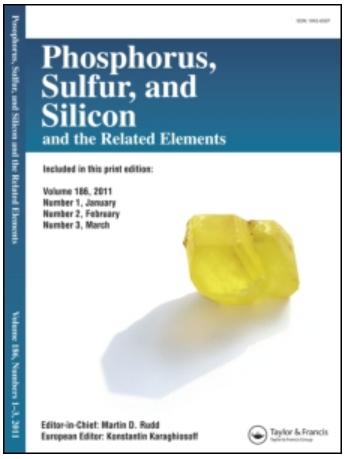


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# SYNTHESIS AND SOME REACTIONS OF NEW BENZO[*b*]PYRAN DERIVATIVES

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# SYNTHESIS AND SOME REACTIONS OF NEW BENZO[*b*]PYRAN DERIVATIVES

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Reaction of cinnamonitriles **1a**, **b** with 3-aminophenol (**2a**) or resorcinol (**2b**) gave the corresponding benzo[*b*] pyran derivatives (**3a–d**). Compound (**3a**) reacted with benzaldehyde to yield monobenzylideneamino derivative **4**. Also, reaction of (**3a**) with benzenesulsulphonyl chloride gave 2-amino-3-cyano-4-phenyl-7-phenylsulphonylamido-4*H*-benzo[*b*]pyran (**6**) which, in turn, underwent some reactions to produce new benzo[b]pyrano[6,5-*d*]pyrimidine derivatives (**7**, **9**) and (**10**).

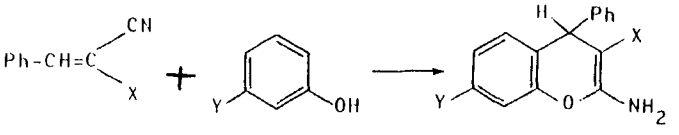
*Key words:* Synthesis, benzo[*b*]pyrans, sulphonamides, and benzopyranopyrimidines.



The importance of pyrans and benzopyrans in medicinal chemistry is well known. For example, some of them are used as antibiotics.[1] Others are reported to possess carcinogenic properties.[2,3] In view of this fact, we wish to report herein the synthesis of some new benzo[*p*]pyran derivatives.

Our approach to the synthesis of the title compounds started from cinnamonitriles (**1a**, **b**) which were readily reacted with 3-aminophenol (**2a**) or resorcinol (**2b**) in an ethanolic solution containing a catalytic amount of piperidine to give the corresponding benzo[*b*]pyran derivatives (**3a–d**) in good yields.

The chemical structures of compounds **3a–d** were confirmed by elemental analyses and spectral data. The IR spectrum of **3a** showed absorption bands at 3420, 3360, 3170 $cm^{-1}$ ($NH_2$) and at 2200 $cm^{-1}$ (C≡N), its $^1$H-NMR spectrum showed the following signals: $\delta$ 3.5 (s, 2H, $NH_2$-arom.), $\delta$ 4.7 (s, 1 H,pyran), $\delta$ 6.3 (s, 2 H, $NH_2$-pyran) and $\delta$ 6.7–7.6 (m, 8 H, Ar-H). The IR spectrum of **3b** showed an




**1a,b** **2a,b** **3a-d**

a; X = CN
b; X = $CO_2Et$

a, Y = $NH_2$
b, Y = OH

| | X | Y |
|---|---|---|
| a | CN | $NH_2$ |
| b | CN | OH |
| c | $CO_2Et$ | $NH_2$ |
| d | $CO_2Et$ | OH |

