HETEROCYCLIC SYNTHESIS USING NITRILIMINES: PART 2[1]. SYNTHESIS OF NEW 1,2,4,5-TETRAZINE DERIVATIVES

Hany M. M. Dalloul
Chemistry Department, Faculty of Science, Al-Aqsa University of Gaza, P. O. Box 4051, Gaza, Palestine.
E-mail: dalloul15@hotmail.com

Abstract: The reaction of C-2-furoyl- and C-2-thenoyl-N-arylnitrilimines 2a,b with 1-substituted-1-methylhydrazines 3-7 led to the formation of the respective amidrazones 8a,b when R = CH_3, Ph and to the acyclic adducts 9-11a,b when R = CHO, $COCH_3$ and COOEt. The acyclic adducts underwent thermal oxidative cyclization at CH_3 to give the unexpected 1,2,4,5-tetrazines 12-14a,b rather than the expected tetrazinones 16a,b when R = COOEt. Dihydro-1,2,4,5-tetrazines 15a,b were also separated when R = CHO.

Introduction

Cyclocondensation reactions of nitrilimines (the reactive 1,3-dipolar speches) with nucleophilic substrates incorporating suitably located electrophilic centers provide various heterocyclic products *via* cyclization of the intermediate acyclic adducts (1-3). 1,2,4,5-Tetrazines represent an important class of heterocyclic compounds that find many practical and synthetic applications (4). Since the formation of N-N bonds is relatively difficult, 1,2,4,5-tetrazines are generally prepared from hydrazine derivatives or from nitrilimines. Dihydro- and tetrahydro-1,2,4,5-tetrazines are prepared from the reaction of nitrilimines with aliphatic keto hydrazones and methyl hydrazones (5-7). The reaction of nitrilimines with different 1-substituted-1-methylhydrazines was recently reported to give acyclic adducts which upon thermal oxidative cyclization produced the tetrahydro-1,2,4,5-tetrazines (1,8). In continuation of our work concerning the utility of nitrilimines in the synthesis of heterocyclic compounds, we investigated the reaction of C-2-furoyl- and C-2-thenoyl-N-arylnitrilimines 2a,b with 1-substituted-1-methylhydrazines 3-7 in an attempt to synthesize new derivatives of 1,2,4,5-tetrazines.

Experimental

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer (KBr discs). NMR spectra were recorded on a Bruker instrument at 400 MHz for ^{1}H-NMR and at 100 MHz for ^{13}C-NMR using TMS as internal reference. Electron impact mass spectra were run on Finnigan Mat 8200 spectrometer at 70 eV. Elemental analysis was performed at Cairo University, Egypt. Hydrazonoyl halides 1a,b (9,10), 1-formyl-1-methylhydrazine 5 (11), 1-acetyl-1-methylhydrazine 6 (12), and 1-ethoxycarbonyl-1-methyl-hydrazine 7 (13) were prepared according to known literature procedures. 1,1-Dimethylhydrazine 3 and 1-methyl-1-phenylhydrazine 4 were purchased from Acros Organics Company, and used without further purification.

Reaction of Nitrilimines 2a,b with 1-Sbstituted-1-methylhydrazines 3-7

To a stirred cold (0 °C) solution of hydrazonoyl halides 1a,b (0.01 mol) and 1-substituted-1-methylhydrazines 3-7 (0.02 mol) in tetrahydrofuran (100 ml) was dropwise added triethylamine (0.05 mol) in tetrahydrofuran (20 ml). Stirring was continued overnight, the precipitated triethylamine salt was filtered off, and the solvent was removed in *vacuo*. The residue was washed with water (100 ml) and the resulting crude solid product was collected and recrystallized from ethanol. The following compounds were prepared by this procedure:

***2-Amino-4-(4-chlorophenyl)-1-(2-furyl)-3,4-diaza-2-buten-1-one* 8a**
^{1}H NMR: 9.95 (s, 1H, NH), 7.76-7.2 (m, 7H, aromatic protons), 5.6 (s, 2H, NH_2); ^{13}C NMR: 173.5 (Ar-C=O), 139.4 (C=N), 144.8, 136.8, 131.7, 130.8, 129.3, 127.5, 123.9, 114.3 (8 aromatic carbons); IR: 3460, 3340, 3300 (NH), 1660 (Ar-C=O), 1605 (C=N).

