ONE POT SYNTHESIS OF 1-N-(ACETYL/BENZOYL)-7-[(SUBSTITUTED PHENYL)-METHYLENE]-2-METHYL-6-OXO-3-THIOXO-1,2,4,5-TETRAAZAPERHYDROEPINS

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Abstract : Cycloaddition of substituted α–acetamido/benzamido cinnam hydrazides **[2(a-g)]** with methyl isothiocyanate (MITC) in presence of methanol, acetic acid mixture (1:1) yielded 1-N-(acetyl/benzoyl)-7-(substituted phenylmethylene)-2-methyl-6-oxo-3-thioxo-1,2,4,5-tetraazaperhydroepins **[3(a-g)]** in good yields.

Introduction

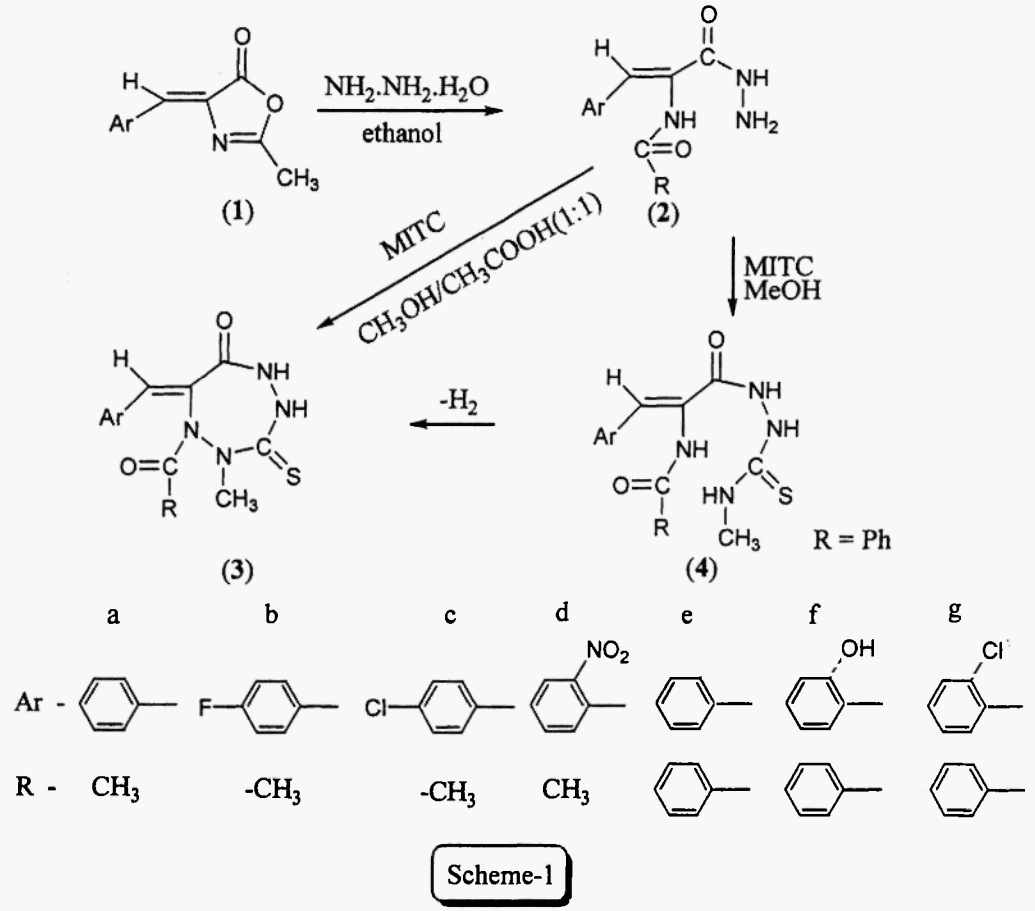
The 1,2,4,5-tetrazepin nucleus is a very significant heterocyclic system, having drug activity on the central nervous system, anticonvulsant activity[1], and carcinoma inhibitory activity[2].

