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Iodine catalyzed simple and efficient synthesis of antiproliferative 2-pyridones

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ABSTRACT

A simple and efficient method for the selective synthesis of 2-pyrdones from 4*H*-pyrans using iodine as catalyst and ethanol as solvent was developed. The present method is equally effective for both aromatic and hetero aromatic ring containing 4*H*-pyrans. The compatibility with various functional groups, mild reaction conditions, high yields and application of inexpensive, readily and easily available iodine as catalyst and formation of 2-pyridones as major products are the advantages of the present procedure. In vitro antiproliferative activity of the final synthesized compounds was evaluated with four different human cancer cell lines (Lung adenocarcinoma-A549, Hepatocarcinoma-HepG2, Breast carcinoma-MCF-7 and Ovarian carcinoma-SKOV3) and normal human lung fibroblast cell line (MRC-5). Compounds **2b** showed better inhibition against MCF-7, HepG2 and A549 cell lines (IC_{50} 8.00 ± 0.11, 11.93 ± 0.01 and 15.85 ± 0.04 μM, respectively) as compared with doxorubicin and also **2e** showed moderate inhibition against MCF-7, HepG2 (IC_{50} 9.32 ± 0.21 and 20.22 ± 0.01 μM, respectively, cell lines, respectively) as compared with doxorubicin. As many clinically used antiproliferative agents induce apoptosis in cancer cells hence, the 2-pyridone analogues were also tested for their ability to induce apoptosis in MCF-7 cells using the caspases-3 and -9 assays.

2-Pyridone moiety is present in a large number of natural and synthetic bioactive molecules. 2-Pyridones and their analogues have attracted considerable interest recently because of their antiproliferative, antiviral and anti-inflammatory properties.[1–3] The drugs Amrinone[4] (I) and Milrinone (II)[5] used as cardiotonic agents for the treatment of heart failure contains 2-pyridone moiety in their structure. Recently, 2-pyridone derivative (III) has been identified as a specific non nucleoside reverse transcriptase inhibitor of human immuno deficiency virus-1 (HIV-1).[6] 2-Pyrdiones are important intermediates in some synthetic approaches for the synthesis of camptothecin family of antitumor agents. 2-Pyridones and their analogues are targeted compounds in a large number of drug discovery programs related to cancer and inflammatory disorders such as CDK4 and FGFR inhibitors and p38 inhibitors (IV–V)[7–10], respectively (Fig. 1). Hence, synthesis of 2-pyridones has gained much chemical and pharmaceutical importance in recent years.

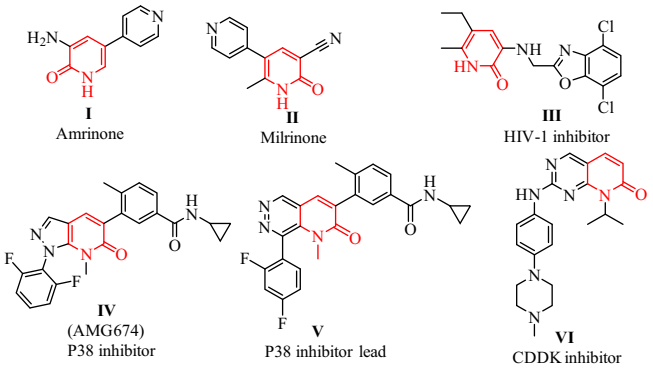

Figure 1. Pyridin-2-one containing compounds of medicinal interest.

So far, only a few methods have been reported for one-pot synthesis of 2-pyridones by condensation of three components, an aldehyde, a β-ketoester and cyano acetate or cyano acetamide under acidic or basic conditions such as HNO_2, H_2SO_4, Piperidine, NH_4OAc, ZnO, $SOCl_2$ etc.[11–14] However, these methods suffers from

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very low yields with a mixture of 2-pyridones as minor and 3,4-dihydro-2-pyridones as major products.

Subsequently, several multistep methods have been reported with somewhat higher yields to synthesize 2-pyridones. In general, these methods involve synthesis of 4*H*-pyrans by condensation of three components using an aldehyde, a β-ketoester and malononitrile in first step, then conversion of the 4*H*-pyrans to 2-pyridones in second step. Several reagents have been reported for the synthesis of 4*H*-pyrans like Al_2O_3/KF, metal oxide nano particles, ionic liquids, solid supported catalysts etc.,[15–20] but for the conversion of 4*H*-pyrans to 2-pyridones, very few methods were reported under strong acidic conditions like H_2SO_4, HNO_2, and mixture of HNO_2 and H_2SO_4 with very low yields with 2-pyridones as minor and 3,4-dihydro-2-pyridones as major or exclusive products.[21–24] However, many of the reported one-pot as well as multistep methods have significant drawbacks such as expensive and toxic reagents, incompatibility with other functional groups, long reaction times, strong acidic conditions, tedious workup procedures and low yields etc. Thus, there is a need for simple, efficient, economic and eco-friendly procedure to synthesize 2-pyridones under mild conditions.

