Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 78 (8) 1119–1125 (2013) UDC 542.913:547.752+547.791+547–304.9
JSCS–4483 *Original scientific paper*

Synthesis of new functionalized derivatives of 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole

SOBHI M. GOMHA[1]* and HATEM A. ABDEL-AZIZ[2]

[1]*Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt and* [2]*Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh 11451, Saudi Arabia*

(Received 14 September, revised 3 October 2012)

Abstract: New functionalized 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives were synthesized *via* reaction of the hydrazonoyl halides with 2,4-dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3-thione or its 3-methylthio derivative. The mechanism and the regioselectivity of the studied reactions are discussed.

Keywords: hydrazonoyl halides; 1,2,4-triazino[5,6-*b*]indole-3-thione; hydrazonothioates.

INTRODUCTION

As a continuation of systematic studies of hydrazonoyl halides devoted to the various aspects of their chemistry,[1–6] it was decided to investigate their use as precursors in the synthesis of the title compounds. In the present contribution, the synthesis is reported of a series of new functionalized derivatives of 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole *via* the reaction of the respective hydrazonoyl halides **5** with either 2,4-dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3-thione **3** or its 3-methylthio derivative. The regiochemistry of the reactions studied and the antimicrobial activity of the products isolated from such reactions were investigated.

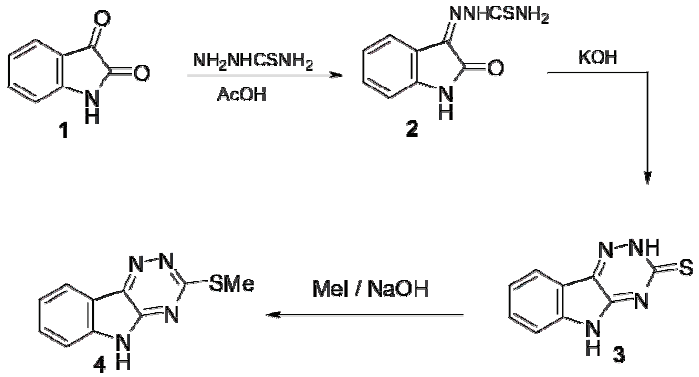
The interest in synthesis of the target compounds is due to the fact that various derivatives of the 5*H*-1,2,4-triazino[5,6-*b*]indoles have aroused considerable interest as a result of their broad spectrum of antibacterial, antifungal, antiparasitic activities and antihypertensive properties.[7–12] Considerable attention has been drawn to the synthesis of several condensed heterocyclic systems derived from triazoles and triazines.[13–18] Furthermore, some triazolo-1,2,4-triazino[5,6-

* Corresponding author. E-mail: s.m.gomha@hotmail.com
doi: 10.2298/JSC120914013G

-*b*]indoles were reported to have medicinal applications, such as antiviral, antibacterial and antimalarial activities.[19–22]

RESULTS AND DISCUSSION

The starting 2,4-dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3-thione **3** or its 3-methylthio derivative **4**[23] were prepared by literature methods (Scheme 1). Reaction of **3** or **4** with **5** was realized in chloroform in the presence of triethylamine under stirring at room temperature. In all cases, hydrogen sulfide was evolved during the course of the reaction and so stirring of the reaction mixture was continued until evolution of hydrogen sulfide ceased. Work-up of the reaction mixture afforded, in each case, one isolable product as evidenced by TLC analysis of the crude product. Elemental analyses and IR, ^{1}H- and ^{13}C-NMR spectroscopy, which showed all the expected signals (see the Supplementary material to this paper), confirmed the structures of the prepared compounds. The regioselectivity of the reaction of **3** with **5** seems consistent with literature reports, which indicated that *N*-2 is the site of preference for cyclization, the isolated products were assigned the structure 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives **8** rather than the isomeric structure **9**.[24–26]