***2-Amino-4-(4-chlorophenyl)-1-(2-thienyl)-3,4-diaza-2-buten-1-one* 8b**
^{1}H NMR: 9.94 (s, 1H, NH-Ar'), 8.3-7.16 (m, 7H, aromatic protons), 5.7 (s, 2H, NH_2); ^{13}C NMR: 176.8 (Ar-C=O), 139.9 (C=N), 143.1, 136.2, 135.7, 131.9, 129.3, 127.2, 125.9, 115.5 (8 aromatic carbons); IR: 3460, 3350, 3310 (NH), 1650 (Ar-C=O), 1600 (C=N).

***6-(4-Chlorophenyl)-4-(2-furyl)-2-methyl-2,3,5,6-tetraaza-4-hexenal* 9a**
^{1}H NMR: 10.4 (s, 1H, NH-Ar'), 8.1 (s, 1H, CHO), 7.74-7.17 (m, 7H, aromatic protons), 6.6 (s, 1H, NH), 3.2 (s, 3H, N-CH_3); ^{13}C NMR: 173.0 (Ar-C=O), 162.0 (H-C=O), 137.1 (C=N), 140.6, 129.0, 128.8, 123.7, 123.0, 119.4, 116.5, 112.4 (8 aromatic carbons), 37.5 (N-CH_3); IR: 3360, 3260 (NH), 1670 (H-C=O), 1650 (Ar-C=O), 1595 (C=N).

***6-(4-Chlorophenyl)-2-methyl-4-(2-thienyl)-2,3,5,6-tetraaza-4-hexenal* 9b**
^{1}H NMR: 10.5 (s, 1H, NH-Ar'), 8.2-7.2 (m, 8H, aromatic protons, CHO), 6.4 (s, 1H, NH), 3.2 (s, 3H, NCH_3); ^{13}C NMR: 176.1 (Ar-C=O), 162.4 (H-C=O), 135.6 (C=N), 141.3, 135.3, 134.7, 132.4, 129.4, 127.6, 127.4, 116.1 (8 aromatic carbons), 37.1 (N-CH_3); IR: 3350, 3280 (NH), 1680 (H-C=O), 1640 (Ar-C=O), 1593 (C=N).

***7-(4-Chlorophenyl)-5-(2-furyl)-3-methyl-3,4,6,7-tetraaza-5-hepten-2-one* 10a**
^{1}H NMR: 11.2 (s, 1H, NH), 7.73-7.16 (m, 10H, aromatic protons), 6.6 (s, 1H, NH), 3.2 (s, 3H, NCH_3), 1.9 (s, 3H, $COCH_3$); ^{13}C NMR: 173.4 (Ar-C=O), 169.9 (CH_3-C=O), 140.0 (C=N), 141.6, 129.3, 129.0, 123.9, 123.2, 119.5, 116.3, 112.2 (8 aromatic carbons), 42.3 (N-CH_3), 21.1 (CH_3-CO); IR: 3380, 3300 (NH), 1670 (CH_3-C=O), 1650 (Ar-C=O), 1594 (C=N).

***7-(4-Chlorophenyl)-3-methyl-5-(2-thienyl)-3,4,6,7-tetraaza-5-hepten-2-one* 10b**
^{1}H NMR: 11.1 (s, 1H, NH-Ar'), 8.15-7.16 (m, 7H, aromatic protons), 6.7 (s, 1H, NH), 3.1 (s, 3H, NCH_3), 1.95 (s, 3H, $COCH_3$); ^{13}C NMR: 176.1 (Ar-C=O), 170.0 (CH_3-C=O), 139.7 (C=N), 141.0, 134.9, 134.7, 129.5, 129.4, 127.6, 127.5, 116.3 (8 aromatic carbons), 42.4 (N-CH_3), 21.1 (CH_3-CO); IR: 3360, 3280 (NH), 1670 (CH_3-C=O), 1660 (Ar-C=O), 1596 (C=N).