Various methods have been employed in literature for the synthesis of substituted 1,2,4,5-tetraazepin derivatives (a) Reaction of vitamin K and pyruvic acid with thiocarbazide (H_2N-NH-CS-NH-NH_2) gave 1,2,4,5-tetrazepin-6-ones[3]. (b) Reaction of α–(1-phenyl hydrazino)alkanone phenyl hydrazones with acylating and sulphonating reagents attacked mostly at the primary amino group of the hydrazine function with carbonyl diimidazole converting it into 1(H)-1,2,4,5-tetrazepin-3-one derivatives[4]. (c) In another method 1,2,4,5-tetrazepin quinazolinone was synthesised by cyclisation of hydrazino quinoline with benzil[5].

In continuation of our synthesis of various heterocyclic compounds with methyl isothiocyanate[6,7,8], we herein report a facile one pot synthesis of the these title compounds.

Synthesis of the title compounds **(3a)** has been envisaged by the reaction of α–acetamido cinnam hydrazide **(2a)** with methyl isothio cyanate (MITC) in the presence of methanol and acetic acid mixture (1:1). The required **2a** was synthesized from 2-methyl oxazolin-5-one **(1)** through a two step synthetic sequence. The compounds were characterised based on its IR, ^{1}H NMR and Mass data. To test the generality, the method has been extended to six other cinnam hydrazides **[2(b-g)]** and in all cases the corresponding 1,2,4,5-tetraazaperhydroepines **[4(b-g)]** were isolated in good yields.

The formation of 1,2,4,5-tetraazaperhydroepines can be rationalised as follows. Addition of MITC over the nucleophilic amino group of **2** in methanol and acetic acid mixture (1:1) would lead to the formation of unstable intermediate which undergoes intramolecular cyclisation resulting 1,2,4,5-tetraazaperhydroepines **[3(a-g)]** by the elimination of hydrogen molecule, whereas the addition of MITC over the nucleophilic amino group of **2(a-g)** in methanol forms the stable intermediate (**4**) which undergo intramolecular cyclisation in presence of methanol:acetic acid mixture (1:1) resulting 1,2,4,5-tetraazaperhydroepins (**3**) by eliminating hydrogen molecule (Scheme – I).



Scheme-1

Experimental

The melting points were uncorrected and taken on sulphuric acid bath. IR spectra were recorded on KBr with Niodel 740 spectrometer FTIR and 1H NMR spectra on a Varian Gemini-200 MHz with TMS as internal standard and mass spectra were recorded on MSPC SCIEX API 3000 instrument.

Elemental analysis was measured by Yamaco CHN MT-3 apparatus and the purity of all the compounds was checked on silica gel G TLC plates using Iodine Vapours as visualising agent.

Synthesis of α–acetamido-cinnam hydrazides (2):

General Procedure: A solution of arylidine (substituted benzilidine)-2-methyl/phenyl-oxazolene-5-ones (**1**) (0.01 mole) in ethanol (30 ml) was added a solution of hydrazine hydrate (99%, 0.02 mole) in ethanol (5 ml). The deep yellow colour of the solution immediately changed to light yellow. The compound that separated out was filtered and recrystallised from methanol with 85% yield..

Synthesis of 1-(N-acetyl/benzoyl)-2-(N-methyl)-6-oxo-7-(substituted phenyl vinyl)-3-thio-1,2,4,5-tetraazapin-4(H),5(H)-perhydroins [4].

General Procedure: Equimolar quantities of cinnam hydrazides (**2**) (0.001M) and methyl isothiocyanate were dissolved in 1:1 mixture of methanol-acetic acid and refluxed for 4-5 hours. The solid that separated out after distilling under reduced pressure was washed with ethanol and dried. The compound gave single spot on TLC (benzene:ethyl acetate; 2:6).

