Journal of Bangladesh Chemical Society, Vol. 25(1), 46-52, 2012

THE EFFECT OF DEACTIVATING GROUPS IN THE FORMATION OF SOME BIOLOGICALLY IMPORTANT LACTAMS (ISATINS) AND THEIR FURTHER DERIVATIZATION

MOHAMMAD M. HOSSAIN*[1], NOOR N. FERDOUS[1], MD HASAN MUHIB[1], MD. SULTAN ALAM[1], MD RABIUL ISLAM[1], MD ABDUL HAI[1] AND WAJDI ZOGHAIB[2]

[1]*Department of Chemistry, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh*

[2]*Department of Chemistry, Sultan Qaboos University, Al Khod, P. C. 123, Sultanate of Oman*

Abstract

Treatment of different aromatic primary amines (7a-b) with chloral hydrate and hydroxylamine hydrochloride under microwave (MW) conditions afforded corresponding isonitrosoacetanilides (6a-b). These intermediate compounds (6a-b) were cyclized in conc.H_2SO_4 medium to give cyclic amides (5a-b) by means of elcetrophilic aromatic substitution reaction. The microwave (MW) mediated treatment of compound 5a with thiosemicarbazide afforded the corresponding Schiff-base 4a, which undergoes cyclization to give thiadiazoline (1). Beside, compound 4a was also treated with aq KOH solution under MW condition to give triazinothione (3). The Sn-HCl mediated reduction of compound 3 afforded the corresponding 6-aminothione (2). On the other hand, compound 5b was treated with o-phenylenediamine under MW condition to give the corresponding quinoxaline derivative 4b in excellent yield.

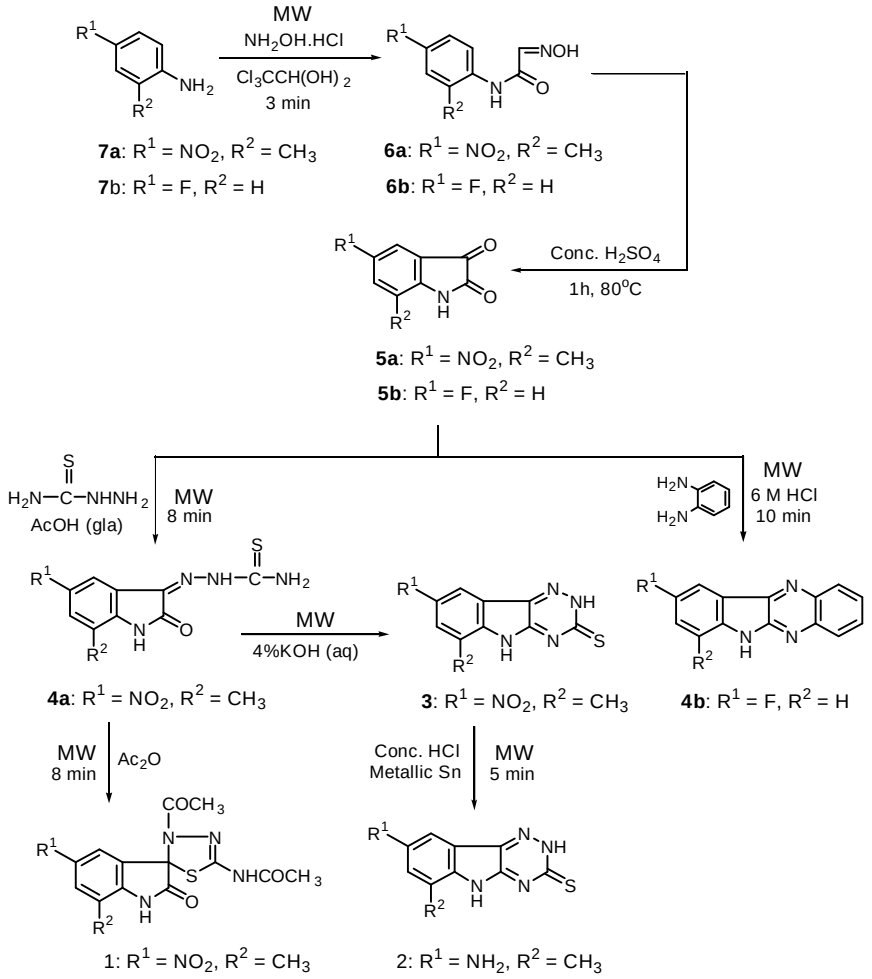
Introduction

The oxidized product of indoles such as isatins (β-lactams) and their related heterocyclic compounds are very useful due to their excellent biological properties such as antiinflammatory, antimicrobial, and anticancer activity.[1-3] In addition, these compounds are very useful synthetic intermediates and can function as suitable building blocks to synthesize some other biologically active compounds such as natural products.[4-6]

