

HETEROCYCLIC SYNTHESIS USING NITRILIMINES PART 15:  
SYNTHESIS OF NEW 1,2,4,5-TETRAZINONE AND  
1,2,4,5-TETRAZEPINONE DERIVATIVES

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## ABSTRACT

The reaction of C-aryl-N-arylnitrilimines II with Girard-reagent P III led to the formation of the 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones IVa-f and 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-ones Va-f, which underwent thermal oxidation to 1,6-dihydro-1,2,4,5-tetrazin-6-ones and 6,7-dihydro-1,2,4,5-tetrazepin-6-ones. The microanalysis and spectral data of the synthesized compounds are in full agreement with their molecular structure.

## KEYWORDS

Nitrilimines, Cyclization, 1,2,4,5-Tetrazinones, 1,2,4,5-Tetrazepinones.

## RESUMO

A reação de C-aroil-N-arilnitriliminas com o reagente de Girard P III levou a formação dos 1,2,3,4-tetrahidro-1,2,4,5-tetrazino-3-onas IVa-f e 1,2,6,7-tetrahidro-1,2,4,5-tetrazepino-6-onas Va-f. Com oxidação térmica formaram 1,6-dihidro-1,2,4,5-tetrazino-6-onas e 6,7-dihidro-1,2,4,5-tetrazepino-6-onas. A microanálise e os dados espectrais dos compostos sintetizados concordam plenamente com a estrutura molecular.

## PALAVRAS-CHAVE

Nitriliminas, Ciclização; 1,2,4,5-Tetrazinonas; 1,2,4,5-Tetrazepinonas.

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## 1. INTRODUCTION

Substituted 1,2,4,5-tetrazines represent significant class of heterocycles that find many useful pharmacological and medicinal applications [1-4]. Azolotetrazinones have been the focus of medicinal chemists in the past decades because of the outstanding antineoplastic activity exhibited by them [5]. Imidazole tetrazinone (Temozolomide: Temodal<sup>®</sup>) has shown promising antitumor activity against low and high-grade glioma [3-6], melanoma [7,8], and mycosis fungoides [8,9]. Furthermore, some pyridopyrrolotetrazine derivatives showed significant activity against leukemia, non-small lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumors cell lines. Different methods were used to synthesize 1,2,4,5-tetrazinone derivatives [6], some of which employed the cyclocondensation of nitrilimines, generated *in situ* from the corresponding hydrazonoyl halides by the action of a suitable base, with nucleophilic substrates incorporating suitably located electrophilic centers. Ottensooser [10] was first reported the synthesis of 1,2,4,6-tetrazepine derivative by the action of dilute potassium hydroxide solution on isobutyl chlorourea. Some derivatives of the fused tetrazepine ring system have been prepared by Sidhu *et al.* [11] by the treatment of 5-(2-aminophenyl)-4,5,6-dihydro-4*H*-1,2,4,6-tetrazepine with ferric chloride or sodium nitrite solution.

In continuation of our research line dealing with the construction of heterocyclic systems by means of nitrilimines cyclocondensation methodology [7-9], we investigated the reaction of C-substituted N-arylnitrilimines **II** with acetylhydrazide pyridinium chloride (Girard-reagent P) **III** in an attempt to synthesize new derivatives of 1,2,4,5-tetrazinones **IVa-f** and 1,2,4,5-tetrazepin-6-ones **Va-f** in anticipation of expected interesting biological activities.

## 2. RESULTS AND DISCUSSION

Recently we found that 1,1-dimethyl- and 1-methyl-1-phenylhydrazine react readily with nitrilimines, generated *in situ* from the action of triethylamine onto the hydrazonoyl halides, yielding the corresponding acyclic electrophilic addition products, which cyclized intramolecularly to the corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazines under thermal conditions [12]. On the other hand, the reaction of the same nitrilimines **II** with acetylhydrazide pyridinium chloride **III** (Girard-reagent P) for 12-18 hours in 1,4-dioxane at room temperature gave a cyclocondensation products, 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones **IVa-f** and 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-ones **Va-f** (Figure 1). The purity of the isolated compounds was checked by TLC in different solvents.