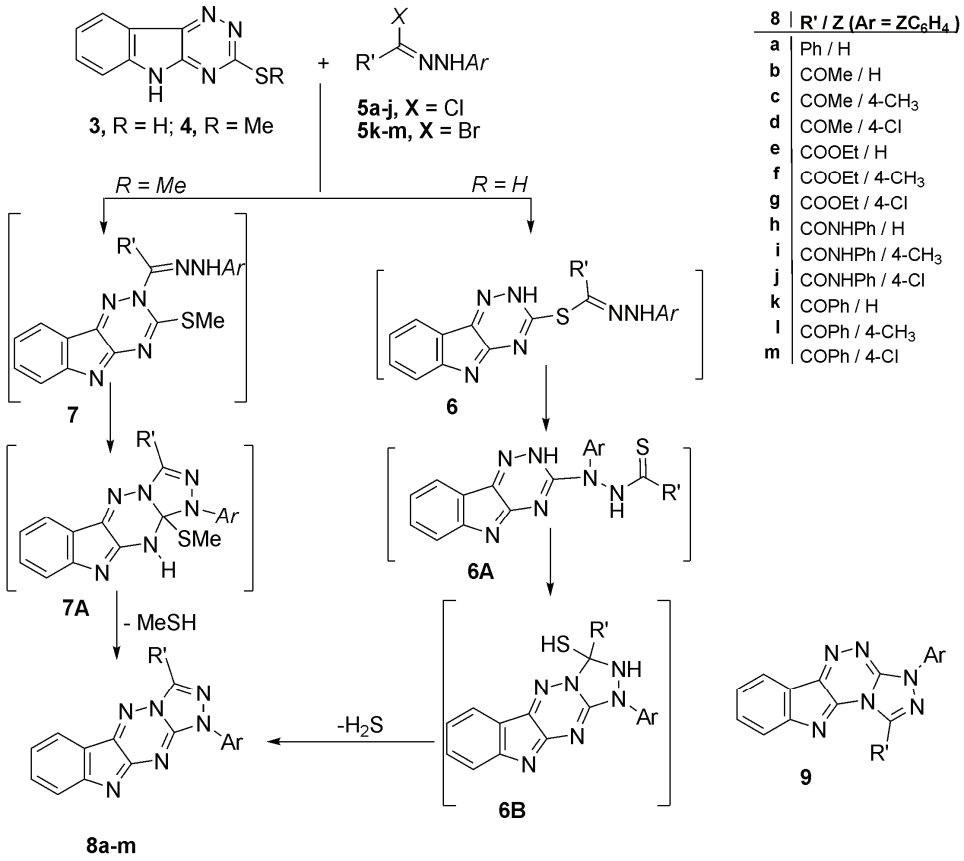


Scheme 1. Synthesis of 5*H*-2,3-dihydro-1,2,4-triazino[5,6-*b*]indole-3-thione (**3**) and its 3-methylthio derivative **4**.

The assignment of structure **8** was further evidenced by an alternate synthesis. Thus, treatment of 2-methylthio derivative **4** with each of the hydrazonoyl halides **5** in chloroform in the presence of triethylamine at room temperature resulted in the evolution of methanethiol and the formation of products that proved identical in all respects (IR, MS, m.p. and mixed m.p.) with **8** (Scheme 2).

Formation of compounds **8** from the thione **3** and hydrazonoyl halides **5** could be accounted for by the hydrazonoylation of **3** to give the hydrazonothioate esters **6**. This is followed by Smiles type rearrangement[27] of the latter esters to form the respective thiohydrazides **6A**, which in turn underwent cyclization to

