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A New One-Step Synthesis of Pyrimido-[1,2-*b*][1,2,4,5]tetrazines

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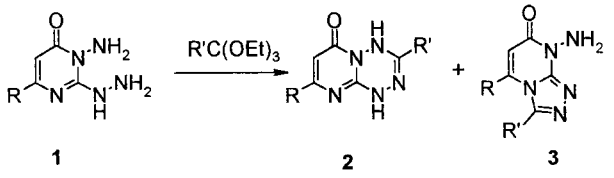
ABSTRACT: *Hydrazonoyl halides* **4** *react readily with either 3-amino-2,3-dihydro-6-methyl-2-thioxo-4(1H)-pyrimidinone* **5** *or 3-amino-6-methyl-2-methylthio-4(3H)-pyrimidinone* **6** *to form 6H-pyrimido[1,2-b][1,2,4,5]tetrazin-6-ones* **9**. *The mechanism of the studied reactions is discussed.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:87–90, 2000

INTRODUCTION

So far, only one method has been reported in the literature for the synthesis of the pyrimido[1,2-*b*][1,2,4,5]tetrazine ring system [1]. Such a method involves the reaction of 3-amino-2-hydrazino-4(3H)-pyrimidinones **1** with *ortho* esters, dimethylformamide dimethyl acetal, or diethoxymethyl acetate in glacial acetic acid at room temperature [1]. Such reactions were reported, however, to yield a mixture of pyrimido[1,2-*b*][1,2,4,5]tetrazines **2** and [1,2,4] triazolo[4,3-*a*]pyrimidines **3**, and the yields of the former were in the range of 15–51% (Equation 1) [1]. Our continued interest in the chemistry of hydrazonoyl halides **4** [2] prompted us to investigate their reactions with *N*-aminoheterocyclic thiols in an attempt to develop a new strategy for synthesis of the title ring system. The interest in developing new simple syntheses of pyrimido[1,2-*b*][1,2,4,5]tetrazines is due to the recent finding that derivatives of such a ring system, for example, 1,4-dihydro-7,8-dimethyl-6H-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one, are among the most potent inhibitors of human cytomegalovirus protease [3]. Here, we wish to report our results utilizing reactions of **4** with 3-amino-2,3-dihydro-6-methyl-2-thioxo-4(1H)-pyrimidinone **5** and 3-amino-6-methyl-2-methylthio-4(3H)-pyrimidinone **6** as a route to 6H-pyrimido[1,2,-*b*][1,2,4,5]tetrazin-6-ones **9** (Scheme 1). The latter can now be readily prepared with a variety of substituents and in good overall yields (see Experimental section).



(1)

Reaction of **4** with **5** in boiling ethanol in the presence of triethylamine gave, in each case, one product, as evidenced by the analysis of the crude reaction product. The same results were obtained when the reactions of **4** with **5** were carried out in pyridine at reflux. It was initially anticipated that such reactions would yield the respective pyrimido[2,1-*b*][1,3,4]thiadiazines by analogy to the reactions of **4** with 2-aminothiophenol, which were reported to afford benzothiadiazine derivatives [4]. Unexpectedly, the products isolated from the reactions of **5** with **4a–h** were found to be free of sulfur. Such products were identified as 1,4-dihydro-1,3,8-trisubstituted-6H-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones, **9a–i.** The structures of the latter products were elucidated on the basis of their spectra (^{1}H NMR, IR, and MS) and microanalyses. For example, the ^{1}H NMR spectra of the products isolated show one NH

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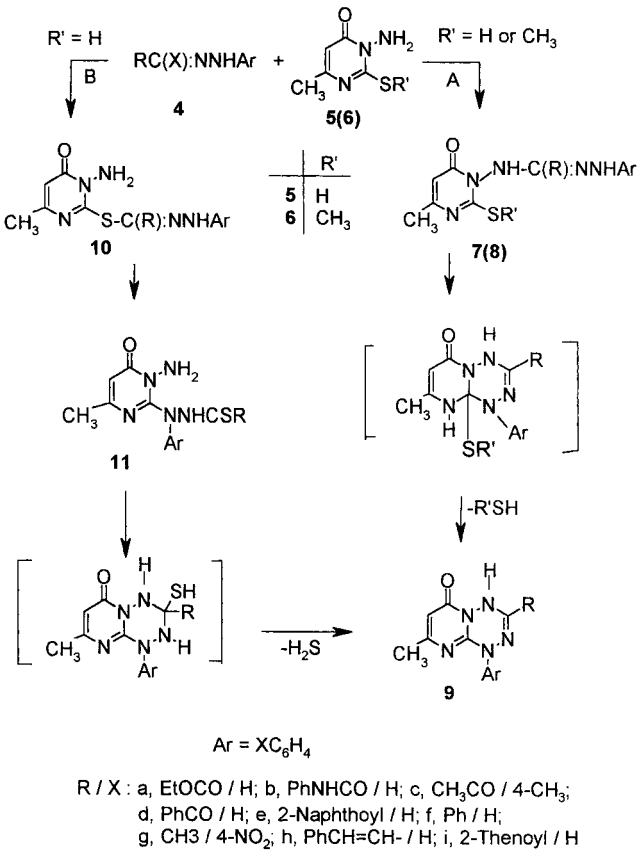
proton signal at δ 9.02–9.9, and they are lacking the N-NH_2 signal at δ 5.6, which is characteristic of the starting substrate **5.** The mass spectra of **9** were also consistent with their assigned structures. In addition to the molecular ion peak, they reveal peaks at *m/z* corresponding to (M^+–R), (M^+–R(NH):NNHAr), (M^+–R(:N)NH), ArN, and Ar fragments.