***Ethyl 6-(4-chlorophenyl)-4-(2-furoyl)-2-methyl-2,3,5,6-tetraaza-4-hexenoate* 11a**
^{1}H NMR: 10.4 (s, 1H, NH-Ar'), 7.76-7.16 (m, 7H, aromatic protons), 6.50 (s, 1H, NH), 4.31-4.25 (q, 2H, CH_2, *J*=7Hz), 3.13 (s, 3H, N-CH_3), 1.34-1.30 (t, 3H, CH_3, *J*=7Hz); ^{13}C NMR: 173.2 (Ar-C=O), 157.7 (O-C=O), 135.5 (C=N), 149.4, 146.8, 141.4, 129.0, 126.7, 121.7, 115.0, 111.9 (8 aromatic carbons), 62.7 (O-CH_2), 36.7 (N-CH_3), 14.2 (CH_3); IR: 3340, 3320 (NH), 1710 (O-C=O), 1650 (Ar-C=O), 1597 (C=N).

***Ethyl 6-(4-chlorophenyl)-2-methyl-4-(2-thenoyl)-2,3,5,6-tetraaza-4-hexenoate* 11b**
^{1}H NMR: 10.4 (s, 1H, NH-Ar'), 8.21-7.17 (m, 7H, aromatic protons), 6.53 (s, 1H, NH), 4.32-4.26 (q, 2H, CH_2, *J*=7Hz), 3.14 (s, 3H, NCH_3), 1.35-1.31 (t, 3H, CH_3, *J*=7Hz); ^{13}C NMR: 176.0 (Ar-C=O), 157.2 (O-C=O), 136.1 (C=N), 141.8, 135.5, 135.3, 129.4, 127.4, 127.1, 124.7, 115.8 (8 aromatic carbons), 63.1 (O-CH_2), 37.1 (N-CH_3), 14.6 (CH_3); IR: 3390, 3300 (NH), 1720 (O-C=O), 1655 (Ar-C=O), 1598 (C=N).

Thermal Cyclization of Compounds 9-11a,b

Compounds 9-11 (0.005 mol) and charcoal (0.5-1.0 g) in benzene (50 ml) were refluxed for 4-6 hours. The reaction mixture was then filtered and the solvent was minimized. Petroleum ether (bp. 40-60 °C) was then added to effect complete crystallization of the desired cyclic compounds 12-14. In case of compounds 12, the oxidation products 15 were also obtained as side reaction products, which were separated on TLC plates, using silica gel as the adsorbent, and CH_2Cl_2/pet.ether (5:1 v/v) as developing solvent. The following compounds were synthesized using this method:

***4-(4-Chlorophenyl)-2-formyl-6-(2-furoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine* 12a**
^{1}H NMR: 8.2 (s, 1H, CHO), 7.75-7.17 (m, 7H, aromatic protons), 6.5 (s, 1H, NH), 5.0 (s, 2H, CH_2); ^{13}C NMR: 173.4 (Ar-C=O), 162.2 (H-C=O), 136.4 (C=N), 143.5, 128.6, 128.1, 126.0, 123.7, 121.5, 119.2, 116.0 (8 aromatic carbons), 44.3 (N-CH_2-N); IR: 3255, (NH), 1670 (H-C=O), 1655 (Ar-C=O), 1596 (C=N).

***4-(4-Chlorophenyl)-2-formyl-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetra-zine* 12b**
^{1}H NMR: 8.4 (s, 1H, CHO), 8.2-7.16 (m, 7H, aromatic protons), 6.5 (s, 1H, NH), 5.1 (s, 2H, CH_2); ^{13}C NMR: 176.3 (Ar-C=O), 162.1 (H-C=O), 136.2 (C=N), 143.3, 128.8, 128.2, 125.9, 123.7, 121.7, 119.4, 116.1(8 aromatic carbons), 44.2 (N-CH_2-N); IR: 3260, (NH), 1675 (H-C=O), 1650 (Ar-C=O), 1597 (C=N).

