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A mild, one-pot synthesis of 3-cyano-4-benzopyrones from 2-hydroxyacetophenones

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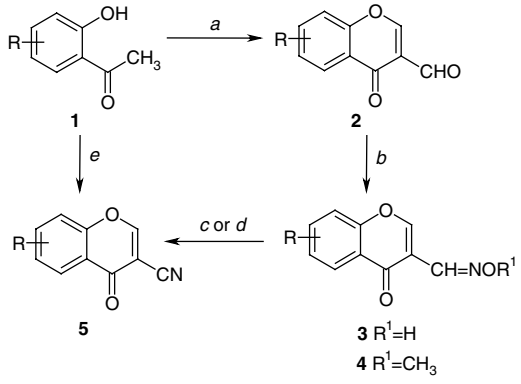
Abstract—A simple one-pot synthesis of 3-cyano-4-benzopyrones directly from 2-hydroxyacetophenones using mild conditions is reported herein.

In connection with developing a library of benzopyrones, we became interested in a general and practical synthesis of 3-cyano-4-benzopyrones. These are important intermediates in the synthesis of therapeutically useful anti-allergic drugs such as Amlexanox.[1] Cyanobenzopyrones are also useful intermediates in the synthesis of benzopyranopyridines with anti-inflammatory activity.[2] They are also reported as useful dienophiles in [4+2] cycloaddition reactions and in the construction of the tricyclic ring of Arisugacin, which is a selective inhibitor of acetylcholine esterase.[3] In view of the synthetic potential of these compounds, and in continuation of our work on benzopyrone derivatives,[4] we herein report a one-pot synthesis of 3-cyano-4-benzopyrones directly from 2-hydroxyacetophenones under mild conditions.

3-Cyano-4-benzopyrones are generally synthesized in three steps starting from 2-hydroxyacetophenones. Thus, Vilsmeier–Haack reaction on 2-hydroxyacetophenones **1** gives 3-formylbenzopyrones **2** in 40–70% yields.[5] These on reaction with hydroxylamine hydrochloride in refluxing ethanol give the corresponding oximes **3**. These oximes undergo facile dehydration to give 3-cyano-4-benzopyrones **5** in 50–70% yields[6] (Scheme 1). The dehydration of oximes is one of the most common ways of preparing 3-cyano-4-benzopyrones and a variety of dehydrating agents such as



Scheme 1. Reagents and conditions: (a) $DMF/POCl_3$; (b) $NH_2OR^1{\cdot}HCl/EtOH$; (c) EtOH/HCl 'or' sodium formate/formic acid 'or' acetic anhydride; (d) benzene/H_2SO_4; (e) $DMF/POCl_3/DCM/NH_2OH{\cdot}HCl$.

hydrochloric acid,[7] sodium formate in formic acid[8] and acetic anhydride[9] have been used. However these methods suffer from certain disadvantages such as the necessity for isolation of the intermediate 3-formylbenzopyrones **2** and corresponding oximes **3**. The dehydration step requires strongly acidic conditions and long reaction periods. In some cases, due to the poor solubilities of the isolated oximes, the yields are very low in the dehydration step. In view of these difficulties Hsung et al.[10] recently reported a practical synthesis of 3-cyano-4-benzopyrones via an acid catalyzed elimination of the corresponding *O*-methyloximes. However this method requires the preparation of the *O*-methyloximes **4** from **2** using expensive *O*-methoxylamine

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Table 1. Physical data on the 3-cyano-4-benzopyrones[11]

Entry	R	Mp, °C (lit., °C)	Yield, %
5a	H	175–177 (177–178)[8]	61
5b	6-CH_3	151–153 (152–153)[6]	55
5c	6-CH_3CH_2	122–124 (123–124)[6]	51
5d	6-$(CH_3)_2CH$	117–119 (118–120)[6]	52
5e	6-Br	218–220 (216–219)[8]	54
5f	6-Cl	210 (210–213)[6]	52
5g	6-F	172–174 (172–174)[10]	69
5h	6,8-diCl	176 (169–174)[10]	72
5i	6,7-diCH_3	230–232 (232–235)[8]	54
5j	6-Cl,7-CH_3	206–208 (207–208)[10]	51

hydrochloride and subjecting the *O*-methyloxime to elimination in refluxing benzene in the presence of sulfuric acid for long reaction periods with low overall yields.†

In view of these observations and the synthetic utility of 3-cyano-4-benzopyrones, we report herein a one-pot mild procedure for the synthesis of 3-cyanobenzopyrones. Thus, various substituted 2-hydroxyacetophenones were subjected to the Vilsmeier–Haack reaction, with dimethylformamide and phosphorus oxychloride at 0 °C and the reaction mixture subsequently treated in situ with hydroxylamine hydrochloride at room temperature[11] to provide the desired 3-cyanobenzopyrones in fair to good yields (**5a**–**j**, Scheme 1, Table 1). All the compounds were characterized by IR, and ^{1}H NMR, and the melting points were compared with authentic samples. It is presumed that the chloroiminium salt $[(CH_3)_2N^+{=}CHCl{\cdot}Cl^-]$ formed under the reaction conditions acts as a dehydrating agent[12] in the conversion of the oximes to cyanobenzopyrones. In support of this, in a separate experiment, when the oximes **3** were treated with the Vilsmeier reagent in dichloromethane at room temperature, 3-cyanobenzopyrones were obtained in good yields.

In summary, we have developed an efficient, simple and one-pot procedure for the synthesis of cyanobenzopyrones directly from 2-hydroxyacetophenones with short reaction times and under mild conditions. The preparative utility and generality of the present procedure is evident from the synthesis of various cyanobenzopyrones (Table 1).

† The overall yields from 2-hydroxyacetophenone to 3-formylbenzopyrone and oxime to 3-cyanobenzopyrone are in the range of 26–46%.

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11. Typical procedure (**2a**): A mixture of dimethylformamide (310 mL, 4.0 mol) and phosphorus oxychloride (186.5 mL, 2.0 mol) was stirred at 0 °C for 30 min. To this solution 2-hydroxyacetophenone (**1a**, 68 g, 0.5 mol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 4 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane (680 mL). The mixture was cooled to 0 °C and hydroxylamine hydrochloride (104.25 g, 1.5 mol) in DMF (300 mL) was added and the mixture stirred at room temperature for 3–4 h. After the reaction was complete, as indicated by TLC, it was diluted with cold water (500 mL) and extracted with DCM (2 × 100 mL). The combined organic phases were washed with water (2 × 100 mL), saturated $NaHCO_3$ solution (10 mL) and finally with water (100 mL). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residual solid was directly crystallized from methanol to give **2a** (52.3 g, 61%). The melting point and IR and ^{1}H NMR spectra were compared with an authentic sample.
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