2CH_3$), 3.25 (t, 2H, CH_2S), 4.05 (t, 2H, CH_2N), ms: m/e 183.
	3	186-187 (Ethanol)	62	ir νmax (Nujol): 1600, 1615, 1530 cm^{-1}; ^{1}Hnmr (DMSO-d_6): 2.20 (m, 2H, $C-CH_2-C$), 3.23 (t, 2H, CH_2S), 4.15 (t, 2H, CH_2N), 7.70 (q, 4H, ArH); ms: m/e 251.
	3	163-164 (Ethanol)	63	ir νmax (Nujol): 1630, 1615, 1530 cm^{-1}; ^{1}Hnmr (DMSO-d_6): 2.25 (m, CCH_2C), 2.45 (s, 3H, CH_3), 3.28 (t, 2H, CH_2S), 4.15 (t, 2H, CH_2N), 7.45 (q, 4H, ArH); ms: m/e 231.
	3	244-245 (Ethanol)	69	ir νmax (Nujol): 3150, 1620; 1530 cm^{-1}; ^{1}Hnmr (DMSO-d_6): 2.20 (m, 2H, $-SCH_2-\underline{CH_2}-CH_2N-$), 3.10 (t, 2H, CH_2S), 3.90 (t, 2H, CH_2N), 4.05 (s, 2H, CH_2S), 6.90 (s, 1H, $C=\underline{CH}$), 7.20 (m, 4H, ArH), 7.50 (s, 1H, NH): ms: m/e 270.

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REFERENCES AND NOTES

Satisfactory analytical data have been obtained for all crystalline compounds described in this communication.

1. L. G. Payne, J. Przytycki, A. A. Patchett and M. T. Wu, J. Heterocyclic Chem., 1979, 16, 391.
2. The only previously know member of this series, 3-phenyl-6,7-dihydro-5H-1,2,4-triazolo-[3,4-b][1,3]thiazine was prepared from 2-benzoylhydrazino-5,6-dihydro-4H-1,3-thiazine by K. S. Dhaka, J. Mohan, V. K. Chadha and H. K. Pujari, Indian J. Chem., 1974, 12, 485.
3. H. Brintzinger, K. Pfannstiel and H. Koddebusch, Ber., 1949, 82, 393.
4. P. Friis, Acta. Chem. Scand., 1965, 19, 766.

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