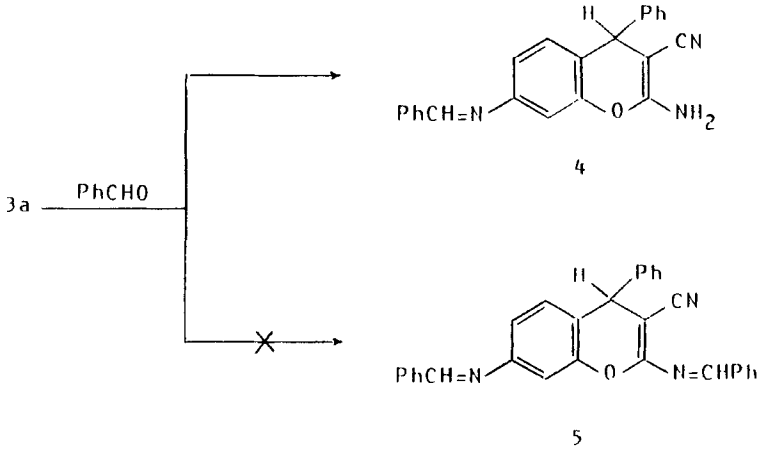
SCHEME 1

absorption band at 3460 $cm^{-1}$ (OH), 3430, 3330 $cm^{-1}$ ($NH_2$) and at 2200 $cm^{-1}$ (C≡N). The IR spectrum of **3c** showed absorption bands at 3420, 3310 $cm^{-1}$ ($NH_2$) and at 1650 (C=O). Also, the IR spectrum of **3d** exhibited absorption bands at 3420 $cm^{-1}$ (OH); 3310, 3220 $m^1$ ($NH_2$), and at 1650 (C=O). $^1$H-NMR spectrum showed the following signals: $\delta$ 1.1–1.3 (t, 3H, $CH_3$), $\delta$ 3.7–4.1 (q, 2 H, $OCH_2$), $\delta$ 4.8 (s, 1 H, pyran), $\delta$ 6.4–7.3 (m, 8 H, Ar-H), $\delta$ 7.5 (s, 2H, $NH_2$-pyran) and $\delta$ 9.5 (s, 1 H, OH). The reactivity of the two amino groups of benzo[*b*]pyran **3a** towards condensation reactions was tested. Thus, interaction of compound **3a** (0.01 mol) with benzaldehyde (0.02 mol) in refluxing *n*-butanol containing a few drops of piperidine afforded a crystalline compound whose elemental analyses and spectral data indicate that the structure was **4** not **5** (Scheme II). The IR spectrum showed absorption bands at 3420,3320 $cm^{-1}$ ($NH_2$), at 2200 $cm^{-1}$ (C≡N) and at 1640 $cm^{-1}$ (C=N); its $^1$H-NMR spectrum exhibited the following signals: $\delta$ 4.9 (s, 1 H, pyran), $\delta$ 7.3–8.2 (m, 15 H, Ar-H and $NH_2$-pyran) and $\delta$ 8.8 (s, 1 H, —CH=N—).

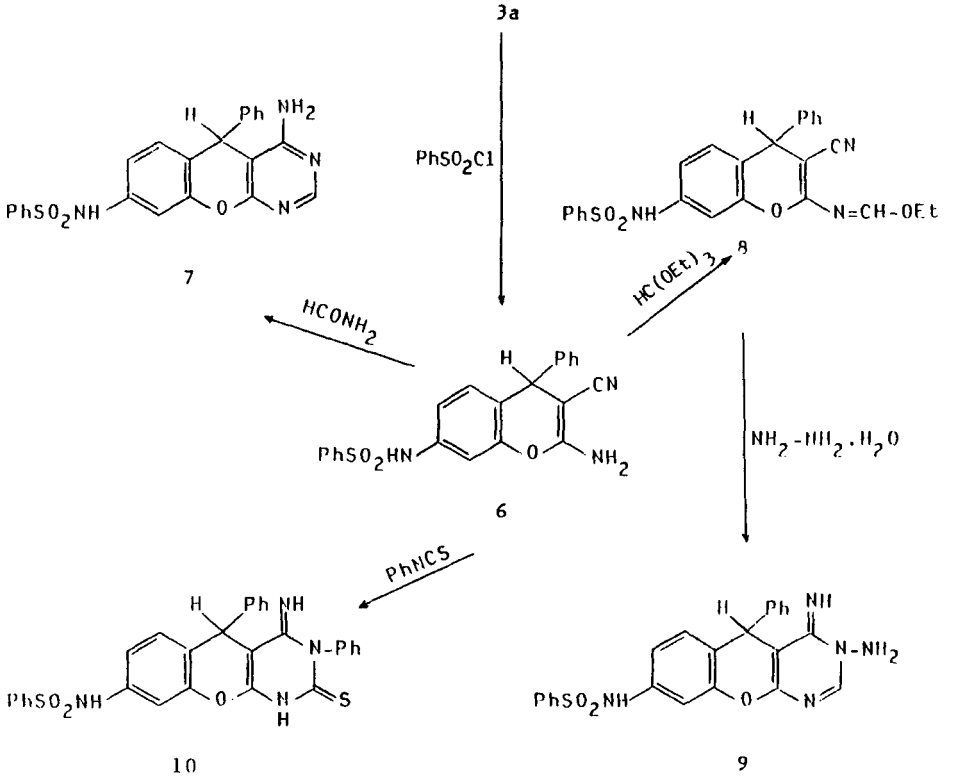
Sulfonamides have attracted special attention for their application as drugs for diseases like cancer,[4] tuberculosis,[5] diabetes[6] and malaria.[7] For this reason, we aimed to incorporate phenylsulfonamido group into a benzo[*b*]pyran structure hoping to obtain compounds **6**–**10** with good biological and medicinal importance.

