Reactions of 5-aminopyrazoles: Synthesis of pyrazolo[5′,1′:2,3] pyrimido[5,4-*b*][1,4]-benzothiazines. a new tetracyclic ring system under microwave irradiation conditions

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Abstract : A series of pyrazolo[5′,1′:2,3]pyrimido[5,4-*b*][1,4]-benzothiazines (4a-f), a new tetracyclic ring system have been prepared under microwave irradiation conditions.

Introduction

The chemistry of 5-Aminopyrazoles has become of recent interest because of medicinal properties associated with this synthon. As a result, a number of fused pyrazoles with interesting biological activities have been synthesized[1]. 5-Aminopyrazoles undergo cyclocondensation reactions with β-functional reagents leading to the formation of pyrazolopyrimidines like Zaleplon, Ocinaplon and Indiplon which are nonbenzodiazepine compounds with activity against anxiety and sleep disorders[2]. Furthermore, a number of 1,4-benzothiazine derivatives are known to exhibit interesting biological activities which include Ca^{+2} antagonist, blood platelet aggregation inhibitory and anticoagulant activities[3]. In view of this and in continuation of our work on reactions of 5 -aminopyrazoles[4], we report herein the synthesis of pyrazolopyrimidines annulated with 1,4-benzothiazine phramacophore.

Results and Discussion

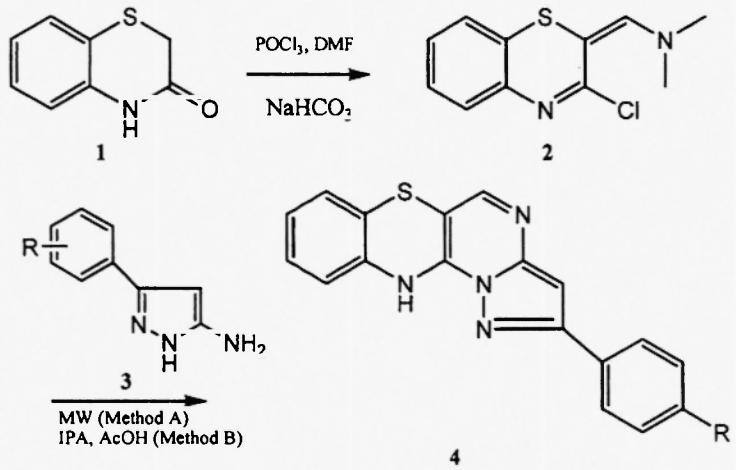
3-Oxo-1,4-benzothiazine (**1**) has got two reactive centers, the lactam carbonyl at position 3 and a methylene group flanked by sulfur and carbonyl at position 2. Reaction of **1** with Vilsmeier reagent derived from dimethylformamide and phosphorousoxychloride results in the formation of 3-chloro-2-dimethylaminoformylidene[1,4]-benzothiazine (**2**)[5]. Although this enamine with an active chloro substituent in β-position forms a reactive synthon it is being relatively unexplored. This can undergo reaction with bifunctional nucleophiles under acidic conditions[6] and requires long reaction times leading to the formation of condensed heterocycles (Scheme 1).

Microwave assisted organic synthesis has gained considerable interest during recent years, because of simplicity, higher yields, purity and drastic reduction in reaction times[7]. In the present work synthon **2** was reacted with various substituted 5-

aminopyrazoles[8] (**3**) in isopropanol under microwave irradiation conditions to give the tetracyclic ring system **4** in good yields. The reaction was also carried out under classical heating conditions in refluxing isopropanol in the presence of acetic acid and montmorillonite K10 as solid acid support[9] for comparison of yields and reaction times. The solution phase reaction under microwave irradiation conditions is much faster and completed in 4-5 minutes time with better yields when compared to 2 hrs under classical heating conditions and does not require any acid support.

The structures of the products reported in Table–1 were based on their ^{1}H NMR, mass spectra and correct elemental analyses. In their, ^{1}H NMR spectra **4** exhibited characteristic signals for pyrimidine and pyrazole protons apart from other signals.

In conclusion, we reported a clean and rapid solution phase synthesis of a new tetracyclic ring system under microwave irradiation condition making use of synthons **2** & **3** and without use of any acid support.



Scheme - 1

Experimental

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra was recorded in KBr pellets. ^{1}H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard, chemical shifts are expressed in δ ppm and Mass spectra on a Hewelett Packard Mass spectrometer operating at 70eV.

