

A Novel Synthesis of 1,2,4-Triazolopteridines

Tayseer A. Abdallah, Manal A. Darwish and Hamdi M. Hassaneen*

Department of Chemistry, Faculty of Science, University of Cairo, Giza, 1263, Egypt.

*Author to whom correspondence should be addressed; e-mail: tiseer123@hotmail.com

Received: 19 March 2002; in revised form: 9 June 2002 / Accepted: 12 June 2002 / Published: 30 June 2002

Abstract: Reaction of 1,2-dihydro-2-thioxopteridin-4(3H)-one, 6,7-dimethyl-1,2-dihydro-2-thioxopteridin-4(3H)-one and 6,7-diphenyl-1,2-dihydro-2-thioxopteridin-4(3H)-one with hydrazonoyl halides affords the title compounds in good yields.

Keywords: Hydrazonoyl halides, 2-thioxopteridine, triazolopteridines.

Introduction

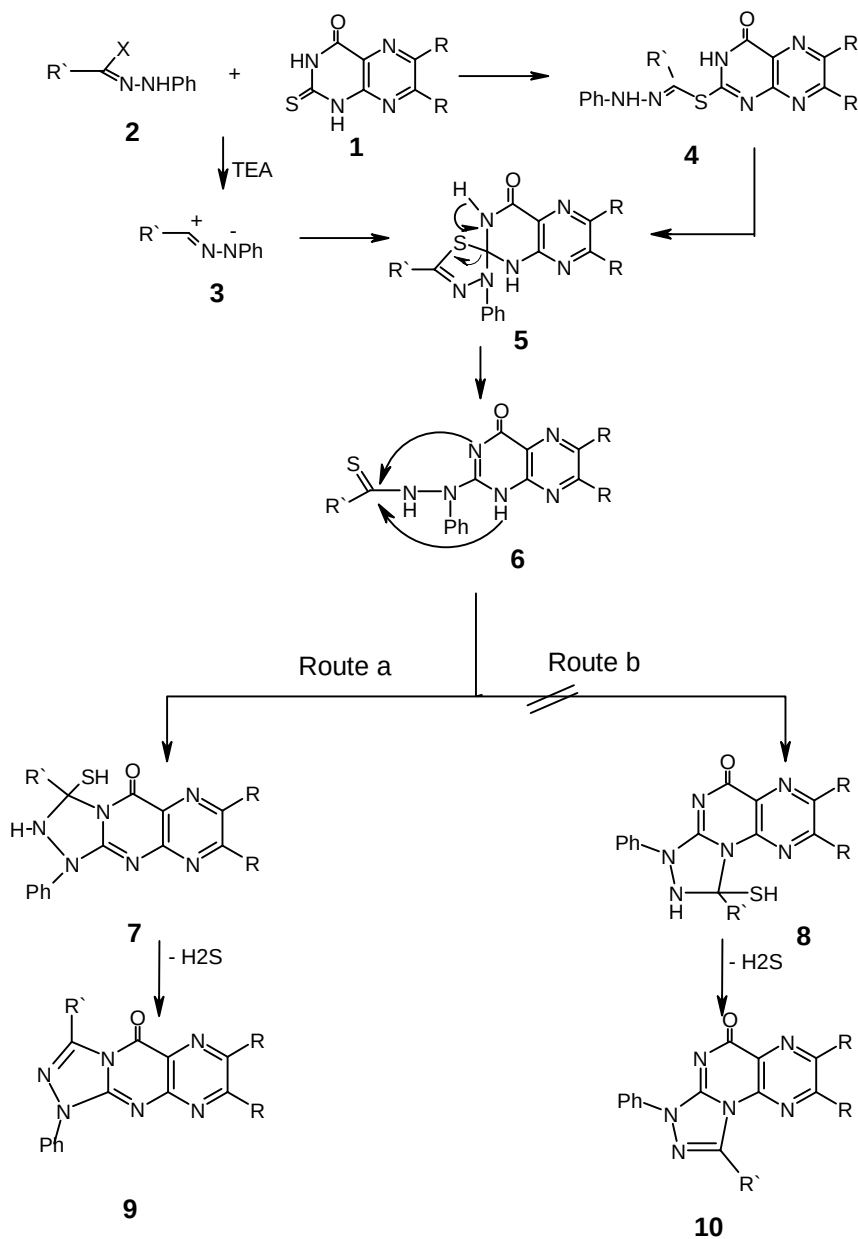
Thiourea reacts with hydrazonoyl halides to give thiadiazoles [1-3], thiazoles [4-6] or triazoles [7] according to the reaction conditions and the type of hydrazonoyl halide used. In a subsequent investigation hydrazonoyl halides were found to react with heterocyclic compounds containing thiourea moieties to give only one of the two isomers possible based on the assumption that ring nitrogen adjacent to carbonyl group is less basic [8-11]. This communication describes the reaction of hydrazonoyl halides with 1,2-dihydro-2-thioxopteridin-4(3H)-one derivatives yielding triazolopteridin-5-ones and not the other isomeric triazolopteridin-9-one products.