The Schiff bases and spiro-thiadiazoline derivatives of isatins have shown remarkable biological activities.[7,8] Therefore, design and consequent synthesis of such lactam based compounds as drugs candidates have been receiving a considerable attention in the field of medicinal organic chemistry.[9,10] The introduction of fluorine in heterocycles is known to modify the course of the reaction beside influencing the biological activity.[11] Moreover, this incorporated fluorine atom or trifluoromethyl group may act as a pharmacophore and enhancing pharmacological properties of the compounds as compared to their non-fluorinated analogues.[12,13] In fact a lot of efforts have been paid to the synthesis of such biologically important lactam based compounds over the decades. But, most of the work was carried out with suitable aromatic amines, having substituents like electron donating groups. Nonetheless a very few papers have reported the synthesis of fluoroisatin in different methods including Sandmeyer procedure.[14-16]As far as nitroisatins concerned there has been no published report of their synthesis in

Author for Correspondence; e-mail: chemmamun2@yahoo.com

andmeryer procedure under microwave conditions. Actually electron withdrawing/donating groups attached to the phenyl ring have a great influence in the Sandmeyer procedure since the second step of the reaction, an intramolecular cyclization, is merely an elcetrophilic aromatic substitution reaction. Therefore, any group attached to the aromatic ring can enhance the stabilization/destabilization of the generating carbonium ion in the ring system depending on its nature whether it is activating or deactivating. We successfully synthesized some crucial isatins from such romatic amines having electron withdrawing groups such as NO_2 and F. It is worth to be mentioned here that most of the reactions were carried out both by MW conditions beside classical heating method.



Scheme 1

Experimental

Fisher-John's electro thermal melting point apparatus was used for recording the melting temperatures of all the synthesized compounds by thin disc method and were not corrected. Infrared spectra were recorded on a Fourier Transform Infra-red Spectrophotometer in KBr disc. Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded using a 400 MHz AVANCE Bruker NMR spectrometer. Mass spectra were acquired on a Quattro Ultima Pt (Waters Corp, Milford MA, USA), Tandem Quadrupole mass spectrometer. The samples were infused using a Harvard syringe pump (Harvard, CA, USA) at a flow rate of 10μL/min into the mass spec.

General procedure for the synthesis of isonitrosoacetanilides (**6a-b**) under MW irradiation:

The appropriate substituted aromatic amines such as 2-methyl-4-nitroaniline (1.00 g, 6.57 mmol) was dissolved in 2M HCl (4 mL), followed by the addition of a solution of hydroxylamine hydrochloride (0.74 g, 10.62 mmol) in water (4 mL). A separate solution of chloral hydrate (1.64 g, 9.91 mmol) and sodium sulphate (saturated solution, 20 mL) was added to the previous solution and the whole reaction mixture was irradiated under microwave for 3 min. The progress of the reaction was monitored by TLC ($CHCl_3$: EtOAc, 3:1). The overnight cooling of the reaction mixture afforded a pale yellow crude solid, which recrystallized from methanol to give **6a** as yellow crystals (89%), Mp. 189°-190° C; IR (KBr, disc**)** ν 3550 (s, O-H), 3325 (s, N-H), 3050 (s, C-H Ar), 1720 (s, C=O), 1635 (s, C=N), 1587, 1490 (s, C=C, Ar); ^{1}H-NMR (CD_3OD) δ 2.31 (s, 3H, CH_3), 6.61 (s, 1H, NH), 7.69 (d, 1H, J_m = 2.5 Hz, H-3, ArH), 7.94 (d, 1H, J_o = 7.5 Hz, H-6, ArH), 8.02 (dd, 1H, J_o = 7.5 Hz, J_m = 2.5 Hz, H-5, ArH), 9.61 (s, 1H, N-OH), 12.35 (1H, s, HC=N); MS: m/z 222 [$(M-H)^+$, $C_9H_9N_3O_4$].

