Studies on Vilsmeier-Haack reaction : Formation of some Heterocyclic Annelated Compounds from 6,7,8,9-tetrahydrobenzocyclohepten-5-ones

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Abstract : Reaction of 5-chloro-7,8,9-trihydrobenzocyclohepten-6-carbaldehyde with ethyl/methyl thioglycolate yielding the corresponding 5,6-dihydro-4[H]thiopheno[2,3-c] benzocycloheptens, with phenylhydrazine gives pyrazolone derivatives. Other reactions were discussed.

In continuation of our interest in Vilsmeier-Haack reaction and its synthetic applications[1-3], we have synthesized the hitherto unreported thiophenes, thionopyrimidines, pyrazoles and Schiff derivatives starting from benzocyclohepten-5-ones.

Reaction of the 3-methyl-benzocyclohepten-5-one (**1a**) with phosphoryl chloride in dimethyl formamide at 0°C gave 5-chloro-3-methyl-7,8,9-trihydro-benzocyclohepten-6-carbaldehyde (**2a**) which cyclised to 2-ethoxy carbonyl-5,6-dihydro-9-methyl-4[H]-thiopheno[2,3-c]benzocyclohepten (**3a**) in good yield upon treatment with ethyl thioglycolate and sodium ethoxide. The infrared spectrum contained a strong C=O peak at 1706 cm^{-1} and the ^1H NMR spectra indicates isolated thiophene proton (3-H) as a singlet at δ 7.60 and the presence of ethyl protons at δ 4.25 and 1.35 as quartet and triplet respectively.

The observation that the chloroaldehydes react with urea, hydrazine and a variety of other diamines to give substituted pyrimidine, pyrazoles and quinolines[4-6] provided further opportunity to examine the fusion pyrimidine and pyrazole nucleus into the system. Reaction of the chloroaldehyde (**2a**) with thiourea and iodine gave the expected 10-methyl-5,6,7-trihydro-[2H]-thionopyrimidino[4,5-c]benzocyclohepten (**4a**). Similarly, condensation of **2a** with phenylhydrazine gave 7-methyl-4,5,6-trihydro-1-phenyl pyrazolo[3,4-c] benzocyclohepten (**5a**).

Analogues **3b-d, 4b** and **5b-d** were similarly obtained by the same procedure. The structure of the compounds were established on the basis of their IR, ^1H NMR and Mass spectra and elemental analysis.

The reactivity of aldehydic group prompted us to investigate the condensation reaction with ethylenediamine. Condensation of **2a** with ethylenediamine in 2:1 molar ratio in refluxing

ethanol resulted in the formation of Schiff bases N,N[1]-bis (5-chloro-3-methylbenzocycloheptен-4-yl-methylene) ethylenediamine (**6a**) as colourless crystals.

Antibacterial activity : The compounds **3, 5** and **6** were evaluated for their antibacterial activity by disc-plate procedure against *Escherichia coli*, *Staphylococcus aureus* in the concentration range 30-40 μg/disc. In comparision with standard drug Nalidixic acid, **3a-d** and **5a-c** showed moderate activity against *E. coli* but **3a-b** resistant towards *S. aureus*. Whereas **5a-c** were approximately 50-80% inhibition against *S. aureus*. **6a-b** showed moderate activity towards *S. aureus* but 80% inhibition against *E. coli*.

Invitro evaluation of anti-tuberculosis activity : Primary screening of all compounds for anti-tubercular activity have been conducted as 12.5 μg/ml against mycobacterium tuberculosis H37RV in BACTEC 12B medium using the BACTEC 460 radiometric system.

The compounds **5a-d** showed 40-50% inhibition against mycobacterium tuberculosis H37RV as compared with standard drug Rifampin as 0.25 to 0.031 g/ml concentration.

Experimental : All Melting points are uncorrected. IR spectra were obtained on a Schimadzu 470 spectrometer, ^{1}H NMR spectra were obtained using a varian FT 80A spectrometer in $CDCl_3$ with TMS as an internal standard and Mass spectra on a VG high resolution 7070H and Funnigan Met 1020 B mass spectrometers.

