HETEROCYCLIC SYNTHESIS USING NITRILIMINES: PART 3 (1). SYNTHESIS OF SUBSTITUTED 1,2,4,5-TETRAZINES AND 1,2,4,5-TETRAAZA-2-PENTENES

Hany M. Dalloul*[a], Peter H. Boyle[b]
a) Chemistry Department, Faculty of Science, Al-Aqsa University of Gaza, Gaza, Palestine.
E-mail: dalloul15@hotmail.com
b) Chemistry Department, Trinity College, Dublin 2, Ireland.

Abstract

The reaction of nitrilimines 2a,b with hydrazones of aliphatic ketones 3 ($RHNN{=}CR^1R^2$) led to the formation of the cyclocondensation products 1,2,4,5-tetrazines 4a-g when R = CH_3, and to acyclic electrophilic addition products 5a-g when R = H, rather than the cyclocondensation tetrazines products 8.

Introduction

The reactive 1,3-dipole nitrilimines are reported to react differently with hydrazones: Their reaction with methyl hydrazones of aliphatic aldehydes and ketones provides the 1,2,3,4-tetrahydro-s-tetrazines (2,3). On the other hand, methyl hydrazones of aromatic aldehydes give a mixture of cyclic and acyclic tetrazines (4). Simple hydrazones of aliphatic aldehydes and ketones react with nitrilimines to give acyclic addition products, which upon treatment with palladium-carbon cyclize to 1,6-dihydro-s-tetrazines (5).

It was recently reported that nitrilimines react with hydrazones carrying electron withdrawing groups to afford the cycloaddition products 1,2,4-triazoles rather than the cyclocondensation 1,2,4,5-tetrazines products, apparently, because of the weak nucleophilicity of the nitrogen atom carrying the electron withdrawing groups (6,7).

This study aims to investigate the reaction of C-phenylaminocarbonyl-N-arylnitrilimines 2a,b with different hydrazones and methyl hydrazones of aliphatic ketones 3.

Experimental

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Satellite 3000 Mid infrared spectrometer (KBr discs). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) spectrometer in $CDCl_3$ using TMS as internal reference. Chemical shifts (δ) are expressed in ppm downfield from internal TMS. Electron impact mass spectra were run on LCT Electrospray mass spectrometer. The NMR and mass spectra were carried out at Trinity College, Dublin 2, Ireland. Elemental analysis was performed at Cairo University, Egypt. Hydrazonoyl halides 1a,b (8), hydrazones (5) and methyl hydrazones 3 (2) were prepared as previously described.

Reaction of Nitrilimines 2a,b with Hydrazones 3

Triethylamine (0.05 mol) in tetrahydrofuran (20 ml) was dropwise added to a stirred solution of hydrazonoyl halides 1a,b (0.01 mol) and hydrazones 3 (0.02 mol) in tetrahydrofuran (100 ml) at -5 to 0 °C. The reaction temperature was allowed to rise slowly to room temperature and stirring was continued for 4-6 hours. The precipitated triethylammonium salt was filtered off, and the solvent was removed in *vacuo*. The residue was washed with water (100 ml) and in a few cases the oily or gummy products were triturated with ethanol (10 ml). The crude solid product was collected and recrystallized from ethanol to give the desired compounds. The following compounds were synthesized using this method:

1,3,3-Trimethyl-4-phenyl-6-phenylaminocarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine 4a

^{1}H NMR (δ/ppm): 9.0 (s, 1H, PhNH), 7.6-7.2 (m, 10H, aromatic), 4.3 (s, 1H, NH), 3.4 (s, 3H, CH_3), 1.4 (s, 6H, CH_3); ^{13}C NMR (δ/ppm): 158.9 (C=O), 136.4 (C=N), 68.7 (quaternary carbon), 42.9 (NCH_3), 22.3 (CH_3); IR (cm^{-1}): 3350, 3255 (NH), 1655 (C=O), 1590 (C=N).

