SYNTHESIS OF 6-(6'-ARYLPYRIDIN-2'-YL) AND 6-(4',6'-DIARYLPYRIDIN-2'-YL)-3(4H)-OXO-1,4-BENZOTHIAZINES UNDER MICROWAVE IRRADIATION CONDITIONS

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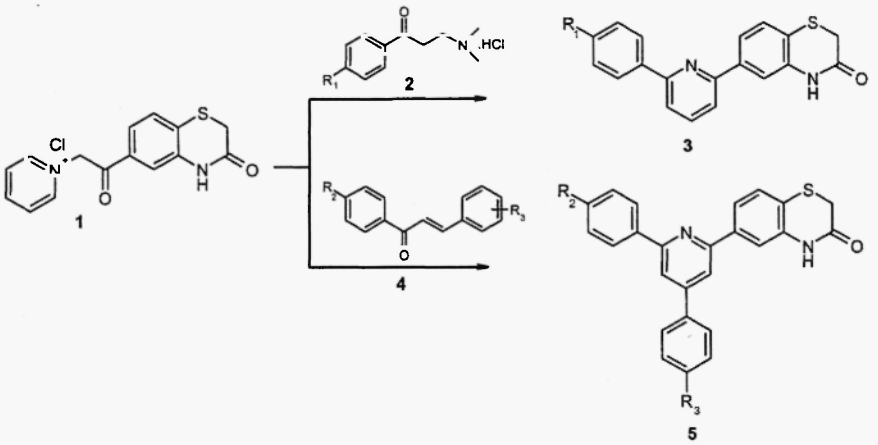
Abstract: A number of 6-(6'-arylpyridin-2-yl) (3a-e) and 6-(4',6'-diarylpyridin-2'-yl)-3(4H)-oxo-1,4-benzothiazines (5a-e) have been synthesized from 2H-3,4-dihydro-3(4H)-oxo-[1,4]benzothiazin-6-acetylpyridinium chloride (1) under Microwave irradiation conditions.

Introduction

Pyridine derivatives posses diverse types of biological activities and found in a number of natural and synthetic pharmaceutical agents[1]. Several di and tri substituted pyridines like Etoricoxib[2], Milrinone and Amrinone[3] have been reported as COX-2 inhibitors and cardiotonic agents for the treatment of congestive heart failure. Many of them are also reported to posses antitumour[4] and antibacterial activities[5]. The synthesis of heterocycles containing this important pharmacophore is of continuing interest to synthetic chemists. Furthermore, 1,4-benzothiazines have been shown to exhibit various kinds of biological activities such as Ca^{2+} antagonist, blood platelet aggregation inhibitors and vascular agents[6]. In view of this and in continuation of our work on various heterocyclic substituted pyridines[7], it was considered of interest to synthesize new derivatives consisting of these two active pharmacophores.

In recent years microwave assisted reaction[8] have become, increasingly important in performing chemical transformations in minutes instead of hours by conventional methods in high purity and yields. This technique has become popular in library synthesis where compounds can be rapidly synthesized by multi component, single step, solution phase or solvent free methods[9].



3 R_1 = a) H b) CH_3 c) SCH_3 d) Cl e) Br
4 & 5 R_3 = H, R_2 = a) H b) F c) Cl d) Br e) CH_3

Scheme - 1

Results and Discussions

Friedel-Crafts reaction of 3-oxo-1,4-benzothiazine with chloroacetylchloride in the presence of aluminium chloride in dichloromethane gave 6-chloroacetyl-2H-3,4-dihydro-3(4H)-oxo-[1,4]-benzothiazine[10]. This on treatment with pyridine at 100°C gave the corresponding 3,4-dihydro-3(4H)-oxo-[1,4]-benzothiazin-6-acetyl pyridinium chloride **1**. The structure of **1** was confirmed by its analytical and spectral data. **1** on reaction with various Mannich bases **2** and α, β unsaturated ketones **4** in the presence of ammonium acetate in refluxing acetic acid under Kroenhke's conditions gave the corresponding 6-(6-aryl and 4,6-diarylpyridin-2-yl)benzothiazines **3** & **5** respectively. Keeping in view of the advantages of microwave irradiation technique, the three component reaction was also carried out under microwave condition. The formation of pyridinyl benzothiazines were completed in 5-10 minutes under microwave condition when compared to 5-6 hrs under conventional heating. The formation **3** & **5** are characterized by the presence of pyridine, $-SCH_2$ and NH-CO protons apart from aromatic protons in their NMR spectra. IR spectra of **3** showed peaks at 3058, 1677, 1594, 1546, 1493, 1401, 1393 and **5** at 3084, 1578, 1567, 1443 and 1383 cm^{-1}. The structures of all the new compounds were established based on their IR, ^{1}H-NMR, mass and correct elemental analyses (**Table-1**).