2-Amino-3-cyano-4-phenyl-7-phenylsulfonamido-4*H*-benzo[*b*]pyran (**6**) was thought to be a suitable intermediate for the desired compounds. This compound **6** was synthesized by reacting equimolar amounts of **3a** and benzenesulfonyl chloride in pyridine (Scheme III). The IR spectrum of **6** showed absorption bands at 3460, 3360 $cm^{-1}$ ($NH_2$), 3150 $cm^{-1}$ (NH), 2200 $cm^{-1}$ (C≡N) and at 1330, 1155 $cm^{-1}$ ($SO_2$); its $^1$H-NMR spectrum showed the following signals: $\delta$ 4.6 (s, 1 H, pyran); $\delta$ 6.7 (s, 2 H, $NH_2$-pyran) and $\delta$ 7.1–7.8 (m, 14 H, Ar-H and NH-sulfonamide).

Reaction of sulfonamide derivative **6** with formamide gave 4-amino-5-phenyl-8-phenylsulfonamido-5*H*-benzo[*b*]pyrano[6,5-*d*]pyrimidine (**7**). Meanwhile, its condensation with triethyl orthoformate, in refluxing acetic anhydride afforded methanimidate derivative **8** which upon treatment with hydrazine hydrate, gave 3-amino-




SCHEME II




SCHEME III

4-imino-5-phenyl-8-phenylsulphonamido-3,4,5-trihydrobenzo[*b*]pyrano-[6,5-*d*]pyrimidine (**9**) in low yield (Scheme III).

The chemical structure of compounds **7**, **8** and **9** was elucidated on the basis of their elemental and spectral analyses. The IR spectrum of **7** revealed the presence of three absorption bands at 3440, 3340 $cm^{-1}$ ($NH_2$), and 3140 (NH) and the absence of the characteristic band at 2200 $cm^{-1}$ due to the nitrile group. The IR spectrum of **8** showed absorption bands at 3260 $cm^{-1}$ (NH) and at 2200 $cm^{-1}$ (C≡N). The IR spectrum of **9** showed the presence of absorption bands at 3440, 3340 $cm^{-1}$ ($NH_2$), and 3140 (NH), 1640 (C≡N), exocyclic) and the absence of the characteristic band due to nitrile group. Its $^1$H-NMR spectrum exhibited the following signals: $\delta$ 4.7 (s, 1 H, pyran); $\delta$ 5.5 (s, 2 H, $NH_2$-pyrimidine); $\delta$ 6.6–7.5 (m, 14 H, Ar-H and NH sulfonamido); $\delta$ 7.8 (s, 1 H, pyrimidine) and $\delta$ 8.1 (s, 1 H, NH).

Refluxing of the sulfonamide derivative **6** with phenyl isothiocyanate in pyridine for a long period produced 3,5-diphenyl-4-imino-1,2,3,4,5-pentahydro 8-phenylsulfonamido-2-thioxo-benzo[*b*]pyrano[6,5-*d*]pyrimidine (**10**) in moderate yield (Scheme III). The identification of this compound was based on its elemental and spectral analyses. The IR spectrum revealed the presence of two absorption bands at 3400, 3160 $cm^{-1}$ (NH) and the absence of a nitrile band near 2200 $cm^{-1}$.

## EXPERIMENTAL

All melting points are uncorrected and measured on a Fisher Johns melting point apparatus. Elemental analyses were performed on a Perkin Elmer 240 C elemental analyzer. IR Spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using KBr wafer technique. $^1$H-NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer using DMSO-$d_6$ as a solvent and TMS as the internal standard.

*Reaction of cinnamonitriles* **1a,b** *with 3-aminophenol* (**2a**) *or resorcinol* (**2b**); *preparation of benzo[b]pyrans* **3a–d**: *General procedure.* To a mixture of cinnamonitrile derivative **1a, b** (0.01 mol) and 3-aminophenol or resorcinol (**2b**) (0.01 mol) in absolute ethanol (50 ml), was added a few drops of piperidine. The resulting mixture was heated under reflux for 5 hr, and left to cool. The precipitated product was collected by filtration and recrystallized from the proper solvent. In this way the following compounds were prepared:

*a) 2,7-Diamino-4-phenyl-4H-benzo[b]pyran-3-carbonitrile* (**3a**): It was obtained from α-cyanocinnamonitrile (**1a**) and 3-aminophenol (**2a**) in 90% yield and recrystallized from acetic acid, m.p. 244–6°C.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96%
Found: C, 72.82; H, 4.92; N, 15.73%.

*b)2-Amino-7-hydroxy-4-phenyl-4H-benzo[b]pyran-3-carbonitrile* (**3b**): It was obtained from α-cyanocinnamonitrile (**1a**) and resorcinol (**2b**) in 85% and recrystallized from acetic acid; m.p. 246–8°C.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60%
Found: C, 72.63; H, 4.43; N, 10.44%.