9-Methyl-6-phenyl-8-phenylaminocarbonyl-6,7,9,10-tetraazaspiro[4.5]dec-7-ene 4b

^{1}H NMR (δ/ppm): 9.0 (s, 1H, PhNH), 7.6-7.2 (m, 10H, aromatic), 4.2 (s, 1H, NH), 3.5 (s, 3H, CH_3), 1.9-1.7 (m, 8H, cyclopentane); ^{13}C NMR (δ/ppm): 158.8 (C=O), 136.6 (C=N), 86.6 (spiro carbon), 42.9 (NCH_3), 31.9, 23.2 (cyclopentane carbons); IR (cm^{-1}): 3385, 3260 (NH), 1650 (C=O), 1592 (C=N).

4-Methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraazaspiro[5.5]undec-2-ene 4c

^{1}H NMR (δ/ppm): 9.0 (s, 1H, PhNH), 7.6-7.2 (m, 10H, aromatic), 4.0 (s, 1H, NH), 3.5 (s, 3H, CH_3), 1.8-1.6 (m, 10H, cyclohexane); ^{13}C NMR (δ/ppm): 158.9 (C=O), 136.8 (C=N), 80.2 (spiro carbon), 42.9 (NCH_3), 32.0, 24.7, 23.3 (cyclohexane carbons); IR (cm^{-1}): 3350, 3250 (NH), 1650 (C=O), 1592 (C=N).

4,9-Dimethyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraazaspiro[5.5]undec-2-ene 4d

^{1}H NMR (δ/ppm): 9.0 (s, 1H, PhNH), 7.6-7.16 (m, 10H, aromatic), 4.1 (s, 1H, NH), 3.4 (s, 3H, CH_3), 2.0-1.2 (m, 9H, cyclohexane), 0.9 (s, 3H, CH_3 at cyclohexane); ^{13}C NMR (δ/ppm): 158.6 (C=O), 136.6 (C=N), 84.5 (spiro carbon), 42.9 (NCH_3), 33.6, 28.1, 22.6 (cyclohexane carbons), 31.2 (CH_3 at cyclohexane); IR (cm^{-1}): 3360, 3265 (NH), 1655 (C=O), 1594 (C=N).

9-tert-Butyl-4-methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraazaspiro[5.5]undec-2-ene 4e

^{1}H NMR (δ/ppm): 9.0 (s, 1H, PhNH), 7.6-7.17 (m, 10H, aromatic), 4.1 (s, 1H, NH), 3.4 (s, 3H, CH_3), 2.0-1.0 (m, 9H, cyclohexane), 0.85 (s, 9H, tert-butyl group); ^{13}C NMR (δ/ppm): 158.7 (C=O), 136.5 (C=N), 84.9 (spiro carbon), 42.9 (NCH_3), 47.0, 35.7, 32.4, 27.5, 24.0 (tert-butyl-cyclohexane carbons); IR (cm^{-1}): 3320, 3255 (NH), 1660 (C=O), 1597 (C=N).

4-Methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraazaspiro[5.6]dodec-2-ene 4f

^{1}H NMR (δ/ppm): 8.9 (s, 1H, PhNH), 7.6-7.2 (m, 10H, aromatic), 4.0 (s, 1H, NH), 3.4 (s, 3H, CH_3), 2.4-1.6 (m, 12H, cycloheptane); ^{13}C NMR (δ/ppm): 158.5 (C=O), 136.7 (C=N), 87.7 (spiro carbon), 42.2 (NCH_3), 39.4, 28.1, 22.2 (cycloheptane carbons); IR (cm^{-1}): 3330, 3245 (NH), 1650 (C=O), 1595 (C=N).