2-Acetyl-4-(4-chlorophenyl)-6-(2-furoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine **13a**

^{1}H NMR: 7.76-7.16 (m, 7H, aromatic protons), 6.7 (s, 1H, NH), 5.0 (s, 2H, CH_2), 2.1 (s, 3H, CH_3); ^{13}C NMR. 173.2 (Ar-C=O), 170.0 (CH_3-C=O), 137.2 (C=N), 144.3, 128.6, 128.3, 125.6, 125.0, 123.3, 119.4, 115.8 (8 aromatic carbons), 43.2 (N-CH_2-N), 26.0 (CH_3); IR: 3280, (NH), 1660 (CH_3-C=O), 1650 (Ar-C=O), 1595 (C=N).

2-Acetyl-4-(4-chlorophenyl)-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetra-zine **13b**

^{1}H NMR: 8.3-7.2 (m, 7H, aromatic protons), 6.8 (s, 1H, NH), 5.0 (s, 2H, CH_2), 2.0 (s, 3H, CH_3); ^{13}C NMR: 176.5 (Ar-C=O), 169.7 (CH_3-C=O), 137.4 (C=N), 144.5, 128.5, 128.1, 125.3, 124.9, 123.6, 119.2, 116.2 (8 aromatic carbons), 43.10 (N- CH_2-N), 26.1 (CH_3); IR: 3260, (NH), 1680 (CH_3-C=O), 1660 (Ar-C=O), 1593 (C=N).

4-(4-Chlorophenyl)-2-ethoxycarbonyl-6-(2-furoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetra-zine **14a**

^{1}H NMR: 7.8-7.2 (m, 7H, aromatic protons), 7.02/6.90 (s, 1H, NH), 5.1/5.0 (s, 2H, NCH_2N), 4.31/4.25 (q, 2H, O-CH_2), 1.36/1.30 (t, 3H, CH_3); ^{13}C NMR: 172.6/172.0 (Ar-C=O), 156.3/153.1 (O-C=O), 142.3/141.2 (C=N), 148.8/144.3, 135.4/134.0, 130.8/129.4, 128.9/126.9, 126.5/124.7, 123.5/121.8, 119.3/115.7, 114.1/112.0 (8 aromatic carbons), 60.4/56.5 (N-CH_2-N), 63.2/62.3 (O-CH_2), 14.8 (CH_3); IR: 3330 (NH), 1702 (O-C=O), 1670 (Ar-C=O), 1595 (C=N).

4-(4-Chlorophenyl)-2-ethoxycarbonyl-6-(2-thenoyl)-1,2,3,4 tetrahydro-1,2,4,5-tetrazine **14b**

^{1}H NMR: 8.4-7.2 (m, 7H, aromatic protons), 7.06/7.04 (s, 1H, NH), 5.1/5.0 (s, 2H, N-CH_2-N), 4.32/4.27 (q, 2H, O-CH_2), 1.38/1.32 (t, 3H, CH_3); ^{13}C NMR: 174.9/174.5 (Ar-C=O), 156.2/152.7 (O-C=O), 143.1/140.9 (C=N), 148.4/144.8, 136.0/135.6, 135.1/134.7, 129.3/128.2, 127.2/127.0, 126.3/124.5, 124.2/123.5, 116.0/115.7 (8 aromatic carbons), 60.6/56.3 (N-CH_2-N), 63.5/62.3 (O-CH_2), 14.7 (CH_3); IR: 3320 (NH), 1705 (O-C=O), 1665 (Ar-C=O), 1594 (C=N).

1-(4-Chlorophenyl-3-(2-furoyl)-1,6-dihydro-1,2,4,5-tetrazine **15a**

^{1}H NMR: 7.40-7.17 (m, 7H, aromatic protons), 5.6 (s, 2H, N-CH_2-N); ^{13}C NMR: 173.1 (Ar-C=O), 143.3 (C=N), 149.0, 139.7, 130.5, 129.3, 123.5, 119.8, 116.9, 113.0 (8 aromatic carbons), 65.3 (CH_2); IR: 1660 (Ar-C=O), 1597 (C=N).

