J. prakt. Chem. 340 (1998) 623 – 626

Journal für praktische Chemie
Chemiker-Zeitung

Full Paper

Reaction of Nitrilimines with Alkoxycarbonyl-hydrazines: Synthesis of 6-Acetyl-4-aryl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-*s*-tetrazines

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Received February 17th, 1998, respectively July 7th, 1998

Abstract. Nitrilimines **2** are found to react with alkoxycarbonylhydrazines **3**–**5** to afford the acyclic adducts **6**–**8**. **6c** is oxidized upon heating with charcoal in refluxing toluene to the corresponding formazan **9c**. Compounds **8** cyclize upon heating with charcoal in refluxing toluene to the corresponding 6-acetyl-4-aryl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-*s*-tetrazines (**10**) rather than to the expected corresponding tetrazinones **11**. NMR study of compounds **10** showed that these compounds exist in a tautomeric equilibrium.

Cyclocondensation reactions of nitrilimines **2** with nucleophilic substrates incorporating suitably located electrophilic centers provide – *via* cyclization of the intermediate acyclic adducts – *various* heterocyclic products [1–3].

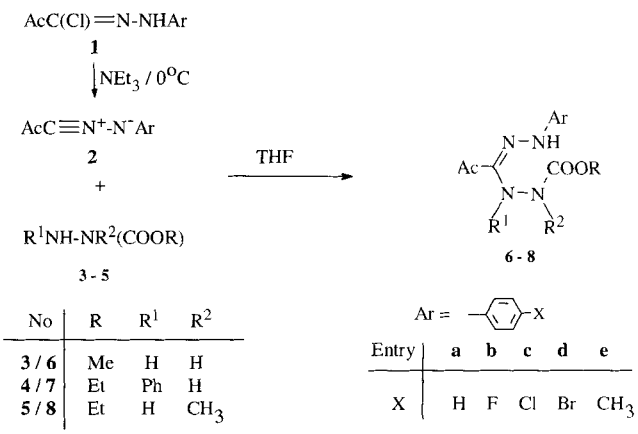
It was recently reported that nitrilimines **2** react with α-amino esters to afford 4,5-dihydro-1,2,4-triazin-6-ones [4]. Similar results are obtained from the cyclo-condensation of nitrile oxides with α-amino acid esters which lead to the formation of 1,2,4-oxadiazin-6-ones [5]. The reaction of nitrile oxides with 1-ethoxycarbonyl-1-methylhydrazine produced -after cyclization of the stable acyclic adducts – the novel 4,5-dihydro-1,2,4,5-oxa-triazin-6-ones [6].

The reaction of nitrilimines **2** with ethoxycarbonylhydrazines remains, however, unexplored in the literature.

As a consequence, it is expected that the reaction of nitrilimines **2** with substituted ethoxy- and methoxycarbonyl hydrazines (aza analogues of amino acid esters) will afford 1,4-dihydro-1,2,4,5-tetrazin-3-(2H)-ones **11**. The precursors of nitrilimines hydrazonoyl chlorides **1** employed in this study were prepared *via* the direct coupling of arenediazonium chlorides with 3-chloropentane-2,4-dione (Japp-Klingmann reaction) [4]. Methylhydrazinocarboxylate **3** was purchased from Aldrich. 1-Ethoxycarbonyl-1-methylhydrazine (**5**) [7] and 1-ethoxycarbonyl-2-phenylhydrazine (**4**) [8] were prepared from coupling of ethyl chloroformate with the corresponding hydrazine according to reported literature procedures.

In the present work, we found that substituted ethoxy- and methoxycarbonylhydrazines **3**–**5** react readily with nitrilimines **2**, generated in situ from the action of NEt_3 onto the hydrazonoyl chlorides (**1**), yielding the corresponding acyclic adducts **6**–**8**.

Structural assignment of **6**–**8** is based on elemental analysis (Table 1) and spectral data. IR spectra of these



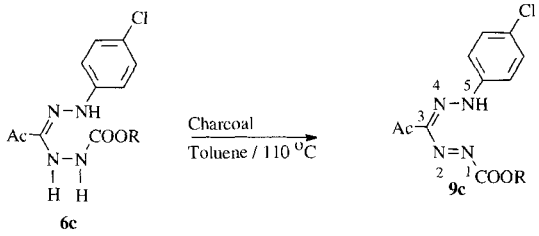
No	R	R^1	R^2
3/6	Me	H	H
4/7	Et	Ph	H
5/8	Et	H	CH_3

Entry	a	b	c	d	e
X	H	F	Cl	Br	CH_3

Scheme 1

compounds reveal the presence of the characteristic functional groups. The signals of the OR (R = -CH_3 or -CH_2CH_3) in both ^{1}H- and ^{13}C NMR spectra are of particular importance in support of the suggested acyclic structure.

