# SYNTHESIS OF PYRAZOLO[5',1':2,3]PYRIMIDO[4,5-*b*][1,4]-BENZOXAZINES, A NEW HETEROCYCLIC RING SYSTEM FROM 5(3)-AMINOPYRAZOLES

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## Abstract

A series of pyrazolo[5',1':2,3]pyrimido[4,5-*b*][1,4]benzoxazines (**4**a-n), a new heterocyclic ring system has been synthesized starting from 2H-3-oxo-[1,4]-benzoxazines (**1**a-d) and 5(3)-aminopyrazoles (**3**a-d) *via* the intermediates 3-chloro-2-formylidine-1,4-benzoxazines (**2**a-d) obtained under Vilsmeier Häack reaction conditions.

## Introduction

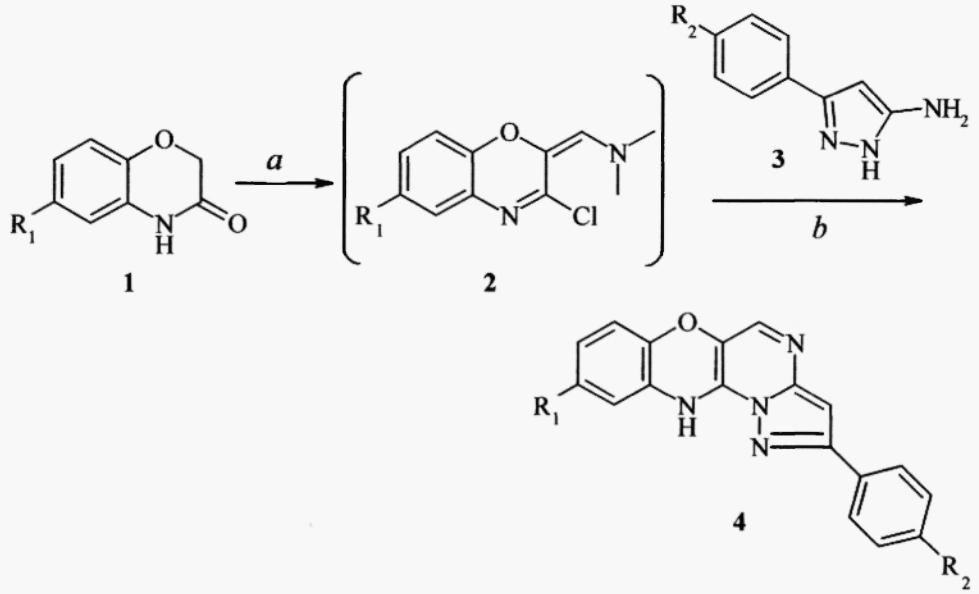
Synthesis of annulated heterocycles is of continuing interest because of the diverse types of biological activities exhibited by them. The pharmacological properties such as anti-inflammatory, antiparasitic and antimicrobial activities associated with 1,4-benzoxazine pharmacophore led to the synthesis of several fused benzoxazine heterocycles[1-4]. Furthermore a number pyrazolo[1,5-a]pyrimidines have been reported as pharmaceutical agents[5,6]. Previous communications from these laboratories described the synthesis of several benzopyrano fused pyrazolo[1,5-a]pyrimidines making use of bifunctional nucleophilic nature of 5(3)-aminopyrazoles[7-8]. Keeping in view of the above observations, it was considered of interest to synthesize some new benzoxazine fused pyrazolopyrimidines from reaction of 5(3)-aminopyrazoles.

## Results and Discussion

The lactam carbonyl at position 3 in 3-oxo-2H-[1,4]-benzoxazine (**1**) readily reacts with phosphorousoxychloride, leading to the formation of highly reactive iminochloride. Condensed benzoxazines are formed when these iminochlorides react with bifunctional nucleophiles, thus making **1** as a versatile synthon[9-11]. Reaction of 3-oxo-2H-[1,4]-benzoxazines (**1**) with phosphorousoxychloride in presence of dimethylformamide under Vilsmeier Häack condition[12] results in the formation of 2-dimethylaminoformylidene-3-chloro[1,4]-benzoxazines (**2**) with two reactive centres at position 2 and 3. Bifunctional nucleophiles such as 5(3)-aminopyrazoles with an exocyclic amino group and a highly reactive ring nitrogen react with **2** forming fused

benzoxazines. Thus treatment of **2** with 5-amino-3-arylpyrazoles (**3**a-d) in refluxing isopropanol in presence of acetic acid gave the desired pyrazolopyrimidobenzoxazines (**4**) (scheme-1) in good yields as yellow crystalline solids. The structures of **4** were established based on their IR, $^1$H NMR and Mass spectra. In the $^1$H NMR spectra compounds **4** exhibited typical signals around δ 6.26-6.4 (H pyrazole) 7.9-8.2 (CH=N) and 9.9-10.1(NH) apart from aromatic protons.

All the compounds reported in Table 1 were based on their correct elemental analyses and mass spectra of representative compounds. The reaction presumably proceeds by the initial attack by the amino group of pyrazole on the carbon bearing dimethyl amino group followed by elimination of dimethylamine and spontaneous cyclization of the ring nitrogen of pyrazole with imino chloride.




*a*) DMF / POCl3 *b*) Isopropanol-Acetic acid

**Scheme -1**

## Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra was recorded in KBr pellets. $^1$H NMR spectra on a varian 200MHz instrument with TMS as internal standard and chemical shifts expressed in δ ppm and Mass spectra Hewlett Packard Mass spectrometer operating at 70ev.