The formation of **9** from **4** and **5** can be rationalized in terms of one of the two pathways outlined in Scheme 1. It is suggested that the reactions begin with the formation of the hydrazidines **7,** which in turn cyclize with concurrent elimination of hydrogen sulfide to give **9** (Route A, Scheme 1). Alternatively, the reaction of **4** with **5** initially gives the respective thiohydrazonate esters **10** that undergo an in situ Smiles rearrangement to yield the thiohydrazides **11** [5]. Cyclization of the latter with concurrent loss of hydrogen sulfide affords **9** (Route B, Scheme 1).

In an attempt to distinguish between these two alternative pathways, the reactions of **4** with **6** were examined in greater detail. Treatment of **4** with **6** in pyridine at reflux afforded products identical in all respects with the products **9** obtained above from **4** and **5.** This finding, together with the fact that all attempts to isolate either the thiohydrazonates **10** or the thiohydrazides **11** failed under the reaction conditions employed, indicate that route-A in Scheme 1 seems to be the more plausible mechanism for the formation of **9** from reactions of **4** with either **5** or **6.**



SCHEME 1

EXPERIMENTAL

All melting points were determined in capillary tubes using a Gallenkamp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer in deuterated chloroform with use of tetramethylsilane (TMS) as an internal reference. IR spectra were determined with a Fourier Transform and Pye Unicam Infrared spectrophotometer using a KBr wafer. Mass spectra were measured on a GCMS-QP 100 EX spectrometer at an ionizing potential of 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory at Cairo University, Giza, Egypt.

The starting hydrazonoyl halides **4a–i** [6] and 2,3-dihydro-3-amino-6-methyl-2-thioxo-4(1H)-pyrimidinone **5** [7] were prepared as previously described.

*3-Amino-6-methyl-2-methylthio-4(3H)-pyrimidinone (**6**)*

To an ethanolic sodium ethoxide solution prepared from sodium metal (2.3 g, 0.01 g atom) and absolute ethanol (100 mL), was added compound **5** (15.7 g, 0.01 mole) with stirring. To the resulting solution was added methyl iodide (15 g, 0.01 mole), and the mixture was refluxed on a water bath for 30 minutes and then left at room temperature overnight. The precipitated solid was collected by filtration and crystallized from water to give pure **6:** Yield 60%, m.p. 178°C; ν (cm^{-1}) 3394, 3305 (NH), 1645 (CO); δ 2.25 (s, 3H), 2.46 (s, 3H), 4.79 (s, 2H), 6.08 (s, 1H); MS *m/z* (%) 171 (54), 155 (100), 109 (16), 94 (18), 82 (20), 67 (37), 54 (81). Anal. Calcd. for $C_6H_9N_3OS$: C, 42.09; H, 5.29; N, 24.54. Found: C, 42.0; H, 5.2; N, 24.5%.

*1,3-Disubstituted-8-methyl-6H-pyrimido[1,2-b][1,2,4,5]tetrazin-6-ones (**9a–i**)*

Method A: To a mixture of equimolar quantities of the appropriate **5** and **4a–e** (5 mmol each) in absolute ethanol (30 mL) was added triethylamine (0.7 mL, 5 mmol), and the resulting mixture was refluxed until hydrogen sulfide ceased to evolve (3–5 hours)

and then cooled. The solid that precipitated was filtered off, washed with water, dried, and crystallized from ethanol to give the corresponding pyrimidotetrazinone **9a–e.**

Method B: A mixture of equimolar quantities of **6** and the appropriate hydrazonoyl halide **4a–e** (5 mmol each) in pyridine was refluxed for 10–15 hours and then cooled. The cold reaction mixture was poured into ice-cold hydrochloric acid with stirring. The solid that precipitated was collected, washed with water, and finally crystallized from ethanol to give **9a–e,** respectively, which were found identical in all respects with the compounds obtained by Method A described previously.

When this method was repeated using **4f–i** with either **5** or **6,** the corresponding pyrimidotetrazinones **9f–i** were obtained in both cases.

The various pyrimidotetrazinones **9a–i** that we prepared, together with their physical constants, are listed subsequently.