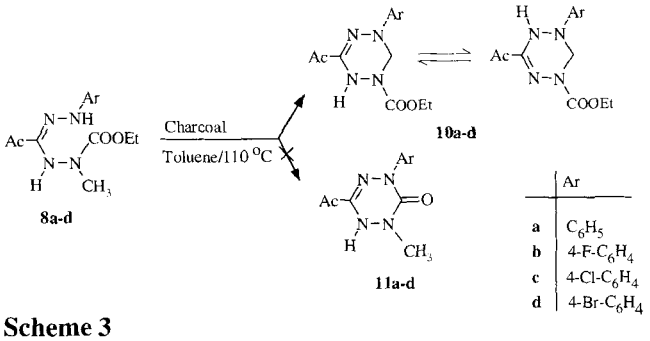
Cyclization of **6–8** was attempted by heating these compounds with active charcoal in refluxing toluene or xylene. This method was recently reported to be efficient for cyclization of similar acyclic adducts which produce tetrazines [9]. Reflux of **6c** with charcoal in toluene for 6 hours gave the oxidized product 3-acetyl-1-methoxycarbonyl-5-arylformazan **9c** in high yield. No other cyclic products were observed using TLC. Mass spectra, elemental analysis (Table 1) and NMR spectral data are in accordance with this acyclic formazan structure.



Scheme 2

Reflux of **7** with charcoal in either toluene of xylene for several hours gave no change, and the starting material was recovered unchanged.

Thermal oxidative cyclization of compounds **8a–d** gave unexpected results: The cyclization products are found to be *s*-tetrazanes **10a–d** rather than the expected tetrazinones **11a–d**. Structural assignment of these compounds is based on elemental analysis, mass spectra and NMR results.



Scheme 3

Elemental analysis (Table 1) and mass spectra show that there is only a loss of a hydrogen molecule rather than the loss of ethanol. Further evidence was obtained from NMR measurements. The ^{1}H NMR spectra indi-

Table 1 Physical properties and elemental analysis of compounds **6–10**

Compd.	Yield (%)	*m.p.* (°C)	Mol. Formula (M. Wt.)	Calcd./Found (%) C	H	N
6c	73	177–178	$C_{11}H_{13}N_4O_3Cl$	46.41	4.60	19.68
			(284.5)	46.37	4.60	19.44
7a	72	90– 92	$C_{18}H_{20}N_4O_3$	63.50	5.93	16.47
			(340.15)	63.77	6.02	16.37
7c	80	178–179	$C_{18}H_{19}N_4O_3Cl$	57.74	5.12	14.97
			(374.7)	57.69	4.95	14.66
7e	70	136–138	$C_{19}H_{22}N_4O_3$	64.39	6.26	15.81
			(354.2)	64.24	5.95	15.65
8a	80	70	$C_{13}H_{18}N_4O_3$	56.10	6.52	20.13
			(278.31)	56.28	6.61	20.35
8b	76	93– 94	$C_{13}H_{17}N_4O_3F$	52.70	5.78	18.91
			(296.30)	52.90	5.78	19.05
8c	93	93– 94	$C_{13}H_{17}N_4O_3Cl$	49.93	5.48	17.91
			(312.76)	49.81	5.43	17.96
8d	90	103–105	$C_{13}H_{17}N_4O_3Br$	43.71	4.80	15.68
			(347.21)	43.70	4.73	15.73
8e	*50*	60– 62	$C_{14}H_{20}N_4O_3$	57.50	6.90	19.17
			(292.15)	57.52	6.78	19.28
9c	81	95– 97	$C_{11}H_{11}N_4O_3Cl$	46.74	3.92	19.82
			(282.5)	46.76	3.96	19.67
10a	65	84– 85	$C_{13}H_{16}N_4O_3$	56.50	5.84	20.29
			(276.1)	56.77	5.64	20.43
10b	55	96– 97	$C_{13}H_{15}N_4O_3F$	53.06	5.14	19.04
			(294.3)	53.10	5.21	19.00
10c	60	121–123	$C_{13}H_{15}N_4O_3Cl$	50.31	4.88	18.06
			(310.80)	50.13	4.88	17.86
10d	57	114–116	$C_{13}H_{15}N_4O_3Br$	44.06	4.27	15.82
			(354.03)	44.06	4.22	15.78