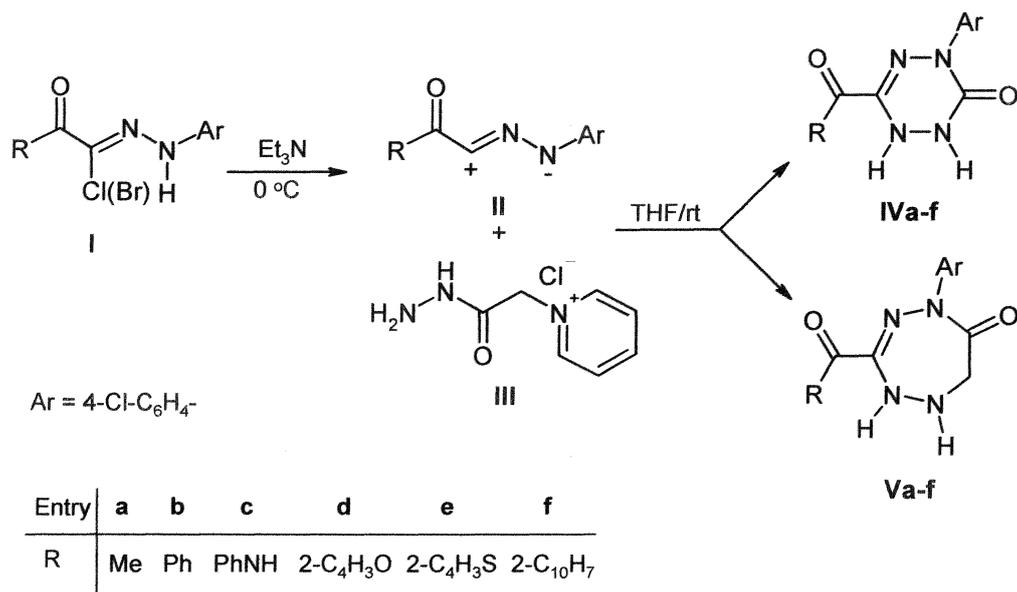


Figure 1. Schematic diagram for the synthesis of compounds IVa-f and Va-f

The formation of compounds IVa-f and Va-f is assumed to involve unisolable nucleophilic addition adducts VIII, which undergo intramolecular cyclization in two pathways as shown in Figure 2. The cyclization at the carbon of amide group (path a) followed with elimination of pyridine methochloride molecule [13] affording the 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one derivatives IVa-f and the cyclization at methylene carbon (path b) followed with losing pyridine hydrochloride molecule yielding the unknown 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one derivatives Va-f as a minor products.

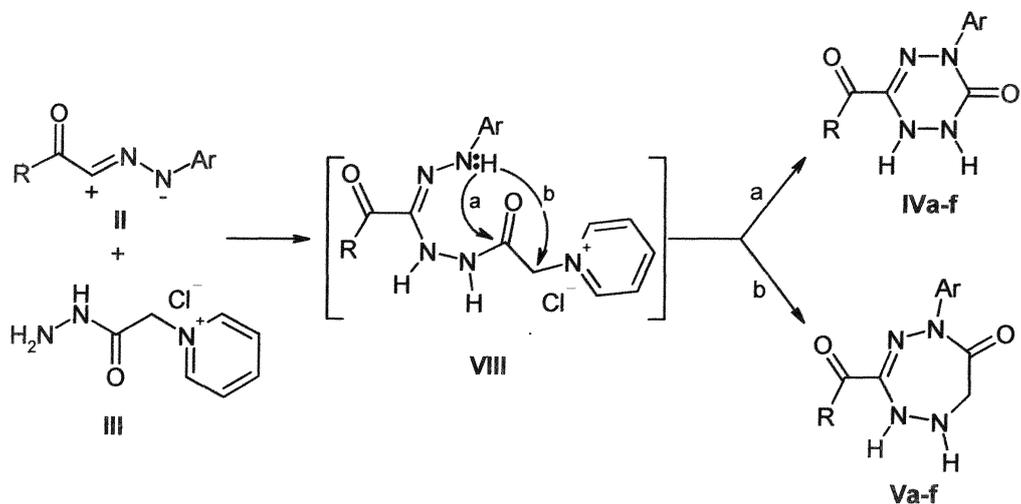
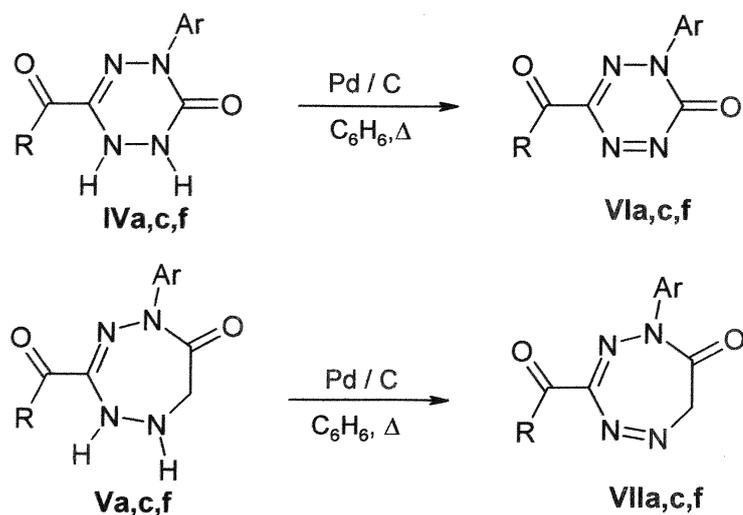


