

# 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  $\alpha$ -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

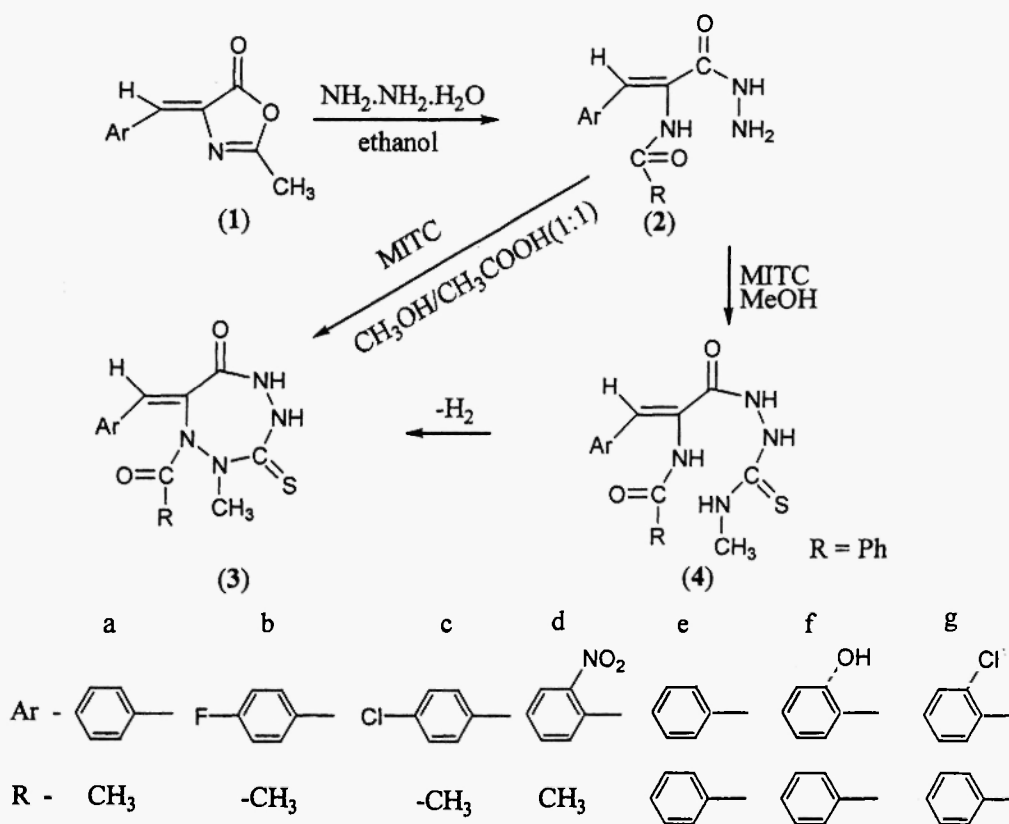
The 1,2,4,5-tetrazepin nucleus is a very significant heterocyclic system, having drug activity on the central nervous system, anticonvulsant activity<sup>1</sup>, and carcinoma inhibitory activity<sup>2</sup>.

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 thiocarbazine ( $\text{H}_2\text{N}-\text{NH}-\text{CS}-\text{NH}-\text{NH}_2$ ) gave 1,2,4,5-tetrazepin-6-ones<sup>3</sup>. (b) Reaction of  $\alpha$ -(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<sup>4</sup>. (c) In another method 1,2,4,5-tetrazepin quinazolinone was synthesised by cyclisation of hydrazino quinoline with benzil<sup>5</sup>.