Table-1: Physical and spectral data of compounds **3** and **5**

Compd*	Yield(%)		Reaction Time		m.p	Mol. formula	Found (Calc.) %			^{1}H NMR δ ppm,
	Method-A	Method-B	Method-A (hr)	Method-B (min)	°C		C	H	N	(DMSO-d_6), MS(70ev)
3a	68	69	5	6	228	$C_{19}H_{14}N_2OS$	71.06 (71.69	4.36 4.40	8.72 8.80)	3.53(s, 2H), 7.32-8.12(m, 11H), 10.64(bs, 1H), MS 318(M^+, 32%)
3b	65	68	5	7	222	$C_{20}H_{16}N_2OS$	72.41 (72.28	4.62 4.81	8.62 8.43)	2.37(s, 3H), 3.51(s, 2H), 7.30-8.12(m, 10H), 10.65(bs, 1H), MS 332(M^+, 100%)
3c	64	65	5	5	218	$C_{20}H_{16}N_2OS_2$	66.26 (65.93	4.67 4.39	8 02 7.69)	3.52(s, 2H), 3.78(s, 3H), 7.31-8.14(m, 10H), 10.67(bs, 1H), MS 364(M^+, 100%)
3d	71	73	4.5	10	209	$C_{19}H_{13}ClN_2OS$	64.82 (64.68	3.82 3.68	8.23 7.94)	3.54(s, 2H), 7.27-8.09(m, 10H), 10.64(bs, 1H), MS 352(M^+, 100%)
3e	72	74	5	8	228	$C_{19}H_{13}BrN_2OS$	57.65 (57.43	3.61 3.27	7.34 7.05)	3.51(s, 2H), 7.28-8.11(m, 10H), 10.67(bs, 1H), MS 398(M^+, 100%)
5a	76	76	5	8	256	$C_{25}H_{18}N_2OS$	75.91 (76.14	4.54 4.56	7.07 7.10)	3.52(s, 2H), 7.23-8.19(m, 15H), 10.59(bs, 1H), MS 395(M+1, 25%)
5b	76	78	5	9	>270	$C_{25}H_{17}FN_2OS$	72.53 (72.87	4.46 4.10	7.08 6.70)	3.51(s, 2H), 7.25-8.12(m, 14H), 10.62(bs, 1H), MS 412(M^+, 100%)
5c	79	82	4.5	7	>270	$C_{25}H_{17}ClN_2OS$	70.26 (70.01	4.23 3.96	6.27 6.53)	3.53(s, 2H), 7.22-8.15(m, 14H), 10.61(bs, 1H), MS 429(M+1,100%)
5d	72	75	5	8	>270	$C_{25}H_{17}BrN_2OS$	63.67 (63.42	3.71 3.59	6.25 5.90)	3.49(s, 2H), 7.24-8.21(m, 14H), 10.59(bs, 1H), MS 474(M^+, 100%)
5e	77	79	5	10	251	$C_{26}H_{20}N_2OS$	76.82 (76.47	5.34 4.90	6.75 6.86)	2.43(s, 3H), 3.48(s, 2H), 7.25-8.23(m, 14H), 10.61(bs, 1H), MS 408(M^+, 100%)

The formation of benzothiazinylpyridines **3** & **5** involves Kröenke's mechanism in which benzothiazinylpyridinium salt **1** undergoes 1,4-Michael addition with **2** & **4**, leading to the formation of 1,5-dicarbonyl system which undergoes spontaneous cyclization in the presence of NH_4OAc leading to the formation of substituted pyridines **3** & **5**.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra was recorded in KBr pellets. ^{1}H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard and chemical

shifts are expressed in δ ppm and Mass spectrum on a Hewelett Packard mass spectrometer operating at 70ev. All the compounds were purified by column chromatography using silica gel.

