SYNTHESIS OF CONDENSED 1,2,4-TRIAZOLO-HETEROCYCLES

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SUMMARY: Cyclization of 2-hydrazino-1, 3-benzothiazole, 2-hydrozinoquioline, 2-hydrazinolepidine, and 2-hydrazino-pyridine with one-carbon cyclizing agents such as triethyl orthoformate, ethyl chloroformate, urea, phenylthiourea, and carbon disulfide gave 3-substituted-1,2,4-triazolo (3,4, -b) 1, 3-benzothiazoles, 3-substituted-1,2,4-triazolo (4,3-a) quinolines, 3-substituted-1,2,4-triazolo (4,3-a) quinolines, 3-substituted-1,2,4-triazolo (4,3-a) lepidines and 3-substituted-1,2,4-triazolo (4,3-a) pyridines respectively. Reactions with acetic acid and acetic anhydride gave the corresponding acetyl hydrazines which were cyclized to the 3-methyl 1,2,4-triazolo-heterocyles. Ring closure with phenyl isocyanate and phenyl isothiocyanate, gave the intermediate 4-phenylsemicarbazides and 4-phenylthiosemicarbazides which, upon fusion, afforded the corresponding 3-oxo- and 3-thioxo-1,2,4-triazolo-heterocyles. The 3-oxo-compounds were also obtained when 2-chloroquinoloni or 2-chlorolepidine was fused with semicarbazide hydrochloride.

Key Words: Synthesis, amidrazones, triazolo-heterocycles.

INTRODUCTION

The synthesis and biological activities of condensed 1,2,4-triazolo (3,4-z) heterocyles have recently been reviewed (14). Several condendes 1,2,4-triazolo-heterocyles exhibit various biological activities such as fungicidal (1,9) bactericidal (1,9) analgesic (4,7,10) anxiolytic (8) and anti-inflammatory (10) activities. Such broad spectrum of activities prompted us to initiate a program for the synthesis of members of these compounds (12, 13). In this paper we describe the results obtained on the synthesis of some 3-substituted-1,2,4-triazolo (3,4-b) 1,3-benzothiasoles, 3-substituted-1,2,4-triazolo (4,3-a) quinolines, 3-substituted-1,2,4-triazolo (4,3-a) lepidines and 3-substituted-1,2,4-triazolo (4,3-a) pyridines.

RESULTS AND DISCUSSION

Reaction of the four cyclic amidrazones 1a–1d with triethyl orthoformate gave the corresponding 1,2,4-triazolo-heterocycle 2a–2d. None of the possible intermediates of this reaction were isolated.

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In an attempt to prepare 3-methyl-1,2,4-triazolo (3,4-b) 1,3-benzothiazole (5a) by heating 2-hydrazino-1, 3-benzothiazole (1a) with an excess of acetic acid or acetic anhydride, 1,1,2-triacetyl-2-(1,3-benzothiazol-2-yl) hydrazine (3a) was obtained. This result is in accordance with those previously reported for similar systems (2). Consequently, the reaction of 1a with acetic acid was carried out at ambient temperature whereupon the monoacetyl derivative 4a was formed. Dehydrative cyclization of the latter by heating above its melting point gave the desired triazolo-benzothiazole 5a. The known mono-acetyl derivatives (ab) and (4d) (3) derived from 2-hydrazinoquinoline and 2-hydrazinopyridine were also cyclodehydrated to the corresponding 3-methyl-1,2,4-triazolo-tehercocycle 5b and 5d respectively. Alternatively, 5c and 5d were directly obtained, without isolating the intermediate mono-acetyl derivatives 4c and 4d by heating the corresponding hydrazines 1c and 1d with acetic acid.

Ring closure of the amidrazones 1b–1d by heating with phenyl isocyanate yielded the intermadiate semicarbazides 7b–7d. Fusion of these semicarbazides proceeded with the elimination of an aniline molecule to give, 3-oxo-1,2,4-triazolo (4,3-a) quinoline (9b), 3-oxo-1,2,4-triazolo (4,3-a) lepidine (9c) and 3-oxo-1,2,4-triazolo (4,3-a) pyridine (9d)

respectively. Each of these compounds was identical to the corresponding one obtained by the alternative route of fusing the appropriate amidrazone (1b–1d) with urea.