Figure 2. Suggested reaction mechanism

**2.1. Spectroscopical Data**

The structures of the titled compounds **IVa-f** and **Va-f** have been confirmed by elemental analysis and their spectral data (experimental part). Their IR spectra showed intense absorption bands within the 3435-3220  $\text{cm}^{-1}$  range that were attributed to HN-NH and 1675-1670  $\text{cm}^{-1}$  assigned to carbonyl of the ring. All these products gave two singlet signals at 6.6-6.4 ppm in their  $^1\text{H}$  NMR spectra, attributed to the HN-NH protons. In compounds **Va-f**, the signal of  $\text{CH}_2$  protons appeared as singlet at 4.3 ppm. The  $^{13}\text{C}$  NMR spectra of the synthesized compounds **IVa-f** and **Va-f** showed all the signals of the proposed structures, specially carbonyl carbon of the ring were found to resonate at about 172 and 171 ppm and the signal at 43.8 ppm are assignable to methylene carbon of the ring in compounds **Va-f**.

The oxidation of compounds **IVa,c,f** and **Va,c,f** was carried out in refluxing benzene in presence of activated charcoal, afforded 1,6-dihydro-1,2,4,5-tetrazin-3-ones **VIa,c,f** and 6,7-dihydro-1,2,4,5-tetrazepin-6-ones **VIIa,c,f** respectively, (Figure 3). Both the analytical and spectral data (IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectra) of the title compounds **VIa,c,f** and **VIIa,c,f** were in full agreement with the proposed structures and depicted in experimental part. Their mass spectra displayed the correct molecular ion peaks ( $M^+$ ) in accordance with the suggested structures. Their IR spectra indicating the disappearance of absorption band in the 3435-3220  $\text{cm}^{-1}$  region due to the HN-NH function. In their  $^1\text{H}$  NMR data, no signals for HN-NH (6.6-6.4 ppm) were observed. Their  $^{13}\text{C}$  NMR spectra revealed all the signals of the proposed structures.



**Figure 3.** Thermal oxidation of compounds **IVa,c,f** and **Va,c,f**

### 3. EXPERIMENTAL SECTION

#### 3.1. General Remarks

Melting points were determined on thermal melting point apparatus and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in  $\text{DMSO-d}_6$  solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as  $\delta$  values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Center of Cairo University, Egypt. Girard-reagent P, tetrahydrofuran (THF), benzene and triethylamine were purchased from Avocado Chemical Company, England. Hydrazoneyl halides I [14] were prepared according to the methods reported in the literature.

#### 3.2. Synthesis of Compounds IVa-f and Va-f

To a mixture of the appropriate hydrazoneyl halide I (10 mmol) and acetylhydrazide pyridinium chloride III (10 mmol) in dry tetrahydrofuran or 1,4-dioxane (100 mL), triethylamine (3 ml, 20 mmol) was added at room temperature and the reaction mixture was controlled by TLC. The stirring continued until the starting substrates were completely consumed (12-18 h). The triethylammonium chloride salt was filtered off, the solvent was removed under reduced pressure and the residue was triturated with methanol. The solid thus obtained was filtered off and chromatographed using silica gel TLC, elution with benzene: ethyl acetate: petroleum ether (40-60 °C) 5:4:1 afforded the desired products IVa-f.