4-Methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraazaspiro[5.7]tridec-2-ene 4g

^{1}H NMR (δ/ppm): 9.1 (s, 1H, PhNH), 7.6-7.2 (m, 10H, aromatic), 4.2 (s, 1H, NH), 3.4 (s, 3H, CH_3), 2.5-1.4 (m, 14H, cyclooctane); ^{13}C NMR (δ/ppm): 158.4 (C=O), 136.5 (C=N), 86.6 (spiro carbon), 42.2 (NCH_3), 34.5, 30.7, 28.4, 23.1 (cyclooctane carbons); IR (cm^{-1}): 3380, 3260 (NH), 1665 (C=O), 1598 (C=N).

5-Cyclopentylidene-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-pentene 5b

^{1}H NMR (δ/ppm): 10.9 (s, 1H, NHAr), 9.1 (s, 1H, PhNH), 8.5 (s, 1H, NH), 7.7-7.2 (m, 10H, aromatic), 1.9-1.6 (m, 8H, cyclopentane); ^{13}C NMR (δ/ppm): 159.9 (C=O), 159.3 (N=CR^1R^2), 136.6 (C=N), 33.5, 26.2, 25.0, 24.9 (cyclopentane carbons); IR (cm^{-1}): 3380, 3260, 3300 (NH), 1660 (C=O), 1618, 1596 (C=N).

5-Cyclohexylidene-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-pentene 5c

^{1}H NMR (δ/ppm): 10.8 (s, 1H, NHAr), 9.1 (s, 1H, PhNH), 8.4 (s, 1H, NH), 7.7-7.2 (m, 10H, aromatic), 2.4-1.5 (m, 10H, cyclohexane); ^{13}C NMR (δ/ppm): 159.9 (C=O), 152.2 (N=CR^1R^2), 136.7 (C=N), 35.7, 26.9, 25.6, 25.5, 24.5 (cyclohexane carbons); IR (cm^{-1}): 3350, 3330, 3280 (NH), 1650 (C=O), 1627, 1592 (C=N).

5-(4-tret-Butylcyclohexylidene-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-pentene 5e

^{1}H NMR (δ/ppm): 10.9 (s, 1H, NHAr), 8.9 (s, 1H, PhNH), 8.5 (s, 1H, NH), 7.7-7.2 (m, 10H, aromatic), 2.1-1.1 (m, 9H, cyclohexane), 0.9 (s, 9H, tert-butyl); ^{13}C NMR (δ/ppm): 159.8 (C=O), 152.3 (N=CR^1R^2), 136.6 (C=N), 46.9, 35.6, 32.5, 32.3, 27.7, 24.4, 23.6 (tert-butylcyclohexane carbons); IR (cm^{-1}): 3360, 3340, 3270 (NH), 1655 (C=O), 1626, 1593 (C=N).

5-Cycloheptylidene-1-phenyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-pentene 5f

^{1}H NMR (δ/ppm): 10.8 (s, 1H, NHAr), 9.0 (s, 1H, PhNH), 8.6 (s, 1H, NH), 7.7-7.2 (m, 10H, aromatic), 2.5-1.6 (m, 12H, cycloheptane); ^{13}C NMR (δ/ppm): 159.7 (C=O), 155.3 (N=CR^1R^2), 136.8 (C=N), 43.6, 30.5, 30.4, 29.1, 27.9, 24.3, (cycloheptane carbons); IR (cm^{-1}): 3450, 3365, 3300 (NH), 1660 (C=O), 1619, 1594 (C=N).

1-(4-Chlorophenyl)-6-methyl-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2,5-pentadiene 5h

^{1}H NMR (δ/ppm): 10.9 (s, 1H, NHAr), 9.0 (s, 1H, PhNH), 8.6 (s, 1H, NH), 7.7-7.2 (m, 9H, aromatic), 1.9 (s, 6H, 2CH_3); ^{13}C NMR (δ/ppm): 159.8 (C=O), 148.9 (N=CR^1R^2), 136.6 (C=N), 25.6 (CH_3), 15.1 (CH_3); IR (cm^{-1}): 3400, 3360, 3260 (NH), 1650 (C=O), 1618, 1596 (C=N).