cate that the NCH_3 (δ = 3.04 ppm) is replaced by a highly deshielded CH_2 (δ = 5.01 and 4.90 ppm). All the NMR signals of the new products **10** are doubled which indicate that the products exist as a pair of tautomers in solution. The tautomer ratio does not affect by changing the NMR-solvent from $CDCl_3$ to DMSO-d_6. However addition of a few drops of trifluoroacetic acid to the DMSO-d_6 solution of compound **10a** in the NMR tube results in complete predominance of one tautomer only. Similar tautomerism was recently reported for *s*-tetrazines (Leuco verdazyles) by Ryabokon *et al.* [10].

Signal doubling was also oberved in ^{13}C NMR spectra of **10a–d**. The NCH_3 signal of **8** at about 37.0 ppm disappeared; meanwhile two new CH_2 signals appeared at 60.4 and 56.9 ppm for both tautomers. Dept NMR spectra were helpful in the differentiation between different types of carbons.

Two dimensional NMR experiments (HMQC & HMBC) gave further support to the assigned structure of **10a–d**. Of interest is the long range coupling in HMBC spectrum of **10a** between the tetrazine CH_2 and both the carbonyl carbon of the ester group and the quaternary carbon of the phenyl ring.

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 [11].

A plausible reaction mechanism for this cyclization starts by the oxidation of the acyclic adducts **8** to formazans, which cyclize as reported by Neugebauer *et al.* [12] to the corresponding tetrahydro-1,2,4,5-tetrazines.

The authors wish to thank Prof. Dr. M. El-Abadelah and Mr. J. A. Zahra for obtaining the NMR-data and for their valuable discussions.

Experimental

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer in KBr discs. Mass spectra (electron impact) were obtained on a Varian CH-7 spectrometer at 70 eV. ^1H- and ^{13}C NMR spectra were recorded on a Bruker-AM 300 MHz instrument for solutions in $CDCl_3$ at 21 °C (Compds. **10b,d** in DMSO-d_6), using TMS as an internal reference. Chemical shifts are expressed downfield from TMS.

Reaction of Nitrilimines with Alkoxycarbonylhydrazines: Synthesis of 6–8

Triethylamine (5.0 g, 0.05 mol) in tetrahydrofuran (10 ml) was dropwise added to a stirred solution of hydrazonoyl chlorides (0.015 mol) and alkoxycarbonyl hydrazines (**3–5**) (0.03 mol) in THF (100 mol) at 0 °C. The temperature of the reaction mixture was then allowed to rise slowly to room temperature, and stirring was continued overnight. The solvent was then evaporated *in vacuo*, and the residue washed with water (100 ml). The resulting crude solid product was then collected and recrystallized from ethanol. The following compounds were prepared by this procedure:

1-Methoxycarbonyl-2-[1-(4-chlorophenyl)hydrazonopropan-2-one]hydrazine (**6c**)

^1H NMR ($CDCl_3$): δ/ppm = 2.39 (s, 3H, CH_3CO), 3.57 (s, 3H, OCH_3), 9.49 (s, 1H, ArNH), 8.86 (s, 1H, NH), 7.55 (s, 1H, NH). – ^{13}C NMR: δ/ppm = 24.01 (CH_3CO), 52.10 (OCH_3), 191.91 (CH_3CO), 139.11 (C=N), 156.91 (O–C=O).

1-Ethoxycarbonyl-2-phenyl-2-(1-phenylhydrazonopropan-2-one)hydrazine (**7a**)

^1H NMR ($CDCl_3$): δ/ppm = 2.50 (s, 3H, CH_3CO), 4.20 (q, 2H, OCH_2, J = 7 Hz), 1.26 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 7.34 (s, 1H, NH), 10.42 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 24.92 (CH_3CO), 62.37 (OCH_2), 14.46 ($-CH_2CH_3$), 193.12 (CH_3CO), 136.61 (C=N), 157.57 (O–C=O).

1-Ethoxycarbonyl-2-phenyl-2[1-(4-chloro-phenyl)hydrazonopropan-2-one]hydrazine (**7c**)

^1H NMR ($CDCl_3$): δ/ppm = 2.49 (s, 3H, CH_3CO), 4.20 (q, 2H, OCH_2, J = 7 Hz), 1.27 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 7.39 (s, 1H, NH), 10.48 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 24.47 (CH_3CO), 62.47 (OCH_2), 14.45 ($-CH_2CH_3$), 193.03 (CH_3CO), 136.96 (C=N), 157.61 (O–C=O).