The following compounds were prepared using this method:

##### **6-Acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one**

(IVa): White solid; yield: 67%; Mp. 178-180 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 2.56 (s, 3H,  $\text{CH}_3$ ), 6.51 (s, 1H, NH), 6.45 (s, 1H, NH), 7.10-7.68 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 192.4 ( $\text{CH}_3\text{C=O}$ ), 171.8 (ring  $\text{C=O}$ ), 146.8 (C=N), 141.6-125.1 (Ar-C), 26.5 ( $\text{CH}_3$ ). IR (KBr disk,  $\text{cm}^{-1}$ ): 3430, 3236 (NH), 1675 (ring  $\text{C=O}$ ), 1690 (C=O), 1598 (C=N). MS, ( $m/z$ ): 252/254 [ $\text{M}$ ] $^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{10}\text{H}_9\text{ClN}_4\text{O}_2$  ( $M_r = 252.66$ ): C, 47.54; H, 3.59; N, 22.17%; Found: C, 47.60; H, 3.50; N, 22.10%.

##### **6-Benzoyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one**

(IVb): White solid, yield: 62%; Mp. 161-163 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 6.52 (s, 1H, NH), 6.47 (s, 1H, NH), 7.13-7.72 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 184.7 ( $\text{PhC=O}$ ), 171.6 (ring  $\text{C=O}$ ), 146.6 (C=N), 141.6-121.4 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 3432, 3224 (NH), 1674 (ring  $\text{C=O}$ ), 1660 ( $\text{PhC=O}$ ), 1596 (C=N). MS,  $m/z$ : 314/316 [ $\text{M}$ ] $^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{15}\text{H}_{11}\text{ClN}_4\text{O}_2$  ( $M_r = 314.73$ ): C, 57.24; H, 3.52; N, 17.80%; Found: C, 57.35; H, 3.45; N, 17.89%.

##### **4-(4-Chlorophenyl)-6-phenylaminocarbonyl-1,2,3,4-tetrahydro-**

**1,2,4,5-tetrazin-3-one (IVc):** Off white solid, yield: 68%; Mp. 189-191 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 6.48 (s, 1H, NH), 6.44 (s, 1H, NH), 7.13-7.71 (m,

9H, Ar-H), 10.2 (s, 1H, NH).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 171.6 (ring C=O), 159.7 (PhNHC=O), 147.6 (C=N), 141.4-121.6 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 3428, 3272, 3227 (NH), 1672 (ring C=O), 1655 (PhC=O), 1599 (C=N). MS,  $m/z$ : 329/331  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{15}\text{H}_{12}\text{ClN}_5\text{O}_2$  ( $M_r = 329.75$ ): C, 54.64; H, 3.67; N, 21.24%; Found: C, 54.55; H, 3.75; N, 21.15%.

**4-(4-Chlorophenyl)-6-(2-furoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVd)**: White solid, yield: 64%; Mp. 147-149 °C,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 6.60 (s, 1H, NH), 6.56 (s, 1H, NH), 7.16-7.80 (m, 7H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 174.6 (C=O), 171.2 (ring C=O), 147.1 (C=N), 142.3-121.4 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 3433, 3237 (NH), 1674 (ring C=O), 1665 (C=O), 1612 (C=N). MS,  $m/z$ : 304/306  $[\text{M}]^+$ . Anal, Calcd for  $\text{C}_{13}\text{H}_9\text{ClN}_4\text{O}_3$  ( $M_r = 304.69$ ): C, 51.25; H, 2.98; N, 18.39%; Found: C, 51.35; H, 3.05; N, 18.30%.

**4-(4-Chlorophenyl)-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVe)**: Yellow solid, yield: 65%; Mp. 195-197 °C,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 6.58 (s, 1H, NH), 6.53 (s, 1H, NH), 7.12-7.82 (m, 7H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 175.4 (C=O), 171.4 (ring C=O), 146.9 (C=N), 142.6-121.7 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 3431, 3228 (NH), 1675 (ring C=O), 1660 (C=O), 1610 (C=N). MS,  $m/z$ : 320/322  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{13}\text{H}_9\text{ClN}_4\text{O}_2\text{S}$  ( $M_r = 320.76$ ): C, 48.68; H, 2.83; N, 17.47%; Found: C, 48.80; H, 2.90; N, 17.55%.

