A One-Pot Synthesis of [1,2,4]Triazino[4,3-*b*]-[1,2,4,5]tetrazines

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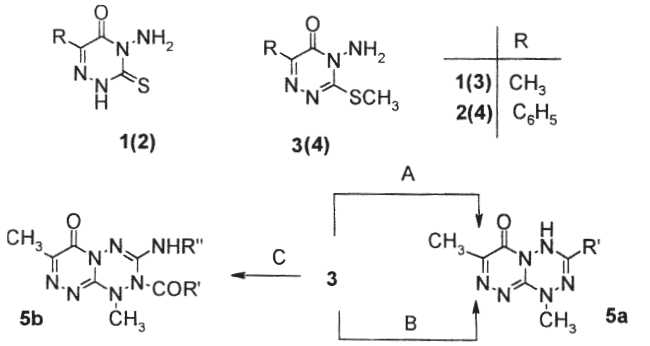
Received May 17th, 1999, respectively July 9th, 1999

Keywords: Heterocycles, Hydrazones, Nitrogen heterocycles, Synthetic methods, Tetrazines

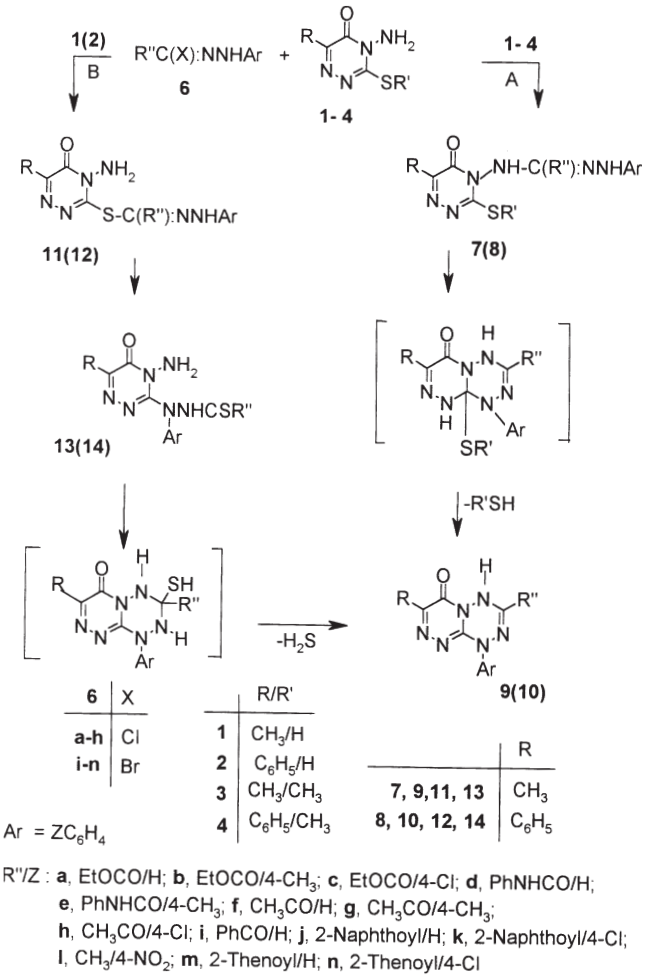
Abstract. Reactions of hydrazonoyl halides **6** with either 4-amino-2,3-dihydro-6-substituted-3-thioxo-[1,2,4]-triazin-5(4*H*)ones **1**(**2**) or 4-amino-3-methylthio-6-substituted-[1,2,4]-triazin-5(4*H*)ones **3**(**4**) gave [1,2,4]-triazino-[4,3-*b*][1,2,4,5]tetrazine derivatives **9**(**10**), respectively. The mechanism of the reactions studied is discussed.