Reaction of 1a or 1c with an excess of ethyl chloroformate under reflux did not afford the corresponding 3-oxo-1,2,4-triazolo-heterocycle (9a or 9c), but gave the di (ethoxycarbonyl) hydrazine derivatives 6a and 6c. Reaction of 1c, however, with one molar equivalent of ethyl chloroformate in pyridine, gave the 3-oxo-1,2,4-triazolo (4,3-a) lepidine 9c. Carrying out the same reaction on 1a and 1b, gave a mixture of inseparable products in each case. In an alternative route, 9b and 9c were obtained by fusion of the two imidoyl chlorides 11b and 11c with semicarbazide hydrochloride.

Reaction of the four hydrazines 1a–1d with phenyl isothiocyanate gave the corresponding 4-phenylthiosemicabazides (8a–8d). In agreement with reported results (5,6,11) the latter compounds underwent eliminative-cyclization upon fusion to give the corresponding 3-thioxo-1,2,4-triazolo-therocycle 10a–10d through the loss of an aniline molecule. When carbon disulfide in pyridine or phenylthiourea were used as cylocondensating agents, the four 3-thioxo compounds 10a–10d were also obtained.

MATERIAL AND METHODS

Melting points were determined with a Kofler Block and are uncorrected. The infrared spectra (IR) were recorded for potassium bromide discs on a Unicam SP-1025 or Pye-Unicam SP-2000 spectrophotometers. Proton magnetic resonance (^{1}H NMR) spectra were carried out at ambient temperature (~25°C) and at 90 MHz with a Varian EM-390 spectrometer for solutions in $CDCl_3$ or $(CD_3)_2SO$. Follow up of the reactions and checking the homogeneity of the prepared compounds were made by performing thin-layer chromatography (TLC) on Silica Gel G (Merck) precoated plates (layer thickness 0.25 mm) used without pretreatment.

All the ratios of the solvent systems used were volume-to-volume (v/v); the distance of solvent travel was 5 cm, and the spots were detected by exposure to iodine vapor for a few minutes. All solvent evaporations were performed in a Buchi rotary evaporator under diminished pressure. Elemental microanalyses were performed in the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, Alexandria University using Perkin-Elmer model PE-240 analyzer or in the Microanalysis Unit, Cairo University, Cairo, Egypt.

1,2,4-Triazolo (3,4-b) 1, 3-benzothiazole (2a), 1,2,4-triazolo (4,3-a) quinoline (2b), 1,2,4-triazolo (4,3-a) lepidine (2c), and 1,2,4-triazolo (4,3-a) pyridine (2d).

A mixture of the cyclic amidrazone (1,0.004 mole) and triethyl orthoformate (10 ml) was heated under reflux for 10 hours and the mixture was evaporated. The obtained residue was crystallized from the suitable solvent to give the title compounds (Table 1).

1,1,2-Triacetyl-2-(1,3-benzothiazol-2-yl) hydrazine (3a)

A solution of 1a (1 g) in acetic acid or acetic anhydride (30 ml) was refluxed for 10 hours. The mixture was evaporated and the obtained residue was crystallized from ethanol to give 1.4 g (78%) of 3a, m.p. 150°; TLC in 19:1 $CHCl_3$ MeOH, R_f: 0.7, IR: 1760, 1728, and 1712 cm^{-1} (CON); ^{1}H NMR ($CDCl_3$): (δ) 7.80-7.50 (m, 2H, aromatic H), 7.50-7.00 (m, 2H, aromatic H), 2.45 (s, 6H, 2 CH_3 groups) and 2.5 (s, 3H, CH_3 group). Anal. $C_{13}H_{13}N_3S$):

	C	H	N
Calc.	53.61	4.47	14.43
Found	53.66	4.59	14.33

1-Acetyl-2-(1,3-benzothiazol-2-yl) hydrazine (4a), 1-acetyl-2-(quinol-2-yl) hydrazine (4b), and 1-acetyl-2-(pyrid-2-yl) hydrazine (4d).