2(a) Molecular formula - $C_{11}H_{13}O_2N_3$, Mol. wt. 219, % yield = 87, melting point 168°C. IR (KBr) λ_{max} cm^{-1} 3472, 3416 (d)NH_2, 3215 (NH), 3022 (C=C aromatic), 1676 (C=O), 1578 (C=N), ^{1}H NMR ($CDCl_3$) δ 2 (s, 3H, CH_3), 3.9 (d, 2H, NH_2), 6.8-7.6 (m, 5H, Ar), 8.4 (s, H, CH-Ar), 9.4 (s, H, CO-NH, D_2O exchangeable), 10.2 (t, H, NH-N, D_2O exchangeable), Mass m/z M^+ -220, Elemental analysis – Cal, C, 60.3, H, 5.94, N, 19.19. Found: C, 60.45; H, 6.0; N, 19.21.

2(b) Molecular formula - $C_{11}H_{12}O_3N_3F$, Mol. wt. 238, % yield = 90, melting point 180°C. IR (KBr) λ_{max} cm^{-1} 3478 (d, NH_2), 3201 (NH), 3061 (C=C aromatic), 1678 (C=O), ^{1}H NMR ($CDCl_3$) δ 2 (s, 3H, CH_3), 2.9 (d, 2H, NH_2), 6.9 (s, H, Ar-CH), 7.2-7.6 (d, 4H, Ar), 9.4 (s, H, NH, D_2O exchangeable), 10.0 (t, H, NH-N, D_2O exchangeable), Mass-m/z M^+237, Elemental Analysis, Cal, C, 55.69; H, 5.06; N, 17.72. Found: C, 55.75; H, 5.1; N, 17.75.

2(c) Molecular formula - $C_{11}H_{12}O_2N_3Cl$, Mol. wt. 254, % yield = 84, melting point 186°C. IR (KBr) λ_{max} cm^{-1} 3463 (d) NH_2), 3066 (NH), 3023 (C=C aromatic), 1652 (C=O), ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3H, CH_3), 3.8 (d, 2H, NH_2), 6.5-7.2 (m, 4H, Ar), 7.8 (s, H, Ar-CH=), 9.8 (s, 2H, NH, D_2O exchangeable), 10.2 (d, H, NH, D_2O

exchangeable), Mass m/z, M^+ 255. Elemental Analysis Cal. C, 51.97; H, 4.72; N, 12.6. Found: C, 52.1; H, 4.75; N, 12.4.

2(d) Molecular formula - $C_{11}H_{12}O_4N_4$, Mol. wt. 264, % yield = 79, melting point 178°C. IR (KBr) λ_{max} cm^{-1} 3400 (d), NH, 3300 (NH), 1700 (C-N), 1650 (C=O), 1550, 1350 (NO_2), ^1H NMR ($CDCl_3$) δ 2.0 (s, 3H, CH_3), 4.0 (d, 2H, NH_2), 7.0-7.9 (m, 4H, Ph), 9.5 (s, H, NH, D_2O exchangeable), 11.2 (t, H, NH-N, D_2O exchangeable), Mass : m/z M^+-264. Elemental Analysis – Cal. C, 50.0, H, 4.55, N, 21.2. Found: C, 50.2, H, 4.6, N, 21.4.

2(e) Molecular formula - $C_{16}H_{15}O_2N_3$, Mol. wt. 281, % yield = 90, melting point 180°C. IR (KBr) λ_{max} cm^{-1} 3486 (d, NH_2), 3310 (NH), 2998 (C=C-Ph), 1678 (C-N), 1587 (C=O), ^1H NMR ($CDCl_3$) δ 3.2 (d, 2H, NH_2), 7.2-7.7 (m, 10H, Ph), 8.0 (s, H, =CH-Ph), 9.4 (s, H, NH, D_2O exchangeable), 9.9 (t, H, -NH-N, D_2O exchangeable), Mass m/z M^+ 282, Elemental analysis – Cal, C, 68.3, H, 5.3, N, 14.95. Found: C, 68.5; H, 5.35; N, 14.91.

