Synthesis of tri- and tetracyclic heterocycles related to cyclohexa- and cyclohepta[b]thiophenes

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Synthesis of a number of tri- and tetracyclic compounds with a fused thiophene ring starting from spiro[benzo[b]thiophene-6(5H), 1'-cycloalkyl]-4(7H)-one I (R = H, Me, Et and n = 4, 5) and cyclohepta[b]thiophenone 2 (R1 = H, R2 = Me and R3R4 = -(CH2)n) is described.

Literature1 abounds with examples of polycondensed heterocycles incorporating a fused thiophene ring, which have been synthesized using 6,7-dihydrobenzo[b]thiophene-4(5H)-one. Many of these compounds2 have proved to be biologically active. To the best of our knowledge reports of such venture with thienspiroketones of the type 1 and cyclohepta[b]thiophenone of the type 2 are lacking in the literature. We have exploited these two key intermediates in the synthesis of hitherto unreported tri- and tetracyclic compounds containing nitrogen, oxygen and sulphur heterocycles.

Intermediates 1a-d and 2a, have been prepared by Friedel-Crafts acylation of the appropriate thiophene with substituted succinic or glutaric anhydride in dichloromethane2 followed by successive reduction (Clemmensen for 1a-d and Huang-Minlon3 for 2a) and cyclisation with polyphosphoric acid4. Here it is relevant to mention our finding2 that acylation of thiophene with substituted succinic anhydrides in dichloromethane yields keto acid with substituent away from the carboxyl group, but in nitrobenzene solvent it is towards the carboxyl group. Intermediate 2b has been prepared by the following sequence of reactions: succinoylation of thiophene in the presence of anhydrous aluminium chloride in dichloromethane at −5 − 0 °C, Huang-Minlon reduction, cyclisation with acetic anhydride - polyphosphoric acid, Clemmensen reduction, glutaroylation, Huang-Minlon reduction and polyphosphoric acid cyclisation.

Formylation of 1 and 2 at the methylene carbon adjacent to the carbonyl group with sodium hydroxide and ethyl formate yielded the formyl derivatives 3 and 8, respectively. The poor yield of 3 may be attributed to the steric factor of the cycloalkyl group. The 1H NMR spectra of the formyl derivatives 3 and 8 showed a one-proton doublet (J = 8-10 Hz) around δ 14.6 proving the predominant existence of the hydroxymethylene form.

The hydroxymethylene compounds 3 and 8 were used as the starting material for the synthesis of two groups of tetracyclic heterocycles (4, 9 and 5, 10). The isoxazole derivatives 4 and 9 were obtained following a nucleophilic attack by hydroxylamine hydrochloride at the aldehydic carbon with successive elimination of two molecules of water. The structures of these condensed heterocycles were established through spectral analyses (vide Experimental). For example, 7-methyl-4,4-spirocyclopentane-4,5-dihydrothieno [1',2':5,6]cyclohexa[2,1-d]isoxazole 5 (R = Me, n = 4) showed a one-proton singlet at δ 8.1 which was assigned to the proton of -N=CH- moiety.

Replacement of hydroxylamine hydrochloride by hydrazine hydrate resulted in the formation of the corresponding pyrazole derivatives (5b, 5d and 10). The structures of these pyrazole fused products were established through spectral analyses. For example, 7-methyl-4,4-spirocyclohexane-4,5-dihydrothieno...
[1',2':5,6]cyclohexa[2,1-d]pyrazole 6 (R = Me, n = 5) showed a one-proton singlet at δ 7.2 owing to –N=C-H moiety (Schemes I and II).

A thiophene ring was annelated to thienospiroketone 1 (R = Me, n = 4) and cyclohepta[b]thiophenone 2 (R' = Me, R'' = H) through Vilsmeier-Haack reaction using phosphorus oxychloride and N,N-dimethylformamide and subsequently treatment of the corresponding chloroaldehydes 6 (R = Me, n = 4) and 11 (R' = Me, R'' = H) with ethyl mercaptoacetate in the presence of sodium ethoxide. The final step in the sequence of reactions involved the nucleophilic displacement of the chlorine atom by ethyl mercaptoacetate followed by intramolecular aldol condensation. The structures of the dithieno compounds 7 and 12 were established through 1H NMR spectra. For example, the 1H NMR spectrum of the dithieno compound 7 (R = Me, n = 4) showed two aromatic proton signals at δ 7.0 and 8.3 due to H3 and H5, respectively (Scheme I).