1-(4-Chlorophenyl)-5-cyclohexylidene-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-pentene 5i

^{1}H NMR (δ/ppm): 10.9 (s, 1H, NHAr), 9.0 (s, 1H, PhNH), 8.4 (s, 1H, NH), 7.7-7.2 (m, 9H, aromatic), 2.4-1.7 (m, 10H, cyclohexane); ^{13}C NMR (δ/ppm): 159.8 (C=O), 152.3 (N=CR^1R^2), 136.7 (C=N), 35.7, 26.9, 25.6, 25.5, 24.5 (cyclohexane carbons); IR (cm^{-1}): 3375, 3360, 3265 (NH), 1665 (C=O), 1628, 1591 (C=N).

1-(4-Chlorophenyl)-5-cyclooctylidene-3-phenylaminocarbonyl-1,2,4,5-tetraaza-2-pentene 5j

^{1}H NMR (δ/ppm): 11.0 (s, 1H, NHAr), 9.1 (s, 1H, PhNH), 8.7 (s, 1H, NH), 7.7-7.2 (m, 9H, aromatic), 2.5-1.5 (m, 14H, cyclooctane); ^{13}C NMR (δ/ppm): 159.8 (C=O), 155.2 (N=CR^1R^2), 136.6 (C=N), 36.7, 27.4, 26.8, 26.6, 25.6, 25.1, 23.7 (cyclooctane carbons); IR (cm^{-1}): 3380, 3360, 3260 (NH), 1655 (C=O), 1620, 1593 (C=N).

2-Amino-4-phenyl-1-phenylamino-3,4-diaza-2-buten-1-one 6

^{1}H NMR (δ/ppm): 9.9 (s, 1H, NHAr), 9.0 (s, 1H, PhNH), 7.6-7.2 (m, 10H, aromatic), 5.7 (s, 2H, NH_2),; ^{13}C NMR (δ/ppm): 159.9 (C=O), 139.9 (C=N); IR (cm^{-1}): 3480-3200 (NH, NH_2, broad), 1650 (C=O), 1593 (C=N).

2-Amino-4-(4-chlorophenyl)-1-phenylamino-3,4-diaza-2-buten-1-one 7

^{1}H NMR (δ/ppm): 9.9 (s, 1H, NHAr), 9.0 (s, 1H, PhNH), 7.6-7.16 (m, 9H, aromatic), 5.6 (s, 2H, NH_2),; ^{13}C NMR (δ/ppm): 159.8 (C=O), 139.7 (C=N); IR (cm^{-1}): 3400-3100 (NH, NH_2, broad), 1650 (C=O), 1594 (C=N).

Results and Discussion

The reaction of nitrilimines 2a,b with alkanone and cycloalkanone hydrazones 3 was carried out by applying a two-fold excess of the hydrazones 3 with hydrazonoyl halides 1a,b -precursors of nitrilimines 2a,b- in tetrahydrofuran in the presence of triethylamine. The reaction is found to give cyclocondensation 1,2,4,5-tetrazines 4a-g when R = CH_3, owing to the high nucleophilicity of the nitrogen atom carrying the methyl group.

The formation of compounds 4a-g involving the nucleophilic addition of the hydrazones 3 to the nitrilimines 2 to give the unisolable acyclic intermediates, which ultimately undergo intramolecular cyclization to yield the tetrazine derivatives 4a-g. Similar intramolecular cyclization, following the initial 1,3-nucleophilic addition step of suitably functionalized nucleophilic substrates onto nitrilimines was reported by El-Abadelah et al. (2,4) (Scheme 1).

The assignment of structures 4a-g is based on analytical and spectral data. The electron impact (EI) mass spectra (Table 1) display the correct molecular ions in accordance with the suggested structures. The IR spectra show characteristic N-H bands in the 3400-3200 cm^{-1} region, in addition to C=O bands at about 1660 cm^{-1}.

