Tetrahedron 65 (2009) 8722–8726

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Heterocyclic synthesis using nitrilimines. Part 13: Synthesis of new 1,2,3,4-tetrahydro-*s*-tetrazine derivatives

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ARTICLE INFO

Article history:
Received 16 May 2009
Received in revised form 30 July 2009
Accepted 13 August 2009
Available online 19 August 2009

Keywords:
s-Tetrazines
Formazanes
Nitrilimines
Electrophilic addition
Cyclization

ABSTRACT

The reaction of *C*-aroyl-*N*-arylnitrilimines with 1,1-dimethylhydrazine or 1-methyl-1-phenylhydrazine led to the formation of the acyclic electrophilic addition products, which underwent thermal oxidative cyclization at CH_3 to 1,2,3,4-tetrahydro-*s*-tetrazines. Both analytical and spectroscopic data of all the synthesized compounds are in full agreement with the proposed structures.

1. Introduction

Tetrazines have been known for long time[1–4] and have been utilized for a diverse range of practical and synthetic applications.[2,5] Tetrazines exhibit dye,[6] insecticide,[7] optical,[8,9] electrochemical,[10] and biomedical[11,12] properties. Some 1,2,4,5-tetrazine derivatives have been reportedly used as anti-tumor[13] and anti-inflammatory[14] agents. Azolotetrazinones have been the focus of medicinal chemists in the past decades because of the outstanding antineoplastic activity exhibited by them. Likewise, imidazotetrazines[15–17] (mitozolomide and temozolomide) have attracted remarkable attention owing to their efficiency against malignant melanoma, mycosis, fungoides, and brain tumors. Recently, it has been reported the synthesis of polymers based upon tetrazine or substituted tetrazine moieties.[18–20] Furthermore, tetrazine chemistries have been useful in the molecular recognition of environmental contaminants,[21] as anion binders[22] and in metal complexation, where 1,4- and 3,6-disubstituted 1,2,4,5-tetrazines have been studied for their complexing behavior toward transition metals.[20,23–25] Several methods have been reported in literature for the synthesis of tetrazine derivatives, 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.[26–28] In continuation of our research line dealing with the construction of the heterocyclic systems by means of the nitrilimines cyclocondensation methodology, we investigated the synthesis of some new 1,2,4,5-tetrazine derivatives **5a–l**.

2. Results and discussion

The precursors of nitrilimines hydrazonoyl halides **1** employed in this study were prepared by a modified literature procedure. Recently, we found that nitrilimines **2** react with 1,1-dimethyl- and 1-methyl-1-phenylhydrazine at room temperature for 6–12 h yielding unexpected amidrazones **6**[26,29,30] (Scheme 1). The same reaction was found time dependent, when stirred for 20–30 min at room temperature gave acyclic electrophilic addition products **4a–l** as indicated by TLC (Scheme 1). Cyclization to the corresponding 1,2,4,5-tetrazines **5a–l** did not occur. This behavior is similar to that reported by Ferwanah et al.,[29] where the treatment of different nitrilimines with 1-formyl-, 1-acetyl-, and 1-ethoxycarbonyl-1-methylhydrazines afforded the corresponding acyclic adducts, which underwent thermal cyclization to tetrazine rings in presence of charcoal. The acyclic adducts **4a–l** were cyclized intramolecularly to the corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazines **5a–l** by heating them with activated charcoal or lithium hydride in refluxing benzene or toluene for 2–4 h (Scheme 1). It is worth noting that the most frequently used method for the preparation of tetrahydro-1,2,4,5-tetrazines is the cyclization of alkylformazanes by heating or base treatment.[31]

