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5-Phenylpyridazinones-A serendipitous route from coumarins

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ABSTRACT

A new route of the ring transformation has been discovered during the reaction of 4-bromomethylcoumarins with hydrazine hydrate leading to the formation of pharmacologically important pyridazinones in a single step with very high yields. These so obtained pyridazinones have the potential for further functional group interconversions.

N-containing heterocycles are of biological importance and design of newer strategies for their synthesis is an important area of research in organic chemistry.[1] Pyridazines are an important class of nitrogen heterocycles, which are known for a wide range of biological activities.[2,3] Introduction of an aryl moiety on the pyridazinone skeleton has resulted in a large number of derivatives exhibiting a plethora of promising pharmacological activities. For example, 6-phenyl pyridazin-3-ones have been found to be useful as cardiotonic,[4] *anti*-hypertensive,[5] antinociceptive agents,[6] as well as platelet aggregation inhibitors[7–9] and their acid–base behaviour has been analyzed theoretically.[10] 5-Phenyl pyridazinones are less common and have been patented[11] for their pronounced β-adreno-receptor antagonist activity. Introduction of a phenyl ring into the pyridazine scaffold has been achieved by Grignard,[12] Sonogoshira,[13] Stille[14] and by Suzuki[15] coupling and palladium[16] catalyzed reactions. In view of the biological importance and the complexity of the existing methods, it is obvious that a simpler method is necessary for the synthesis of aryl pyridazinones.

We have been exploring the reactivity of coumarins to construct biologically active oxygenated bi-heterocycles,[17] unsymmetrical triheterocycles[18] and pentacyclic heterocycles[19] as well. An attempted reaction of 4-bromomethylcoumarins **1** with hydrazine hydrate in refluxing ethanol resulted in a product which did not correspond to the allylic substitution by aromatic amines.[20] Interestingly, the product obtained did not show any band around 1700 cm^{-1} in the IR spectrum, indicating the absence of coumarin carbonyl. Instead, a band around 1660 cm^{-1} characteristic of amides was found. Furthermore, the ^1H NMR showed no signals in the region of 3–6 ppm, which indicated a clear absence of the

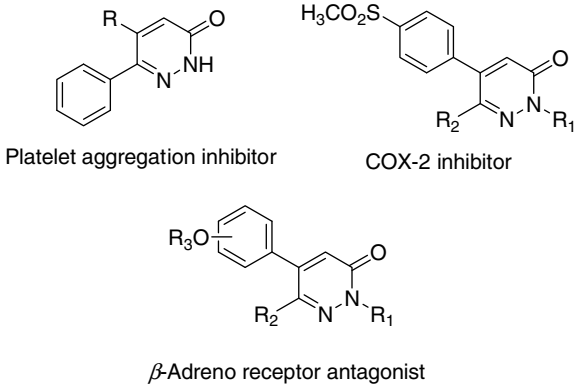

Figure 1. Biologically active phenyl pyridazin-3-ones.

C_4-methylene protons, observed around 4.6 ppm in 4-bromomethyl-coumarins (Fig. 1).

These spectral observations led us to think in terms of a possible ring opening of the lactone followed by a ring closure involving the thermodynamically favoured amide bond formation and aromatization leading to pyridazinones **2**. When the reaction of hydrazine hydrate with **1** was carried out in refluxing acetic acid, a different product was obtained. In the IR spectrum, this compound exhibited two bands around 1650 cm^{-1} and 1700 cm^{-1}. In the ^1H NMR, an extra upfield signal around 2.4 ppm was observed corresponding to acetyl protons. This led us to infer that in acetic acid the product is N-acetylated pyridazinone **3**.

With a view to introduce a phenyl group on the N-2 of pyridazinone, we tried the reaction of phenyl hydrazine with 4-bromomethyl coumarins **1**. This reaction resulted in the expected nucleophilic substitution similar to our earlier work on other

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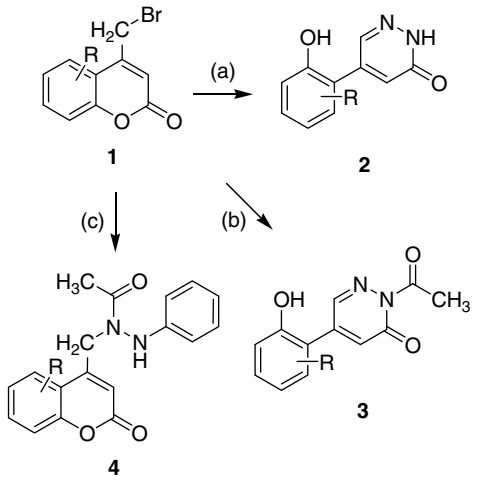

Scheme 1. Reagents and conditions: (a) NH_2–NH_2/EtOH, reflux; (b) NH_2–NH_2/AcOH, reflux; (c) Ph–NH–NH_2/AcOH, reflux.

