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

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Z. Naturforsch. **61b,** 65 – 68 (2006); received September 26, 2005

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

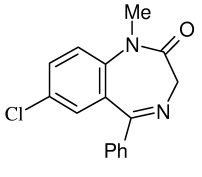
The synthetic interest in 1,4-benzodiazepines (*e.g.* diazepam/valium (**1**)) arising from their well-established role as potential psychotherapeutics [1] has promoted investigations of their nitrogen homologues, the benzotriazepines. Several studies have reported the preparation of members of the 1,3,4-benzotriazepine 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(3*H*)-thieno[3,2-*d*]pyrimidinones (**5**), but the isomeric thieno[3,2-*e*][1,2,4]triazepin-5-ones (**6**) were not isolated [5].

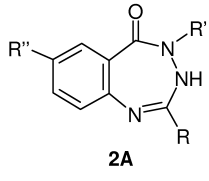
Accordingly, the present work aims at the synthesis of some thienotriazepinones (**10a – c**) *via* a two-step route utilizing available reactants: methyl 3-aminothiophene-2-carboxylate (**4**) and appropriate *N*-arylhydrazonoyl chlorides **7a – c** (Scheme 2).

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*

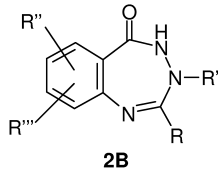


1



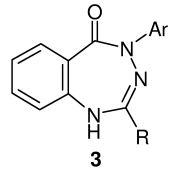
2A

R = H; Me; Et; Bu; Ph, 2-Py
R'= H; Me
R"= H; Me; Cl; Br; NO_2



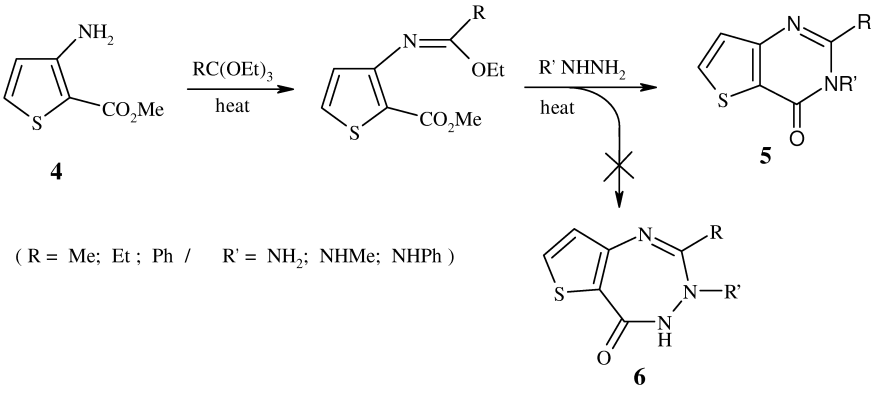
2B

R = NH_2; alkylthio
R'= 2-furoyl
R" and R"' = H; alkoxy

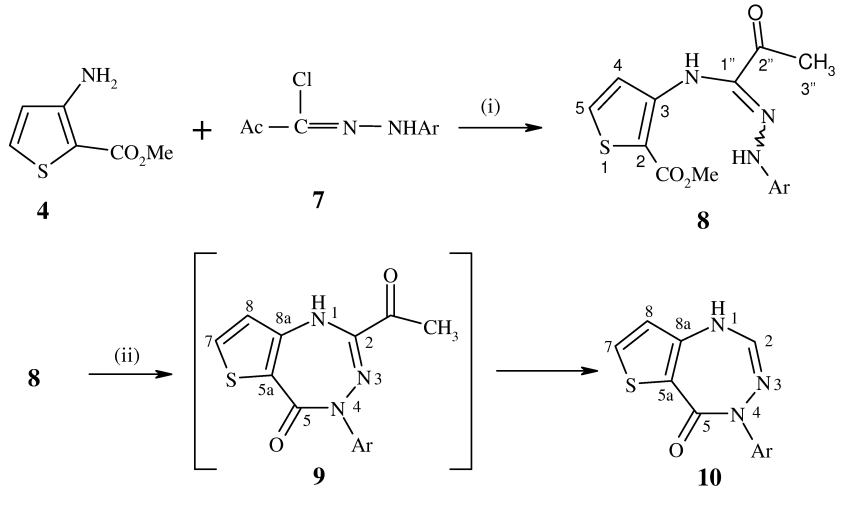


3

Ar = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4



Scheme 1.