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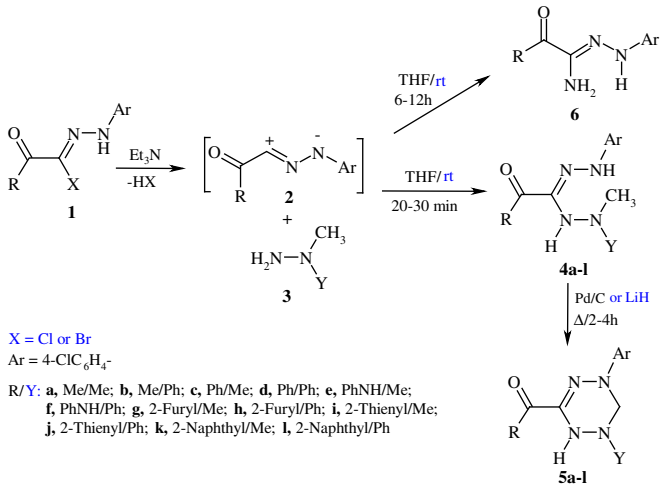
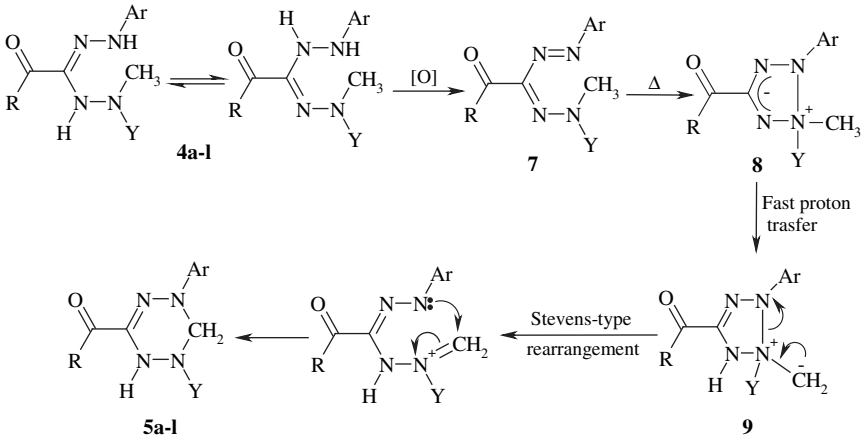
doi:10.1016/j.tet.2009.08.036



Scheme 1. Synthetic pathway for the preparation of compounds **4a–l** and **5a–l**.

A plausible reaction mechanism for this cyclization started by the oxidation of the acyclic adducts **4a–l** to formazanes **7**, which cyclized as reported by Neugebauer and McConnachie[31] to the corresponding tetrahydro-*s*-tetrazines **5a–l**. The formazane **7** cyclized to the delocalized zwitterionic tetrazoles **8**, which changed through fast proton transfer to the isomeric ylid **9**. This ylid cyclized to the tetrazines **5a–l** in Stevens-type rearrangement (Scheme 2).



Scheme 2. The suggested reaction mechanism for compounds **5a–l**.

2.1. Spectral data analysis

The characteristic data of acyclic compounds **4a–l** are given in detail in Experimental section. All compounds gave satisfactory combustion analysis for the proposed structures, which were confirmed on the basis of their spectroscopic data. The mass spectra showed the correct molecular ion peaks ($M^{+\bullet}$) in accordance with the suggested structures. The IR spectra of title compounds **4a–l** revealed two absorption bands at the 3380–3200 cm^{-1} region and the carbonyl absorption band at the 1690–1640 cm^{-1} region. Their ^1H NMR spectra showed two signals for Ar–NH and NH proton appeared as singlet at 10.5–10.3 ppm and 6.5–6.2 ppm, respectively. The *N*-methyl protons in all compounds appeared as singlet at 3.2–3.0 ppm. The ^{13}C NMR spectra also illustrated that compounds **4a–l** have the assigned acyclic structures. The *N*-methyl carbon appeared at about 43–38 ppm, and the signal at 139–136 ppm is attributed to the C=N carbon atom.

Structure elucidation of the obtained tetrahydro-1,2,4,5-tetrazines **5a–l** was achieved by analytical and spectral data, which summarized in Experimental section. Their mass spectra displayed the correct molecular ion peaks (M^+) in accordance with the suggested structures and showed the loss of hydrogen molecule. The IR spectra exhibited only one absorption band in the 3260–3220 cm^{-1} region for NH of the tetrazine ring. The ^1H NMR spectra of compounds **5a–l** showed all the signals of the proposed structures, indicating the disappearance of Ar–NH proton and the N–CH_3 signal (δ=3.2–3.0 ppm) of acyclic adducts **4a–l** is replaced by a highly deshielded CH_2 signal (δ=5.2–5.0 ppm) in compounds **5a–l**. This is similar to reported values of CH_2 flanked by two nitrogens in six-membered heterocycles.[26,29,30] Finally, also the ^{13}C NMR data illustrated that compounds **5a–l** have the assigned cyclic structure, where the *N*-methyl carbon signal of **4a–l** at about 42–38 ppm disappeared; meanwhile new methylene signal appeared at about 61–56 ppm,[26,29,30] whereas the signal of the C=N carbon was recorded at 143 ppm. The ^1H and ^{13}C NMR data for compounds **5a–l** were presented in Experimental section.

3. Experimental

3.1. General

All melting points were determined on an A. Krüss Melting Point Meter and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in $CDCl_3$ solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per million (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at Cairo University, Egypt. The hydrazonoyl halides **1a–l**[32,33] were prepared according to literature procedures. 1,1-Dimethylhydrazine and 1-methyl-1-phenylhydrazine were purchased from Across Organics Company, Belgium, and used without further purification.