The synthesis of [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine ring system **5** was first reported by Molina *et al*. [1, 2] a few years ago. As outlined in Scheme 1, their approach is based on the use of 4-amino-6-methyl-3-methylthio-[1,2,4]triazin-5(4*H*)-ones 3 as a starting reagent. The latter is usually prepared by methylation of 4-amino-6-methyl-2,3-dihydro-3-thioxo-[1,2,4]triazin-5(4*H*)-one (**1**) [3]. The conversion of **3** into [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine derivatives was achieved by three alternative procedures A–C, each of which requires at least three consecutive reactions (Scheme 1). As



Scheme 1

a part of our research program to explore the synthetic applications of hydrazonoyl halides [4], we now wish to present herein a one-pot procedure for synthesis of a variety of [1,2,4]triazino-[4,3-*b*][1,2,4,5]tetrazine derivatives *via* direct reaction of hydrazonoyl halides **6** with either 4-amino-2,3-dihydro-6-substituted-3-thioxo-[1,2, 4]triazin-5(4*H*)-ones **1**(**2**) or 4-amino-3-methylthio-6-substituted-[1,2,4]-triazin-5(4*H*)-ones **3**(**4**) (Scheme 2).



Scheme 2

Results and Discussion

The requisite starting [1,2,4]triazin-5(4*H*)-ones **1**–**4** and hydrazonoyl halides **6** for this study were prepared by previ-

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ous literature methods [3, 5]. Refluxing of **1** with **6** in chloroform (or ethanol) in the presence of triethylamine for 6 hr and work up the reaction mixture gave, in each case, one product as evidenced by tlc analysis. Similar results were obtained when **2** was refluxed with **6** under the same reaction conditions. At first, it was anticipated that such reactions would yield the respective [1,2,4]-triazino[4,3-*b*][1,3,4]thiadiazine derivatives by analogy to the reactions of **6** with 2-aminothiophenols, which were reported to give benzothiadiazine derivatives [6]. Surprisingly, however, the products isolated from the reactions of **6a**–**l** with **1** and **2** were free of sulfur. Repetition of these reactions in pyridine at reflux also yielded the same products. All such products display in their IR spectra absorption bands in the regions 3 200–3 260 and 1 670–1 700 cm^{-1} due to the NH and C=O groups, respectively. Their ^1H NMR spectra, while they show a common characteristic singlet signal in the region δ 9.0–9.4 assignable to the NH proton, they reveal the absence of $N–NH_2$ proton signal present in the spectra of **1** and **2** at δ 6.1–6.2. Their mass spectra show in addition to the expected molecular ions, peaks at *m/z* [M^+–28], [PhCN], [R], [ArN] and [Ar] (see Experimental). On the basis of these spectral data together with their microanalyses, the isolated products from the reactions of **6** with **1** and **2** were assigned [1,2,4]-triazino[4,3-*b*][1,2,4,5]tetrazine structures **9** and **10**, respectively (Scheme 2).

To account for the formation of **9** and **10**, the two possible pathways A and B depicted in Scheme 2 were considered. Thus, it is suggested that reactions of **6** with **1** or **2** presumably proceed through the initial formation of the respective hydrazidine derivatives **7** or **8**, which subsequently undergo cyclization with concurrent elimination of hydrogen sulfide to give **9** and **10**, respectively (Route A). The formation of either **7** or **8** is analogous to the reactions of **6** with hydrazines which were reported to give the corresponding hydrazidines [7]. Alternatively, reaction of **6** with **1** or **2** may start with the formation of the thiohydrazonate esters **11** or **12**, which undergo *in situ* Smiles rearrangement [8] under the reaction conditions employed to afford the corresponding thiohydrazides **13** or **14**. Then the thiohydrazides **13** and **14** undergo cyclization as soon as they are formed with concurrent elimination of hydrogen sulfide to give **9** and **10** as the end products, respectively (Route B, Scheme 2). All attempts to isolate any of the aforementioned intermediates **11**–**14** were unsuccessful, however. Presumably, such intermediates are converted under the employed reaction conditions to the final products **9** and **10** as soon as they are formed.

To distinguish between these two alternative pathways, the reactions of **6** with 4-amino-2-methylthio-6-substituted-1,2,4-triazin-5(4*H*)-one derivatives **3** and **4** were investigated. Thus, refluxing a mixture of **6** with **3** (or **4**) in pyridine afforded, in each case, one product whose ^1H NMR spectrum showed the absence of the methylthio δ 2.55–2.65 and amino δ 5.0–5.03 proton signals present in the spectra of the respective 4-amino-3-methylthio-1,2,4-triazinones **3** and **4**. Instead, the spectra of the products isolated revealed in each case, a characteristic one NH proton singlet in the region δ 9.0–9.4. Furthermore, such products proved identical in all respects (*m.p.*, mixed *m.p.*, IR) with those obtained above from **6** and **1** and **2**, respectively. These findings indicate that route A in Scheme 2 seems to be the most plausible mechanism for the studied reactions of **6** with either **1**–**4**.

