SYNTHESIS OF SOME ISATIN-3-SUBSTITUTED DERIVATIVES

Navabeh Nami* and Masoumeh Hosseinzadeh
Department of Chemistry, Islamic Azad University, Ghaemshahr,
Mazandaran, Iran.

Abstract: The reaction of isatin-3-(6-methoxycarbonyl-1,3-thiazin-4-one-2-yl)hydrazone **2** with hydrazine hydrate in methanol afforded isatin-3-(6-hydrazincarbonyl-1,3-thiazin-4-one-2-yl)hydrazone **3**. Carbon disulfide and then hydrazine hydrate with **3** afforded isatin-3-[6-(4-amino-1,2,4-triazolo-5-thiol)-1,3-thiazin-4-one-2-yl]hydrazone **5**. The latest reacted with DMAD to give isatin-3-[6-(8-methoxycarbonylmethylen-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazin-7-one)-1,3-thiazin-4-one-2-yl]hydrazone 6.

Introduction

Isatin is an endogenous indole present in mammalian tissues and Fluids (1). Isatin has shown wide variety of biological such as CNS (2), and antiviral activity (3). Schif base, imines of isatin and its derivatives are reported to show a wide variety of biological activities such as antibacterial (4), antifungal (5), antiviral (6), anti-HIV (7) and anticonvulsant (8) activities.

Triazoles and condensed triazole system are reported to possess diverse types of biological activities. Including antifungal, antibacterial, antiparasitic, hypocholesteremic, hypotensive and anti-inflammatory properties (9-11). In continuation of our work on the synthesis of heterocyclic systems containing nitrogen and sulfur (12), we describe here the synthesis of new isatin derivatives with thiazine and triazolo[3,4-*b*]-1,3,4-thiadiazine nucleus.

Results and Discussion

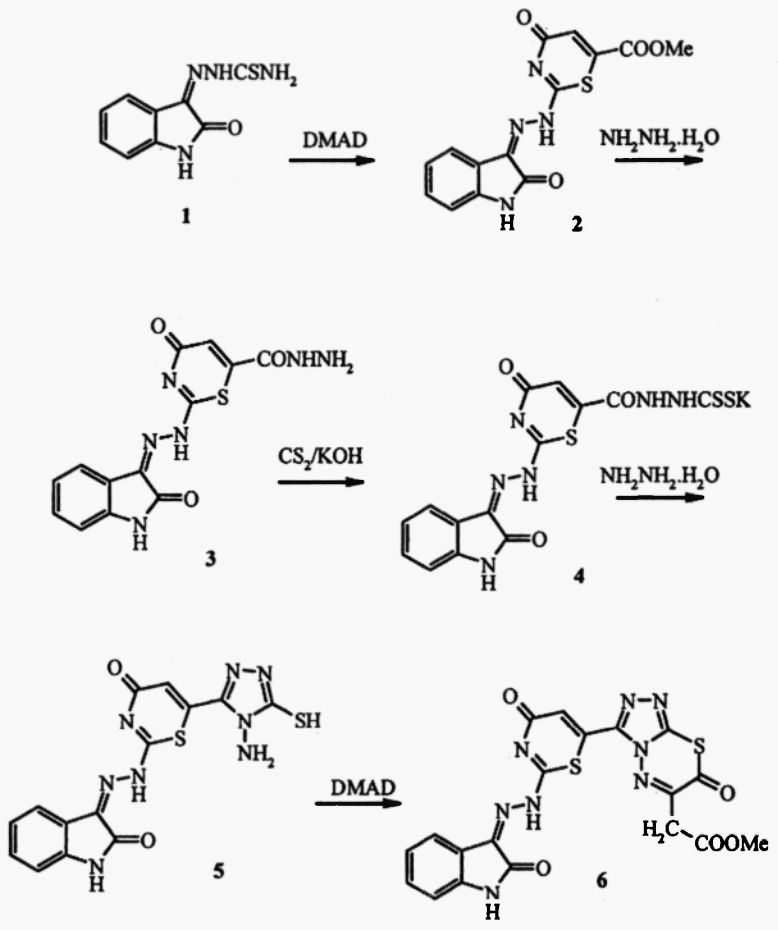
Reaction of isatin-3-thiosemicarbazone **1** with DMAD (dimethylacetylenedicarboxylate) yielded isatin-3-(6-methoxycarbonyl-1,3-thiazin-4-one-2-yl)hydrazone **2** (13). The reaction of **2** with hydrazine hydrate in methanol afforded isatin-3-(6-hydrazincarbonyl-1,3-thiazin-4-one-2-yl)hydrazone **3**. Carbon disulfide was then added to a solution of potassium hydroxide / ethanol and **3** to give 4. A suspension of **4** and hydrazine hydrate in water refluxed while stirring to give isatin-3-[6-(4-amino-1,2,4-triazolo-5-thiol)-1,3-thiazin-4-one-2-yl]hydrazone **5**. The condensation of **5** with DMAD in methanol gave isatin-3-[6-(8-methoxycarbonylmethylen-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazin-7-one)-1,3-thiazin-4-one-2-yl]hydrazone **6** (Scheme-1).