**Experimental Section**

**General:** All mps and bps are uncorrected. Infra-red spectra were taken on Pye Unicam SP 200G and Perkin Elmer 298 spectrometers in KBr or liquid film (υmax in cm–1). 1H NMR spectra were recorded on Varian-60 MHz, Jeol FX-90, 90 MHz and Bruker AC 200 MHz and Bruker AM 300L, 300 MHz. Super Con Spectrometers. Chemicals shifts are expressed in δ, ppm using tetramethylsilane as internal standard. C, H and N analyses of the unknown compounds are within experimental error.

Alkylthiophenes6,5 and cycloalkyl-1-carboxy-1-acetic and their corresponding anhydrides5 were prepared by the standard literature method. The characteristics of the cyclic ketones have already been described7.

**General procedure for the formylation of the cyclic ketones 1 and 2.** Ethyl formate (0.005 mole) in sodium-dried benzene (5 mL) was added dropwise over a period of 10 min under nitrogen atmosphere to the oil-free sodium hydride (0.01 mole) in dry benzene (10 mL) with continuous stirring at 0 °C. The cyclic ketone (0.005 mole) in dry benzene (5 mL) was then added during a period of 10 min. After stirring for 5 hr at that temperature the reaction mixture was
decomposed with ice-cold water. The organic layer was separated, washed with water and dilute sodium hydroxide solution. Acidification of the combined aqueous layer in the cold condition afforded the formylated product which was crystallised from ethanol.

5-Formylspiro[benzo[b]thiophen-6(5H), 1'-cyclopentan]-4(7H)one 3a (R=H, n=4): Yield 59%, oil (crude); IR (Neat): 1670, 1625; 1H NMR (60 MHz, CCl4): δ 1.80 (8H, br s, cyclopentane ring), 2.90 (2H, s, ArCH2), 7.10 (1H, d, J = 5 Hz, Ar-H), 7.35 (1H, d, J = 5 Hz, Ar-H), 7.60 (1H, br s, CHO).

5-Formyl-2-methylspiro[benzo[b]thiophen-6(5H), 1'-cyclohexan]-4(7H)one 3b (R=Me, n=4): Yield 55%, mp 121°C; IR (KBr): 3660-3220, 1665, 1628; 1H NMR (300 MHz, CDCl3): δ 1.50-1.80 (10H, m, cyclohexane ring), 2.45 (3H, s, ArCH), 2.85 (2H, s, ArCH2), 7.05 (1H, s, Ar-H), 7.35 (1H, d, J = 5 Hz, Ar-H), 7.58 (1H, d, J = 5 Hz, CHO).

2-Ethyl-5-formylspiro[benzo[b]thiophen-6(5H), 1'-cyclopentan]-4(7H)one 3c (R=Et, n=4): Yield 49%, mp 86 °C; IR (KBr): 1622; 1H NMR (300 MHz, CDCl3): δ 1.30 (3H, t, J = 5Hz, CH2CH3), 1.60-1.80 (8H, m, cyclopentane ring), 2.80 (2H, q, J = 5 Hz, CH2CH3), 2.90 (2H, s, ArCH2), 7.10 (1H, s, Ar-H), 7.60 (1H, d, J = 10 Hz, CHO).

9-Hydroxymethylene-1,2,3,4-tetrahydrobenzo-[2,3-e]cyclohepta[2',3'-j]thiophen-10-one 8: Yield 81%, mp 82-83 °C; IR (KBr): 1620; 1H NMR (200 MHz, CDCl3): δ 1.50-2.10 (6H, m, ArCH2CH2CH2 and HOHC=CHCH2), 2.60-2.90 (8H, m, 3 × ArCH2 and HOHC=CHCH2), 8.00 (1H, d, J = 8 Hz, CHO).

General procedure for the conversion of the formyl derivatives 3 and 8 to the isoxazole derivatives 4 and 9. A mixture of hydroxymethylene compound (0.004 mole) in rectified spirit (10 mL) and hydroxylamine hydrochloride (0.0045 mole) in water (1 mL) was refluxed on a water-bath for 1 hr after which the reaction mixture was cooled and poured into ice-cold water. The solid obtained was extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulphate. Removal
of ether afforded a solid which was crystallized from ethanol.