3.2. Reaction of nitrilimines 2 with 1-substituted-1-methylhydrazines 3

Triethylamine (7 mL, 50 mmol) was added at room temperature to stirred mixture of 1-substituted-1-methylhydrazines **3** (20 mmol) and the appropriate hydrazonoyl halides **1** (10 mmol) in

tetrahydrofuran (100 mL). The reaction mixture was monitored by TLC and stirred for 20–30 min at rt, then the precipitated triethylamine salt was filtered off and the solvent was removed under reduced pressure. The residue was washed with water (100 mL) and extracted with chloroform (3×20 mL) and the combined extracts were washed with water (50 mL), dried over anhydrous sodium sulfate. The solvent ($CHCl_3$) was evaporated in vacuo, and the crude product was triturated with ethanol (5–10 mL). The crude solid products were collected and recrystallized from ethanol to afford the desired compounds.

*3.2.1. 3-Acetyl-1-(4-chlorophenyl)-5-methyl-1,2,4,5-tetraaza-2-hexene (**4a**).* Yield 1.9 g, 75% as a pale yellow solid, mp 146–148 °C. Found: C, 52.15; H, 6.05; N, 21.90. $C_{11}H_{15}ClN_4O$ (254.72) requires: C, 51.87; H, 5.94; N, 22.00%. ν_{max} (KBr) 3385, 3240 (NH), 1690 (C=O), 1598 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.51 (s, 1H, ArNH), 7.22–7.05 (m, 4H, Ar–H), 6.20 (s, H, NH), 3.15 (s, 6H, $2NCH_3$), 2.56 (s, 3H, CH_3) ppm; δ_C (300 MHz, $CDCl_3$) 193.2 (C=O), 137.9 (C=N), 141.4, 129.3, 126.9, 115.3 ($C_{arom.}$) 37.9 (NCH_3), 24.9 (CH_3) ppm; *m/z* (254/256$M^{+\bullet}$, chlorine isotopes).

*3.2.2. 3-Acetyl-1-(4-chlorophenyl)-5-phenyl-1,2,4,5-tetraaza-2-hexene (**4b**).* Yield 2.5 g, 79% as a pale yellow solid, mp 186–188 °C (ethanol). Found: C, 60.45; H, 5.25; N, 17.80. $C_{16}H_{17}ClN_4O$ (316.79) requires: C, 60.66; H, 5.41; N, 17.69%. ν_{max} (KBr) 3386, 3238 (NH), 1687 (C=O), 1596 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.50 (s, 1H, ArNH), 7.34–7.20 (m, 9H, Ar–H), 6.24 (s, H, NH), 3.25 (s, 3H, NCH_3), 2.54 (s, 3H, CH_3) ppm; δ_C (300 MHz, $CDCl_3$) 193.3 (C=O), 138.6 (C=N), 142.2, 137.2, 132.5, 130.4, 129.4, 128.0, 127.3, 115.4 ($C_{arom.}$), 38.4 (NCH_3), 24.9 (CH_3) ppm; *m/z* (316/318 $M^{+\bullet}$, chlorine isotopes).

*3.2.3. 3-Benzoyl-1-(4-chlorophenyl)-5-methyl-1,2,4,5-tetraaza-2-hexene (**4c**).* Yield 2.4 g, 76% as a pale yellow solid, mp 159–161 °C (ethanol). Found: C, 60.40; H, 5.30; N, 17.85. $C_{16}H_{17}ClN_4O$ (316.79) requires: C, 60.66; H, 5.41; N, 17.69%. ν_{max} (KBr) 3365, 3250 (NH), 1655 (C=O), 1594 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.30 (s, 1H, ArNH), 8.12–7.10 (m, 9H, Ar–H), 6.40 (s, 1H, NH), 3.07 (s, 6H, $2NCH_3$) ppm; δ_C (300 MHz, $CDCl_3$) 187.8 (C=O), 138.5 (C=N), 141.3, 136.4, 132.2, 130.7, 129.4, 127.9, 127.1, 115.8 ($C_{arom.}$), 38.8 (NCH_3) ppm; *m/z* (316/318 $M^{+\bullet}$, chlorine isotopes).