Results and Discussion

The reaction of **1** with hydrazonoyl halides **2** was carried out in THF under reflux in the presence of triethylamine. After workup of the reaction mixtures only a single product was isolated in each case. The spectral and elemental analysis data of these products are listed in Table I. The pathways leading

to the subsequent products **9** or **10** are outlined in Schemes 1 and 2. In Scheme 1 it is suggested that the studied reactions involve an initial formation of thiohydrazone esters **4**, which undergo a $S \rightarrow N$ migration to give the thiohydrazides **6** via the spirocycloadduct **5**. Compounds **6** can also be formed via 1,3-dipolar cycloadditions of nitrilimines **3** (generated in situ from the reaction of hydrazoneyl halides **2** with triethylamine) onto the $C=S$ thione group of **1**.

Scheme 1

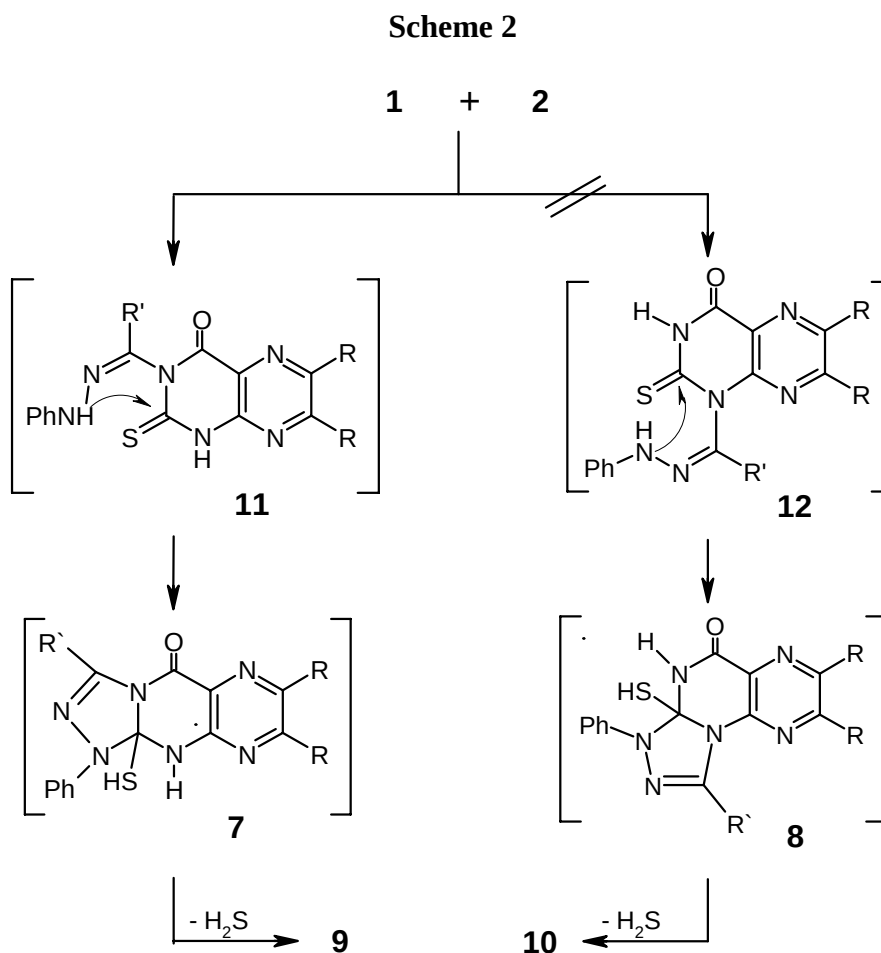


g	R'/R
a	PhCH=CH/H
b	PhCH=CH/CH ₃
c	PhCH=CH/Ph
d	Ph/H
e	Ph/CH ₃
f	Ph/Ph

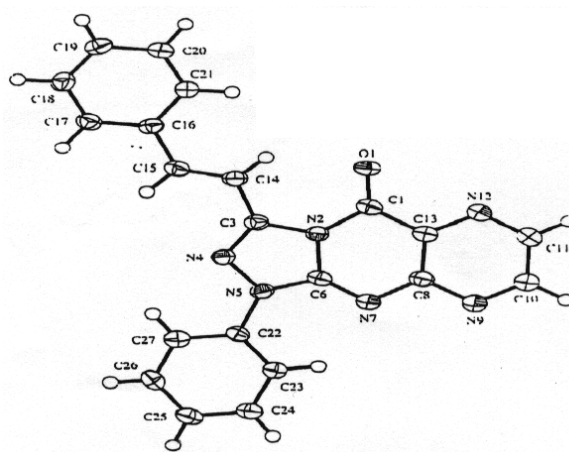
g	R'/R
g	COOC ₂ H ₅ /H
h	COOC ₂ H ₅ /CH ₃
i	COOC ₂ H ₅ /Ph
j	PhCO/CH ₃
k	PhCO/Ph
l	CH ₃ CO/CH ₃
m	CH ₃ CO/Ph

Attempts to isolate the thiohydrazone ester **4** or the thiohydrazide open chain intermediates **6** did not succeed even under mild conditions as they readily undergo *in situ* cyclization followed by elimination of hydrogen sulfide to give the final products, that may have either structure **9** or **10** depending on the cyclization step involved (Routes a or b as depicted in Scheme 1).

In Scheme 2 it is suggested that reaction of **1** with **2** starts with nucleophilic attack on N3 or N1 to give the substitution products **11** or **12** respectively. Cyclization of the latter intermediates and elimination of hydrogen sulfide would then give the end products **9** or **10** respectively.