1-(4-Chlorophenyl)-3-(2-thenoyl)-1,6-dihydro-1,2,4,5-tetrazine **15b**

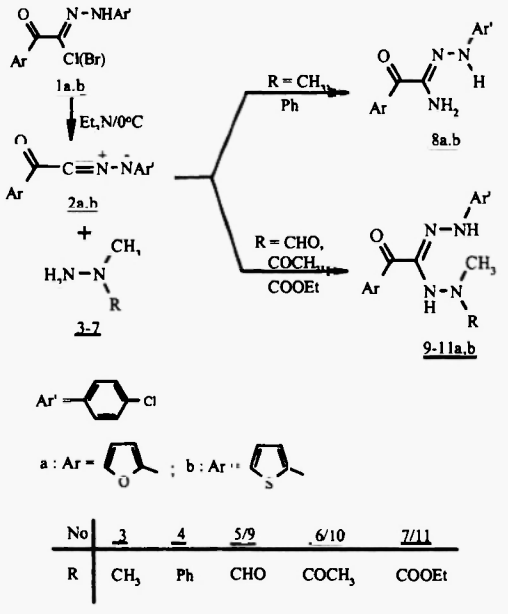
^{1}H NMR: 8.40-7.20 (m, 7H, aromatic protons), 5.7 (s, 2H, N-CH_2-N); ^{13}C NMR: 176.4 (Ar-C=O), 143.6 (C=N), 148.2, 136.8, 133.9, 130.3, 129.6, 127.8, 123.7, 116.2 (8 aromatic carbons), 65.5 (CH_2); IR: 1650 (Ar-C=O), 1598 (C=N).

Results and Discussion

In the present work, we found that 1-substituted-1-methylhydrazines 3-7 react readily with nitrilimines 2a,b- generated in *situ* from the action of triethylamine onto the hydrazonoyl halides 1a,b- yielding the corresponding amidrazones 8a,b when R = CH_3, Ph, and the acyclic adducts 9-11a,b when R = CHO, $COCH_3$ and $COOC_2H_5$ (Scheme 1).

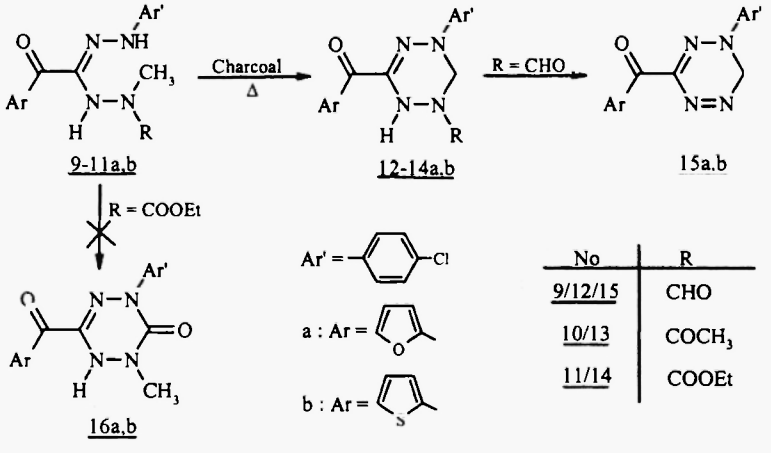
Thermal cyclization of later acyclic adducts gave tetrahydro-1,2,4,5-tetrazines 12-14a,b (Scheme 2). Dihydro-1,2,4,5-tetrazines 15a,b were also obtained upon elimination of formaldehyde from compounds 12a,b (Scheme 2, Table 1).

A plausible reaction mechanism for this cyclization starts by the oxidation of the acyclic adducts 9-11a,b to formazanes, which cyclize as reported by Neugebauer et al. (14) to corresponding tetrahydro-1,2,4,5-tetrazines. It is worth mentioning this kind of cyclization of alkyl formazanes is the most frequently used method for the preparation of tetrahydro-1,2,4,5-tetrazines (4).



Scheme 1 : Synthesis of amidrazones 8a,b and compounds 9-11a,b.