*3.2.4. 3-Benzoyl-1-(4-chlorophenyl)-5-phenyl-1,2,4,5-tetraaza-2-hexene (**4d**).* Yield 2.8 g, 74% as a pale yellow solid, mp 132–134 °C (ethanol). Found: C, 66.35; H, 4.92; N, 14.90. $C_{21}H_{19}ClN_4O$ (378.86) requires: C, 66.58; H, 5.05; N, 14.79%. ν_{max} (KBr) 3356, 3245 (NH), 1656 (C=O), 1696 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.33 (s, 1H, ArNH), 8.10–7.09 (m, 14H, Ar–H), 6.38 (s, 1H, NH), 3.15 (s, 3H, NCH_3) ppm; δ_C (300 MHz, $CDCl_3$) 187.2 (C=O), 139.6 (C=N), 141.9, 137.2, 136.7, 132.6, 131.3, 130.9, 130.1, 129.4, 127.9, 127.1, 125.3, 115.9 ($C_{arom.}$), 42.3 (NCH_3) ppm; *m/z* (378/380 $M^{+\bullet}$, chlorine isotopes).

*3.2.5. 1-(4-Chlorophenyl)-5-methyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-hexene (**4e**).* Yield 2.4 g, 72% as a pale yellow solid, mp 178–180 °C (ethanol). Found: C, 59.15; H, 5.35; N, 21.30. $C_{16}H_{18}ClN_5O$ (331.81) requires: C, 58.92; H, 5.47; N, 21.11%. ν_{max} (KBr) 3380, 3270, 3235 (NH), 1665 (C=O), 1597 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.41 (s, 1H, ArNH), 9.80 (s, 1H, amide), 8.52–7.25 (m, 9H, Ar–H), 6.24 (s, 1H, NH), 3.05 (s, 6H, $2NCH_3$) ppm; δ_C (300 MHz, $CDCl_3$) 187.1 (C=O), 137.9 (C=N), 141.1, 134.8, 129.4, 129.1, 126.9, 124.3, 119.7, 116.1 ($C_{arom.}$), 38.3 (NCH_3) ppm; *m/z* (331/333 $M^{+\bullet}$, chlorine isotopes).

*3.2.6. 1-(4-Chlorophenyl)-5-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-hexene (**4f**).* Yield 2.8 g, 71% as a pale yellow solid, mp 187–189 °C (ethanol). Found: C, 63.85; H, 4.95; N, 17.90. $C_{21}H_{20}ClN_5O$ (393.88) requires: C, 64.04; H, 5.12; N, 17.78%. ν_{max} (KBr) 3382, 3276, 3240 (NH), 1660 (C=O), 1594 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.43 (s, 1H, ArNH), 9.84 (s, 1H, amide), 8.52–7.25 (m, 14H, Ar–H), 6.30 (s, 1H, NH), 3.13 (s, 1H, NCH_3) ppm; δ_C (300 MHz, $CDCl_3$) 187.1 (C=O), 138.7 (C=N), 141.9, 135.2, 134.7, 132.4, 129.7, 129.2, 128.0, 127.5, 127.1, 124.8, 122.2, 116.5 ($C_{arom.}$), 39.7 (NCH_3) ppm; *m/z* (393/395 $M^{+\bullet}$, chlorine isotopes).

*3.2.7. 1-(4-Chlorophenyl)-3-(2-furoyl)-5-methyl-1,2,4,5-tetraaza-2-hexene (**4g**).* Yield 2.5 g, 78% as a white solid, mp 151–153 °C (ethanol). Found: C, 55.55; H, 6.11; N, 17.25. $C_{15}H_{19}ClN_4O_2$ (322.80) requires: C, 55.81; H, 5.93; N, 17.36%. ν_{max} (KBr) 3378, 3254 (NH), 1655 (C=O), 1597 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.35 (s, 1H, ArNH), 8.52–7.25 (m, 7H, Ar–H), 6.35 (s, 2H, 2NH), 3.14 (s, 6H, $2NCH_3$) ppm; δ_C (300 MHz, $CDCl_3$) 175.3 (C=O), 138.8 (C=N), 140.9, 136.9, 135.4, 134.9, 128.9, 128.1, 120.6, 114.9 ($C_{arom.}$), 38.6 (NCH_3) ppm; *m/z* (322/324 $M^{+\bullet}$, chlorine isotopes).