*c) Ethyl-2,7-diamino-4-phenyl-4H-benzo[b]pyran-3-carboxylate* (**3c**): It was obtained from ethyl α-cyanocinnamate (**1b**) and 3-aminophenol (**2a**) in 60% yield and recrystallized from ethanol, m.p. 218–20°C.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.67; H, 5.80; N, 9.02%
Found: C, 69.42; H, 5.63; N, 9.23%.

*d) Ethyl 2-amino-7-hydroxy-4-phenyl-4H-benzo[b]pyran-3-carboxylate* (**3d**): It was obtained from ethyl α-cyanocinnamate (**1b**) and resorcinol (**2b**) in 55% yield and recrystallized from ethanol, m.p. 234–6°C.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.50; N, 4.50%
Found: C, 69.11; H, 5.32; N, 4.31%.

*Condensation of compound* **3a** *with benzaldehyde: preparation of compound 4:* To a suspension of **3a** (0.01 mol) and benzaldehyde (0.02 mol) butanol (50 ml), a few drops of piperidine was added. The resulting mixture was refluxed for 2 hr. The crystalline product that precipitated on cooling was collected and recrystallized from acetic acid as pale yellow crystals. This product was identified as 2-amino-7-benzylideneamino-4-phenyl-4*H*-benzo[*b*]pyran-3-carbonitrile (**4**), in 87%; m.p. 198–200°C.

Anal. Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.87; N, 11.95%
Found: C, 78.32; H, 4.73; N, 11.73%.

*3-Amino-4-phenyl-7-phenylsulphonamido-4H-benzo[b]pyran 3-carbonitrile* (**6**): A mixture of **3a** (0.01 mol) and benzenesulphonyl chloride (0.01 mol) in dry pyridine (25 ml) was heated on a water bath for one hour. After cooling, the reaction mixture was poured into cold water (40 ml) whereby a white solid separated. It was filtered off and crystallized from acetic acid to give **6** in (70%), m.p. 248–50°C.

Anal. Calcd. for $C_{22}H_{17}N_3O_3S$: C, 65.50; H, 4.25; N, 10.42; S, 7.95%
Found: C, 65.21; H, 4.11; N, 10.23; S, 7.75.

*4-Amino-5-phenyl-8-phenylsulphonamido-5H-benzo[b]pyrano-[6,5-d]pyrimidine* (**7**): A solution of compound **6** (0.01 mol) in formamide (15 ml) was heated under reflux for one hour. After cooling, the precipitated solid was filtered off, washed with ethanol and recrystallized from acetic acid to give **7** in (60%), m.p. >300°C.

Anal. Calcd. for $C_{22}H_{18}N_4O_3S$: C, 64.18; H, 4.21; N, 13.02; S, 7.44%
Found: C, 63,89; H, 4.11; N, 13.21; S, 7.32%.

*Ethyl N-(3-cyano-4-phenyl-7-phenylsulphonamido-4H-benzo[b]pyran-2-yl)methanimidate* (**8**): A mixture of **6** (0.01 mol) and triethyl orthoformate (2 ml) in acetic anhydride (15 ml) was refluxed for 3 hr. On cooling, the solid product was collected and recrystallized from ethanol to give compound **8** in (65%), m.p. 218–20°C.

Anal. Calcd. for $C_{25}H_{21}N_3O_4S$: C, 65.45; H, 4.61; N, 9.15; S, 6.98%
Found: C, 65.13; H, 4.42; N, 8.92; S, 6.73%.

*3-Amino-4-imino-5-phenyl-8-phenylsulphonamido-3,4,5-trihydrobenzo[b]pyrano[6,5-d]pyrimidine* (**9**): To a suspension of compound **8** (0.003 mol) in benzene (40 ml), hydrazine hydrate (12 ml, 30%) was added. The reaction mixture was stirred at room temperature for 6 hr. The product formed was filtered off and recrystallized from ethanol to give **9** in (25%), m.p. >300°C.

Anal. Calcd. for $C_{23}H_{19}N_5O_3S$: C, 62.00; H, 4.30; N, 15.72; S, 7.20%
Found: C, 61.88; H, 4.11; N, 15.63; S, 6.98%.

*3,5-Diphenyl- 4 -imino-8 -1,2,3,4,5-pentahydro-8 -phenylsulphonamidobenzo[b]pyrano[6,5-d]pyrimidine* (**10**): A mixture of **6** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in dry pyridine (20 ml) was heated under reflux for 20 hr and allowed to cool. The reaction mixture was poured into cold water (40 ml), whereby a solid product was separated. It was collected and recrystallized from dioxane to give compound **9** in (60%), m.p. >300°C.

Anal. Calcd. for $C_{29}H_{22}N_4O_3S_2$: C, 64.67; H, 4.11; N, 10.40; S, 11.90%
Found: C, 64.42; H, 3.99; N, 10.22; S, 11.63%.



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