**4-(4-Chlorophenyl)-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVf)**: Pale yellow solid, yield: 60%; Mp. 201-203 °C,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 6.60 (s, 1H, NH), 6.54 (s, 1H, NH), 7.22-8.42 (m, 11H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 184.5 (C=O), 170.8 (ring C=O), 146.7 (C=N), 142.2-120.9 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 3428, 3221 (NH), 1675 (ring C=O), 1650 (C=O), 1605 (C=N). MS, ( $m/z$ ): 364/366  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{19}\text{H}_{13}\text{ClN}_4\text{O}_2$  ( $M_r = 364.79$ ): C, 62.56; H, 3.59; N, 15.36%; Found: C, 62.45; H, 3.70; N, 15.30%.

**3-Acetyl-5-(4-chlorophenyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Va)**: White solid, yield: 32%; Mp. 134-136 °C,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 2.54 (s, 3H,  $\text{CH}_3$ ), 4.34 (s, 2H,  $\text{CH}_2$ ), 6.50 (s, 1H, NH), 6.41 (s, 1H, NH), 7.10-7.68 (m, 4H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 192.4 ( $\text{CH}_3\text{C=O}$ ), 170.8 (ring C=O), 147.8 (C=N), 142.6-125.6 (Ar-C), 43.8 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_3$ ). IR (KBr disk,  $\text{cm}^{-1}$ ): 3430, 3236 (NH), 1675 (ring C=O), 1687 (C=O), 1598 (C=N). MS,  $m/z$ : 266/268  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{11}\text{H}_{11}\text{ClN}_4\text{O}_2$  ( $M_r = 266.69$ ): C, 49.54; H, 4.16; N, 21.01%; Found: C, 49.65; H, 4.05; N, 20.90%.

**3-Benzoyl-5-(4-chlorophenyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vb)**: White solid, yield: 31%; Mp. 154-156 °C,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 4.33 (s, 2H,  $\text{CH}_2$ ), 6.47 (s, 1H, NH), 6.43 (s, 1H, NH), 7.13-7.72 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 184.7 (PhC=O), 171.6 (ring C=O), 146.6 (C=N), 141.6-121.4 (Ar-C), 43.7 ( $\text{CH}_2$ ). IR (KBr disk,  $\text{cm}^{-1}$ ): 3430, 3236 (NH), 1674 (ring C=O), 1665 (PhC=O), 1596 (C=N). MS,  $m/z$ : 328/330  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{O}_2$  ( $M_r = 328.76$ ): C, 58.46; H, 3.99; N, 17.04%; Found: C, 58.36; H, 4.07; N, 16.95%.

**5-(4-Chlorophenyl)-3-phenylaminocarbonyl-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vc)**: White solid, yield: 30%; Mp. 179-181 °C,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ : 4.32 (s, 2H,  $\text{CH}_2$ ), 6.48 (s, 1H, NH), 6.42 (s, 1H, NH), 7.13-7.71 (m, 9H, Ar-H), 10.3 (s, 1H, NH).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ , TMS)  $\delta$ :

184.7 (PhC=O), 171.6 (ring C=O), 159.7 (PhNHC=O), 147.6 (C=N), 141.4-121.6 (Ar-C), 43.5 (CH<sub>2</sub>). IR (KBr disk, cm<sup>-1</sup>): 3430, 3275, 3236 (NH), 1672 (ring C=O), 1655 (PhC=O), 1599 (C=N). MS, m/z: 343/345 [M]<sup>+</sup> chlorine isotopes. Anal, Calcd for C<sub>16</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>2</sub> (M<sub>r</sub> = 343.78): C, 55.90; H, 4.10; N, 20.37%; Found: C, 55.88; H, 3.91 N, 20.25%.

**5-(4-Chlorophenyl)-3-(2-furoyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vd):** White solid, yield: 33%; Mp. 149-151 °C, <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 4.30 (s, 2H, CH<sub>2</sub>), 6.52 (s, 1H, NH), 6.47 (s, 1H, NH), 7.16-7.80 (m, 7H, Ar-H). <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 174.6 (C=O), 171.2 (ring C=O), 147.1 (C=N), 142.3-121.4 (Ar-C), 43.6 (CH<sub>2</sub>). IR (KBr disk, cm<sup>-1</sup>): 1674 (ring C=O), 1665 (C=O), 1612 (C=N). MS, m/z: 318/320 [M]<sup>+</sup> chlorine isotopes. Anal, Calcd for C<sub>14</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>3</sub> (M<sub>r</sub> = 318.72): C, 52.76; H, 3.48; N, 17.58%; Found: C, 52.65; H, 3.40 N, 17.65%.