Structural assignment of 8-15a,b is based on elemental analysis and spectral data (experimental part).
The electron impact spectra (Table 1) display the correct molecular ions in accordance with the suggested structures. The IR spectra of each of the amidrazones 8a,b exhibits characteristic NH_2 bands in the 3400-3300 cm^{-1} region, in addition to N-H and C=O bands near 3450 and 1650 cm^{-1}, respectively.
The IR of the acyclic adducts 9-11a,b reveal two N-H bands at about 3300 and 3200 cm^{-1}, and two C=O bands at about 1700 and 1600 cm^{-1} assignable to lactam C=O and ArC=O, respectively.
One of the N-H bands is absent in the spectra of cyclic compounds 12-14a,b. The N-H band and C=O band of the formyl group disappear in IR spectra of compounds 15a,b.
^{1}H- and ^{13}C-NMR spectra of compounds 8-15a,b are consistent with the assigned structures (experimental part).
The ^{1}H-NMR spectra indicate that the N-CH_3 signal (δ = 3.2-3.0 ppm) of compounds 9-11a,b is replaced by a highly deshielded CH_2 signal (δ = 5.7-5.1 ppm) in compounds 12-15a,b. This is similar to reported values of CH_2 flanked by two nitrogens in six-membered heterocycles (1,8).
All the NMR signals of compounds 14a,b are doubled which indicate that the products exist as a pair of tautomers in solution. Similar tautomerism was reported for s-tetrazines by Ryabokon et al. (15).



Scheme 2 : Thermal cyclization of compounds 9-11a,b.

Table 1 Physical Data and Elemental Analysis for Compounds 8-15

Compd.	m.p (°C)	Yield (%)	Mol. Formula $M^{+\cdot}$	Calculated / Found (%)		
				C	H	N
8a	158-160	60	$C_{12}H_{10}ClN_3O_2$	54.66	3.82	15.94
			263/265	54.50	3.90	15.80
8b	149-151	63	$C_{12}H_{10}ClN_3OS$	51.52	3.60	15.02
			279/281	51.40	3.70	14.90
9a	119-121	74	$C_{14}H_{13}ClN_4O_3$	52.43	4.09	17.47
			320/322	52.30	3.90	17.60
9b	140-142	75	$C_{14}H_{13}ClN_4O_2S$	49.93	3.89	16.63
			336/338	50.10	4.80	16.80
10a	175-177	71	$C_{15}H_{15}ClN_4O_3$	53.82	4.52	16.74
			334/336	54.10	4.60	16.80
10b	133-135	72	$C_{15}H_{15}ClN_4O_2S$	51.35	4.31	15.97
			350/352	51.60	4.50	16.10
11a	102-104	76	$C_{16}H_{17}ClN_4O_4$	52.68	4.70	15.36
			364/366	52.50	4.80	15.50
11b	115-117	78	$C_{16}H_{17}ClN_4O_3S$	50.46	4.50	14.71
			380/382	50.30	4.70	14.80
12a	145-147	67	$C_{14}H_{11}ClN_4O_3$	52.76	3.48	17.58
			318/320	52.90	3.30	17.70
12b	132-134	69	$C_{14}H_{11}ClN_4O_2S$	50.23	3.31	16.74
			334/336	50.10	3.40	16.60
13a	186-188	72	$C_{15}H_{13}ClN_4O_3$	54.15	3.94	16.84
			332/334	54.30	4.10	16.70
13b	180-182	74	$C_{15}H_{13}ClN_4O_2S$	51.65	3.76	16.06
			348/350	51.80	3.60	15.90
14a	153-155	78	$C_{16}H_{15}ClN_4O_4$	52.97	4.17	15.44
			362/364	52.90	4.30	15.50
14b	145-147	77	$C_{16}H_{15}ClN_4O_3S$	50.73	3.99	14.79
			378/380	50.60	4.20	14.90
15a	174-176	34	$C_{13}H_9ClN_4O_2$	54.09	3.14	19.41
			288/290	53.90	3.20	19.50
15b	168-170	35	$C_{13}H_9ClN_4OS$	51.24	2.98	18.38
			304/306	51.40	3.10	18.40

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