4-Fluoroisonitrosoacetanilide (6b)

Yield**:** (86%), mp**.** 167-168°C; IR (KBr, disc) ν 3535 (s, O-H), 3326 (N-H amide), 3115 (s, C-H, Ar), 1715 (s, C=O), 1653 (s, C=N), 1605, 1558 (s, C=C, Ar); ^{1}H-NMR (CD_3OD) δ 7.08 (d, 1H, J_o = 8.8 Hz, Ar-H), 7.11 (d, 1H, J_o = 8.8 Hz, Ar-H), 7.65 (d, 1H, J_o = 8.2 Hz, Ar-H), 7.67 (d, 1H, J_o = 8.2 Hz, Ar-H), 7.60 (s, 1H, =CH)**,** no data for NH as it is exchangeable; MS: m/z 182 [M^+, $C_8H_7FN_2O_2$].

General procedure for the synthesis of β-lactams (5a-b)

The appropriate isonitrosoacetanilides such as compound **6a** (2.00g, 8.96 mmol) was dissolved in conc. H_2SO_4 (6.0 mL) and the resulting mixture was heated between 70°-80°C for an hour. Besides, the same reaction was also carried out under MW conditions and the reaction mixture was irradiated (20% radiation of the total power) for 20 sec (5 sec×4). In both cases the progress of the reactions was monitored by TLC (CH_2Cl_2 : EtOAc, 5:1). Finally neutralization of the reaction mixture with 20% aq. Na_2CO_3 solution gave a red solid mass, which was recrystallized from methanol afforded the titled compound (88%), mp. 254°-255°C; IR (KBr, disc) ν 3425 (s, N-H, lactam), 3031 (C-H, Ar), 1750 (C=O, lactam), 1728 (s, C=O) cm^{-1}; ^{1}H-NMR (CD_3OD) δ 2.21 (s, 3H, CH_3), 8.09 (d, 1H, J_m = 2.7 Hz,

ArH), 8.47 (d, 1H, J_m = 2.7 Hz, ArH), 11.35 (s, 1H, NH), **MS**: m/z 206 [M^+, $C_9H_6N_2O_4$].

5-Fluoroindole-2,3-dione (**5b**)

Yield (84%), mp. 220°-221°C; IR (KBr, disc) ν 3390 (s, lactam N-H), 3050 (C-H, Ar), 1762 (s, C=O, lactam), 1709 (s, C=O, keto), 1624 and 1616 (C=C, Ar); ^{1}H-NMR (CD_3OD) δ 7.20 (d, 1H, J_m = 2.3Hz, C_4-H, ArH), 7.87 (dd, 1H, J_o = 7.7Hz, J_m = 2.3Hz, C_6-H, ArH), 7 .94 (d, 1H, J_o = 7.7Hz, C_7-H, ArH), 9.83 (s, 1H, NH), **MS**: m/z 165 [M^+, $C_8H_4FNO_2$].

Microwave-assisted synthesis of 7-methyl-5-nitroisatin-3-thiosemicarbazone (**4a**) from **5a**:

The titled compound was synthesized as per literature method.[3]

Yield (74%), mp. 269°-270°C; IR (KBr, disc) ν 3325 (s, N-H), 3122 (w, C-H, aromatic), 2990 (s, C-H, aliphatic), 1720 (s, lactam C=O), 1635 (s, C=N), 1587, 1490 (s, C=C, Ar); ^{1}H-NMR (CD_3OD) δ 2.22 (s, 3H, CH_3), 8.09 (d, 1H, J_m = 1.5Hz, ArH), 8.46 (d, 1H, J_m = 1.5Hz, ArH), 11.35 (s, 1H, N-N<u>H</u>), 13.82 (s, 1H, lactam NH), no data for -NH_2 as they are exchangeable; MS**:** m/z 278 [$(M-H)^+$, $C_{10}H_9N_5O_3S$].