**5-(4-Chlorophenyl)-3-(2-thenoyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Ve):** White solid, yield: 31%; Mp. 171-173 °C, <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 4.33 (s, 2H, CH<sub>2</sub>), 6.50 (s, 1H, NH), 6.46 (s, 1H, NH), 7.12-7.82 (m, 7H, Ar-H). <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 175.4 (C=O), 171.4 (ring C=O), 146.9 (C=N), 142.6-121.7 (Ar-C), 43.5 (CH<sub>2</sub>). IR (KBr disk, cm<sup>-1</sup>): 3430, 3236 (NH), 1675 (ring C=O), 1660 (C=O), 1610 (C=N). MS, m/z: 334/336 [M]<sup>+</sup> chlorine isotopes. Anal, Calcd for C<sub>14</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub>S (M<sub>r</sub> = 334.79): C, 50.23; H, 3.31; N, 16.74%; Found: C, 50.30; H, 3.21 N, 16.65%.

**5-(4-chlorophenyl)-3-(2-naphthoyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vf):** White solid, yield: 28%; Mp. 162-164 °C, <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 4.32 (s, 2H, CH<sub>2</sub>), 6.45 (s, 1H, NH), 6.41 (s, 1H, NH), 7.22-8.42 (m, 11H, Ar-H). <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 184.5 (C=O), 170.8 (ring C=O), 146.7 (C=N), 142.2-120.9 (Ar-C), 43.7 (CH<sub>2</sub>). IR (KBr disk, cm<sup>-1</sup>): 3430, 3236 (NH), 1675 (ring C=O), 1650 (C=O), 1605 (C=N). MS, m/z: 378/380 [M]<sup>+</sup> chlorine isotopes. Anal, Calcd for C<sub>20</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>2</sub> (M<sub>r</sub> = 378.82): C, 63.41; H, 3.99; N, 14.79%; Found: C, 63.30; H, 4.10 N, 14.85%.

### 3.3. Thermal Oxidation of Compounds 4a,c,f and 5a,c,f

A compounds 4a,c,f or 5a,c,f (5 mmol) and Pd/charcoal in benzene (50 mL) were heated to reflux for 2-4 hours and monitored by TLC. The reaction mixture was cooled, then filtered and the solvent evaporated. The residual solid was collected and recrystallized from ethanol to give the desired compounds 4a,c,f and 5a,c,f. The following compounds were prepared using this method:

**3-Acetyl-5-(4-chlorophenyl)-1,6-dihydro-1,2,4,5-tetrazin-3-ones (VIa):** White solid, yield: 77%; Mp. 230-232 °C, <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 2.54 (s, 3H, CH<sub>3</sub>), 7.10-7.68 (m, 4H, Ar-H). <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 192.8 (RC=O), 172.5 (ring C=O), 147.8 (C=N), 142.6-126.0 (Ar-C), 26.7 (CH<sub>3</sub>). IR (KBr disk, cm<sup>-1</sup>): 1690 (RC=O), 1675 (ring C=O), 1610 (C=N). MS, m/z: 250/252 [M]<sup>+</sup> chlorine isotopes. Anal, Calcd for C<sub>10</sub>H<sub>7</sub>ClN<sub>4</sub>O<sub>2</sub> (M<sub>r</sub> = 250.65): C, 47.92; H, 2.82; N, 22.35%; Found: C, 47.80; H, 2.90 N, 22.25%.

**5-(4-Chlorophenyl)-3-phenylaminocarbonyl-1,6-dihydro-1,2,4,5-tetrazin-3-ones (VIc):** White solid, yield: 54%; Mp. 230-232 °C, <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 7.10-7.68 (m, 9H, Ar-H), 9.96 (s, 1H, NH). <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>, TMS) δ: 172.3 (ring C=O), 160.3 (PhNHC=O), 147.3 (C=N),

142.3-126.2 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 3277 (NH), 1672 (ring C=O), 1660 (RC=O), 1615 (C=N). MS, m/z: 327/329  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{15}\text{H}_{10}\text{ClN}_5\text{O}_2$  ( $M_r = 327.73$ ): C, 54.97; H, 3.08; N, 21.37%; Found: C, 55.10; H, 2.95 N, 21.25%.