*3.2.8. 1-(4-Chlorophenyl)-3-(2-furoyl)-5-phenyl-1,2,4,5-tetraaza-2-hexene (**4h**).* Yield 2.8 g, 74% as a white solid, mp 162–164 °C (ethanol). Found: C, 62.15;H, 5.35; N, 14.72. $C_{20}H_{21}ClN_4O_2$ (384.87) requires: C, 62.42; H, 5.50;N, 14.56%. ν_{max} (KBr) 3375, 3255 (NH), 1650 (C=O), 1593 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.42 (s, 1H, ArNH), 8.52–7.25 (m, 12H, Ar–H), 6.32 (s, 1H, NH), 3.19 (s, 3H, NCH_3) ppm; δ_C (300 MHz, $CDCl_6$) 175.6 (C=O), 139.4 (C=N), 141.8, 140.2, 137.3, 135.5, 135.1, 129.3, 128.6, 128.3, 127.7, 126.2, 120.1, 115.9 ($C_{arom.}$) 43.2 (NCH_3) ppm; *m/z* (384/386 $M^{+\bullet}$, chlorine isotopes).

*3.2.9. 1-(4-Chlorophenyl)-5-methyl-3-(2-thenoyl)-1,2,4,5-tetraaza-2-hexene (**4i**).* Yield 2.5 g, 75% as a yellow solid, mp 172–174 °C (ethanol). Found: C, 52.95; H, 5.75; N, 16.70. $C_{15}H_{19}ClN_4OS$ (338.86) requires: C, 53.17; H, 5.65; N, 16.53%. ν_{max} (KBr) 3375, 3260 (NH), 1665 (C=O), 1596 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.39 (s, 1H, ArNH), 8.52–7.25 (m, 7H, Ar–H), 6.04 (s, 1H, NH), 3.25 (s, 6H, $2NCH_3$) ppm; δ_C (300 MHz, $CDCl_3$) 174.6 (C=O), 138.5 (C=N), 141.9, 136.9, 135.4, 128.9, 128.1, 127.9, 120.6, 115.8 ($C_{arom.}$), 38.6 (NCH_3) ppm; *m/z* (338/340 $M^{+\bullet}$, chlorine isotopes).

*3.2.10. 1-(4-Chlorophenyl)-5-phenyl-3-(2-thenoyl)-1,2,4,5-tetraaza-2-hexene (**4j**).* Yield 3.1 g, 77% as a yellow solid, mp 179–181 °C (ethanol). Found: C, 60.15; H, 5.12; N, 14.10. $C_{20}H_{21}ClN_4OS$ (400.93) requires: C, 59.92; H, 5.28; N, 13.97%. ν_{max} (KBr) 3370, 3265 (NH), 1662 (C=O), 1595 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.45 (s, 1H, ArNH), 8.52–7.25 (m, 12H, Ar–H), 6.07 (s, 1H, NH), 3.18 (s, 3H, NCH_3) ppm; δ_C (300 MHz, $CDCl_3$) 174.2 (C=O), 139.3 (C=N), 142.5, 137.4, 135.9, 135.2, 134.9, 129.2, 128.4, 128.1, 127.0, 124.7, 120.8, 116.1 ($C_{arom.}$) 42.8 (NCH_3) ppm; MS *m/z* (400/402 $M^{+\bullet}$, chlorine isotopes).

*3.2.11. 1-(4-Chlorophenyl)-5-methyl-3-(2-naphthoyl)-1,2,4,5-tetraaza-2-hexene (**4k**).* Yield 2.6 g, 71% as a pale yellow solid, mp 192–194 °C (ethanol). Found: C, 65.75; H, 5.05; N, 15.40. $C_{20}H_{19}ClN_4O$ (366.85) requires: C, 65.48; H, 5.22; N, 15.27%. ν_{max} (KBr) 3360, 3225 (NH), 1645 (C=O), 1595 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.46 (s, H, ArNH), 8.65–7.05 (m, 11H, Ar–H), 6.50 (s, H, NH), 3.22 (s, 6H, $2NCH_3$) ppm; δ_C (300 MHz, $CDCl_3$) 187.2 (C=O), 137.9 (C=N), 141.1, 135.2, 133.6, 132.7, 132.3, 129.7, 129.4, 128.2, 127.7, 127.5, 127.0, 126.6, 126.4, 115.9 ($C_{arom.}$) 38.9 (NCH_3) ppm; *m/z* (366/368 $M^{+\bullet}$, chlorine isotopes).

*3.2.12. 1-(4-Chlorophenyl)-3-(2-naphthoyl)-5-phenyl-1,2,4,5-tetraaza-2-hexene (**4l**).* Yield 3.0 g, 70% as a pale yellow solid, mp 203–205 °C (ethanol). Found: C, 69.80; H, 5.05; N, 12.95. $C_{25}H_{21}ClN_4O$ (428.93) requires: C, 70.01; H, 4.93; N, 13.06%. ν_{max} (KBr) 3365, 3230 (NH), 1644 (C=O), 1592 (C=N) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.44 (s, H, ArNH), 8.72–7.10 (m, 16H, Ar–H), 6.47 (s, 2H, 2NH), 3.25 (s, 3H, NCH_3) ppm; δ_C (300 MHz, $CDCl_3$) 187.4 (C=O), 139.2 (C=N), 141.2,

135.2, 134.2, 133.3, 132.5, 132.4, 130.5, 129.6, 129.4, 129.1, 128.3, 127.8, 127.6, 127.4, 127.1, 126.8, 126.1, 116.3 ($C_{arom.}$), 43.4 (NCH_3) ppm; *m/z* (428/430 $M^{+\bullet}$, chlorine isotopes).