Microwave-assisted synthesis of spiro-7-methyl-5-nitroisatin-4-N-acetyl-2-acetamido-Δ^2*-1,3,4-thiadiazoline (**1**) from **4a***

Isatin-3-thiosemicarbazone 4a (1.00 g, 3.58 mmol) was dissolved in freshly distilled acetic anhydride (2.5 mL) and the whole reaction mixture was irradiated under microwave condition for 8 min. The progress of the reaction was monitored by TLC (EtOAc : $CHCl_3$, 1:3). The reaction mixture was cooled over-night at room temperature. A deep brown solid was obtained, which was filtered off and washed with hexane and dried. The compound **1** was recrystallized from methanol to give a brown solid (86%), mp. 234°-235°C; IR (KBr, disc) ν 3334 (s, N-H), 2990 (s, C-H, aliphatic), 3074(w, C-H, aromatic), 1720 (s, lactam C=O), 1635 (s, C=N), 1587, 1490 (s, C=C, Ar); ^{1}H-NMR (CD_3OD) δ 2.01 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.22 (s, 3H, CH_3), 7.94 (d, 1H, J_m = 1.5Hz, Ar-H), 8.01 (d, 1H, J_m = 1.5Hz, Ar-H), 11.37 (s, 1H, NH), 11.97 (s, 1H, NH); MS**:** m/z 362 [$(M-H)^+$, $C_{14}H_{13}N_5O_5S$].

*Microwave-assisted synthesis of 8-methyl-6-nitro-3,9-dihydro-1,3,4,9-tetraaza-2-thione (**3**) from **4a***

Compound **4a** (1 g, 2.75 mmol) was taken in a round bottomed flask followed by the addition of freshly prepared 4% aq. KOH solution (7.0 mL) and the whole reaction mixture was irradiated under microwave for 8 minutes. The progress of the reaction was monitored by TLC (EtOAc: Methanol, 1:1). The reaction mixture was cooled overnight at room temperature. A yellowish brown solid was obtained, which was filtered off and washed with hexane and dried under vacuum. The obtained crude solid was recrystallized from methanol to give a yellowish crystalline solid, (90%), mp. 279°-281°C; IR (KBr, disc) ν 3315 (s, N-H), 3090 (w, C-H, aromatic), 2970, 2835 (s, C-H aliphatic), 1730 (s, lactam C=O), 1628 (s, C=N), 1587, 1490 (s, C=C, Ar); ^{1}H-NMR (CD_3OD) δ 2.22 (s, 3H, CH_3), 8.09 (d, 1H, J_m= 1.2Hz, Ar-H), 8.46 (d, 1H, J_m = 1.2Hz,

Ar-H), 11.35 (s, 1H, NH), 13.82 (s, 1H, NH); MS**:** m/z 261 [(M-H)$^+$, $C_{10}H_7N_5O_2S$].

*Microwave-assisted synthesis of 6-amino-8-methyl-3,9-dihydro-1,3,4,9-tetraaza-2-thione (**2**) from **3***

Compound **3** (1.00 g, 3.82 mmol) and metallic tin (100 mg) were taken in a round bottomed flask followed by the addition of conc. HCl (10 mL) and the whole reaction mixture was irradiated under microwave for 5 min (30 sec × 10). The progress of the reaction was monitored by TLC (EtOAc : Methanol, 1:1). The reaction mixture was poured onto crushed ice. A wine red solid was obtained, which was filtered off and washed with hexane and dried under vacuum. The crude solid was recrystallized from methanol to give the titled compound **2** (80%), mp 284^o-286^{o}C; **IR** (KBr, disc) ν 3325 (s, N-H), 2990, 2871 (s, C-H, aliphatic), 1720 (s, lactam C=O), 1635 (s, C=N), 1587, 1490 (s, C=C, Ar); ^{1}H-NMR (CD_3OD) δ 2.36 (s, 3H, CH_3), 5.57 (s, 1H, NH), 5.58 (s, 1H, NH), 7.32 (d, 1H, J_m= 1.6Hz, Ar-H), 7.00 (d, 1H, J_m =1.6 Hz, Ar-H), 8.41 (s, 2H, -NH_2).