In continuation of our synthesis of various heterocyclic compounds with methyl isothiocyanate<sup>6,7,8</sup>, 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  $\alpha$ -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, <sup>1</sup>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-tetraazaperhydroepines (**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 Nidel 740 spectrometer FTIR and <sup>1</sup>H 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 $\alpha$ -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  $168^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3472, 3416 (d)  $\text{NH}_2$ , 3215 (NH), 3022 (C=C aromatic), 1676 (C=O), 1578 (C=N),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2 (s, 3H,  $\text{CH}_3$ ), 3.9 (d, 2H,  $\text{NH}_2$ ), 6.8-7.6 (m, 5H, Ar), 8.4 (s, H, CH-Ar), 9.4 (s, H, CO-NH,  $\text{D}_2\text{O}$  exchangeable), 10.2 (t, H, NH-N,  $\text{D}_2\text{O}$  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  $180^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3478 (d,  $\text{NH}_2$ ), 3201 (NH), 3061 (C=C aromatic), 1678 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2 (s, 3H,  $\text{CH}_3$ ), 2.9 (d, 2H,  $\text{NH}_2$ ), 6.9 (s, H, Ar-CH), 7.2-7.6 (d, 4H, Ar), 9.4 (s, H, NH,  $\text{D}_2\text{O}$  exchangeable), 10.0 (t, H, NH-N,  $\text{D}_2\text{O}$  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 -  $C_{11}H_{12}O_2N_3\text{Cl}$ , Mol. wt. 254, % yield = 84, melting point  $186^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3463 (d)  $\text{NH}_2$ , 3066 (NH), 3023 (C=C aromatic), 1652 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.6 (s, 3H,  $\text{CH}_3$ ), 3.8 (d, 2H,  $\text{NH}_2$ ), 6.5-7.2 (m, 4H, Ar), 7.8 (s, H, Ar-CH=), 9.8 (s, 2H, NH,  $\text{D}_2\text{O}$  exchangeable), 10.2 (d, H, NH,  $\text{D}_2\text{O}$