3.3. Thermal cyclization of compounds 5a–l

Acyclic compounds **4a–l** (5 mmol) and Pd/charcoal (0.1 w/w%) or LiH (0.5–1.0 g) in benzene or toluene (50 mL) were heated to reflux for 2–4 h and monitored by TLC. The reaction mixture was cooled, then filtered and the solvent was minimized to one-third amount. Petroleum ether (bp 40–60 °C) was slowly added to effect complete crystallization of the desired cyclic compounds **5a–l**.

The following compounds were synthesized using this method:

*3.3.1. 6-Acetyl-4-(4-chlorophenyl)-2-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5a**).* Yield 1.9 g, 76% as a yellow solid, mp 138–140 °C (toluene/pet. ether). Found: C, 52.50; H, 5.08; N, 22.30. $C_{11}H_{13}ClN_4O$ (252.71) requires: C, 52.28; H, 5.19; N, 22.17%. ν_{max} (KBr) 3225 (NH), 1695 (C=O), 1596 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.35–7.07 (m, 4H, Ar–H), 6.67 (s, 1H, NH), 5.23 (s, 2H, CH_2), 3.56 (s, 3H, NCH_3), 2.61 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 193.3 (Ar–C=O), 143.7 (C=N), 141.5, 129.5, 127.1, 116.8 ($C_{arom.}$), 57.3 (CH_2), 42.9 (NCH_3), 24.5 (CH_3) ppm; *m/z* (252/254 $M^{+\bullet}$, chlorine isotopes).

*3.3.2. 6-Acetyl-4-(4-chlorophenyl)-2-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5b**).* Yield 2.3 g, 74% as a yellow solid, mp 150–152 °C (toluene/pet. ether). Found: C, 61.25; H, 4.66; N, 17.91. $C_{16}H_{15}ClN_4O$ (314.78) requires: C, 61.05; H, 4.80; N, 17.80%. ν_{max} (KBr) 3224 (NH), 1698 (C=O), 1598 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.38–7.10 (m, 9H, Ar–H), 6.70 (s, 1H, NH), 5.26 (s, 2H, CH_2), 2.63 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 193.3 (Ar–C=O), 143.7 (C=N), 141.3, 133.1, 132.9, 129.7, 129.0, 127.4, 125.2, 116.1 ($C_{arom.}$), 57.3 (CH_2), 24.5 (CH_3) ppm; *m/z* (314/316 $M^{+\bullet}$, chlorine isotopes).

*3.3.3. 6-Benzoyl-4-(4-chlorophenyl)-2-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5c**).* Yield 2.3 g, 72% as a pale green solid, mp 178–180 °C (toluene/pet. ether). Found: C, 60.85; H, 4.70; N, 17.92. $C_{16}H_{15}ClN_4O$ (314.78) requires: C, 61.05; H, 4.80; N, 17.80%. ν_{max} (KBr) 3250 (NH), 1650 (C=O), 1595 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.95–7.16 (m, 7H, Ar–H), 6.52 (s, 1H, NH), 5.12 (s, 2H, CH_2), 3.51 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 185.3 (Ar–C=O), 143.5 (C=N), 142.6, 132.9, 129.9, 129.0, 128.2, 125.8, 121.8, 115.8 ($C_{arom.}$), 56.2 (CH_2), 42.3 (CH_3) ppm; *m/z* (314/316 $M^{+\bullet}$, chlorine isotopes).

*3.3.4. 6-Benzoyl-4-(4-chlorophenyl)-2-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5d**).* Yield 2.8 g, 74% as a dirty green solid, mp 154–156 °C (toluene/pet. ether). Found: C, 67.20; H, 4.42; N, 14.75. $C_{21}H_{17}ClN_4O$ (376.85) requires: C, 66.93; H, 4.55; N, 14.87%. ν_{max} (KBr) 3255 (NH), 1655 (Ar–C=O), 1598 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.90–7.12 (m, 14H, Ar–H), 6.57 (s, 1H, NH), 5.19 (s, 2H, CH_2) ppm; δ_C (300 MHz, DMSO-d_6) 185.2 (Ar–C=O), 142.9 (C=N), 142.5, 134.5, 133.7, 132.2, 131.3, 130.2, 129.7, 128.9, 128.3, 126.1, 121.4, 116.2 ($C_{arom.}$), 56.3 (CH_2) ppm; *m/z* (376/378 $M^{+\bullet}$, chlorine isotopes).