*Microwave-assisted synthesis of 8-fluoro-1H-indolo [2,3-b] quinoxaline (**4b**) from **5b***

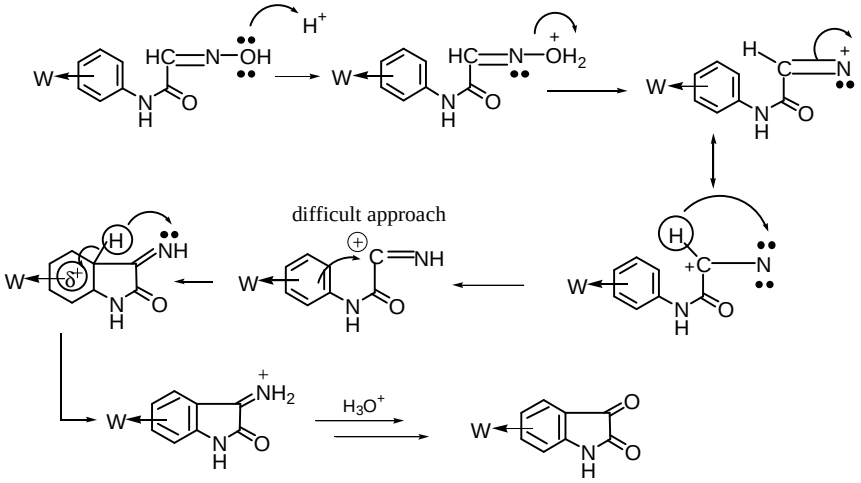
Compound **5b** (500 mg, 2.74 mmol) and *o*-phenylenediamine (470 mg, 2.74 mmol) were dissolved in 6M HCl (25 mL) and the whole mixture was irradiated under 40% microwave irradiation for 10 min ((30 sec×20 times irradiation). The extent of the reaction observed by TLC (EtOAc: $CHCl_3$, 1:8). The crude solid was purified by column chromatography using (EtOAc: $CHCl_3$, 1:5) as eluent. Finally the obtained crude solid was recrystallized from methanol to give the titled quinoxaline **4b** (71%), mp 240^o-242^{o}C; IR (KBr, disc) ν 3300 (N-H amide), 3100 (s, C-H, Ar), 1653(s, C=N), 1558 (s, C=C, Ar); ^{1}H-NMR (DMSO) δ 8.06 (d, 1H, J_o=8.4Hz, H-11, ArH), 8.14 (dd, 1H, J_o=8.4Hz, J_m=1.2Hz, H-10, ArH), 8.24 (d, 1H, J_m=1.2Hz, H-8, ArH), 7.84-7.51 (m, 4H, ArH), 12.07 (s, 1H, lactam NH).

Results and Discussion

The formation of isonitrosoacetanilides (**6a-b**) from the respective aromatic amines under MW conditions gave excellent yield. The lactam ring (**5a-b**) formation by means of ring closure reaction was conveniently carried out by conventional heating method rather than MW irradiation method. The limit and scope of the latter method as well as the pros and cons of both methods (MW vs. classical heating) were explained great detail in our previous paper.[17] Compound **4a** obtained from **5a** with thiosemicarbazide, was converted into thiadiazoline (**1**) under MW condition in excellent yield. On the other hand, Schiff base **4a** was also transformed into triazinothione (**3**), which was reduced to the corresponding triaza-6-aminothione (**2**) in fairly good yield. Furthermore, compound **5b** was converted into quinoxaline under MW irradiation in good yield. Compounds **5a-b** such as **5a** showed clear peaks in the ^{1}H-NMR spectrum at δ 8.09 for an aromatic proton as a doublet and the remaining aromatic proton appeared at δ 8.47 as also a doublet because both are in meta coupling with each other. The CH_3 protons attached to the phenyl ring appeared at δ 2.21 as a singlet. The spectral data of all

other compounds were found to be consistent with their assigned structures (experimental section).