Table 1
Pyridazinones synthesized from coumarins

Entry	R	Compound	Mp (°C)	Yield (%)
1	5-CH_3	**2a**	136–138	78
2	4-CH_3	**2b**	140–142	75
3	5,6-Benzo	**2c**	161–163	70
4	3,4-Benzo	**2d**	152–154	68
5	5-Br	**2e**	147–149	64
6	5-Cl	**2f**	208–210	70
7	4-Cl	**2g**	178–180	75
8	5-OCH_3	**2h**	168–170	78
9	5-CH_3	**3a**	184–186	72
10	4-CH_3	**3b**	190–192	68
11	5,6-Benzo	**3c**	170–172	66
12	3,4-Benzo	**3d**	185–187	66
13	5-Br	**3e**	190–192	71
14	5-Cl	**3f**	184–186	70
15	5-OCH_3	**3h**	275–277	69
16	4-Cl	**3g**	170–172	65

Acetylation of the initially formed hydrazide.

nitrogen nucleophiles[20] and was carried out in acetic acid, which resulted in N-acetylated product **4** (Scheme 1).

To the best of our knowledge there are no reports on the transformations of coumarins to pyridazines. Recently, it has been observed that tricyclic trifluoromethyl dihydro thienosulfonyl coumarins obtained in a multistep sequence reacted with hydrazine hydrate to yield 3-hydrazino-6-*o*-hydroxy phenyl pyridazines.[21] A probable mechanistic pathway for the formation of pyridazines is given in Scheme 2.

Nucleophilic attack of hydrazine hydrate on the lactone carbonyl and the C-4 methylene is equally probable, since excess of this reagent is employed and would produce a hydrazino hydrazide. Hydrazine hydrate and other double nucleophiles like amidines and thiourea are known to bring about similar ring opening of coumarins which have resulted in the formation of *o*-hydroxyphenyl substituted pyrazoles[22] and pyrimidines.[23] Further, an intramolecular nucleophilic attack of the hydrazine on the carbonyl group of the hydrazide followed by the expulsion of hydrazine results in the intermediates **5** which undergo in situ dehydrogenation to give pyridazinones **2**. In acetic acid medium the corresponding intermediate can result from the acetylation of the initially formed hydrazide).

The proposed acetylation of hydrazides is in agreement with the recent literature reports.[24] Further, intramolecular nucleophilic attack on the carbonyl group and elimination of acetic acid hydrazide would result in a similar intermediate **5a**. Dehydrogenation of the intermediate **5a** can lead to the generation of aromatic pyridazinones **3**. Intra-molecular expulsion of acetic acid hydrazide has been proposed in the formation of 3-hydrazinopyridazinones.[21] The driving force for this nucleophilic substitution, followed by ring opening and ring closure (SNRORC) seems to be the stability of the aromatic pyridazinones.

In conclusion, the present work has demonstrated a novel transformation that can be used as a new method for the synthesis of 5-substituted phenyl pyridazin-3-ones.[25] Ease of preparing the starting materials and simple reaction conditions provided a new route for the introduction of the aryl moiety in pyridazinones. The functional groups generated in this reaction have the potential for further transformations, and hence this reaction has a wide range of applicability.

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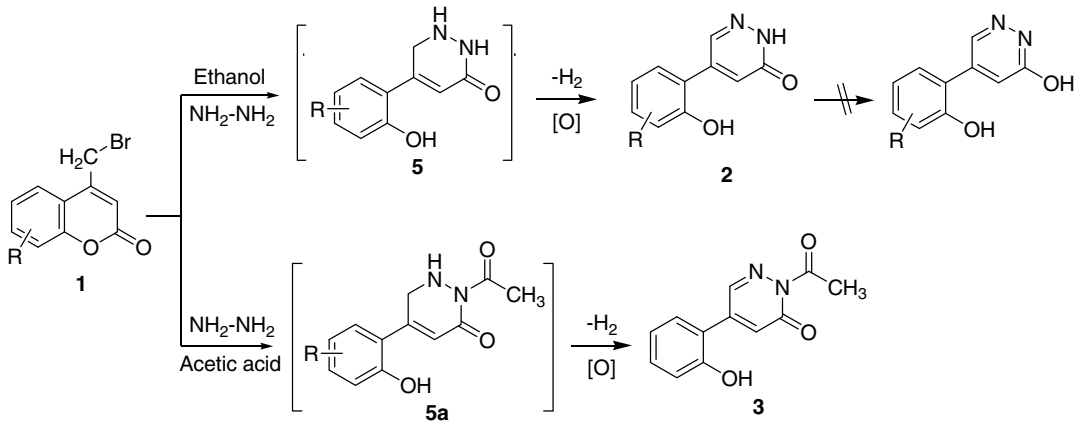