1-Ethoxycarbonyl-2-phenyl-2-[1-(4-methylphenyl)hydrazonopropan-2-one]hydrazine (**7e**)

^1H NMR ($CDCl_3$): δ/ppm = 2.50 (s, 3H, CH_3CO), 4.19 (q, 2H, OCH_2, J = 7 Hz), 1.27 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 7.38 (s, 1H, NH), 10.40 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 24.87 (CH_3CO), 62.33 (OCH_2), 14.47 ($-CH_2CH_3$), 192.98 (CH_3CO), 136.23 (C=N), 157.54 (O–C=O).

1-Ethoxycarbonyl-1-methyl-2-(1-phenylhydrazonopropan-2-one)hydrazine (**8a**)

^1H NMR ($CDCl_3$): δ/ppm = 2.52 (s, 3H, CH_3CO), 3.04 (s, 2H, NCH_3), 4.25 (q, 2H, OCH_2, J = 7 Hz), 1.30 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 6.32 (s, 1H, NH), 10.05 (s, 1H, ArNH). – ^{13}C NMR δ/ppm = 23.69 (CH_3CO), 36.94 (NCH_3), 62.96 (OCH_3), 14.64 ($-CH_2CH_3$) = 193.60 (CH_3CO), 136.46 (C=N), 158.05 (O–C=O).

1-Ethoxycarbonyl-1-methyl-2-[1-(4-fluorophenyl)hydrazonopropan-2-one]hydrazine (**8b**)

^1H NMR ($CDCl_3$): δ/ppm = 2.50 (s, 3H, CH_3CO), 3.05 (s, 3H, NCH_3), 4.24 (q, 2H, OCH_2), J = 7 Hz), 1.30 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 6.30 (s, 1H, NH), 10.09 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 23.64 (CH_3CO), 36.97 (NCH_3), 62.65 (OCH_2), 14.61 ($-CH_2CH_3$), 193.43 (CH_3CO), 136.47 (C=N), 158.12 (O–C=O).

1-Ethoxycarbonyl-1-methyl-2-[1-(4-chlorophenyl)hydrazonopropan-2-one]hydrazine (**8c**)

^1H NMR ($CDCl_3$): δ/ppm= 2.51 (s, 3H, CH_3CO), 3.04 (s, 3H, NCH_3), 4.24 (q, 2H, OCH_2), J = 7 Hz), 1.03 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 6.28 (s, 1H, NH), 10.10 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 23.71 (CH_3CO), 37.08 (NCH_3), 63.04 (OCH_3), 14.62 (-

CH_2CH_3), 193.56 (CH_3CO), 136.83 (C=N), 158.15 (O–C=O).

1-Ethoxycarbonyl-1-methyl-2-[1-(4-bromophenyl)hydrazonopropan-2-one]hydrazine (**8d**)

^{1}H NMR ($CDCl_3$): δ/ppm = 2.51 (s, 3H, CH_3CO), 3.04 (s, 2H, NCH_3), 4.25 (q, 2H, OCH_2, J = 7 Hz), 1.29 (t, 3H, -CH_2CH_3, J = 7 Hz), 6.31 (s, 1H, NH), 10.11 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 23.72 (CH_3CO), 37.10 (NCH_3), 63.10 (OCH_2), 14.62 (-CH_2CH_3), 193.55 (CH_3CO), 136.91 (C=N), 158.13 (O–C=O).

1-Ethoxycarbonyl-1-methyl-2-[1-(4-methylphenyl)hydrazonopropan-2-one]hydrazine (**8e**)

^{1}H NMR ($CDCl_3$): δ/ppm = 2.50 (s, 3H, CH_3CO), 3.03 (s, 3H, NCH_3), 4.24 (q, 2H, OCH_2, J =7 Hz), 1.29 (t, 3H, -CH_2CH_3, J = 7 Hz), 6.27 (s, 1H, NH), 10.05 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 23.63 (CH_3CO), 36.85 (NCH_3), 62.89 (OCH_2), 14.64 (-CH_2CH_3), 193.43 (CH_3CO), 136.07 (C=N), 158.02 (O–C=O).

