Synthesis and Properties of Some New 1,4-Dihydrothieno[3,2-e][1,2,4]triazepin-5-ones

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Methyl 3-aminothiophene-2-carboxylate reacts readily, in the presence of triethylamine, with hydrazonoyl chlorides (7a–c) to afford good yields of the corresponding N-arylamidrazones (8a–c). The latter acyclic adducts undergo, in the presence of t-BuOK/t-BuOH, cyclocondensation accompanied by elimination of the acetyl group present in 8, to deliver the respective thieno-1,3,4-triazepin-5-ones 10a–c.

Key words: Methyl 3-Amino-2-thiophenecarboxylate, Nitrile Imines, Amidrazone Adducts, Cyclocondensation, Thieno[3,2-e][1,2,4]triazepinones

Introduction

The synthetic interest in 1,4-benzodiazepines (e.g. diazepam/valium (1)) arising from their well-established role as potential psychotherapeutics [1] has promoted investigations of their nitrogen homologues, the benzotriazepines. Several studies have reported the preparation of members of the 1,3,4-benzotriazepine family [2, 3], exemplified by 2A, 2B [2] and 3 [3]. Compounds 2A and 2B were reported as useful antihypertensives, cardiotonics and fungicides [4].

On the other hand, thieno[3,2-e]triazepinones, such as 6 (bioisosteres of benzotriazepinones 2) are hitherto undescribed in the literature. The only attempt to prepare this new bicyclic heteroring system from methyl 3-aminothiophene-2-carboxylate (4) according to Scheme 1 was reported in 1992 [5]. However, this route yielded 4(3H)-thieno[3,2-d]pyrimidinones (5), but the isomeric thieno[3,2-e][1,2,4]triazepin-5-ones (6) were not isolated [5].

Accordingly, the present work aims at the synthesis of some thienotriazepinones (10a–c) via a two-step route utilizing available reactants: methyl 3-aminothiophene-2-carboxylate (4) and appropriate N-arylhydrazonoyl chlorides 7a–c (Scheme 2).

Results and Discussion

The synthetic methodology involves interaction between methyl 3-aminothiophene-2-carboxylate (4) and the appropriate hydrazonoyl chloride (7a–c) in the presence of triethylamine, to furnish the corresponding acyclic amidrazone adducts (8a–c, Scheme 2). Herein compound 4, acting as a nitrogen nucleophile, adds readily onto nitrile imines [Ac–C≡N+–N−–Ar] (the reactive 1,3-dipolar intermediates, generated in situ.
from their precursors 3a-c to form 8a–c. This mode of nucleophilic addition reaction of various nucleophiles onto 1,3-dipoles is well-documented, and several adducts related to 8 were obtained from the reaction of primary and secondary amines with various hydrazonoyl halides (such as 7) [6, 7]. Intramolecular cyclization of the adducts 8a–c was accomplished using potassium tert-butoxide in tert-butanol under reflux. These reaction conditions led to the production of the respective bicyclic heterocycles, namely 1,4-dihydrothieno[3,2-e][1,3,4]triazepin-5-ones (10a–c). The latter compounds lack the acetyl group present in 8 as evidenced from their 1H / 13C NMR and MS spectral data that are given in the Experimental Section. Elimination of the acetyl group might have occurred from substrate 8 (prior to its cyclization) or from the presumed intermediates 9a–c (Scheme 2) which, however, were not isolated.

**Experimental Section**

Methyl 3-aminothiophene-2-carboxylate, 3-chloropentane-2,4-dione and potassium tert-butoxide were purchased from Acros. Melting points (uncorrected) were determined on an electrothermal melting point apparatus. 1H and 13C NMR spectra were measured on a Bruker DPX-300 instrument with Me3Si as internal reference. EIMS spectra
Methyl 3-[(1-(4-chlorophenylhydradono)-2-oxopropan-1-yI)amino]thiophene-2-carboxylate (8e)