5-Chloro-3-methyl-7,8,9-trihydrobenzocyclohepten-6-carbaldehyde (2a-b) :

General Procedure : Freshly distilled phosphorous oxychloride (0.6 ml, 6 mmol) was added at 0°C to stirred DMF (4 ml), followed by 3-methyl benzocycloheptenone[7] (1 g, 6 mmol). After 30 minutes at 0°C and 90 minutes at 80°C, the cooled reaction mixture was poured into crushed ice and neutralised with sodium acetate. Extraction with ether, drying and removal of solvent afforded compound **2a** (0.9 g, 78%) as an oil which was used directly to the next step without further purification, IR : 1665 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 2.18-2.25 (2H, m, 8-CH_2), 2.40 (3H, s, CH_3), 2.65-3.05 (4H, m, 7 & 9-CH_2), 7.10-7.40 (3H, m, aromatic), 10.37 (1H, s, CHO) [Found : C, 70.93; H, 5.91. $C_{13}H_{13}ClO$ requires C, 70.90 ; H, 5.90%].

Compound 2b : Obtained as liquid (1.02 g, 80%), IR : 1665 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 2.16-2.25 (2H, m, 8-CH_2), 2.65-3.00 (4H, m, 7 & 9-CH_2), 7.05-7.40 (4H, m, aromatic), 10.35 (1H, s, CHO); [Found : C, 69.95, H, 5.35. $C_{12}H_{11}ClO$ requires C, 69.90; H, 5.33%].

9-Methyl-2-Ethoxy/methoxy carbonyl-5-6-dihydro-4[H]thiopheno [2,3-c] benzocyclohepten (3a-d):

General Procedure : Ethyl/methyl thioglycolate (0.1 ml) was added to a cooled, stirred solution of sodium (0.05 g) in dry ethanol/methanol (5 ml). A solution of 5-chloro-3-methyl-7,8,9-

trihydrobenzocyclohepten-6-carbaldehyde (**2a**) (0.22 g, 1 mmol) in methanol (5 ml) was added drop wise during 0.5 h at 0-5°C, and the mixture was stirred overnight at room temperature, boiled for 0.5 h, cooled and poured into water. The ester **3a** was filtered off, and obtained as amorphous powder (0.2 g, 75%), which was crystallised from methanol, m.p. 215°C, IR (KBr): 1706 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) : δ 1.35 (3H, t, OCH_2-$\underline{CH_3}$), 2.10 (2H, m, 5-CH_2), 2.40 (3H, s, CH_3), 2.59-2.75 (4H, m, 4 & 6-CH_2), 4.25-4.42 (2H, q, -$\underline{OCH_2}$-CH_3). 7.05-7.30 (3H, m, aromatic), 7.60 (1H, s, 3-H); m/z 286 ($M^{+\cdot}$) [Found C, 71.30; H, 6.30. $C_{17}H_{18}O_2S$ requires C, 71.32; H, 6.29%].

Compound 3b : Yield (75%), m.p. 230°C (decomp); IR (KBr) : 1705 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.32 (3H, t, OCH_2-$\underline{CH_3}$), 2.09 (2H, m, 5-CH_2), 2.56-2.72 (4H, m, 4 & 6-CH_2), 4.20-4.39 (2H, q, -$\underline{OCH_2}$-CH_3), 7.25-7.40 (4H, m, aromatic), 7.62 (1H, S, 3-H); m/z 272 ($M^{+\cdot}$) [Found : C, 70.60; H, 5.87. $C_{16}H_{16}O_2S$ requires C, 70.58; H, 5.88%].