Preparation of 3,4-Dihydro-3(4H)-oxo-[1,4]benzothiazin-6-acetylpyridinium chloride 1

A mixture of 6-chloroacetyl-1,4-benzoxazin-3-one (0.01 mole) and pyridine (25 ml) was heated at 100°C with stirring for 2 hrs. The separated solid was filtered, washed with ethylacetate and dried to obtain a pure product **1**. Yield (92%), mp>300°C. IR: 3314, 3052, 1689, 1666, 1568, 1489, 1361 cm^{-1}. ^1H NMR (D_2O): δ 3.61(s, 2H), 4.80(s, 2H), 7.60(m, 2H), 7.80(dd, 1H), 8.28(m, 2H), 8.82(m, 3H).

Method A: Preparation of 6-Aryl-2-(3-oxo-1,4-benzothiazin-6-yl)pyridines 3 & 4,6-Diaryl-2-(3-oxo-1,4-benzothiazin-6-yl)pyridines 5: by conventional heating.

General procedure

A mixture of **1** (0.001 mole), ammonium acetate (0.01 mole), Mannich base/ (**2** or **4**, 0.001 mole) and α,β-unsaturated ketone glacial acetic acid (10 ml) was refluxed for 4-5 hrs. The reaction mixture was poured onto crushed ice, the solid obtained was filtered, washed with water and extracted with dichloromethane. The organic extract was washed with water, 5% $NaHCO_3$, water, dried and purified by column chromatography (Hexane : Ethyl acetate, 90:10) to give pure **3** as crystalline solid. **5** was also prepared using similar procedure.

Method B : Preparation of 3 & 5 under microwave irradiation conditions

General procedure.

A mixture of **1** (0.001 mole), ammonium acetate (0.01 mole), Mannich base / α,β unsaturated ketone (**2** or **4**, 0.001 mole), acetic acid (5 ml) was irradiated for 5 minutes in 5x1 with 1 minute intervals using domestic microwave oven the progress of the reaction was monitored by TLC and at the end of the reaction it was poured onto ice and worked up as described above.

References

1. a) H. J. Roth, A. Kleemann, *Pharmaceutical Chemistry Volume I Drug Synthesis*, John Wiley & Sons, New York, (1988).

   b) T. Honkel, R. M. Brunne, H. Müller, F. Reichel, *Angew. Chem. Int. Ed. Engl.* **38**, 643, (1999).

2. R. W. Frussen, C. Brideau, C. C. Chan, S. Charleson, D. Deschenes, D. Dubé, D. Ethier, R. Fortin, J. Y. Ganthier, Y. Girand, R. Gordon, G. M. Greig, D. Riendeau, C. Savoie, Z. Wang, E. Wong, J. L. Xu, R. R. Young, *Bioorg. Metr. Lett* 8, 2777, (1998).

3. G. Pasterin, R. Mendez, E. Kabela, A. Farah, *Life Sci.* **33**, 1787, (1983).

4. a) D. M. Balitz, L. Bush, W. T. Bradner, T. W. Doyee, F. A. O'Herron, D. E. Nettleton, *J. Antibiot* **35**, 256, (1982).

5. M. C. Bagley, J. W. dare, X. Xiong, J. Bower, *J. Org. Lett.* **5**, 4421, (2003).

6. a) C. Brown, R. M. Davidson, *Adv. Heterocycl. Chem.* **38**, 135, (1985).

b) M. O. Lozinskü, A. M. Demehenko, A. F. Shivanuk, *Synthesis and properties of Derivatives of 1,4-Benzothiazines. In Advanced Methods of Synthesis and Modifications of Heterocycles*, Vol 2, Edited by G. V. Karev. JBS Press, Moscow (2003).

7. a) G. Jagath Reddy, K. Pallavi, R. Shailaja Reddy, K. Srinivasa Rao, *Indian. J. Chem.* **44B**, 812, (2005).

b) P. S. N. Reddy, Pragati Reddy, G. Jagath Reddy, K. Srinivasa Rao, *Heterocycl. Commun.* **11**, 135, (2005).

8. V. K. Ahluwalia, M. Kidwai, *New Trends in Green Chemistry*, Anamaya, New Delhi, 59, (2004).

9. L. H. Britteny, *Aldrichim. Acta* **37**, 66, (2004).

10. K. N. Jayaveera, S. Sailaja, G. Jagath Reddy, K. Srinivasa Rao, *Heterocycl. Commun.* **11**, 105, (2005).

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