2(f) Molecular formula - $C_{16}H_{15}O_3N_3$, Mol. wt. 297, % yield 80, melting point 189°C. IR (KBr) λ_{max} cm^{-1} 3486 (d) NH_2, 3216-NH, 3056 (OH), 1794 (C-N), 1652 (C=O), ^1H NMR ($CDCl_3$) δ 3.1 (s, H, OH), 5.8 (d, 2H, NH_2), 7.2-7.6 (m, 9H, Ph), 7.9 (s, H, =CH-Ph), 8.8 (s, H, NH, D_2O exchangeable), 9.0 (t, H, NH-N, D_2O exchangeable), Mass-m/z M^+-298, Elemental Analysis, Cal, C, 64.65; H, 5.05; N, 16.2. Found: C, 64.7; H, 5.1; N, 16.1.

2(g) Molecular formula - $C_{16}H_{14}O_2N_3Cl$, Mol. wt. 316, % yield = 60, melting point 184°C. IR (KBr) λ_{max} cm^{-1} 3408 (d) NH_2, 3325 (NH), 1710 (C-N), 1636 (C=O), ^1H NMR ($CDCl_3$) δ 5.8 (d, 2H, NH_2), 7.0-7.9 (m, 9H, Ph), 8.0 (s, H, Ph-CH=), 8.9 (s, H, NH, D_2O exchangeable), 9.0 (t, H, NH, D_2O exchangeable), Mass m/z M+ 316, Elemental Analysis – Cal. C, 60.76; H, 4.43; N, 13.29. Found: C, 60.8; H, 4.45; N, 13.3.

3(a) Molecular formula - $C_{13}H_{14}N_4O_2S$, Mol. wt. 292, % yield = 77, melting point 177°C. IR (KBr) λ_{max} cm^{-1} 3369 (sharp NH), 2684 (sharp CH_3, SP^3), 1791 (C-N), 1666 (C=O), 1256 (C=S), ^1H NMR (DMSO) δ 2.0 (s, 3H, CH_3), 3.8 (s, 3H, N-CH_3), 7.0-7.8 (m, 5H, Ph), 8.2 (s, H, =CH-Ph), 9.2 (d, H, NH, D_2O exchangeable), 11.4 (d, H, NH-D_2O exchangeable), Mass m/z M^+ -291. Elemental analysis, Cal. C, 53.79; H, 2.55; N, 19.3. Found: C, 53.8; H, 2.53; N, 19.4.

3(b) Molecular formula - $C_{13}H_{13}N_4O_2FS$, Mol. wt. 309, % yield = 80, melting point 189°C. IR (KBr) λ_{max} cm^{-1} 3301 (NH), 2360 (SP^3-CH_3), 1652 (C=O), 1257 (C=S), ^1H NMR ($CDCl_3$) δ 2.4 (S, 3H, -$COCH_3$), 4.4 (S, 3H, NCH_3), 6.8 (s, H, =CH-Ph), 7.0-7.8 (m, 4H, Ph), 8.2 (d, H, NH-D_2O exchangeable), 9.4 (d, H, NH-D_2O exchangeable), Mass m/z M^+ 308. Elemental analysis, Cal. C, 50.65; H, 4.22; N, 18.18. Found: C, 50.7; H, 4.2; N, 18.2.

3(c) Molecular formula - $C_{13}H_{13}N_4O_2SCl$, Mol. wt. 325, % yield = 80, melting point 203°C. IR (KBr) λ_{max} cm^{-1} 3301 (NH), 2360 (CH_3-SP^3), 1710 (C-N), 1662 (C=O), 1257 (C=S), ^1H NMR ($CDCl_3$) δ 2.1 (s, 3H, $COCH_3$), 3.8 (s, 3H, NCH_3), 7.0-7.9 (m, 4H, Ph), 8.2 (s, H, =CH-Ph), 9.4 (d, H, NH, D_2O exchangeable), 11.2 (d, H, D_2O exchangeable), Mass, m/z M^+ -323, Elemental analysis – Cal. C, 48.0; H, 4.0; N, 17.24. Found: C, 48.2; H, 4.2; N, 17.28.