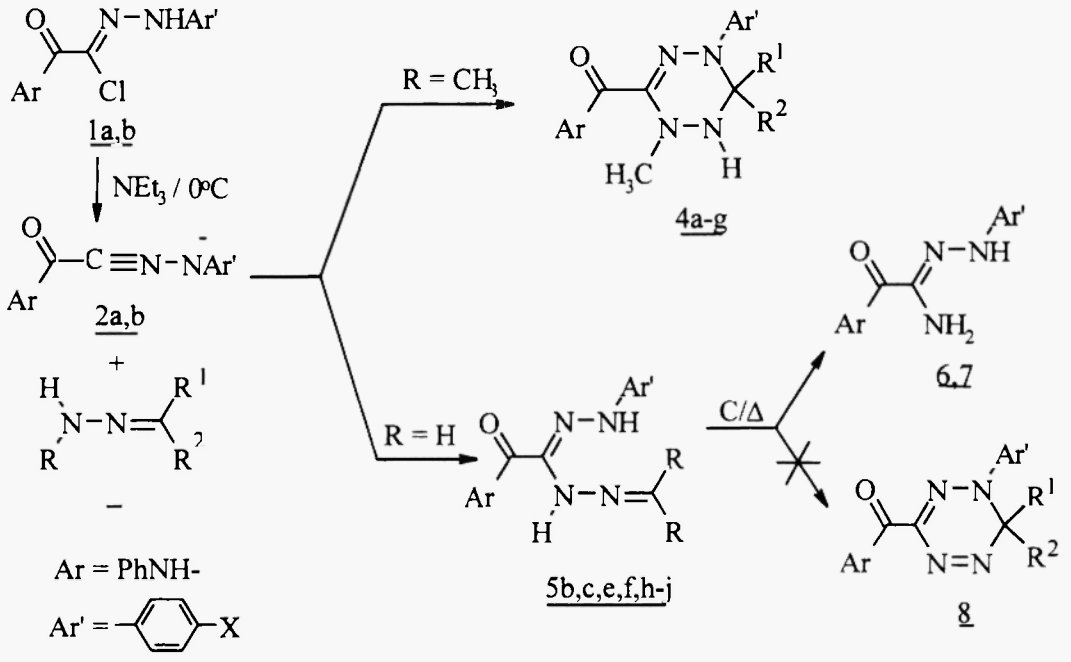
^1H and ^{13}C NMR spectra of compounds 4a-g show all the signals of the proposed structures. ^1H-NMR shows characteristic signals for N-H of the ring at about (δ = 4.0-4.3 ppm) and N-CH_3 (3.4 ppm) in addition to the multiplets resulting from the aliphatic at about (2.5-0.8 ppm) and aromatic hydrogens at about (7.6-7.2 ppm) The detailed ^1H NMR data is shown in the experimental part.

The ^{13}C NMR spectra of products 4a-g exhibit a signal at 70-90 ppm attributed to C_6 (quaternary or spiro carbon). This is similar to reported values of quaternary or spiro carbons flanked by tow nitrogens in six-membered heterocycles (2-4,9). This provides strong evidence in support of structures 4a-g rather than acyclic structures.

On the other hand, the reaction with simple hydrazones is found to afford the acyclic adducts 5. Trials to cyclize the later adducts were performed by heating them with activate charcoal in refluxing toluene. This method was recently reported to be efficient for cyclization of similar acyclic adducts which produce tetrazines (5).

A compounds give complicated mixture of products as indicated by TLC, among which amidrazones 6,7 were separated, rather than the expected 1,6-dihydro-s-tetrazines 8 (Scheme 1). The assignment of structures 5-7 is based on their analytical and spectral data (Tables 1). The complete spectral data are presented in the experimental part.

Scheme 1: Synthesis of compounds 4-7.