In conclusion, the foregoing results indicate collectively that the studied reactions of **6** with either 4-amino-2,3-dihydro-6-substituted-3-thioxo-[1,2,4]triazin-5 (4*H*)-ones **1**(**2**) or 4-amino-3-methylthio-6-substituted-[1,2,4]-triazin-5(4*H*)-ones **3**(**4**) provide easy access to [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazine derivatives.

Experimental

Melting points were determined in capillary tubes in a Gallenkamp Electrothermal apparatus and are uncorrected. IR spectra were measured in potassium bromide with Fourier Transform and Pye-Unicam SP300 instruments. The ^1H NMR spectra were recorded on a Varian Gemini spectrometer. All pmr spectra were recorded in deuterated chloroform (or dimethyl sulfoxide) as solvents, chemical shifts being given as δ values downfield from internal tetramethylsilane. Mass spectra were obtained with a GCMS-Q1000-EX spectrometer. Microanalyses were performed by the Microanalytical Center of Cairo University.

4-Amino-3-thioxo-6-methyl-2,3-dihydro-[1,2,4]triazin-5(1*H*)-one, (**1**) and its 6-phenyl analog **2** were prepared from thiocarbohydrazide and benzoylformic acid and pyruvic acid, respectively following known methods [3]. 4-Amino-3-methylthio-6-methyl-4,5-dihydro-[1,2,4]triazin-5(3*H*)-thione, (**3**) and its 6-phenyl analogue **4** were prepared by methylation of **1** and **2**, respectively with methyl iodide in methanol in the presence of sodium methoxide as previously described [3]. The hydrazonoyl halides **6a**–**n** were prepared according to literature methods [5].

Table 1 Physical constants of the products **9**

Compd. no.	Yield (%)	*m.p.* (°C) (Solvent) [a]	Molecular formula [b] (molecular weights)
9a	69	162 (b)	$C_{14}H_{14}N_6O_3$ (314.3.)
9b	72	185 (b)	$C_{15}H_{16}N_6O_3$ (328.3)
9c	72	230 (c)	$C_{14}H_{13}ClN_6O_3$ (348.7)
9d	95	280 (a)	$C_{18}H_{15}N_7O_2$ (361.3)
9e	85	263–264 (a)	$C_{19}H_{17}N_7O_2$ (375.4)
9g	78	223–225 (a)	$C_{14}H_{14}N_6O_2$ (298.3)
9k	49	198–200 (a)	$C_{22}H_{15}ClN_6O_2$ (430.8)
9m	40	223–224 (a)	$C_{16}H_{12}N_6O_2S$ (352.3)
9n	50	> 300 (c)	$C_{16}H_{11}N_6O_2S$ (386.8)

[a]) Solvent: (a) DMF-EtOH; (b) EtOH; (c) DMF
[b]) All compounds gave satisfactory elemental analyses