Although it is difficult at present to distinguish between the two mechanisms, the one proposed in Scheme 2 was discarded on the following basis: (1) although amidrazones of type **11** or **12** are known to be stable [12-14], all attempts to separate them from the reaction mixture failed; (2) reaction of 2-thiouracil derivatives with various halogen compounds yielded in all reported cases S-substituted products [15-18]. Thus, the mechanism proposed in Scheme 1 seems to be more acceptable. As the spectroscopic data alone does not allow one to distinguish between possible products **9** or **10**, conclusive evidence was obtained by X-ray crystallographic analysis of compound **9a** (Figure 1), thus confirming the structure **9** of the products.

Figure 1. Diagram of compound **9a** with crystallographic numbering system

Experimental

General

All melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. $^1\text{H-NMR}$ spectra were recorded in CDCl_3 and $(\text{CD}_3)_2\text{SO}$ solutions on a Varian Gemini 200 MHz spectrometer and chemical shifts are expressed in δ units using TMS as internal reference. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer, operating at 70 eV. Elemental analyses were carried out at Microanalytical Center of the University of Cairo, Giza, Egypt.

General procedure for the synthesis of 2-aryl-3-styryl-1,2,4-triazolo[4,3-a]7,8-pteridin-5-ones (9). A suspension of pteridine **1** [19] (5 mmol) in tetrahydrofuran (25 mL) was refluxed with hydrazonoyl halides **2** [4,6,20-22] (5 mmol) and triethylamine (0.7 mL, 5 mmol) for 10 h. The excess solvent was evaporated and the residue was triturated with methanol (10 mL). The solid formed was collected and crystallized from dimethylformamide to give analytically pure product. The physical and spectral data of the compounds **9a-m** thus prepared is summarized in Table 1.

X-ray structural analysis of compound 9a. Crystal data $\text{C}_{21}\text{H}_{14}\text{N}_6\text{O}$, $M=366.4$, monoclinic P_2^1 , $a=8.874$ (3), $b=17.978$ (4), $c=11.229$ (3), Å, $\alpha=90$, $\beta=108.97$ (2), $\gamma=90$. The alkene substituent has the E conformation. The non-hydrogen atoms were refined anisotropically. Refinement of the structure was carried out on F using full-matrix least square procedure, which minimized the function $\sum w(|F_o| - |F_c|)^2$ [23].