The structures of these compounds were confirmed by their ^{1}H NMR, FT-IR, mass spectra and by elemental analyses.

Experimental

The melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (CsI disks for the range 4000-500 cm^{-1}). The ^{1}HNMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H,

300.134 MHz) using TMS as internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system.



Scheme-1

Isatin-3-(6-hydrazincarbonyl-1,3-thiazin-4-one-2-yl)hydrazone 3

A mixture of **2** (1 mmol) and hydrazine hydrate (1.5 mmol, 85%) in 20 mL of methanol was heated at reflux for 4 h. The methanol, water and excess hydrazine hydrate were removed in vacuo, and the residual solid recrystallized from ethanol. Yield 88%, mp 142-143 °C; MS: *m/z* 330 (M^+); FT-IR: NH_2 3294, CO 1725, 1695 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.59 (s, 1H, C=CH), 6.82 (d, J = 7.5 Hz, 1H, Ar-H), 6.98 (m, 1H, Ar-H), 7.13 (br, 1H, NH), 7.30 (m, 1H, Ar-H), 7.59 (d, J = 7.5 Hz, 1H, Ar-H), 8.05 (br, 2H, NH_2), 8.22 (br, 1H, NH), 10.63 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{10}N_6O_3S$: C, 47.27; H, 3.03; N, 25.45. Found: C, 47.25; H, 3.02; N, 25.49.

Isatin-3-[6-(4-amino-1,2,4-triazolo-5-thiol)-1,3-thiazin-4-one-2-yl]hydrazone 5

Carbon disulfide (1.4 mmol) was added dropwise to an ice-cold solution of potassium hydroxide (1.5 mmol) and **3** (0.9 mmol) in 15 mL absolute ethanol. The mixture was stirred at room

temperature for 14 h. Dry ether 20 mL was then added and the separated solid was filtered and washed with ether (2x5 mL). The product 4 obtained in nearly quantitative yield was employed in the next reaction without further purification. A suspension of **4** (about 0.8 mmol) and hydrazine hydrate 85% (1.6 mmol) in 10 mL of water refluxed while stirring for 4 h. Hydrogen sulfide was evolved. On dilution with 50 mL of cold water and acidification with concentrated HCl, the solid was precipitated. The product was filtered, washed with water and recrystallized from ethanol. Yield 85%, mp > 300 °C; MS: *m/z* 386 (M^+); FT-IR: NH_2 3223, SH 2849, CO 1699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.27 (s, 2H, NH_2), 5.83 (s, 1H, C=CH), 6.93 (d, J = 8.0 Hz, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 7.30 (m, 1H, Ar-H), 7.51 (d, J = 7.5 Hz, 1H, Ar-H), 11.17 (s, 1H, NH), 12.90 (s, 1H, NH), 14.03 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{10}N_8O_2S_2$: C, 43.52; H, 2.59; N, 29.02. Found: C, 43.57; H, 2.55; N, 29.06.