Entery	a	b	c	d	e	f	g	h	i	j
R^1 / R^2	M / M							M / M		
X	H	H	H	H	H	H	H	C	C	C

Table 1: Physical Data and Elemental Analysis for Compounds 4-7

Compd.	Mp (°C)	Yield (%)	Mol. Formula	Calculated / Found (%)		
			$M^{+\cdot}$	C	H	N
4a	130-132	80	$C_{18}H_{21}N_5O$	66.85	6.55	21.66
			323	67.10	6.40	21.60
4b	142-144	76	$C_{20}H_{23}N_5O$	68.75	6.63	20.04
			349	68.50	6.80	19.90
4c	139-141	82	$C_{21}H_{25}N_5O$	69.40	6.93	19.27
			363	69.50	7.20	19.20
4d	144-146	80	$C_{22}H_{27}N_5O$	70.00	7.21	18.55
			377	69.80	7.10	18.70
4e	152-154	79	$C_{25}H_{33}N_5O$	71.57	7.93	16.69
			419	71.70	8.10	16.60
4f	121-123	75	$C_{22}H_{27}N_5O$	70.00	7.21	18.55
			377	69.90	7.40	18.40
4g	110-112	73	$C_{23}H_{29}N_5O$	70.56	7.47	17.89
			391	70.80	7.60	18.00
5b	107-109	69	$C_{19}H_{21}N_5O$	68.04	6.31	20.88
			335	67.80	6.10	21.00
5c	120-122	73	$C_{20}H_{23}N_5O$	68.75	6.63	20.04
			349	69.00	6.80	19.90
5e	144-146	71	$C_{24}H_{31}N_5O$	71.08	7.70	17.27
			405	70.90	7.60	17.20
5f	118-120	63	$C_{21}H_{25}N_5O$	69.40	6.93	19.27
			363	69.60	7.10	19.10
5h	128-130	71	$C_{17}H_{18}ClN_5O$	59.39	5.28	20.37
			343/345	59.50	5.30	20.50
5i	141-143	65	$C_{20}H_{22}ClN_5O$	62.58	5.78	18.24
			383/385	62.40	5.70	18.10
5j	150-152	65	$C_{22}H_{26}ClN_5O$	64.15	6.36	17.00
			411/413	64.00	6.50	16.80
6	218-220[a]	60	$C_{14}H_{14}N_4O$	66.13	5.55	22.03
			254	65.90	5.40	21.80
7	229-231[b]	61	$C_{14}H_{13}ClN_4O$	58.24	4.54	19.40
			288/290	58.10	4.60	19.60

a: Lit. mp. 216 °C (10); b: Lit. mp. 230 °C (10)

References

1) H. M. Dalloul, Heterocyclic Comm. (submitted).

2) M. M. El-Abadelah, A. Q. Hussein, M. A. Kamal, K. H. Al-Adhami, Heterocycles **27**, 917 (1988).

3) E. A. El-Sawi, A. M. Awadallah, A. S. Ferwanah, H. M. Dalloul, Asian J. Chem. **14**, 1225 (2002).

4) A. Q. Hussein, M. M. El-Abadelah, K. H. Al-Adhami, A. S. Abushamleh, Heterocycles **29**, 1163 (1989).

5) A. Q. Hussein, J. Chem. Res. (**S**), 174 (1996); J. Chem. Res. (**M**), 949 (1996).

6) A. M. Awadallah, E. A. El-Sawi, A. S. Ferwanah, H. M. Dalloul, Asian J. Chem. **14**, 1230 (2002).

7) B. M. Awad, A. S. Ferwanah, A. M. Awadallah, N. M. El-Halabi, Asian J. Chem. **14**, 1235 (2002).

8) A. S. Shawali, H. M. Hassaneen, A. A. Fahmi, N. M. AbuNada, Phosphorous, Sulfur and Silicon **53**, 259 (1990).

9) A. S. Shawali, C. Parkanyi, J. Heterocyclic Chem. **17**, 833 (1980), and references therein.

10) N. M. Abu Nada, M.Sc. Thesis, Faculty of Science, Cairo University (1989).

Received on March 29, 2003.