**5-(4-chlorophenyl)-3-(2-naphthoyl)-1,6-dihydro-1,2,4,5-tetrazin-3-ones (VI f):** White solid, yield: 76%; Mp. 230-232 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 7.10-7.68 (m, 11H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 185.2 (RC=O), 171.7 (ring C=O), 147.7 (C=N), 143.4-121.8 (Ar-C). IR (KBr disk,  $\text{cm}^{-1}$ ): 1675 (ring C=O), 1650 (RC=O), 1610 (C=N). MS, m/z: 362/364  $[\text{M}]^+$ . Anal, Calcd for  $\text{C}_{19}\text{H}_{11}\text{ClN}_4\text{O}_2$  ( $M_r = 362.78$ ): C, 62.91; H, 3.06; N, 15.44%; Found: C, 62.80; H, 2.95 N, 15.55%.

**3-Acetyl-5-(4-chlorophenyl)-6,7-tetrahydro-1,2,4,5-tetra-zepin-6-one (VII a):** White solid, yield: 74%; Mp. 201-203 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 4.44 (s, 2H,  $\text{CH}_2$ ), 7.22-8.42 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 192.0 (C=O), 172.2 (ring C=O), 148.3 (C=N), 142.9-124.8 (Ar-C), 44.7 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_3$ ). IR (KBr disk,  $\text{cm}^{-1}$ ): 1693 (C=O), 1675 (ring C=O), 1605 (C=N). MS, m/z: 264/266  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{11}\text{H}_9\text{ClN}_4\text{O}_2$  ( $M_r = 264.67$ ): C, 49.92; H, 3.43; N, 21.17%; Found: C, 50.05; H, 3.50 N, 21.10%.

**5-(4-Chlorophenyl)-3-phenylaminocarbonyl-6,7-tetrahydro-1,2,4,5-tetra-zepin-6-one (VII c):** White solid, yield: 71%; Mp. 201-203 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 4.43 (s, 2H,  $\text{CH}_2$ ), 7.22-8.42 (m, 9H, Ar-H), 9.98 (s, 1H, NH).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 172.8 (ring C=O), 160.5 ( $\text{PhNHC=O}$ ), 147.7 (C=N), 143.2-124.9 (Ar-C), 44.2 ( $\text{CH}_2$ ). IR (KBr disk,  $\text{cm}^{-1}$ ): 3273 (NH), 1673 (ring C=O), 1655 (C=O), 1610 (C=N). MS, m/z: 341/343  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}_5\text{O}_2$  ( $M_r = 341.76$ ): C, 53.23; H, 3.54; N, 20.49%; Found: C, 53.35; H, 3.60 N, 20.55%.

**5-(4-chlorophenyl)-3-(2-naphthoyl)-6,7-tetrahydro-1,2,4,5-tetra-zepin-6-one (VII f):** White solid, yield: 70%; Mp. 201-203 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 4.46 (s, 2H,  $\text{CH}_2$ ), 7.22-8.42 (m, 11H, Ar-H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO-d}_6$ , TMS)  $\delta$ : 184.8 (C=O), 172.4 (ring C=O), 147.4 (C=N), 143.6-121.4 (Ar-C) 44.8 ( $\text{CH}_2$ ). IR (KBr disk,  $\text{cm}^{-1}$ ): 1675 (ring C=O), 1650 (C=O), 1600 (C=N). MS, m/z: 376/378  $[\text{M}]^+$  chlorine isotopes. Anal, Calcd for  $\text{C}_{20}\text{H}_{13}\text{ClN}_4\text{O}_2$  ( $M_r = 376.81$ ): C, 63.75; H, 5.48; N, 14.87%; Found: C, 63.80; H, 5.55 N, 14.95%.

#### 4. CONCLUSION

In conclusion, the cyclocondensation of several nitrilimines with Girard-reagent P leads to formation of 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones **IV a-f** and 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-ones **V a-f**, which thermally oxidized in presence of activated charcoal to 1,6-dihydro-1,2,4,5-tetrazin-3-ones **VI a,c,f** and 6,7-dihydro-1,2,4,5-tetrazepin-6-ones **VII a,c,f**.

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