4,4'-Spirocyclopentane-4,5-dihydrothiieno[1',2':5,6']cyclohexa[2,1-d]pyrazole 5a: Yield 87%, mp 196 °C; 1H NMR (300 MHz, CDCl3): 1.30-1.55 (10H, m, cyclopentane ring), 2.45 (3H, s, ArCH3), 2.65 (1H, s, ArCH2), 2.85 (1H, s, ArCH), 7.15 (1H, s, Ar-I), 7.25 (1H, s, N=CH).

7-Methyl-4,4'-spirocyclopentane-4,5-dihydrothiieno[1',2':5,6']cyclohexa[2,1-d]pyrazole 5b (R=Me, n=5): Yield 87%, mp 196 °C; 1H NMR (300 MHz, CDCl3): 1.30-1.55 (10H, m, cyclopentane ring), 2.45 (3H, s, ArCH3), 2.65 (1H, s, ArCH2), 2.85 (1H, s, ArCH), 7.15 (1H, s, Ar-I), 7.25 (1H, s, N=CH).

8,9,10,11-Tetrahydrobenzo[b]thieno[1',2':6,7']cyclohepta[2,1-d]pyrazole 10: Yield 82%, mp 140-43 °C; 1H NMR (300 MHz, CDCl3): 1.30 80-1.95 (6H, m, ArCH2CH2CH2 and C=C=CH2CH2), 2.00-2.15 (2H, m, C=CH2), 2.65-3.10 (6H, m, 3 × ArCH2), 7.40 (1H, s, N=CH).

General procedure for the chloroformylation of the cyclic ketones 1b and 2a. Freshly distilled phosphorus oxychloride (0.11 mole) was added dropwise during a period of 10 min to the freshly distilled dimethylformamide (20 mL) while stirring magnetically and cooling in an ice-salt bath. The mixture was then stirred for a period of 15 min followed by the addition of the cyclic ketone (0.01 mole) in dry dimethylformamide (10 mL) during 20 min under the same condition. Stirring was continued for a further period of 30 min after which it was heated on a water-bath for 2 hr. The reaction mixture was cooled and poured into ice-cold sodium acetate solution (25 mL, 10% w/v). The oily material was extracted with ether. Usual work-up afforded a dark brown viscous liquid which was distilled under reduced pressure.

2-Methyl-4-chloro-5-formyl-6,7-dihydrospiro[benzo[b]thiophen-6,1'-cyclopentane 6 (R=Me, n=4): Yield 81% (crude); IR (KBr): 1673; 1H NMR (90 MHz, CDCl3): 1.75-1.95 (6H, m, ArCH2CH2CH2 and C=C=CH2CH2), 2.01 (2H, m, C=CH2CH2), 2.65-2.80 (4H, m, 2 × ArCH2), 3.05 (2H, m, ArCH), 8.05 (1H, s, N=CH).
added dropwise to it at the same temperature and the mixture stirred further for a period of 5 min. This was followed by the addition of the chloroaldehyde (0.006 mole) and stirring for 3 hr. The reaction mixture was kept overnight at room temperature and then extracted with ether. Usual work-up afforded a yellow liquid which was distilled under reduced pressure.

**Compound 7 (R=Me, n=4):** Yield 63%, bp 138-40 °C/2.2 mm; IR (KBr) : 1710; ¹H NMR (60 MHz, CDCl₃) : δ 1.30 (3H, t, J = 6 Hz, CO₂CH₂CH₃), 1.40-1.80 (8H, m, cyclopentane ring), 2.45 (3H, s, ArCH₃), 2.85 (2H, s, ArCH₂), 4.20 (2H, t, J = 6 Hz, CO₂CH₂CH₃), 7.00 (1H, br s, Ar-H), 8.30 (1H, br s, EtCO₂C=CH)

**2- Carbethoxy-8-methyl-5,6-dihydro-4(H)-thieno[1',2':6,7]cyclohepta[1,2-d]thiophene 12(R=Me):** Yield 73%, bp 210-12 °C/2.5 mm; IR (KBr): 1710; ¹H NMR (300 MHz, CDCl₃) : δ 1.35 (3H, t, J = 6 Hz, CO₂CH₂CH₃), 2.05 (2H, m, ArCH₂CH₂), 2.40 (3H, s, ArCH₃), 2.95 (2H, t, J = 6 Hz, ArCH₂CH₂CH₃), 3.05 (2H, t, J = 6 Hz, ArCH₂CH₂CH₃), 6.90 (1H, s, CH=CS), 7.45 (1H, s, HIC=CCO₂Et).

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**References**