This compound was prepared from 4 (2.2 g, 14 mmol) and 7c (3.7 g, 16 mmol), following the same procedure and experimental conditions as described above for obtaining 8a. Yield: 3.7 g (75%), m.p. 187 – 188 °C. – 1H NMR (300 MHz, CDCl3): δ = 2.51 (s, 3H, O=CH3), 3.82 (s, 3H, OCH3), 6.19 (d, J = 5.4 Hz, 1H, 4-H), 7.11 (d, J = 8.7 Hz, 2H, 2’-H / 6’-H), 7.25 (d, J = 8.7 Hz, 2H, 3’-H / 5’-H), 7.28 (d, J = 5.4 Hz, 1H, 5-H), 8.11 (s, 1H, CH=N=), 8.37 (s, 1H, C3=N=). – 13C NMR (75 MHz, CDCl3): δ = 24.4 (O=CH3), 51.9 (OCH3), 106.0 (C-2), 115.3 (C-2’/C-6’), 119.9 (C-4), 127.3 (C-4’), 129.4 (C-3’/C-5’), 131.9 (C-5), 135.6 (C-3), 141.3 (C-1’), 148.4 (C-1”), 164.6 (O=CH=), 192.9 (O=CH=). – C24H19ClN3O3S (351.81): calcd. C 51.21, H 4.01, Cl 10.08, N 11.94, S 9.11; found C 51.10, H 3.92, Cl 9.96, N 11.84, S 9.03.

4-Phenyl-1,4-dihydro-5H-thieno[3,2-e][1,2,4]triazepin-5-one (10a)

Potassium tert-butoxide (0.36 g, 3.2 mmol) was added to a stirred solution of 8a (0.51 g, 1.6 mmol) in dry tert-butanol (30 ml). The resulting orange-colored mixture was refluxed for 1 h during which the solution gradually acquired a dark-red coloration. The reaction mixture was cooled and treated with cold water (2 ml) and acetic acid (1 ml). The organic solvents were evaporated from the reaction mixture, the residue was treated with water (50 ml) and extracted with dichlormethane (3 x 30 ml). The combined organic extracts were dried (MgSO4), decolorized with norite, and the solvent was evaporated. The residual solid was finally purified on preparative thick-layer chromatography (Merek silica gel 60 HF-254 glass plates) using dichlormethane/methanol (50:1, v/v) as solvent mixture. Yield of 10a: 0.14 g (36%), m.p. 173 – 174 °C. – 1H NMR (300 MHz, CDCl3): δ = 6.75 (dd, J = 8.5 Hz, 1.1 Hz, 2H, 2’-H / 6’-H), 7.00 (br t, J = 7.6 Hz, 1.1 Hz, 1H, 4’-H), 7.23 (dd, J = 8.5 Hz, 7.6 Hz, 2H, 3’-H / 5’-H), 7.26 (br s, 1H, N(1)-H), 7.39 (d, J = 5.3 Hz, 1H, 8-H), 7.84 (d, J = 5.3 Hz, 1H, 7-H), 8.31 (br s, 1H, 2-H). – 13C NMR (75 MHz, CDCl3): δ = 114.6 (C-2’/C-6’), 123.2 (C-5a + C-4’), overlapped signals), 125.5 (C-8), 129.5 (C-3’/C-5’), 135.4 (C-7), 146.4 (C-1’), 149.6 (C-2), 156.7 (C-8a), 157.0 (C=O). – C21H15N3O5S (423.29): calcd. C 59.24, H 3.66, N 17.14, S 9.42; found C 59.02, H 3.73, N 17.27, S 9.42.
4-(4-Methylphenyl)-1,4-dihydro-5H-thieno[3,2-e][1,2,4]triazepin-5-one (10b)

10b was obtained via cyclocondensation of 8b (0.53 g, 1.6 mmol) with potassium tert-butoxide (0.36 g, 3.2 mmol), following the same procedure and experimental conditions as described above for the preparation of 9a. Yield: 0.14 g (34%), m. p. 168 – 169 °C. – 1H NMR (300 MHz, CDCl3): δ = 2.24 (s, 3H, CH3), 6.67 (d, J = 8.4 Hz, 2H, 2'-H/6'-H), 7.02 (d, J = 8.4 Hz, 2H, 2'-H/6'-H), 7.33 (br s, 1H, N(1)-H), 7.38 (d, J = 5.3 Hz, 1H, 8-H), 7.82 (d, J = 5.3 Hz, 1H, 7-H), 8.32 (brs, 1H, 1H, 2-H). – 13C NMR (75 MHz, CDCl3): δ = 20.7 (CH3), 115.1 (C-2'/C-6'), 123.8 (C-5a), 125.5 (C-8), 128.2 (C-4'), 129.5 (C-8a), 132.8 (C-4'), 135.3 (C-7), 144.0 (C-1'), 149.6 (C-2), 156.8 (C-8-a), 57.0 (C=O) – C13H11N3O S (257.31): calcd. C 60.68, H 4.31, N 16.33, S 12.46; found C 60.42, H 2.94, N 15.01, S 12.33.

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