Table 2 Spectral data of [1,2,4]triazino-[4,3-*b*][1,2,4,5]tetrazines **9**

Compd. no.	Spectral data IR ν/cm^{-1}	^{1}H NMR δ/ppm	MS *m/z* (%)
9a	3265 (NH), 1716, 1685 (CO), 1172 (C-O-C)	1.40 (t, 3H), 2.43 (s, 3H), 4.45 (q, 2H), 7.26–7.57 (m, 5H)	315 (M^+, 100), 314(87), 287(28), 258(15), 240(42), 212(9), 172(31), 117(69), 103(50), 91(21), 77(99)
9b	3223 (NH), 1735, 1697 (CO), 1176 (C-O-C)	1.40 (t, 3H), 2.37 (s, 3H), 2.42 (s, 3H), 4.43 (q, 2H), 7.24 (d, 2H), 7.4 (d, 2H), 8.77 (s, 1H)	328 (M^+), 100), 300(8), 265(41), 186(21), 172(21), 131(35), 117(21), 105(16), 91(36), 77(16)
9c	3223 (NH), 1734, 1697 (CO), 1180 (C-O-C)	1.40 (t, 3H), 2.43 (s, 3H), 4.44 (q, 2H), 7.20—7.6 (m, 4H), 8.83 (s, 1H)	
9d	3232, 3134 (NH), 1689, 1641 (CO)	2.31 (s, 3H), 7.1–7.77 (m, 10H), 9.3 (s, 1H), 10.56 (s, 1H)	361 (M^+, 86), 334(42), 172(31), 117(31), 103(36), 91(29), 77(100)
9e	3265, 3223 (NH), 1697, 1651 (CO)	2.39 (s, 3H), 2.42 (s, 3H), 7.18–7.60 (m, 9H), 8.58 (s, 1H), 9.08 (s, 1H)	375 (M^+, 100), 186(28), 146(12), 137(15), 119(45), 105(21), 103(18), 91(72), 77(57)
9g	3244 (NH), 1697, 1633 (CO)	2.39 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 7.25 (d, 2H), 7.42 (d, 2H), 8.86 (s, 1H)	298 (M^+), 100), 270(78), 186(59), 131(59), 91(64), 77(32), 64(98)
9k	3257 (NH), 1697, 1641 (CO)	2.48 (s, 3H), 7.26–7.9 (m, 11H), 9.31 (s, 1H)	430 (M^+, 29), 277(45), 155(71), 128(36), 127(100), 114(33), 111(23), 76(26)
9m	3216 (NH), 1702, 1639 (CO)	2.46 (s, 3H), 7.2–7.84 (m, 8H), 9.32 (s, 1H)	352 (M^+, 24), 324(16), 240(5), 117(15), 111(100), 91(4), 77(21)
9n	3182 (NH), 1699, 1637 (CO)	2.52 (s, 3H), 7.32–8.29 (m, 7H), 9.44 (s, 1H)	386 (M^+, 12), 358(5), 323(5), 137(6), 126(2), 117(4), 111(100), 77(5)

Table 3 Physical constants of the products **10a**–**n**

Compd. no.	Yield (%)	*m.p.* (°C) (Solvent) [a]	Molecular formula [b] molecular weights
10a	70	178–179 (a)	$C_{19}H_{16}N_6O_3$ (376.3)
10b	74	150–151 (b)	$C_{20}H_{18}N_6O_3$ (390.4)
10c	75	160–161 (b)	$C_{19}H_{15}ClN_6O_3$ (410.8)
10d	95	220 (a)	$C_{23}H_{17}N_7O_2$ (423.4)
10e	90	256 (a)	$C_{24}H_{19}N_7O_2$ (437.4)
10f	80	180 (b)	$C_{18}H_{14}N_6O_2$ (346.3)
10g	85	165 (b)	$C_{19}H_{16}N_6O_2$ (360.3)
10h	80	192 (c)	$C_{18}H_{13}ClN_6O_2$ (380.8)
10i	50	190 (a)	$C_{23}H_{16}N_6O_2$ (408.4)
10j	54	172–174 (a)	$C_{27}H_{18}N_6O_2$ (458.4)
10k	50	236–238 (a)	$C_{27}H_{17}ClN_6O_2$ (492.9)
10l	70	260 (a)	$C_{17}H_{13}N_7O_3$ (363.3)
10m	46	192–193 (a)	$C_{21}H_{14}N_6O_2S$ (414.4)
10n	48	223–225 (a)	$C_{21}H_{13}ClN_6O_2S$ (448.9)

[a]) Solvent: (a) DMF-EtOH; (b) EtOH; [c]) DMF
[b]) All compounds gave satisfactory elemental analyses

*[1,2,4]Triazino-[4,3-*b*][1,2,4,5]tetrazines* **9** and **10**

Method A To a mixture of the appropriate hydrazonoyl halide **6** (0.01 mole) and triazinethione **1** (0.01 mole) in chloroform or ethanol (30 ml) was added triethylamine (1.4 ml, 0.01 mole). The mixture was refluxed till hydrogen sulfide ceased to evolve (5–9 h). The excess solvent was then removed under reduced pressure. The solid produced upon cooling the residue left was collected, washed with water and crystallized from the proper solvent to give the corresponding triazinotetrazines **9**. Use of **2** in place of **1** in this procedure yielded the respective triazinotetrazines **10**.