*3.3.5. 4-(4-Chlorophenyl)-2-methyl-6-phenylaminocarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5e**).* Yield 2.3 g, 70% as a white solid, mp 158–160 °C (benzene/pet. ether). Found: C, 58.55; H, 5.00; N, 21.11. $C_{16}H_{16}ClN_5O$ (329.79) requires: C, 58.27; H, 4.89; N, 21.24%. ν_{max} (KBr) 3290, 3235 (NH), 1660 (C=O), 1592 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.89 (s, 1H, amide NH), 7.8–7.2 (m, 9H, Ar–H), 6.49 (s, 1H, NH), 4.96 (s, 2H, CH_2), 3.48 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 172.6 (Ar–C=O) 144.0 (C=N), 143.1, 128.9, 128.1, 126.1, 123.8, 121.7, 119.2, 114.9 ($C_{arom.}$), 60.4 (CH_2), 42.5 (CH_3) ppm; *m/z* (329/331 $M^{+\bullet}$, chlorine isotopes).

*3.3.6. 4-(4-Chlorophenyl)-2-phenyl-6-phenylaminocarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5f**).* Yield 2.8 g, 73% as a white solid, mp 198–200 °C (benzene/pet. ether). Found: C, 64.60; H, 4.55; N, 18.01. $C_{21}H_{18}ClN_5O$ (391.86) requires: C, 64.37; H, 4.63; N, 17.87%. ν_{max} (KBr) 3287, 3230 (NH), 1665 (Ar–C=O), 1594 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 9.10 (s, 1H, amide NH), 8.4–7.2 (m, 14H, Ar–H), 6.46 (s, 1H, NH), 4.98 (s, 2H, CH_2) ppm; δ_C (300 MHz, DMSO-d_6) 174.5 (Ar–C=O), 144.1 (C=N), 143.4, 141.3, 135.4, 133.9, 131.7, 130.6, 128.9, 128.0, 127.4, 125.1, 122.2, 116.7 ($C_{arom.}$), 60.6 (CH_2) ppm; *m/z* (391/393 $M^{+\bullet}$, chlorine isotopes).

*3.3.7. 4-(4-Chlorophenyl)-6-(2-furoyl)-2-methyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5g**).* Yield 2.4 g, 76% as off white solid, mp 133–135 °C (toluene/pet. ether). Found: C, 55.90; H, 5.47; N, 17.35. $C_{15}H_{17}ClN_4O_2$ (320.78) requires: C, 56.17; H, 5.34; N, 17.47%. ν_{max} (KBr) 3255 (NH), 1656 (C=O), 1597 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.20–7.18 (m, 7H, Ar–H), 6.58 (s, 1H, NH), 5.17 (s, 2H, CH_2) 3.51 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 173.5 (Ar–C=O), 143.9 (C=N), 141.5, 137.3, 135.2, 131.9, 129.1, 128.0, 120.8, 115.5 ($C_{arom.}$), 61.2 (CH_2), 42.2 (CH_3) ppm; *m/z* (320/322 $M^{+\bullet}$, chlorine isotopes).

*3.3.8. 4-(4-Chlorophenyl)-6-(2-furoyl)-2-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5h**).* Yield 2.9 g, 75% as off white solid, mp 152–154 °C (toluene/pet. ether). Found: C, 62.60; H, 4.85; N, 14.76. $C_{20}H_{19}ClN_4O_2$ (382.85) requires: C, 62.75; H, 5.00; N, 14.63%. ν_{max} (KBr) 3250 (NH), 1652 (C=O), 1593 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.25–7.20 (m, 12H, Ar–H), 6.60 (s, 1H, NH), 5.19 (s, 2H, CH_2) ppm; δ_C (300 MHz, DMSO-d_6) 173.6 (Ar–C=O), 143.9 (C=N), 141.9, 137.8, 136.7, 134.9, 132.3, 129.4, 128.9, 128.0, 125.2, 121.6, 116.1, 114.9 ($C_{arom.}$), 61.2 (CH_2) ppm; *m/z* (382/384 $M^{+\bullet}$, chlorine isotopes).