Scheme 2.

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 ^{1}H / ^{13}C 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. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument with Me_3Si as internal reference. EIMS spectra

were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 °C. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were preformed at the Microanalytical Laboratory of the Inorganic Chemistry Department, Tübingen University, Germany.

*1-(N-Arylhydrazono)-1-chloropropanones (**7a** – **c**)*

The hydrazonoyl chlorides **7a** [8 – 10], **7b** [8, 9] and **7c** [8 – 10] were previously characterized, and were prepared in this study *via* the Japp-Klingemann reaction [11, 12] that involves direct coupling of the appropriate arenediazonium chloride with 3-chloropentane-2,4-dione in aqueous pyridine, following standard procedures [8, 9].

*Methyl 3-{[2-oxo-1-(N-phenylhydrazono)propan-1-yl]-amino}thiophene-2-carboxylate (**8a**)*

A homogeneous solution of methyl 3-aminothiophene-2-carboxylate (**4**, 2.2 g, 14 mmol) in methanol (10 ml) and triethylamine (5 ml) was added dropwise to a stirred and cooled (0 °C) solution of 1-chloro-1-(*N*-phenylhydrazono)propanone (**7a**, 3.1 g, 16 mmol) in THF (40 ml) and triethylamine (4 ml). The resulting mixture was further stirred at 5 – 10 °C for 4 h and then at r. t. for 30 – 40 h. The organic solvents were then evaporated from the reaction mixture, and the remaining solid product was collected, washed with water, soaked in cold ethanol (5 ml) and finally recrystallized from ethanol. Yield of **8a**: 3.2 g (72%), m. p. 176 – 177 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.52$ (s, 3H, O=C-CH_3), 3.82 (s, 3H, OCH_3), 6.21 (d, $J = 5.4$ Hz, 1H, 4-H), 6.99 (t, $J = 7.1$ Hz , 1H, 4'-H), 7.18 (d, $J = 7.7$ Hz, 2H, 2'-H/6'-H), 7.29 (d, $J = 5.4$ Hz, 1H, 5-H), 7.35 (dd, $J = 7.1$ Hz, 7.7 Hz, 2H, 3'-H/5'-H), 8.20 (s, 1H, C1'-N*H*), 8.35 (s, 1H, C3-N*H*). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.4$ (O=C-*C*H_3), 51.8 (OCH_3), 105.8 (C-2), 114.1 (C-2'/C-6'), 119.1 (C-4), 122.5 (C-4'), 129.5 (C-3'/C-5'), 131.8 (C-5), 135.2 (C-3), 142.6 (C-1'), 148.8 (C-1"), 164.7 (O=*C*-OMe), 193.0 (O=*C*-CH_3). – $C_{15}H_{15}N_3O_3S$ (317.36): calcd. C 56.77, H 4.76, N 13.24, S 10.10; found C 56.48, H 4.65, N 13.06, S 9.94.

*Methyl 3-{[1-(4-methylphenylhydrazono)-2-oxopropan-1-yl]amino}thiophene-2-carboxylate (**8b**)*

This compound was prepared from **4** (2.2 g, 14 mmol) and **7b** (3.14 g, 16 mmol), following the same procedure and experimental conditions as described above for obtaining **8a**. Yield: 3.1 g (67%), m. p. 174 – 175 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.33$ (s, 3H, Ar-CH_3), 2.52 (s, 3H, O=C-CH_3), 3.85 (s, 3H, OCH_3), 6.20 (d, $J = 5.4$ Hz, 1H, 4-H), 7.07 (d, $J = 8.6$ Hz, 2H, 2'-H/6'-H), 7.11 (d, $J = 8.6$ Hz, 2H, 3'-H/5-H'), 7.27 (d, $J = 5.4$ Hz, 1H, 5-H), 8.05 (s, 1H, C1'-N*H*), 8.33 (s, 1H, C3-N*H*). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.8$ (Ar-*C*H_3), 24.4 (O=C-*C*H_3), 51.8 (OCH_3), 105.2 (C-2), 114.1 (C-2'/C-6'), 119.2 (C-4), 129.9 (C-3'/C-5'), 131.7 (C-5), 132.2 (C-4'), 134.9 (C-3), 140.2 (C-1'), 148.8 (C-1"), 164.7 (O=*C*-OMe), 192.9 (O=*C*-CH_3). – $C_{16}H_{17}N_3O_3S$ (331.39): calcd. C 57.99, H 5.17, N 12.68, S 9.68; found C 58.07, H 5.20, N 12.55, S 9.42.