Method B To a solution of the appropriate 3-methylthiotriazine **3** (0.01 mole) in pyridine (30 ml) was added the hydrazonoyl halide **6** (0.01 mole), and the resulting mixture was refluxed for 15 h, then cooled and poured onto cold hydrochloric acid. The crude solid that precipitated was filtered off, washed with water, dried and finally crystallized from ethanol to give **9**. Use of **4** istead of **3** afforded the respective derivatives **10**. Also, use of **2** instead of **3** in this method afforded also the corresponding **10**.

The physical constants and spectral data of the various triazinotetrazines **9** and **10** prepared by the foregoing two methods are listed in Tables 1–4.

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Table 4 Spectral data of products **10a–n**

Compd. no.	Spectral data IR (ν/cm^{-1})	^{1}H NMR (δ/ppm)	MS (*m*/*z*/%)
10a	3249 (NH), 1716, 1693 (CO), 1209 (C–O–C)	1.42 (t, 3H), 4.7 (q, 2H), 7.26–8.26 (m, 10H), 9.04 (s, 1H)	376 (M^+, 100), 348(49), 117(98), 103(70), 91(19), 77(96)
10b	3257 (NH), 1712, 1691 (CO), 1209 (C–O–C)	1.41 (t, 3H), 2.39 (s, 3H), 4.45 (q, 2H), 7.0–8.25 (m, 9H), 9.01 (s, 1H)	390 (M^+, 100), 363(46), 131(93), 117(42), 103(68), 105(17), 91(64), 77(50)
10c	3265 (NH), 1719, 1685 (CO), 1199 (C–O–C)	1.42 (t, 3H), 4.47 (q, 2H), 7.2–8.26 (m, 9H), 9.05 (s, 1H)	
10d	3271, 3190 (NH), 1693, 1651 (CO)	6.90–7.97 (m, 16H), 9.45 (s, 1H)	423 (M^+, 94), 395(55), 146(6), 120(17), 117(39), 103(63), 91(32), 77(100)
10e	3261, 3191 (NH), 1691, 1645 (CO)	2.42 (s, 3H), 7.2–8.0 (m, 14H), 8.5 (s, 1H), 9.35 (s, 1H)	
10f	3238 (NH), 1690, 1685 (CO)	2.55 (s, 3H), 7.26–8.26 (m, 10H), 9.1 (S, 1H)	346 (M^+, 100), 318(57), 117(69), 103(43), 91(21), 77(99)
10g	3257 (NH), 1697, 1685 (CO)	2.41 (s, 3H), 2.53 (s, 3H), 7.27–8.26 (m, 9H), 9.1 (s, 1H)	
10h	3259 (NH), 1697, 1654 (CO)	2.55 (s, 3H), 7.26–8.25 (m, 9H), 9.11 (s, 1H)	380 (M^+, 50), 352(60), 281(29), 270(29), 228(27), 169(99), 152(100), 125(55), 111(59), 99(54), 77(51)
10i	3294 (NH), 1678, 1647 (CO)	7.26–8.30 (m, 15H), 9.44 (s, 1H)	408 (M^+, 43), 380(22), 118(20), 105(100), 89(10), 77(80)
10j	3232 (NH), 1693, 1658 (CO)	7.49–8.16 (m, 17H), 9.84 (s, 1H)	458 (M^+, 13), 430(12), 181(40), 155(100), 127(67), 103(16), 91(21), 77(21)
10k	3234 (NH), 1693, 1660 (CO)	7.51–8.12 (m, 16H), 9.90 (s, 1H)	492 (M^+, 33), 464(14), 155(100), 127(74), 111(8), 103(7), 77(16)
10l	3236 (NH), 1697 (CO)	2.06 (s, 3H), 7.26–8.10 (m, 9H), 10.35 (s, 1H)	363 (M^+, 100), 335(69), 219(21), 163(22), 133(16), 117(7), 103(30), 89(22), 76(24)
10m	3275 (NH), 1683, 1637 (CO)	7.0–8.34 (m, 13H), 9.4 (s, 1H)	414 (M^+, 24), 386(14), 117(23), 111(100), 103(17), 91(4), 77(29)
10n	3274 (NH), 1685, 1643 (CO)	7.3–8.3 (m, 12H), 9.57 (s, 1H)	448 (M^+, 25), 420(12), 151(15), 111(100), 103(17), 77(25)

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