Thermal Oxidation of 6c: Synthesis of 3-Acetyl-1-methoxycarbonyl-5-(4-chloro-phenyl)formazan (9c)

(1.0 g, 0.0035 mol) of **6c** was refluxed in toluene (30 ml) and charcoal (0.5 g) for 6 hours. The reaction mixture was then filtered and the solvent evaporated *in vacuo*. The residue was crystallized from chloroform/petroleum ether (*b.p.* 40–60 °C) to give 0.8 g of purple crystals of the oxidized product (formazan **9c**). – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.60 (s, 3H, CH_3CO), 3.91 (s, 3H, OCH_3), 12.29 (s, 1H, ArNH). – ^{13}C NMR: δ/ppm = 26.59 (CH_3CO), 53.93 (OCH_3), 193.94 (CH_3CO), 150.54 (C=N), 153.80 (O–C=O).

Thermal Cyclization of Compounds 8a–d to *s*-Tetrazines 10a–d

0.005 mol of **8a–d** was refluxed in toluene (30 ml) and charcoal (0.5 g) for 4 hours. The reaction mixture was then filtered and the solvent evaporated *in vacuo*. The residue was crystallized from diethylether/petroleum ether (*b.p.* 40–60 °C) to give the tetrazines **10a–d**. The following compounds were prepared by this method:

6-Acetyl-4-phenyl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**10a**)

^{1}H NMR ($CDCl_3$): δ/ppm = 2.40, 2.36 (s, 3H, CH_3CO), 5.01, 4.90 (s, 2H, CH_2-ring), 4.25, 4.22 (q, 2H, OCH_2, J = 7 Hz), 1.17, 1.15 (t, 3H, -CH_2CH_3), J = 7 Hz), 9.33, 8.84 (s, 1H, NH-ring). – ^{13}C NMR: δ/ppm = 23.77, 23.43 (CH_3CO), 60.40, 56.95 (CH_2-ring), 63.50, 62.75 (OCH_2), 14.28 (-CH_2CH_3), 192.86, 191.60 (CH_3CO), 142.81, 139.60 (C=N), 156.32, 152.51 (O–C=O).

6-Acetyl-4-(4-fluorophenyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**10b**)

^{1}H NMR (DMSO-d_6): δ/ppm = 2.53, 2.48 (s, 3H, CH_3CO), 4.89, 4.84 (s, 2H, CH_2-ring), 4.25, 4.22 (q, 2H, OCH_2, J = 7 Hz), 1.29, 1.27 (t, 3H, -CH_2CH_3, J = 7 Hz), 9.36, 8.90 (s, 1H, NH-ring). – ^{13}C NMR: δ/ppm = 23.78, 23.46 (CH_3CO), 60.62, 56.86 (CH_2-ring), 63.61, 62.91 (OCH_2), 14.41 (-CH_2CH_3), 193.34, 191.39 (CH_3CO), 142.00, 138.57 (C=N), 156.41, 153.00 (O–C=O).

6-Acetyl-4-(4-chlorophenyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**10c**)

^{1}H NMR ($CDCl_3$): δ/ppm = 2.49, 2.38 (s, 3H, CH_3CO), 5.00, 4.90 (s, 2H, CH_2-ring), 4.13, 4.10 (q, 2H, OCH_2, J = 7 Hz), 1.17, 1.15 (t, 3H, -CH_2CH_3, J = 7 Hz), 9.39, 8.99 (s, 1H, NH-ring). – ^{13}C NMR δ/ppm = 23.77, 23.46 (CH_3CO), 60.50, 56.77 (CH_2-ring), 63.63, 62.94 (OCH_2), 14.41 (-CH_2CH_3), 193.34, 191.91 (CH_3CO), 141.87, 138.55 (C=N), 156.41, 153.00 (O–C=O).

6-Acetyl-4-(4-bromophenyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (**10d**)

^{1}H NMR (DMSO-d_6): δ/ppm = 2.39, 2.36 (s, 3H, CH_3CO), 5.01, 4.90 (s, 2H, CH_2-ring), 4.17, 4.13 (q, 2H, OCH_2, J = 7 Hz), 1.19, 1.17 (t, 3H, -CH_2CH_3, J = 7 Hz), 9.39, 8.99 (s, 1H, NH-ring). – ^{13}C NMR: δ/ppm = 23.77, 23.43 (CH_3CO), 60.40, 56.95 (CH_2-ring), 62.75, 63.50 (OCH_2), 14.42 (-CH_2CH_3), 193.45, 192.02 (CH_3CO), 142.13, 138.40 (C=N), 156.44, 153.26 (O–C=O).

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