*Methyl 3-{[1-(4-chlorophenylhydrazono)-2-oxopropan-1-yl]amino}thiophene-2-carboxylate (**8c**)*

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. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.51$ (s, 3H, O=C-CH_3), 3.82 (s, 3H, OCH_3), 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, C1'-N*H*), 8.37 (s, 1H, C3-N*H*). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.4$ (O=C-*C*H_3), 51.9 (OCH_3), 106.0 (C-2), 115.3 (C-2'/C-6'), 119.1 (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=*C*-OMe), 192.9 (O=*C*-CH_3). – $C_{15}H_{14}ClN_3O_3S$ (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 dichloromethane (3×30 ml). The combined organic extracts were dried ($MgSO_4$), decolorized with norite, and the solvent was evaporated. The residual solid was finally purified on preparative thick-layer chromatography (Merck silica gel 60 HF-254 glass plates) using dichloromethane/methanol (50 : 1, v/v) as solvent mixture. Yield of **10a**: 0.14 g (36%), m. p. 173 – 174 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.75$ (dd, $J = 8.5$ Hz, 1.1 Hz, 2H, 2'-H/6'-H), 7.00 (tt, $J = 7.6$ 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). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 114.6$ (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). – $C_{12}H_9N_3O$ S (243.29): calcd. C 59.24, H 3.73, N 17.27, S 13.18; found C 59.02, H 3.66, N 17.14, S 12.95.

*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. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.24$ (s, 3H, CH_3), 6.67 (d, $J = 8.4$ Hz, 2H, 2'-H/6'-H), 7.02 (d, $J = 8.4$ Hz, 2H,3'-H/5'-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, 2-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.7$ (CH_3), 115.1 (C-2'/C-6'), 123.8 (C-5a), 125.5 (C-8), 130.0 (C-3'/C-5'), 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). – $C_{13}H_{11}N_3O$ S (257.31): calcd. C 60.68, H 4.31, N 16.33, S 12.46; found C 60.42, H 4.18, N 16.05, S 12.33.

*4-(4-Chlorophenyl)-1,4-dihydro-5H-thieno[3,2-e][1,2,4]triazepin-5-one (***10c***)*

10c was obtained *via* cyclocondensation of **8c** (0.56 g, 1.6 mmol) with potassium *tert*-butoxide (0.36 g, 3.2 mmol) in *tert*-butanol (30 ml) under reflux for 2 h. The reaction mixture was worked-up, following the same procedure as described above for the preparation of **9a**, and the crude solid product was purified on preparative silica gel plates, using dichloromethane / methanol (50 : 2, v/v) as solvent. Yield: 0.11 g (25%), m. p. 154 – 155 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.65$ (d, $J = 8.6$ Hz, 2H, 2'-H/6'-H), 7.16 (d, $J = 8.6$ Hz, 2H, 3'-H/5'-H), 7.39 (d, $J = 5.3$ Hz, 1H, 8-H), 7.53 (br s, 1H, N(1)-H), 7.85 (d, $J = 5.3$ Hz, 1H, 7-H), 8.28 (br s, 1H, 2-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 115.9$ (C-2'/C-6'), 123.7 (C-5a), 125.6 (C-8), 128.2 (C-4'), 129.5 (C-3'/C-5'), 135.6 (C-7), 145.0 (C-1'), 149.5 (C-2), 156.7 (C-8a), 157.1 (C=O). – $C_{12}H_8ClN_3O$ S (277.73): calcd. C 51.90, H 2.90, Cl 12.77, N 15.13, S 11.55; found C 51.72, H 2.94, Cl 12.56, N 15.01, S 11.28.

Acknowledgement

We wish to thank Internationales Büro des Bundesministeriums für Bildung und Forschung (Bonn, Germany) for financial support.

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