The main objective of the work was to synthesize isatins and their analogues where the aromatic moiety contains an electron withdrawing group. Electron withdrawing groups such as -NO_2, F, -C=O etc. directly attached to the phenyl ring lowering the aromaticity by net deactivation through decreasing the electron density on the π-electron by means of inductive effect. Synthesis of isatins by Sandmeyer procedure[17] from aromatic amines with electron withdrawing substituents especially nitroaniline was thought to be a difficult task due to the net deactivation in the aromatic ring system. But the method applies well to anilines with lectron-withdrawing substituents, such as2-fluoroaniline, and to some heterocyclic amines, such as 2-aminophenoxathine.[18,19]



Scheme 2

Scheme 2. a complicated situation in electrophilic cycliztion due to electron withdrawing group

The aspect of nitroisatin made us interested in doing further work to see the competence of the said method on the electron withdrawing effect using MW and classical heating methods in some extent. As attempted substituted isatins were synthesized in which the aromatic moiety contains powerful electron withdrawing group such as -NO_2 and F. We were succeeded in synthesizing the lactam (isatin) from the condensation of corresponding nitroaniline with chloral hydrate and hydroxylamine hydrochloride followed by the addition of concentrated sulfuric acid (Sandmeyer Procedure). It is clear from the scheme 2 that for the formation of the intermediate oximinoacetanilide, the substitutents attached to the aromatic ring, has less or no effect at all. But when the ring closure takes place, it is a clean case of electrophilic aromatic substitution reaction. The nitro/fluoro group should destabilize the generated carbonium ion in the aromatic

ring system, as it tends to draw the π-electron cloud toward itself. But the reaction takes place readily maybe because of the presence of the electron donating methyl group in the aromatic ring in the case of **5a**. But, the reaction is also smoothly run for the formation of compound **5b** though there is no further activating group in the aromatic ring system.

Conclusion

Acknowledgement

We are thankful to Mr. Golam Sarwar, a Ph. D. candidate, Department of Chemistry, Toronto University, Canada, for providing us with spectral support of some compounds.

References

1. C. Giselle and A. Ferreira, *J. Braz. Chem. Soc.*, 2006, **17,** 1.
2. V. Chazeau, M. Cussac and A. Boucherle, *J. Med. Chem.*, 1990, **27** (6), 615.
3. M. M. Hossain, N. Islam, R. Khan and M. R. Islam, *Bangladesh J. Pharmacol*, 2007, **2,** 66.
4. P. Salvam, N. Murugesh, M. Chandramohan and D. E. Clereq, *Ind. J. Pharm. Sci.* 2004, **66**, 465.
5. F. A. Barile, P. J. Dierickx and U. Kristen, *Cell Biol Toxicol*, 1994, **10**, 155.
6. M. R. Islam and M. Mohsin, *Bangladesh J. Pharmacol*., 2007, **2**, 7.
7. P. N. Solis, C. W. Wright, M. M. Anderson, M.P. Gupta and J. D. Phillipson, *Planta Med.*, 2007, **59**, 250.
8. B. S. Joshi, M. A. Likhate and N. Viswanathan, *Indian J. Chem., Sect.*, 1984, **B23,** 114.
9. Y. Teitz, E. Ladizensky, N. Barko and N. Burstein, *Antimicrob. Agents Chem. Ther.* 1993, 2483.
10. M. M. Hossain, S. K. Saha, Foysal Aziz, *Bangladesh Medical Research Council Bulletin*, 2009, **35**, 2, 48.
11. A. Danida , S. Ruby, S. Harshita and A. S. Kapil, *J Fluorine Chemistry*, 2001, **111**, 61.
12. Y. Torisawa, T. Nishi and M. Jun-Ichi, *Bioorg Med. Chem. Lett*., 2001, **11**, 829.
13. J. S. Yadav, B. Reddy, C. Reddy and A. Krishna, *Synthesis*, 2007, **5**, 693.
14. A. K. Erica, E. E. Jackline and C. A. Federico, *Tetrahedron Lett*, 1998, 7679.
15. J. Collino and S. Volpe, *Ital. Boll. Chim. Farm*, 1982, 121, 408.
16. I. Akira and M. Yutaka, *Heterocylces*, 1982, **19** (11), 2139.
17. M. M. Hossain, M. R. Islam, S. K. Shaha, K. I. Mohammad, *Tetrahedron Lett*, 2010, **51**, 1155.
18. R. R. Smolders, A. Waefelaer and D. Francart, *Ing. Chim. (Brussels)* 1982, **64**, 5.
19. G. Loloiu, T. Loloiu, O. Maior, *Khim. Geterosilk. Soedin.* 1998, 396.

(Received: 10 March, 2011; Accepted : 3 April, 2012)