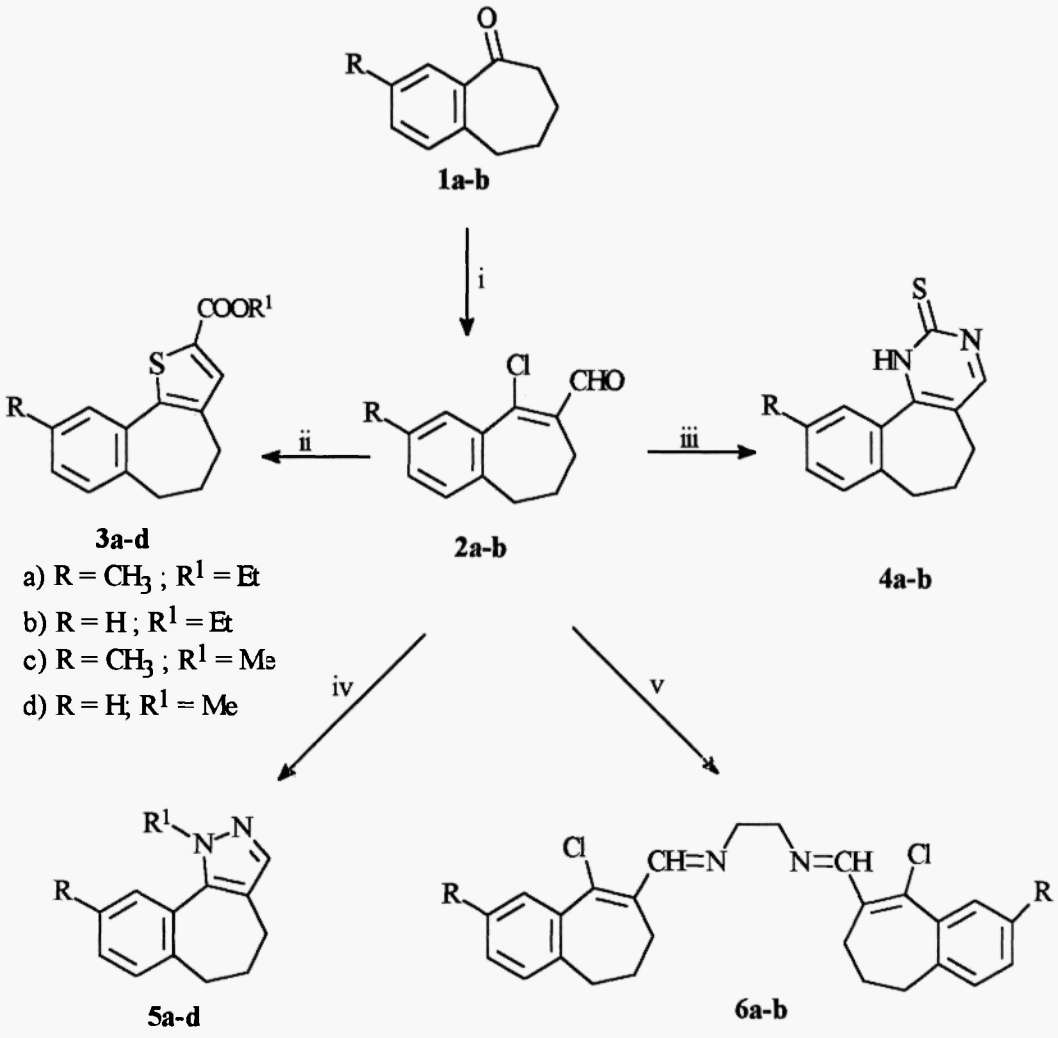
Compound 3c : Yield (74%), IR (KBr) : 1706 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.10 (2H, m, 5-CH_2), 2.40 (3H, s, CH_3), 2.59-2.75 (4H, m, 4 & 6-CH_2), 3.95 (3H, s, OCH_3), 7.00-7.30 (3H, m, aromatic), 7.65 (1H, s, 3-H); m/z 272 ($M^{+\cdot}$) [Found : C, 70.61; H, 5.89. $C_{16}H_{16}O_2S$ requires C, 70.58 ; H, 5.88%].

Compound 3d : Yield (73%), b.p. 147-150°C / 0.05 mm (lit.[8] 148-150 / 0.05 mm), IR (KBr) : 1705 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.20 (2H, m, 5-CH_2), 2.55-2.70 (4H, m, 4 & 6-CH_2), 3.90 (3H, s, -OCH_3), 7.22-7.35 (4H, m, aromatic), 7.65 (1H, s, 3-H); m/z 258 ($M^{+\cdot}$) [Found : C, 69.79; H, 5.44. $C_{15}H_{14}O_2S$ requires C, 69.76; H, 5.42%].