A mixture of the amidrazone (1, 0.004 mole) and acetic anhydride or acetic acid (5 ml) was stirred at ambient temperature for one hour. The mixture was evaporated under reduced pressure at 40°. The obtained product was crystallized from the suitable solvent to give the title compounds (Table 1).

3-Methyl-1,2,4-triazolo (3,4-b) 1, 3-benzothiazole (5a), 3-methyl-1,2,4-triazolo (4,3-a) quinoline (5b), 3-methyl-1,2,4-triazolo (4,3-a) lepidine (5c), and 3-methyl-1,2,4-triazolo (4,3-a) pyridine (5c).

Method (A)

Each of the mono-acetyl derivatives 3 (0.004 mole) was heated at 10° above its melting point for 30 minutes and the obtained product was crystallized from the suitable solvent (Table 1).

Method (B)

A mixture of the amidrazone 1 (0.004 mole) in acetic anhydride (20 ml) was heated under reflux for 2–4 hours and then evaporated. The obtained residue was crystallized from the suitable solvent to give the title compounds (Table 1).

4-Phenyl-1-(quinol-1-yl) semicarbazide (7b), 4-phenyl-1-(lepid-2-yl) semicarbazide (7c), and 4-phenyl-1 (pyrid-2-yl) semicarbazide (7d).

A solution of the amidrazone 1 (0.004 mole) in ethanol (25 ml) was treated with phenyl isocyanate (0.004 mole) and heated under reflux for 30 minutes. The product, which separated upon cooling, was filtered, washed with ethanol, and crystallized from the appropriate solvent to give the title compounds (Table 1).

4-Phenyl-1-(1,3-benzothiazol-2-yl) thiosemicarbazide (8a), 4-Phenyl-1-(quinol-2-yl) thiosemicarbazide (8b), 4-phenyl-1-(lepid-2-yl) thiosemicarbazide (8c), and 4-phenyl-1-(pyrid-2-yl) thiosemicarbazide (8d).

Table 1: Physical and elemental analysis data of the prepared compounds.

Compd. No.	MP (°C)	Solvent of Cryst	Yield (%)	Molecular Formula	Analyses (%) Calc. / Found		
					C	H	N
2a	168	A	61	$C_3H_3N_3S$	54.86 55.21	2.86 3.17	24.00 23.74
2b	171	A	67	$C_{10}H_7N_3$	71.01 70.89	4.14 4.17	24.85 25.00
2c	233	A	83	$C_{11}H_9N_3$	72.13 71.87	4.92 5.19	22.95 23.01
2d	72	C	71	$C_9H_5N_3$	60.50 60.90	4.20 4.10	
4a	226	A	79	$C_9H_9N_3OS$	52.17 52.51	4.35 4.37	
4b	196	A	78	$C_{11}H_{11}N_3O$	65.67 65.40	5.48 5.30	
4d	149	C	71	$C_7H_9N_3O$	55.63 55.40	5.96 5.50	
5a	150	A	67	$C_9H_7N_3S$	57.14 56.90	3.70 3.2	
5b	175	C	67	$C_{11}H_9N_3.1/2H_2O$	68.75 68.80	5.21 4.70	
5c	180	A	56	$C_{12}H_{11}N_3.1/2H_2O$	64.29 64.20	6.25 6.53	
5d	125	C	77	$C_7H_9N_3$	63.16 63.30	5.26 4.70	
7b	215	C	67	$C_{10}H_{14}N_4O.1/2H_2O$	66.90 67.51	5.23 4.99	19.51 19.92
7c	225	A	75	$C_{17}H_{16}N_4O.1/2H_2O$	67.77 68.04	5.68 5.57	18.60 19.02
7d	180	A	62	$C_{12}H_{12}N_4O.1/2H_2O$	60.76 61.20	5.49 4.90	- -
8a	298	B	73	$C_{14}H_{14}N_4S.1/2H_2O$	54.37 55.00	4.21 3.90	18.12 17.30
8b	138	A	64	$C_{16}H_{14}N_4S$	65.31 64.70	4.76 5.00	
8c	300	A	73	$C_{17}H_{16}N_4S$	66.23 66.90	5.19 4.80	
8d	185	A	73	$C_{12}H_{12}N_4S.1/2H_2O$	56.92 56.50	5.14 4.60	
9b	242	A	67	$C_{10}H_7N_3O.1/2H2O$	61.86 61.97	4.12 3.90	21.65 21.88
9c	298	A	57	$C_{11}H_9N_3O.1/2H_2O$	63.46 63.56	4.81 4.47	
9d	235	A	50	$C_6H_3N_3O$	53.33 52.80	3.70 3.50	
10a	255	A	75	$C_6H_5N_3S_2$	46.38 46.40	2.42 2.80	
10b	270	A	67	$C_{10}H_7N_3S.1/2H_2O$	57.14 57.27	3.81 3.60	20.00 20.45
10c	298	A	86	$C_{11}H_9N_3S$	61.40 61.88	4.19 4.12	19.53 19.19
10d	211	A	50	$C_6H_5N_3S$	47.68 48.09	3.31 3.36	27.81 27.66