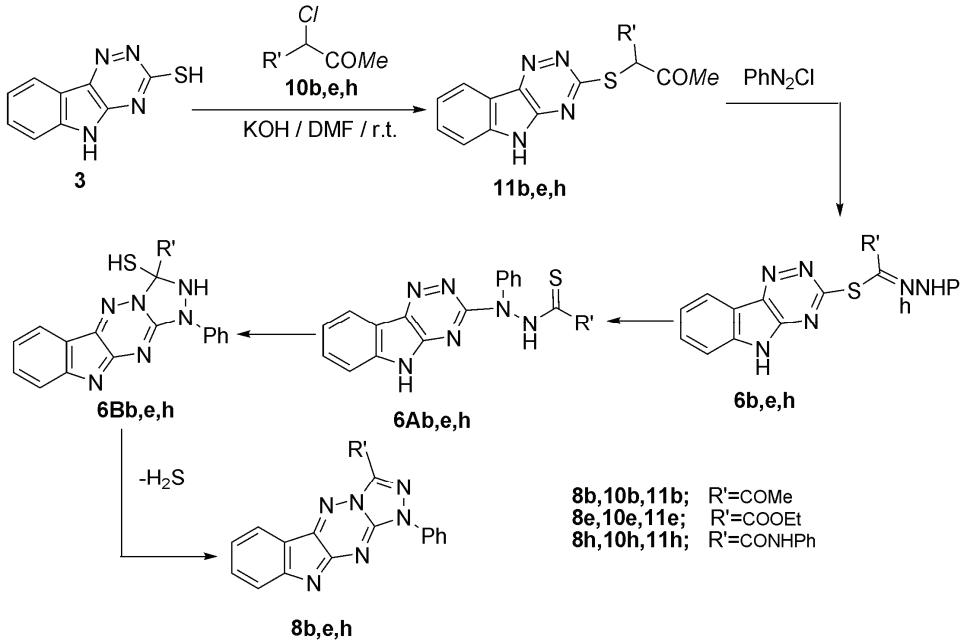
give **8** as the end products (Scheme 2). Under the employed reaction conditions, it seems that both intermediates **6** and **6A** are consumed immediately after formation since all attempts to isolate them failed.



Scheme 2. Synthesis of 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives **8a**–**m**.

The involvement of **6** and **6A** as intermediates in the formation of **8** was evidenced by alternate synthesis of **8b**, **8e** and **8h** (Scheme 2). Thus, treatment of **3** with each of 3-chloro-2,4-pentanedione, ethyl *α*-chloroacetoacetate and *α*-chloroacetoacetanilide in ethanol in the presence of sodium ethoxide afforded the respective substituted products **11b**, **11e** and **11h**. Coupling of each of the latter with benzenediazonium chloride in ethanol in the presence of sodium acetate yielded the thiohydrazonates **6b**, **6e** and **6h**, respectively (Scheme 3), *via* Japp–Klingemann cleavage of the acetyl group.[28] Treatment of the latter products **7** with sodium ethoxide in ethanol afforded the respective compounds **8b**, **8e** and **8h**, which were identical in all respects with those obtained from the reactions of **3** with each of **5b**, **5e** and **5h**, respectively. These findings indicate that **6** and **6A**

are intermediates in the studied reactions of **3** with **5** and that they are consumed as soon as they are formed under the employed reaction conditions.



Scheme 3. Alternate synthesis of 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives **8a**–**m**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in potassium bromide using a Pye-Unicam SP300 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 using a Varian Gemini 300 NMR spectrometer (300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR) and the chemical shifts were related to that of the solvent DMSO-d_6. The mass spectra were recorded on GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses of the products were performed at the Microanalytical Centre of Cairo University, Giza, Egypt. 2,4-Dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3-thione **3** and its 3-methylthio derivative **4**[24] and the hydrazonoyl halides **5**[28–34] were prepared as described in the literature.

*General procedure for the synthesis of 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives (**8a**–**m**)*

Method A. To a mixture of 2,4-dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3-thione **3** (2.02 g, 0.01 mol) and an appropriate hydrazonoyl halide (**5**) (0.01 mol) in chloroform (40 mL), triethylamine (1.4 mL, 0.01 mol) was added. The reaction mixture was stirred at room temperature until cessation of H_2S evolution (4–6 h). The solvent was evaporated and the residue was treated with an ice/ HCl mixture. The solid product was collected, washed with water and crystallized from the appropriate solvent to give the respective derivatives **8**.