3(d) Molecular formula - $C_{13}H_{13}N_5O_4S$, Mol. wt. 335, % yield = 67, melting point 207°C. IR (KBr) λ_{max} cm^{-1} 3301 (NH), 2360 (CH-SP^3), 1652 (C=O), 1550, 1350 (strong, NO_2), 1257 (C=S), ^1H NMR ($CDCl_3$) δ 2.1 (s, 3H, $COCH_3$), 3.8 (s, 3H, N-CH3), 7.0-7.8 (m, 4H, Ph), 8.2 (s, H, =CH-Ph), 9.4 (d, H, NH, D_2O exchangeable), 11.2 (d, H, NH, D_2O exchangeable), Mass m/z M^+ 333. Elemental analysis, Cal. C, 46.57; H, 3.9; N, 17.91. Found: C, 46.6; H, 3.98; N, 17.9.

3(e) Molecular formula - $C_{18}H_{16}N_4O_2S$, Mol. wt. 352, % yield = 84, melting point 190°C. IR (KBr) λ_{max} cm^{-1} 3346 (NH), 3076 (C=C-Ph), 1798 (C-N), 1659 (C=O), 1258 (C=S), ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H, N-CH_3), 7.2-7.7 (m, 10H, Ph), 8.0 (s, H, =CH-Ph), 8.1 (d, H, NH, D_2O exchangeable), 9.3 (d, H, NH-D_2O exchangeable), Mass m/z M^+ -353, Elemental analysis Cal. C, 61.36; H, 4.55; N, 15.91. Found: C, 61.38; H, 4.5; N, 15.95.

3(f) Molecular formula - $C_{18}H_{16}N_4O_3S$, Mol. wt. 368, % yield 80, melting point 204°C. IR (KBr) λ_{max} cm^{-1} 3400 (NH), 3010 (broad-OH), 1709 (C-N), 1664 (C=O), 1254 (C=S), ^1H NMR ($CDCl_3$) δ 3.2 (s, H, OH), 4.0 (s, 3H, N-CH3), 6.9-8.0 (m, 9H, Ph), 8.4 (s, H, =CH-Ph), 9.4 (d, H, NH, D_2O exchangeable), 11.4 (s, H, NH, D_2O exchangeable), Mass m/z M^+ 366. Elemental analysis – Cal. C, 58.7; H, 4.35; N, 15.22. Found: C, 58.71; H, 4.34; N, 15.21.

3(g) Molecular formula - $C_{18}H_{15}N_4O_2SCl$, Mol. wt. 387 % yield = 70, melting point 212°C. IR (KBr) λ_{max} cm^{-1} 3241 (NH), 1649 (C=O), 1253 (C=S), ^1H NMR ($CDCl_3$) δ 2.0 (s, 3H, -CH3), 6.6-8.0 (m, 9H, Ph), 8.2 (s, H, =CH-Ph), 9.8 (d, H,

NH, D_2O exchangeable), 11.8 (d, H, NH, D_2O exchangeable), Mass m/z M^+ -388, Elemental analysis, Cal. C, 55.8; H, 3.88; N, 14.47. Found: C, 55.9; H, 3.9; N, 14.5.

4 Molecular formula - $C_{18}H_{18}N_4O_2S$, Mol. wt. 354 % yield = 80, melting point 162^0C, IR (KBr) λ_{max} cm^{-1} 3422 (NH), 3291 (NH), 3170 (NH), 1815 (C-N), 1597 (C=O), 1253 (C=S); 1H NMR ($CDCl_3$) δ 2 (s, 3H, N-CH_3), 6.7-7.8 (m, 10H, Ph), 7.9 (s, 1H, CH-Ph), 8.8 (s, 1H, NH, D_2O exchangeable), 9.4 (s, 1H, NH, D_2O exchangeable), 11.2 (d, 1H, NH, D_2O exchangeale), 11.8 (d, 1H, NH, D_2O exchangeable), Mass m/z 356.

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