General procedure for the preparation of 3-chloro-2-dimethylaminoformylidene-1,4-benzothiazine[5] 2.

To a cooled mixture of phosphorousoxychloride (0.06 moles) and anhydrous dimethylformamide (0.06 moles), 3-oxo-1,4-benzothiazne (0.02 moles) in $CHCl_3$ (25 ml) was added drop wise at 0-5°C and the mixture was stirred at 0°C for 30 minutes and for 2 hrs at reflux. It was then poured into cold water, organic layer was separated, washed with saturated $NaHCO_3$ solution, water, dried (Na_2SO_4) and solvent removed *in vacuo* to give **2**. It was used as such in the next step without further purification.

Table - 1 : Physical data of compounds **4a-f**

Compd	R	M. p °C	Reaction time Method A/min	Method B/hr	Yield %	Mol. formula	^{1}H NMR (200 MHz) $CDCl_3$, δ ppm
4a	H	209	5	2	76	$C_{18}H_{12}N_4S$	6.74(m, 2H), 6.95-7.13(m, 4H), 7.28(d, 2H), 7.76(s, 1H), 7.86(m, 2H), 9.96(bs, 1H)
4b	F	245	5	2	82	$C_{18}H_{11}FN_4S$	6.91-7.16(m, 4H), 7.25(d, 1H), 7.59(d, 2H), 7.94(s, 1H), 8.12(d, 2H), 10.09(bs, 1H)
4c	Cl	261	4	1.5	81	$C_{18}H_{11}ClN_4S$	6.92-7.16(m, 4H), 7.24(d, 1H), 7.58(d, 2H), 7.94(s, 1H), 8.13(d, 2H), 10.18(bs 1H)
4d	Br	263	4	1.5	79	$C_{18}H_{11}BrN_4S$	7.01-7.19(m, 4H), 7.25(d, 1H), 7.61(d, 2H), 7.96(s, 1H), 8.14(d, 2H), 10.16(bs, 1H)
4e	CH_3	223	5	2	77	$C_{19}H_{14}N_4S$	2.41(s, 3H), 6.76(m, 2H), 6.94-7.10(m, 3H), 7.28(d, 2H), 7.76(s, 1H), 7.86(m, 2H), 10.13(bs, 1H)
4f	OCH_3	221	5	2	80	$C_{19}H_{14}N_4OS$	3.84(s, 3H), 6.71(s, 1H), 6.82(d, 1H), 6.94-7.06(m, 4H), 7.74(s, 1H), 7.92(m, 3H), 10.14(bs, 1H)

2-(*p*-Chlorophenyl)pyrazolo[5',1':2,3]pyrimido[5,4-*b*][1,4]benzoxazine 4c: Micro-wave irradiation method. Method A

A mixture of **2** (2.38 g, 0.01 mol), 3(5)-(4-chlorophenyl)- 5(3)-aminopyrazole (**3**, R = Cl, 1.93 g, 0.01 mol), isopropanol (5 ml) was irradiated under microwave irradiation conditions for 5 minutes with 2 minutes interval between each irradiation. After cooling, a crystalline precipitate was formed, it was filtered and recrystallized from dimethylformamide to give pure **4c** as yellow crystalline solid. Yield: 2.83 gm (81%); m.p: 261, ms (70eV) m/z (%): 350(M^+, 100%) ^{1}H NMR ($CDCl_3$): δ 6.92-7.16(m, 4H), 7.24(d, 1H), 7.58(d, 2H), 7.96(s, 1H), 8.13(d, 2H), 10.18(bs, 1H). (Found: C, 61.46; H, 3.27; N, 15.64 $C_{18}H_{11}ClN_4S$ requires C, 61.62; H, 3.13; N, 15.97%).

Synthesis of 4c by conventional heating, Method B

a) In presence of glacial acetic acid. A mixture of **2**, (0.01 mol), **3** (0.01 mol), isopropanol (25 ml), glacial acetic acid (3 ml) was refluxed for 1-2 hrs. At the end of the reaction (as monitored by TLC) solvent was removed and the residue was filtered, washed with water, dried and recrystallized from DMF to give pure **4c** Yield 67%.

b) In presence of montmorillonite K10: A mixture of **2**, (0.01 mol), **3** (0.01 mole), isopropanol (25 ml), montmorillonite K10 as solid acid support (250 mg) was refluxed for 1-2 hrs. At the end of the reaction, the clay was filtered, solvent removed and the residue was recrystallized from DMF to give pure **4c** yield 74%.

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