A = Ethanol, B = Ethanol-chloroform, C = Benzene-petroleum ether.

The title compounds were prepared from the corresponding amidrazones 1 (0.004 mole) and phenyl isothiocyanate (0.004 mole) as just described for the preparation of their oxygen analogs 7 (Table 1).

3-oxo-1,2,4-triazolo (4,3-a) quinoline (9b), 3-oxo-1,2,4-triazolo (4,3-a) lepidine (9c) and 3-oxo-1,2,4-triazolo (4,3-a) pyridine (9d).

Method (A)

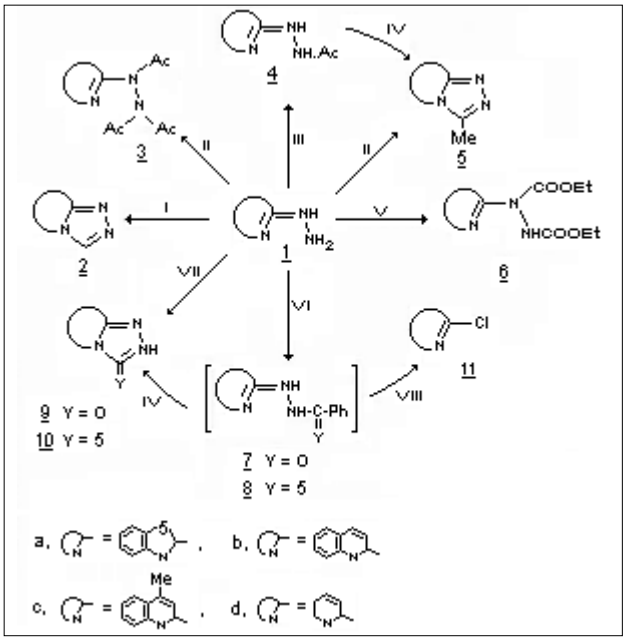
The individual semicarbazide derivative 7 (0.004 mole) was heated at 10° above its melting point for 30 minutes in an oil bath. The mass obtained after cooling, was crystallized from the suitable solvent to give the title compound (Table 1).

Method (B)

A mixture of the amidrazone 1 (0.004 mole) and urea (0.07 mole) was heated at 180° for 30 minutes in an oil bath followed by cooling and crystallization of the obtained solid mass (Table 1).

Method (C)

A solution of the amidrazone 1c (0.004 mole) in pyridine (15 ml) was treated with ethyl chloroformate (0.004 mole) and the mixture was heated under reflux for 6 hours. The solvent was evaporated and the obtained residue was crystallized from the suitable solvent to give 9c (Table 1).