Isatin-3-[6-(8-methoxycarbonylmethylen-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazin-7-one)-1,3-thiazin-4-one-2-yl]hydrazone 6

A solution of **5** (1 mmol) and DMAD (1 mmol) in 20 mL of MeOH was heated at reflux for 2 h. The solution was cooled and the crystals that formed were separated. Yield 73%, mp 285-286 °C; MS: *m/z* 496 (M^+); FT-IR: OH 3407, CO 1734cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.28 (s, 2H, CH_2), 3.77 (s, 3H, OMe), 6.91 (s, 1H, C=CH), 6.94 (d, J = 8.0 Hz, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.33 (d, J = 7.5 Hz, 1H, Ar-H), 8.31 (br, 1H, NH), 10.75 (br, 1H, NH). *Anal.* Calcd. for $C_{19}H_{12}N_8O_5S_2$: C, 45.97; H, 2.42; N, 22.58. Found: C, 45.93; H, 2.38; N, 22.61.

Acknowledgment

The authors are thankful to the Islamic Azad University of Ghaemshahr for their support.

REFERENCES

1. N. Igosheva, S. Matta and V. Glover, Physiology and Behavior, **80**, 665 (2004).
2. V. Glover, J.M. Halket, P.J. Watkins, A. clow, B.L. Goddwin and M.J. Sandler, Neurochemistry, **51**, 656 (1988).
3. R.L. Chen, Y.C. Wang, Y.W. Lin, S.Y. Chou, S.F. Chen, L.T. Liu, Y.T. Wu, C.J. Kuo, T.S.S. Chen and S.H. Juang, Bioorg. Med. Chem. Lett. **15**, 3058 (2005).
4. S.N. Pandeya, D. Sriram, G. Nath and E. De Clercq, Eur. J. Med. Chem. 9, 25 (1999).
5. A. Bacchi, M. Carcelli, P. Pelagatti, G. Pelizzi, M.C. Rodriguez-arguelles, D. Rogolino, C. Solinas and F.J. Zani, Inorg. Biochem. 99, 397 (2005).
6. N. Karali, N. Terzioglu and A. Gursoy, Arzneim. Forsch. **48**, 758 (1998).
7. S.N. Pandeya, D. Sriram, G. Nath and E. De Clercq, Eur. J. Med. Chem. **35**, 249 (2000).
8. M. Varma, S.N. Pandeya, K. Singh and J.P. Stables, Acta Pharm. **54**, 49 (2004).
9. M.B. Talawar, U.V. Laddi, Y.S. Somannavar, R.S. Bennur and S.C. Bennur, Indian J. Heterocyclic Chem. **4**, 297 (1995).
10. S.B. Hallo, B. Kalluraya, K.R. Sridhar, E. Drake, K.K. Bhandary and M. Levine, Eur. J. Med. Chem. **29**, 301 (1994).
11. M.S. Chande and B.M. Kamik., J. Indian Chem. Soc. **70**, 268 (1993).
12. M.M. Heravi, N. Nami, H.A. Oskooie and R. Hekmatshoar, Phosphorus, Sulfur and Silicon, **181**, 87 (2006); H.A. Oskooie, M.M. Heravi, N. Nami and A. Nazari, Heterocyclic Comm. **11**, 101 (2005); M.M. Heravi, Y.S. Beheshtiha, N. Nami and M. Ghassemzadeh, Phosphorus, Sulfure and Silicon, **161**, 71 (2000); M.M. Heravi, Y.S. Beheshtiha, N. Nami and R. Hekmatshoar, Phosphorus, Sulfur and Silicon, **165**, 285 (2000).
13. J.E. Lown, Canadian Journal of Chemistry, **45**, 938 (1967); J.E. Lown, Canadian Journal of Chemistry, **45**, 953 (1967).

Received on April 10, 2007.