10-Methyl-5,6,7-trihydro-2[H]-thionopyrimidino[4,5-c]benzocyclohepten (4a-b) :

General procedure : A mixture of **2a** (0.22 g, 1 mmol), thiourea (0.15 g, 2 mmol) and iodine (0.127g, 1 mmol) were refluxed for 2-3 h in absolute ethanol (5 ml). Thin layer chromatography showed the absence of the ketone and the resulting hydroiodide was dissolved in hot water. The solution was filtered while hot and the clear filterate was neutralised with a strong solution of ammonia. The precipitate was collected and recrestallized from petroleum ether / benzene (1:1) gave 4a (50 mg, 22%), as colourless crystals, m.p. 260°C (decomp.); ^1H NMR ($CDCl_3$) : δ 2.15 (2H, m, 6-CH_2), 2.35 (3H, s, CH_3), 2.65 (2H, t, 5-CH_2), 2.80 (2H, t, 7-CH_2), 7.00-7.28 (3H, m, aromatic), 8.20 (1H, s, 4-H pyrimidine); m/z 242 ($M^{+\cdot}$) [Found : C, 69.45; H, 5.80; N, 11.58. $C_{14}H_{14}N_2S$ requires C, 69.42; H, 5.78; N, 11.57%].

Compound 4b : Yield 15%, m.p. 210°C (decomp); ^1H NMR ($CDCl_3$) : δ 2.17 (2H, m, 6-CH_2), 2.65 (2H, t, 5-CH_2), 2.80 (2H, t, 7-CH_2), 7.00-7.30 (4H, m, aromatic), 8.15 (1H, s, 4-



Reagents : i) DMF / $POCl_3$, 0°C; ii) NaOMe, Ethyl / methylthioglycolate in ethanol / methanol R.T, 24 h; iii) Thiourea / Iodine, Ethanol reflux, 36 h; iv) Phenylhydrazine / Hydrazine hydrate, ethanol reflux, 8-9 h. v) Ethylenediamine, ethanol reflux 24 h.

H pyrimidine); m/z 228 (M^+) [Found: C, 68.45; H, 5.25; N, 12.30. $C_{13}H_{12}N_2S$ requires C, 68.42; H, 5.26; N, 12.28%].

9-Methyl-1-phenyl-4,5,6-trihydro pyrazolo [3,4-c] benzocyclohepten (5a-d) :

General procedure : To ethanolic solution of **2a** (0. 22g, 1 mmol) an excess of phenylhydrazine (1.5 mmol) was added, triethylamine was added as catalyst and refluxed 8-9 h. It was then filtered and the filterate was concentrated. The resulting gummy solid was purified by chromatography on silica gel in petroleum ether (b.p. 60-80°C) gave **5a** (0.15 g, 54%). The solid was recrystallised from ethanol, m.p. 80-82°C; ^{1}H NMR ($CDCl_3$) : δ 2.18 (2H, m, 5-CH_2), 2.40 (3H, s, CH_3), 2.60 (2H, t, 4-CH_2), 2.81 (2H, t, 6-CH_2), 7.22 (1H, s, 3-H), 7.32-7.50 (8H, m, aromatic); m/z 274 (M^+) [Found: C, 83.24; H, 6.58; N, 10.25. $C_{19}H_{18}N_2$ requires. C, 83.21; H, 6.56; N, 10.21%].

Compound 5b : Yield 60%, m.p. 95-97°C; ^{1}H NMR ($CDCl_3$) : δ 2.62 (2H, t, 4-CH_2), 2.80 (2H, t, 6-CH_2), 7.23 (1H, s, 3-H), 7.30-7.55 (9H, m, aromatic). m/z 260 (M^+) [Found: C, 83.10; H, 6.18; N, 10.80. $C_{18}H_{16}N_2$ requires C, 83.07; H, 6.15; N, 10.76%].