I = $HC(OEt)_3$, II = AcOH/Heat, III = AcOH/room temperature, IV = Fusion, V = ClCOOEt (excess), VI = PhNCY, VII = ClCOOEt, H_2NCONH_2, $PhNHCONH_2$ or CS_2, VIII = $H_2N.CSNHNH_2.HCl$

Method (D)

A mixture of the imidoyl chloride 11 (0.004 mole) and semicarbazide hydrochloride (0.004 mole) was heated at 180° for 30 minutes in an oil-both. The solid mass obtained after cooling was crystallized from the suitable solvent to give the title compounds (Table 1).

1, 2-Diethoxycarboyl-1-(benzothiazol-2-yl) hydrazine (6a).

A mixture of 1a and ethyl chloroformate (30 ml) was heated under reflux for 4 hours. The mixture was evaporated and the obtained residue was crystallized from ethanol to give 1.5 g (79%) of 6a, m.p. 125°; TLC in 29: 1 $CHCl_3$: MeOH, R_p, 0.52; IR:3210 (NH), 1760, (ester-carbonyl) and 1605 cm^{-1} (C=N), ^1H NMR ($CDCl_3$: (~) 7.80–7.50, 7.40–7.00 (2m, 2H each, aromatic H), 4.23 (2 overlapping q, 4H, $2CH_2$) and 1.33 (overlapping t, 6H, $2CH_3$ groups). Anal. ($C_{13}N_{15}N_3O_4S$):

	C	H	N
Calc.	50.49	4.85	13.59
Found	49.87	4.87	13.16

1,2-Diethoxycarbonyl-2-(lepid-2-yl) hydrazine (6c).

The title compound was prepared from 1c (1 g) and ethyl chloroformate 530 ml) as just described for the preparation of 6a. The product was crystallized to give 1.5 g (81%) of 6c, m. p. 135°; TLC in 19:1 $CHCl_3$: MeOH, Zr: 0.71; IR: 3180 (NH), 1740 (broad, ester-carbonyl), and 1605 cm^{-1} (C=N). Anal. ($C_{16}H_{19}N_3O_4$):

	C	H	N
Calc.	60.57	6.00	13.20
Found	60.18	6.51	13.20

3-Thioxo-1,2,4-triazolo (3,4-b) 1, 3-benzothiazole (10a) 3-thioxo-1,2,4-triazolo (4,3-a) quinoline (10b), 3-thioxo-1,2,4-triazolo (4,3-a) lepidine (10c), and 3-thioxo-1,2,4-triazolo (4,3-a) pyridine (10d).

Method A

The individual thiosemicarbazide derivative 8 (0.004 mole) was heated above its melting point for 30 minutes followed by cooling and crystallization from the suitable solvent to give the title compounds (Table 1).

Method B

To a stirred suspension of the amidrazone 1 (0.004 mole) in pyridine (5 ml), carbon disulfide (2 ml) was added and the mixture was stirred at room temperature for 30 mins. The product, which separated, was filtered, washed with water, dried, and crystallized form the suitable solvent to give the title compounds (Table 1).

Method C

A mixture of the amidrazone 1 (0.004 mole) and phenylthiourea (0.004 mole) was heated at 200° for 30 minutes followed by cooling and crystallization of the obtained product from the suitable solvent to give the title compounds (Table 1).

Table 2: Spectral data of the prepared compounds.