Compound **9a:** Yield 75%, m.p. 135–136°C (EtOH), ν(cm^{-1}) 3259 (NH), 1759, 1686 (CO); δ 1.40 (t, 3H), 2.09 (s, 3H), 4.44 (q, 2H), 6.05 (s, 1H), 7.26–7.55 (m, 5H), 8.99 (s, 1H); MS *m/z* (%) 313 (M^+, 100), 240 (5), 200(9), 185 (37), 109 (16), 91 (8), 77 (95). Anal. Calcd. for $C_{15}H_{15}N_5O_3$: C,57.50; H, 4.83; N, 22.35. Found: C, 57.3; H, 4.5; N, 22.2%.

Compound **9b:** Yield 90%, m.p. 204–206°C (EtOH/DMF), ν (cm^{-1}) 3384, 3265 (NH), 1701, 1647 (CO); δ 2.09 (s, 3H), 6.05 (s, 1H), 7.06–7.70 (m, 10H), 9.03 (s, 1H), 11.80 (s, 1H); MS *m/z* (%) 360 (M^+, 90), 240 (25), 185 (28), 157 (100), 145 (21), 129 (76), 125 (39), 91 (19), 77 (49). Anal. Calcd. for $C_{19}H_{16}N_6O_2$: C, 63.33; H, 4.48; N, 23.32. Found: C, 63.2; H, 4.2; N, 23.2%.

Compound **9c:** Yield 70%, m.p. 206–207°C (EtOH), ν (cm^{-1}) 3253 (NH), 1714, 1683 (CO); δ 1.61 (s, 3H), 2.08 (s, 3H), 2.40 (s, 3H), 2.51 (s, 3H), 6.03 (s, 1H), 7.16–7.43 (m, 4H), 9.03, (s, 1H); MS *m/z* (%) 297 (M^+, 100), 254 (69), 240 (4), 214 (14), 157 (49), 109 (21), 105 (20), 91 (50), 84 (26), 77 (9). Anal. Calcd. for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.55. Found: C, 60.2; H, 4.8; N, 23.2%.

Compound **9d:** Yield 55%, m.p. 197–198°C (EtOH), ν (cm^{-1}) 3307, 3192 (NH), 1685, 1647 (CO); δ 2.11 (s, 3H), 6.09 (s, 1H), 7.26–7.67 (m, 10H), 9.38 (s, 1H). Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.2; H, 4.4; N, 20.1%.

Compound **9e:** Yield 40%, m.p. 190–191°C (EtOH), ν (cm^{-1}) 3303 (NH), 1716, 1682 (CO); δ 2.13 (s, 3H), 6.11 (s, 1H), 7.15–7.93 (m, 17H), 9.54 (s, 1H); MS *m/z* (%) 395 (M^+, 27), 200 (6), 155 (100), 127 (69), 109 (3), 91 (2), 77 (27). Anal. Calcd. for $C_{23}H_{17}N_5O_2$: C, 69.86; H, 4.33; N, 17.71. Found: C, 69.5; H, 4.1; N, 17.5%.

Compound **9f:** Yield 80%, m.p. 176°C (EtOH), ν (cm^{-1}) 3178 (NH), 1683 (CO); δ 2.14 (s, 3H), 6.05 (s, 1H), 7.26–7.86 (m, 10H), 8.99 (s, 1H); MS *m/z* (%) 317 (M^+, 66), 200 (5), 185 (10), 108 (12), 91 (7), 77 (100). Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.1; H, 4.5; N, 22.0%.

Compound **9g:** Yield 35%, m.p. 240°C (EtOH), ν (cm^{-1}) 3209 (NH), 1680, (CO); δ 2.09 (s, 3H), 2.13 (s, 3H), 6.13 (s, 1H), 7.85 (d, 2H), 8.23 (d, 2H), 10.38 (s, 1H); MS *m/z* (%) 300 (M^+, 100), 286 (5), 230 (14), 155 (3), 136 (4), 122 (74), 109 (29), 76 (28). Anal. Calcd. for $C_{13}H_{12}N_6O_3$: C, 51.99; H, 4.03; N, 27.99. Found: C, 51.7; H, 4.0; N, 27.8%.

Compound **9h:** Yield 50%, m.p. 220–222°C (EtOH), ν (cm^{-1}) 3224 (NH), 1681, (CO); δ 2.02 (s, 3H), 6.06 (s, 1H), 7.03 (d, 1H), 7.63 (d, 1H), 7.27–7.57 (m, 10H), 9.97 (s, 1H); MS *m/z* (%) 343 (M^+, 51), 240 (1), 200 (10), 129 (14), 109 (11), 91 (6), 77 (100). Anal. Calcd. for $C_{20}H_{17}N_5O$: C, 69.96; H, 4.99; N, 20.39. Found: C, 69.8; H, 4.6; N, 20.1%.

Compound **9i:** Yield 50%, m.p. 200–201°C (EtOH), ν (cm^{-1}) 3209 (NH), 1690, 1650 (CO); δ 2.11 (s, 3H), 6.08 (s, 1H), 7.16–7.80 (m, 8H), 9.33 (s, 1H); MS *m/z* (%) 351 (M^+, 22), 240 (2), 200 (2), 109 (3), 111 (100), 91 (8), 77 (22). Anal. Calcd. for $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93. Found: C, 58.0; H, 3.7; N, 19.6%.

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