Compound 5c : Yield 50%, m.p. 158-160°C; IR (KBr) 3300 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 2.28 (2H, m, 5-CH_2), 2.35 (3H, s, CH_3), 2.50 (2H, t, 4-CH_2), 2.65 (2H, t, 6-CH_2), 7.08 - 7.35 (3H, m, aromatic), 7.40 (1H, s, 3-H), 8.89 (1H, s, NH); m/z 198 (M^+) [Found: C, 78.95; H, 7.10; N, 14.15. $C_{13}H_{14}N_2$ requires C, 78.93; H, 7.07; N, 14.14%].

Compound 5d : Yield 50%, m.p. 145-48°C; IR (KBr) 3300 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 2.28 (2H, m, 5-CH_2), 2.50 (2H, t, 4-CH_2), 2.60 (2H, t, 6-CH_2), 7.08-7.40 (4H, m, aromatic), 7.42 (1H, s, 3-H), 8.89 (1H, s, NH); m/z 184 (M^+) [Found: C, 78.25; H, 6.53; N, 15.23. $C_{12}H_{12}N_2$ requires C, 78.26; H, 6.52; N, 15.21%].

N,N^1-bis(5-Chloro-3-methylbenzocyclohepten-6-yl-methylene)ethylenediamine [6a-b] :

General procedure : To a suspension of **2a** (0.22 g, 1 mmol) in ethanol (10 ml) was added ethylenediamine (0.5 mmol). The reaction mixture was heated at reflux for 24 h and then cooled to room temperature. The solid was collected by filteration and recrystallised from ethanol to give 10 a (0.3 g, 57%) as colourless crystals, m.p > 260°C (decomp); ^{1}H NMR ($CDCl_3$) : δ 2.10 (4H, m,-CH_2), 2.4 (10H, m,-CH_3 & -CH_2), 2.58 (4H, m,-CH_2), 3.98 [4H, s, (-N-$(CH_2)_2$], 7.08-7.40 (6H, m, aromatic), 8.55 [2H, s, (-CH=N)$_2$]; m/z 464 (M^+) [Found: C, 72.40; H, 6.48; N, 6.01. $C_{28}H_{30}N_2Cl_2$ requires C, 72.41; H, 6.46; N, 6.03%].

Compound 6b : Yield (30%), m.p. 238°C (decomp); ^{1}H NMR ($CDCl_3$) : δ 2.00 (4H, m,-CH_2), 2.38 (4H, m, -CH_2), 2.58 (4H, m, -CH_2), 3.98 [4H, s, (-N-$(CH_2)_2$], 7.00-7.45 (8H, m,

aromatic), 8.54 [2H, s, $(-CH=N)_2$]; m/z 436 (M^+) [Found: C, 71.52; H, 5.98; N, 6.44. $C_{26}H_{26}N_2Cl_2$ requires C, 71.55; H, 5.96; N, 6.42%].

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References

(1) J. Mc Lean, V. Peesapatic, G.R. Proctor, J. Chem. Soc., Perkin Trans.1, 98 (1979).

(2) V. Peesapati, N. Lingaiah, Org. Prep. Proced. Int., 25, 602 (1993).

(3) V. Peesapati, K. Anurdha. Indian J. Chem., 35B, 1287 (1996).

(4) J.K. Yay, S. Sharma, B. G. Chattergi. Synthesis. 326 (1980).

(5) R.A. Pawar, A.A. Patil. Indian J. Chem., 33B, 156 (1994).

(6) O. Meth-Cohn, B. Narine and B. Tarnowski, J. Chem. Soc., Perkin Trans. 1, 1520 (1981).

(7) a) S.G.S. Gupta, P. K. Sen, Sci. Cult. (Culcutta), 28, 343 (1992). b) L.F. Somerville, C.F.H. Allen, Org. Syn. Collective volumes 2, 81 (1941). c) R.C. Gilmore, Jr., and N.J. Harton, J. Am. Chem. Soc., 73, 1411 (1951).

(8). Asish De, S. Bhattacharya, S.S. Jash, S. Mukherjee, J. Heterocyclic Chem., 29, 1213 (1992).

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