	IR(KBr) cm^{-1}				
Compd. No.	NH	C=O	C=N	C=S	^{1}H NMR(δ) ppm
2a	-	-	1580	-	8.93 (s, 1H, CH=N), 7.77-7.40 (m, 4H, aromatic H)*
2b	-	-	1610	-	8.13 (s, 1H, CH=N), 8.00-7.10 (m, 6H, aromatic H)*
2c	-	-	1632	-	9.17 (s, 1H, CH=N), 8.07-7.50 (m, 5H, aromatic H). 2.67 (s, 3H, CH_3)*
2d	-	-	1640	-	9.13 (s, 1H, CH=N), 8.80-7.28 (m, 4H, aromatic H)*
4a	3360	1665	1600	-	
4b	3500	1650	1600	-	
4d	3260	1680	1610	-	
5a	-	-	1590	-	
5b	-	-	1620	-	
5c	-	-	1635	-	8.17-7.33 (m, 6H, aromatic H), 3.10, 2.57 (s, 3H each, 2 CH_3)*
	-	-	1640	-	
7b	3380	1630	1610	-	
7c	3380	1685	1630	-	
7d	3220	1645	1585	-	
8a	3340	-	1630	1235	7.60-6.77 (m, 9H, aromatic H)**
8b	3110	-	1587	1260	
8c	3250	-	1655	1220	
8d	3200	-	1650	1250	
9b	-	1725	1648	-	
9c	3130	1680	1618	-	12.33 (s, 1H, deuteratable, NH)**
9d	3160	1712	1625	-	
10a	3080	-	1580	1265	
10b	3100	-	1640	1260	
10c	3120	-	1650	1238	
10d	3130	-	1655	1255	

* = $CDCl_3$, ** = $(CD_3)_2SO$

REFERENCES

1.Deshpande DS : Synthesis of some substituted s-triazola (3-4-b) benzothiazoles as patent antibacterials. Acta Cienc Indica (Ser) Chem, 6:80-82, 1980; Chem Abstr: 94, 65568, 1985.

2. Hajos G, Massner A : Linearly fused isoquinolines. Part II. The synthesis of the s-triazolo (4, 3-b) isoquinoline systems. J Heterocycl Chem, 15:463-466, 1978.

3. Fargher RG, Furness R : Derivatives of 2-pyridylhydrazine and 2-quinolyhydrazine. J Chem Soc, pp 688-699, 1915.

4. Kamal A, Sattur PB : Synthesis and biological activity of 1-substituted-5-aryl-s-triazolo (4,3-a) quinazolines. Indian J Chem Sect B23B: 1293-1294, 1984; Chem Abstr: 102, 166690, 1985.

5. Marckwald W, Meyer E : Uleber das δ-chinolylhydrazin und seine derivate. Chem Ber, 33:1885-1895, 1900.

6. Marchwald W, Meyer E : Ueber das γ--chinolylhydrazin und seine derivate. Chem Ber, 33:1895-1899, 1900.

7. Morogues J, Vega A, Prieto J, Marquez M, Roberts DJ : Potential anti-inflammatory agents. Farmaca Ed Sci, 31:126-132, 1976; Chem Abstr: 84, 180138, 1976.

8. Moran DB, Dusza JP, Albright JD : 6-and-8-Heteroaryl-s-triazolo (4,3-b) pyridazines. US Patent 4, 260, 756, 1981; Chem Abstr: 95, 97829, 1981.

9. Paget CJ Jr, Wikl JH : s-Triazolo (3,4-b) benzothiazoles, G Often 2, 509, 843, 1975; Chem Abstr: 84, 44070, 1976.

10. Prasad AR, Ramalingam T, Rao AB, Diwan PV, Sattur PB : Synthesis and biological activity of 2-(aryloxyalkyl)-5-(3,4-methylene dioxyphenyl)-s-triazolo (3,4-b)-1,3,4-thiadiazoles, Indian J Chem Sect B 25B:566-668, 1986; Chem Abstr:106, 84500, 1987.

11. Reynolds GA, Van Allan JA : Synthesis of polyazaindines. J Org Chem, 24:1478-1486, 1959.

12. Shaban MAE, Ali RS, El-Badry SM : The synthesis of 3-(alditol-1-yl)-1,2,4-triazolo (3,4-a) phthalazines. Carbohydr Res, 95:51-60, 1981.

13. Shaban MAE, Taha MAM : The synthesis of C-nucleoside precursors II: Synthesis and conformational analysis of 3-(pentahydroxypentyl)-6-phenyl-1,2,4-triazolo(3,4-a) phthalazines. Bull Chem Soc Japan, 1989 (in press).

14. Shaban MAE, Nasr AZ : The synthesis of condensed 1,2,4-triazolo (3,4-z) heterocycles. Advances in Heterocyclic Chemistry , 1989 (in press).

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