Method B. To a solution of 3-(methylthio)-5*H*-1,2,4-triazino[5,6-*b*]indole (**4**) (3.9 g, 0.01 mol) in chloroform (30 mL) containing triethylamine (1.4 mL, 0.01 mol), the appropriate hydrazonoyl halide (**5**) was added (0.01 mol) and the resulting solution was stirred at room temperature overnight. The product was collected, washed with water and crystallized from an appropriate solvent to give the respective products **8**, which are identical in all respects (m.p., mixed m.p. and IR) to those prepared by method A.

Method C. To a stirred ethanolic sodium ethoxide solution, prepared from Na metal (0.23 g, 10 mg atom) and absolute ethanol (20 mL), was added each of the compound **6b**, **6e** and **6h** (10 mmol) and the reaction mixture was stirred at room temperature for 12 h, during which time, the starting reactants **6** dissolved and the crude products precipitated. The latter was filtered, washed with H_2O, dried and finally crystallized from the appropriate solvent to give products, identified as **8b**, **8e** and **8h**, respectively. The latter products proved to be identical in all respects (m.p., mixed m.p. and IR) with those obtained from **3** and the respective hydrazonoyl halides **5**.

*Synthesis of the hydrazonothioates (**6**)*

To a solution of each of **8b**, **8e** and **8h** (10 mmol) in ethanol (40 mL) was added sodium acetate trihydrate (1.38 g, 10 mmol) and the mixture was cooled to 0–5 °C in an ice bath. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride, prepared by diazotizing aniline (10 mmol) dissolved in 6 mL HCl (6 M) with a solution of sodium nitrite (0.7 g, 10 mmol) in 10 cm^3 H_2O. After complete addition of the diazonium salt, the reaction mixture was stirred for a further 12 h at room temperature. The solid precipitate was filtered off, washed with water, dried and crystallized from the appropriate solvent to give the respective pure **6b**, **6e** and **6h**.

*Reactions of **3** with active chloromethylene compounds*

To a solution of **3** (2.02 g, 0.01 mol) in chloroform was added triethylamine (1.4 mL, 0.01 mol) and the mixture was stirred for 10 min at room temperature. To the resulting clear solution was added an active chloromethylene compound (0.01 mol) drop-wise under stirring. After complete addition, the reaction mixture was stirred for further 24 h at room temperature. The solid that precipitated was filtered off, washed with H_2O, dried and finally crystallized from the appropriate solvent to give pure **11b**, **11e** and **11h**.

CONCLUSION

In summary, the reactivity of 2,4-dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3--thione or its 3-methylthio derivative is a versatile and readily accessible building block for the synthesis of new 1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives.

SUPPLEMENTARY MATERIAL

Analytic and spectral data of the prepared compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА НОВИХ ФУНКЦИОНАЛИЗОВАНИХ ДЕРИВАТА 1,2,4-ТРИАЗОЛО[4′,3′:2,3][1,2,4]ТРИАЗИНО[5,6-*b*]ИНДОЛА

SOBHI M. GOMHA[1] и HATEM. A. ABDEL-AZIZ[2]

[1]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt и [2]Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

Нови функционализовани деривати 1,2,4-триазоло[4′,3′:2,3][1,2,4]триазино[5,6-*b*]индола синтетисани су реакцијом хидразоноил-халогенида и 2,4-дихидро-3*H*-1,2,4-триазино[5,6-*b*]индол-3-тиона или одговарајућег 3-метилтио деривата. У раду су разматрани механизам и региоселективност испитиваних реакција.