- 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  $178^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3400 (d), NH, 3300 (NH), 1700 (C-N), 1650 (C=O), 1550, 1350 ( $\text{NO}_2$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.0 (s, 3H,  $\text{CH}_3$ ), 4.0 (d, 2H,  $\text{NH}_2$ ), 7.0-7.9 (m, 4H, Ph), 9.5 (s, H, NH,  $\text{D}_2\text{O}$  exchangeable), 11.2 (t, H, NH-N,  $\text{D}_2\text{O}$  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  $180^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3486 (d,  $\text{NH}_2$ ), 3310 (NH), 2998 (C=C-Ph), 1678 (C-N), 1587 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.2 (d, 2H,  $\text{NH}_2$ ), 7.2-7.7 (m, 10H, Ph), 8.0 (s, H, =CH-Ph), 9.4 (s, H, NH,  $\text{D}_2\text{O}$  exchangeable), 9.9 (t, H, -NH-N,  $\text{D}_2\text{O}$  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  $189^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3486 (d)  $\text{NH}_2$ , 3216-NH, 3056 (OH), 1794 (C-N), 1652 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.1 (s, H, OH), 5.8 (d, 2H,  $\text{NH}_2$ ), 7.2-7.6 (m, 9H, Ph), 7.9 (s, H, =CH-Ph), 8.8 (s, H, NH,  $\text{D}_2\text{O}$  exchangeable), 9.0 (t, H, NH-N,  $\text{D}_2\text{O}$  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 -  $C_{16}H_{14}O_2N_3\text{Cl}$ , Mol. wt. 316, % yield = 60, melting point  $184^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3408 (d)  $\text{NH}_2$ , 3325 (NH), 1710 (C-N), 1636 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.8 (d, 2H,  $\text{NH}_2$ ), 7.0-7.9 (m, 9H, Ph), 8.0 (s, H, Ph-CH=), 8.9 (s, H, NH,  $\text{D}_2\text{O}$  exchangeable), 9.0 (t, H, NH,  $\text{D}_2\text{O}$  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 -  $C_{13}H_{14}N_4O_2\text{S}$ , Mol. wt. 292, % yield = 77, melting point  $177^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3369 (sharp NH), 2684 (sharp  $\text{CH}_3$ ,  $\text{SP}^3$ ), 1791 (C-N), 1666 (C=O), 1256 (C=S),  $^1\text{H}$  NMR ( $\text{DMSO}$ )  $\delta$  2.0 (s, 3H,  $\text{CH}_3$ ), 3.8 (s, 3H, N- $\text{CH}_3$ ), 7.0-7.8 (m, 5H, Ph), 8.2 (s, H, =CH-Ph), 9.2 (d, H, NH,  $\text{D}_2\text{O}$  exchangeable), 11.4 (d, H, NH- $\text{D}_2\text{O}$  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  $189^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3301 (NH), 2360 ( $\text{SP}^3\text{-CH}_3$ ), 1652 ( $\text{C=O}$ ), 1257 ( $\text{C=S}$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.4 (s, 3H,  $\text{-COCH}_3$ ), 4.4 (s, 3H,  $\text{NCH}_3$ ), 6.8 (s, H,  $\text{=CH-Ph}$ ), 7.0-7.8 (m, 4H, Ph), 8.2 (d, H,  $\text{NH-D}_2\text{O}$  exchangeable), 9.4 (d, H,  $\text{NH-D}_2\text{O}$  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 -  $C_{13}H_{13}N_4O_2\text{SCl}$ , Mol. wt. 325, % yield = 80, melting point  $203^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3301 (NH), 2360 ( $\text{CH}_3\text{-SP}^3$ ), 1710 (C-N), 1662 ( $\text{C=O}$ ), 1257 ( $\text{C=S}$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.1 (s, 3H,  $\text{COCH}_3$ ), 3.8 (s, 3H,  $\text{NCH}_3$ ), 7.0-7.9 (m, 4H, Ph), 8.2 (s, H,  $\text{=CH-Ph}$ ), 9.4 (d, H,  $\text{NH, D}_2\text{O}$  exchangeable), 11.2 (d, H,  $\text{D}_2\text{O}$  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  $207^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3301 (NH), 2360 ( $\text{CH-SP}^3$ ), 1652 ( $\text{C=O}$ ), 1550, 1350 (strong,  $\text{NO}_2$ ), 1257 ( $\text{C=S}$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.1 (s, 3H,  $\text{COCH}_3$ ), 3.8 (s, 3H,  $\text{N-CH}_3$ ), 7.0-7.8 (m, 4H, Ph), 8.2 (s, H,  $\text{=CH-Ph}$ ), 9.4 (d, H,  $\text{NH, D}_2\text{O}$  exchangeable), 11.2 (d, H,  $\text{NH, D}_2\text{O}$  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  $190^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3346 (NH), 3076 ( $\text{C=C-Ph}$ ), 1798 (C-N), 1659 ( $\text{C=O}$ ), 1258 ( $\text{C=S}$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.8 (s, 3H,  $\text{N-CH}_3$ ), 7.2-7.7 (m, 10H, Ph), 8.0 (s, H,  $\text{=CH-Ph}$ ), 8.1 (d, H,  $\text{NH, D}_2\text{O}$  exchangeable), 9.3 (d, H,  $\text{NH-D}_2\text{O}$  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  $204^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3400 (NH), 3010 (broad-OH), 1709 (C-N), 1664 ( $\text{C=O}$ ), 1254 ( $\text{C=S}$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.2 (s, H, OH), 4.0 (s, 3H,  $\text{N-CH}_3$ ), 6.9-8.0 (m, 9H, Ph), 8.4 (s, H,  $\text{=CH-Ph}$ ), 9.4 (d, H,  $\text{NH, D}_2\text{O}$  exchangeable), 11.4 (s, H,  $\text{NH, D}_2\text{O}$  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 -  $C_{18}H_{15}N_4O_2\text{SCl}$ , Mol. wt. 387 % yield = 70, melting point  $212^\circ\text{C}$ . IR (KBr)  $\lambda_{\text{max}}$   $\text{cm}^{-1}$  3241 (NH), 1649 ( $\text{C=O}$ ), 1253 ( $\text{C=S}$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.0 (s, 3H,  $\text{-CH}_3$ ), 6.6-8.0 (m, 9H, Ph), 8.2 (s, H,  $\text{=CH-Ph}$ ), 9.8 (d, H,

NH, D<sub>2</sub>O exchangeable), 11.8 (d, H, NH, D<sub>2</sub>O exchangeable), Mass m/z M<sup>+</sup> -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<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S, Mol. wt. 354 % yield = 80, melting point 162°C, IR (KBr) λ<sub>max</sub> cm<sup>-1</sup> 3422 (NH), 3291 (NH), 3170 (NH), 1815 (C-N), 1597 (C=O), 1253 (C=S); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2 (s, 3H, N-CH<sub>3</sub>), 6.7-7.8 (m, 10H, Ph), 7.9 (s, 1H, CH-Ph), 8.8 (s, 1H, NH, D<sub>2</sub>O exchangeable), 9.4 (s, 1H, NH, D<sub>2</sub>O exchangeable), 11.2 (d, 1H, NH, D<sub>2</sub>O exchangeable), 11.8 (d, 1H, NH, D<sub>2</sub>O exchangeable), Mass m/z 356.

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