Scheme 2. Mechanism of formation of pyridazinones.

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25. *Typical procedures*: *Synthesis of 5-(2-hydroxy-5-methyl-phenyl)-2H-pyridazine-3-one* (**2a**). A mixture of 6-methyl-4-bromomethylcoumarin (**1a**, 0.5 g, 0.002 mmol) was refluxed with hydrazine hydrate (99%) (0.5 g, 0.01 mmol) in ethanol (10 ml) for 2 h. The reaction mixture was cooled and poured on ice-cold water, and separated solid was filtered off. It was washed several times with aqueous ethanol, dried and recrystallized from ethanol to give **2a** as a colourless crystalline solid (0.31 g, 78%), mp 138–140 °C; IR (KBr) cm^{-1} 3191 (br), 1661; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.41 (s, 3H, CH_3), 6.23 (s, (br), 2H, D_2O exchangeable, NH and OH), 6.43 (s, 1H, C4–H of pyridazine), 8.18 (s, 1H, C6–H of pyridazine), 7.13 (s, 1H, C6′–H), 7.20 (d, 1H, C4′-H, J = 8.6 Hz), 7.35 (d, 1H, C3′–H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 22, 114, 121, 122, 128, 129, 130, 148, 154.3, 154.6, 162; mass (EI) m/z M^+ 202 (8%), M–CO 174 (100%); Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.38; H, 4.95; N, 13.89. Identical procedure was used in all the cases (Table 1). *Synthesis of 2-acetyl-5-(2-hydroxy-5-methyl-phenyl)-2H-pyridazine-3-one* (**3a**). A mixture of 6-methyl-4-bromomethylcoumarin (0.5 g, 0.002 mmol) was refluxed with hydrazine hydrate (0.5 g, 0.01 mmol) in glacial acetic acid (10 mL) for 1 h. The crystalline product separated was filtered off and washed with aqueous ethanol and recrystallized from ethanol to give colourless solid (0.30 g, 64%), mp 186–188 °C; IR (KBr) cm^{-1} 3400 (br), 1701, 1654; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.43 (s, 3 H, C5′–CH_3), 2.46 (s, 3H, $NCOCH_3$), 7.49 (d, 1H, J = 8.0 Hz, C3′–H of phenyl), 7.98 (d, 1H, J = 8.0 Hz, C4′–H of phenyl), 8.21 (s, 1H, C6–H of pyridazine), 6.15 (s, 1 H, C4–H of pyridazine), 7.22 (s, 1 H, C6–H of pyridazine), 7.28 (s (br), 1 H, OH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$,75 MHz, TMS) δ 17, 21, 120, 122, 123, 133, 126, 127, 144, 148, 157, 168, 169; mass m/z M^+ 244 (10%), M–CO, 216 (25%), 43 (100%); Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.97; H, 4.99; N, 11.44. Similar procedure was used in all other cases (Table 1). *Synthesis of 4-[2′-acetylphenylhydrazino)-methyl]-5,6-benzocoumarin* (**4**). A mixture of 6-methyl-4-bromomethylcoumarins (0.7 g, 0.002 mmol) and phenyl hydrazine(0.2 ml, 0.002 mmol) was refluxed in glacial acetic acid (10 ml) for 4 h at a temperature of 120 °C in an oil bath. The reaction mixture was concentrated and poured over crushed ice (100 ml). The solid separated was filtered, dried and recrystallized from ethanol to give colourless solid (0.65 g, 65 %); mp 222–224 °C. IR (KBr) cm^{-1} 3298, 2990, 1696, 1640; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.11 (s, 3H, $NCOCH_3$), 5.31 (s, 2H, CH_2–N), 6.57 (s, C3–H of coum), 8.34 (s (br), 1H, NH), 6.75–8.30 (m, 11H, Ar–H).; mass m/z 358 (12%), 315 (10%), 77 (100%). Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.77; H, 5.02; N, 7.86.