Table I. Physical and spectral data of new Triazolopteridines

Compound	m.p. (°C) (solvent)	Yield (%)	IR (v)	MS(70 ev) <i>m/e</i> (M ⁺)	Molecular Formula	Analysis			¹ H NMR
						Calcd	Found		
9a	253 (DMF)	80	1709	366	C ₂₁ H ₁₄ N ₆ O (366)	C H N	68.8 3.8 22.9	68.8 3.8 22.7	7.2-7.6 (m, 8H); 7.9 (d, J=5 Hz, 1H); 8.1 (d, J=5 Hz, 1H); 8.3 (s, 1H); 8.4 (s, 1H); 8.8 (d, J=14 Hz, 1H) and 8.9 (d, J=14 Hz, 1H).
9b	277 (DMF)	75	1705	394	C ₂₃ H ₁₈ N ₆ O (394)	C H N	70.0 4.6 21.3	69.8 4.7 21.4	2.7 (s, 3H); 2.8 (s, 3H) and 7.2-8.4 (m, 12H).
9c	302 (DMF)	82	1714	518	C ₃₃ H ₂₂ N ₆ O (518)	C H N	76.4 4.2 16.2	76.4 4.3 16.0	7.3-8.5 (m, Ar-H).
9d	314 (DMF)	78	1727	340	C ₁₉ H ₁₂ N ₆ O (340)	C H N	67.1 3.5 24.7	67.3 3.3 24.4	7.2-7.9 (m, 10H); 8.7 (d, J=14 Hz, 1H) and 8.8 (d, J=14 Hz, 1H).
9e	287 (DMF)	75	1708	368	C ₂₁ H ₁₆ N ₆ O (368)	C H N	68.5 4.4 22.8	68.7 4.4 22.6	2.7 (s, 3H); 2.7 (s, 3H) and 7.3-8.4 (m, 10H).
9f	308 (DMF)	75	1725	492	C ₃₁ H ₂₀ N ₆ O (492)	C H N	75.6 4.1 17.1	75.6 4.0 16.9	7.3-8.5(m,Ar-H)
9g	199 (DMF)	77	1745 1707	336	C ₁₆ H ₁₂ N ₆ O ₃ (336)	C H N	57.1 3.6 25.0	57.1 3.6 24.9	1.5 (t, J=7 Hz, 3H); 4.7 (q, J=7 Hz, 2H); 7.3-7.6 (m, 5H); 8.3 (d, J=14 Hz, 1H) and 8.8 (d, J=14Hz, 1H).
9h*	211 (DMF)	77	1714 1675		C ₁₈ H ₁₆ N ₆ O ₃	C H N	59.3 4.4 23.1	59.4 4.2 22.9	1.4 (t, J=7 Hz, 3H); 2.7 (s, 3H); 2.8 (s, 3H); 4.6 (q, J=7Hz, 2H) and 7.3-8.3 (m, 5H).
9i	206 (DMF)	84	1730 1640	488	C ₂₈ H ₂₀ N ₆ O ₃ (488)	C H N	68.9 4.1 17.2	68.7 3.9 16.9	1.5 (t, J=7Hz, 3H); 4.6 (q, J=7 Hz, 2H) and 7.2-8.3 (m, 15H).
9j	298 (DMF)	78	1723 1683	396	C ₂₂ H ₁₆ N ₆ O ₂ (396)	C H N	66.7 4.0 21.2	66.5 3.9 21.2	2.7 (s, 3H); 2.8 (s, 3H) and 7.3-8.3 (m, 10H).

9k	183 (DMF)	72	1773 1637	520	C ₃₂ H ₂₀ N ₆ O ₂ (520)	C H N	73.9 3.9 16.2	73.9 3.9 16.1	7.2-8.3 (m, Ar-H)
9l	197 (DMF)	66	1710 1680	334	C ₁₇ H ₁₄ N ₆ O ₂ (334)	C H N	61.1 4.2 25.1	61.1 4.3 25.0	2.6 (s, 3H), 2.7 (s, 6H) and 7.3-8.2 (m, 5H).
9m	196 (DMF)	70	1762 1640	458	C ₂₇ H ₁₈ N ₆ O ₂ (458)	C H N	70.7 3.9 18.3	70.8 3.6 18.2	2.6 (s,3H) and 7.2-7.8 (m, 15H).

* ¹³C-NMR of compound **9h**: 15.6, 23.9, 25.2, 66.1, 122.7, 126.2, 129.7, 131.4, 137.9, 138.3, 147.0, 153.5, 156.0, 156.4, 158.4, 163.5).

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Sample Availability: Samples of entries **1**, **5**, **7** and **11** are available from MDPI

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