(Примљено 14. септембра, ревидирано 3. октобра 2012)

REFERENCES

1. A. S. Shawali, S. M. Gomha, *J. Pract. Chem.* **342** (2000) 599
2. S. M. Gomha, *Monatsh. Chem.* **140** (2009) 213
3. I. M. Abbas, S. M. Riyadh, M. A. Abdallah, S. M. Gomha, *J. Heterocycl. Chem.* **43** (2006) 935
4. A. S. Shawali, S. M. Gomha, *Tetrahedron* **58** (2002) 8559
5. S. M. Gomha, H. M. E. Hassaneen, *Molecules* **16** (2011**)** 6549
6. S. M. Gomha, S. M. Riyadh, *ARKIVOC* (2009) 58
7. V. J. Ram, *Arch. Pharm.* **313** (1980) 108
8. J. M. Gwaltney, *Proc. Soc. Exp. Biol. Med.* **133** (1970) 1148
9. J. M. Z. Gladych, R. Hornby, J. Hunt, D. Jack, J. J. Boyle, R. J. Ferlauto, R. Haff, C. Kormendy, F. Stanfield, R. Stewart, *J. Med. Chem.* **15** (1972) 277
10. R. F. Haff, J. J. Boyle, R. Stewart, R. Ferlando, J. M. Z. Gladych, J. Hunt, D. Jack, *Nature* **221** (1969) 286
11. J. M. Z. Gladych, R. Hornby, J. H. Hunt, D. Jack, J. J. Boyle, R. J. Ferlauto, R. F. Haff, C. G. Kormendy, F. J. Stanfield, R. C. Stewart, *J. Med. Chem.* **15** (1972) 277
12. J. M. Gwaltney, *Proc. Soc. Exp. Biol. Med.* **133** (1970) 1148
13. R. Mardronero, S. Vega, *J. Heterocycl. Chem.* **15** (1978) 1127
14. S. W. Schneller, D. G. Barthdomew, *J. Heterocycl. Chem.* **15** (1978) 439
15. E. J. Gray, M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1* (1977) 1492
16. M. Robba, D. Maume, J. C. Lancelot, *J. Heterocycl. Chem.* **15** (1978) 1209
17. K. C. Joshi, A. Dandi, S. Baweia, *J. Indian Chem. Soc.* **66** (1989) 690
18. M. I. Younes, H. H. Abbas, S. A. Metwally, *Arch. Pharm. (Weinheim)* **320 (**1987) 1191
19. A. Dorn, S. R. Vippagunta, H. Matile, C. Jaquet, J. L. Vennerstrom, R. G. Ridley, *Biochem. Pharmacol.* **55** (1998) 727
20. T. J. Egan, D. C. Ross, P. A. Adams, *Afr. J. Sci.* **92** (1996) 11
21. C. D. Fitch, R. Chevli, H. S. Banyal, G. Phillips, M. A. Pfaller, D. J. Krogstad, *Antimicrob. Agents Chemother.* **21**(1982) 819
22. P. A. Adams, P. A. M. Berman, T. J. Egan, P. J. Marsh, J. J. Silver, *Inorg. Biochem.* **63** (1996) 69
23. J. Mohan, G. S. R. Anjaneyulu, D. Kiran, *Indian J Chem.* **27B** (1988) 346
24. V. J. Ram, V. Dube, A. Vlietinck, *J. Heterocycl. Chem.* **24** (1987) 1435
25. F. F. Abdel-Latif, R. M. Shaker, M. Mahgoub, Z. A. A. Bader, *J. Heterocyl. Chem.* **26** (1989) 769

26. E. S. H. El Ashry, N. Rashed, H. Abdel-Hamid, E. S. Ramadan, *Z. Naturforsch., B* **52** (1997) 873
27. K. Ishii, M. Hatanaka, I. Ueda, *Chem. Pharm. Bull.* **39** (1991) 3331
28. A. S. Shawali, A. O. Abdelhamid *Bull. Chem. Soc. Jpn.* **49** (1976) 321
29. P. Wolkoff, *Can. J. Chem*. **53** (1975) 1333
30. C. Bullow, E. King, *Liebigs Ann.* **439** (1924) 211
31. G. Favrel, *Bull. Soc. Chim. Fr*. **31** (1904) 150
32. W. Dieckmann, O. Platz, *Ber. Dtsch. Chem. Ges*. **38** (1906) 2989
33. H. M. Hassaneen, A. S. Shawali, N. M. Abunada, *Org. Prep. Proced. Int.* **24** (1992) 171
34. T. Curtius, *J. Prakt. Chem.* **51** (1899) 168.