*3.3.9. 4-(4-Chlorophenyl)-2-methyl-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5i**).* Yield 2.6 g, 78% as a pale yellow solid, mp 148–150 °C (toluene/pet. ether). Found: C, 53.25; H, 4.90; N, 16.75. $C_{15}H_{17}ClN_4OS$ (336.85) requires: C, 53.49; H, 5.09; N, 16.63%. ν_{max} (KBr) 3261 (NH), 1662 (C=O), 1593 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.25–7.15 (m, 7H, Ar–H), 6.55 (s, 1H, NH), 5.03 (s, 2H, CH_2), 3.55 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 174.3 (Ar–C=O), 143.9 (C=N), 141.5, 137.8, 135.6, 133.7, 131.4, 129.6, 124.3, 115.6 ($C_{arom.}$), 60.5 (CH_2), 42.1 (CH_3) ppm; *m/z* (336/338 $M^{+\bullet}$, chlorine isotopes).

*3.3.10. 4-(4-Chlorophenyl)-2-phenyl-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5j**).* Yield 2.9 g, 72% as pale green solid, mp 191–193 °C (toluene/pet. ether). Found: C, 60.50; H, 4.92; N, 13.95. $C_{20}H_{19}ClN_4OS$ (398.92) requires: C, 60.22; H, 4.80; N, 14.04%. ν_{max} (KBr) 3256 (NH), 1665 (C=O), 1595 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.30–7.20 (m, 12H, Ar–H), 6.56 (s, 1H, NH), 5.07 (s, 2H, CH_2) ppm; δ_C (300 MHz, DMSO-d_6) 174.4 (Ar–C=O), 143.9 (C=N), 141.4, 137.8, 136.1, 135.6, 133.7, 131.4, 129.6, 128.6, 128.1, 124.3, 121.3, 115.6 ($C_{arom.}$), 60.5 (CH_2) ppm; *m/z* (398/400 $M^{+\bullet}$, chlorine isotopes).

*3.3.11. 4-(4-Chlorophenyl)-2-methyl-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5k**).* Yield 2.7 g, 73% as a yellow solid, mp 172–174 °C (benzene/pet. ether). Found: C, 66.05; H, 4.55; N, 15.45. $C_{20}H_{17}ClN_4O$ (364.84) requires: C, 65.84; H, 4.70; N, 15.36%. ν_{max} (KBr) 3232 (NH), 1645 (C=O), 1597 (C=N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.60–7.17 (m, 11H, Ar–H), 6.53 (s, 1H, NH), 5.00 (s, 2H, CH_2), 3.52 (s, 3H, CH_3) ppm; δ_C (300 MHz, DMSO-d_6) 183.9

(Ar–C═O), 143.9 (C═N), 141.3, 135.4, 134.1, 132.4, 132.2, 130.0, 129.6, 129.1, 128.4, 128.2, 127.5, 126.3, 125.8, 115.5 ($C_{arom.}$), 56.8 (CH_2), 42.3 (CH_3) ppm; *m*/*z* (364/366 $M^{+\bullet}$, chlorine isotopes).

*3.3.12. 4-(4-Chlorophenyl)-6-(2-naphthoyl)-2-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**5l**).* Yield 3.0 g, 70% as a dirty green solid, mp 184–186 °C (benzene/pet. ether). Found: C, 70.55; H, 4.40; N, 12.95. $C_{25}H_{19}ClN_4O$ (426.91) requires: C, 70.34; H, 4.49; N, 13.12%. ν_{max} (KBr) 3235 (NH), 1648 (C═O), 1596 (C═N) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.58–7.15 (m, 16H, Ar–H), 6.58 (s, 1H, NH), 5.02 (s, 2H, CH_2) ppm; δ_C (300 MHz, DMSO-d_6) 184.2 (Ar–C═O), 143.6 (C═N), 141.7, 135.4, 134.3, 132.9, 132.4, 132.2, 131.9, 130.2, 129.7, 129.0, 128.7, 128.7, 127.9, 127.5, 126.7, 125.6, 121.7, 116.2 ($C_{arom.}$), 56.9 (CH_2) ppm; *m*/*z* (426/428 $M^{+\bullet}$, chlorine isotopes).

4. Conclusion

The reaction of several nitrilimines with 1,1-dimethylhydrazine or 1-methyl-1-phenylhydrazines leads to formation of 1,3,5-trisubstituted 1,2,4,5-tetraaza-2-hexene, which underwent thermal cyclization to corresponding 1,2,3,4-tetrahydro-*s*-tetrazine derivatives.

Acknowledgements

The author is thankful to the Union Arab Universities, Supporting Box of Palestinian Universities, Amman, Jordan, for partial finance support.

References and notes

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