### General Procedure for the preparations of 3-Aryl-5-aminopyrazole[13] (3)

To a solution benzoylacetonitrile (0.01 mole) in isopropanol (50ml) hydrazine hydrate (0.015 mole) and a catalytic amount of acetic acid was added and the mixture was heated under reflux for 4-6 hrs. The reaction was monitored by TLC. At the end of the reaction solvent was removed **in Vacuo** and the residue was treated with ice water to give crude **3**. It was crystallized from methanol to give pure **3** as crystalline solids.

**2-(p-tolyl)pyrazolo[5',1':2,3]pyrimido[4,5-b][1,4]-benzoxazine 4**

To a cooled mixture of phosphorousoxychloride (4.6 ml, 0.06 moles) and dimethylformamide (4.6 ml, 0.06 moles), 3-oxo-2H-[1,4]-benzoxazine[14] (1, $R_1$=H, 3.0 gm, 0.02 moles) in $CHCl_3$(30ml) was added drop wise at 0-5°C and the mixture was stirred for 30 minutes at 0°C and for 2 hrs as reflux. It was then poured into cold water, organic layer was separated and washed with saturated $NaHCO_3$ solution, water and dried over anhydrous $Na_2SO_4$. Solvent was removed **in Vacuo**. To the residue 3-p-tolyl-5-aminopyrazole (**3**, $R_2$ = $CH_3$, 3.46 gm, 0.02 mole), isopropanol (30 ml) and acetic acid (1 mole) was added and the mixture was refluxed for 4-6 hrs till the completion of the reaction as followed by TLC (Ethylacetate : Hexane, 25 : 75) during which period yellow crystalline solid separates out. It was filtered washed with water, methanol and recrystallized from DMF to give pure **4c** 2.95 gm (47%): m.p: >300°C; IR(KBr): 3087, 1654, 1590cm$^{-1}$ ; ms (70ev) m/z ( %) 315(46)(M+1). $^1$H NMR(DMSO-$d_6$): δ 2.2(s, 3H, $ArCH_3$), 6.2(s, 1H, $C_3$-H), 6.7(m, 3H, ArH), 7.2(d, 2H, ArH), 7.7(m, 3H, ArH); 7.95(s, 1H, CH=N), 9.95(bs, 1H, NH). Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.61; H, 4.45; N, 17.83% found C, 72.45; H, 4.67; N, 17.56%).

Compounds **4a**, **4b** and **4d-n** reported in Table –1 were similarly prepared.

Table –1: Characterization data of compounds **4a**

| Compound | $R_1$ | $R_2$ | m.p °C | Yield % | Mol. Formula |
|---|---|---|---|---|---|
| **4a** | H | H | >300 | 43 | $C_{18}H_{12}N_4O$ |
| **4b** | H | $OCH_3$ | 270 | 45 | $C_{19}H_{14}N_4O_2$ |
| **4c** | H | $CH_3$ | >300 | 47 | $C_{19}H_{14}N_4O$ |
| **4d** | H | Cl | >300 | 51 | $C_{18}H_{11}ClN_4O$ |
| **4e** | F | H | >300 | 54 | $C_{18}H_{11}FN_4O$ |
| **4f** | F | $OCH_3$ | >300 | 52 | $C_{19}H_{13}FN_4O_2$ |
| **4g** | F | $CH_3$ | >300 | 49 | $C_{19}H_{13}FN_4O$ |
| **4h** | F | Cl | >300 | 47 | $C_{18}H_{10}FClN_4O$ |
| **4i** | Cl | H | >300 | 52 | $C_{18}H_{11}ClN_4O$ |
| **4j** | Cl | $OCH_3$ | 264 | 55 | $C_{19}H_{13}ClN_4O_2$ |
| **4k** | Cl | $CH_3$ | >300 | 56 | $C_{19}H_{13}ClN_4O$ |
| **4l** | $CH_3$ | H | >300 | 46 | $C_{19}H_{14}N_4O$ |
| **4m** | $CH_3$ | $OCH_3$ | >300 | 42 | $C_{20}H_{16}N_4O_2$ |
| **4n** | $CH_3$ | $CH_3$ | >300 | 49 | $C_{20}H_{16}N_4O$ |

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15. Representative $^1$H NMR Spectra: **4a** (DMSO-$d_6$): δ 6.4(s, 1H, $C_3$-H), 6.7(m, 3H, ArH); 7.3(m, 3H, ArH), 7.75(d, 2H, ArH); 8.0(s, 1H, ArH), 8.13(s, 1H, CH=N), 10.07(bs, 1H, NH); **4b** (DMSO-$d_6$): δ 3.8(s, 3H, $CH_3$), 6.32(s, 1H, $C_3$-H); 6.8-7.1(m, 5H, ArH); 7.65-7.9(m, 3H, ArH); 8.23(s, 1H, CH=N); 10.1(bs, 1H, NH); **4d** (DMSO-$d_6$): δ 6.3(s, 1H, $C_3$-H), 6.7(m, 3H, ArH); 7.0(m, 1H, ArH), 7.35(m, 2H, ArH), 7.8(m, 3H, ArH), 9.95(bs, 1H, NH); **4i** (DMSO-$d_6$): δ 3.8(s, 3H, $CH_3$); 6.2(s, 1H, $C_3$-H), 6.5-7.0(m, 5H, ArH); 7.7(d, 1H, ArH); 7.8(d, 1H, ArH); 7.9(s, 1H, CH=N), 10.0(bs, 1H, NH); **4g** (DMSO-$d_6$): δ 6.5-6.9(m, 3H, $C_3$-H & ArH), 7.5(m, 2H, ArH), 8.0(m, 3H, ArH); 8.42(s, 1H, CH=N); 10.3(bs, 1H, NH).

**Received on September 19, 2003.**