As a part of our ongoing work of novel methodologies for the synthesis of bioactive molecules, we were interested to synthesize 2-pyridone derivatives due to their biological importance. Recently, iodine has received considerable attention as an inexpensive, readily available mild and efficient catalyst for various organic reactions such as Suzuki-Miyaura coupling reaction,[25] Michael addition,[26,27] protection[28] and deprotection[29] of acetals, synthesis of bis-indols,[30] β-keto enol ethers,[31] chalcones,[32] and quinolines[33] etc. Here, we report a simple, efficient and mild method for the synthesis of 2-pyridones selectively from 4-H pyrans using iodine as catalyst.

It is well known that cancer deaths are more than those caused by AIDS, malaria, and tuberculosis combined. The drugs like Indomethacin, doxorubicin has created some hope for the life of cancer patients. However, the chemotherapeutic agents under present use suffer from various drawbacks. This undoubtedly underscores the need of developing new chemotherapeutic agents for more effective and economical treatment of cancer.

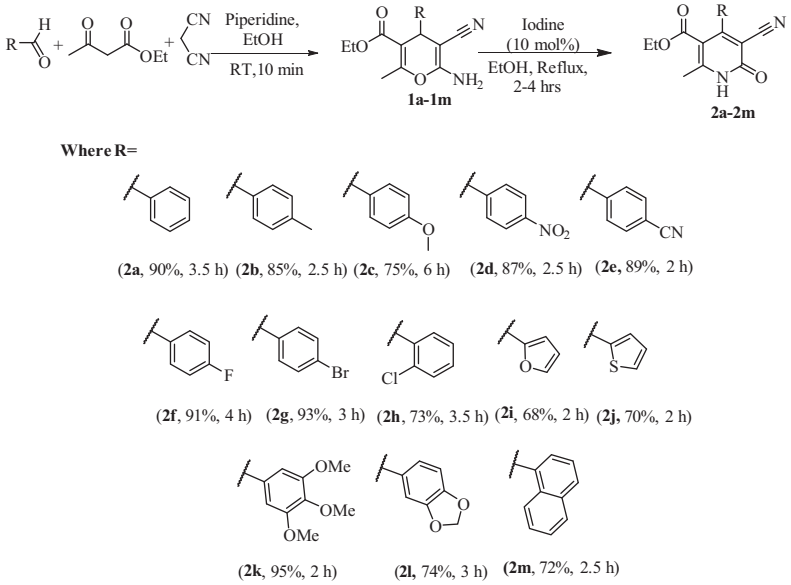
In this Letter, we report a novel methodology for the synthesis of various 2-pyridones and the resulting analogues were also screened for in vitro antiproliferative activity using four different human cancer cell lines and normal human cell line. Because of many clinically used antiproliferative agents induce apoptosis in cancer cells,[34] we tested the 2-pyridone analogues for their ability to induce apoptosis in MCF-7 cells using the caspases-3 and 9 assays.

Initial attempt of one pot synthesis of 2-pyridones by condensation of an aldehyde, a β-keto ester and malononitrile with either molecular Iodine (I_2) or metal iodides like HgI, NaI, CuI and KI was not successful. Then two step method was devised in which first 4*H*-pyrans were prepared by condensation of an aldehyde, malononitrile and ethylacetoacetate as per the reported methods[35,36] but with slight modifications. In the second step, different 2-pyridones were synthesized selectively from the 4*H*-pyrans under reflux conditions in the presence of iodine as catalyst and ethanol as a solvent (Scheme 1).

The reaction proceeded via iodination at benzylic position of 4*H*-pyran in the presence of iodine at 80 °C to form intermediate **I**, which further underwent formation of oxonium ion **II** by leaving iodide ion and shifting of the double bond. Further rearrangement took place by instantaneous opening of pyran to give pyridonium ion **III** and finally removal of hydrogen iodide (HI) resulted 2-pyridone (Fig. 2).

The method was also optimized with respect to different catalysts, solvents and catalyst load etc. It was observed that molecular iodine and ethanol are the most effective catalyst and solvent in terms of yields and reaction times than other catalyst sources such as HgI, NaI, CuI and KI (Table 1) and solvents such as toluene, DCM, dichloroethane, $CHCl_3$, acetone, methanol, ethanol, CH_3CN, THF, propane-2-ol, ethanol + water, etc (Table 2, entry 4). When catalyst load increased from 2.5 to 10 mol%, yields were steadily increased and thereafter no significant change was observed from 10 to 20 mol%. But, further increase in catalyst load, led to significant decrease in the yields of the final product. This may be due to the coagulation of I_2.

The above methodology was tolerant to a wide variety of electron releasing as well as electron withdrawing 4*H*-pyrans to give the corresponding products (**2a**–**m**) in excellent yields selectively. The reaction with ethyl-6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-4*H*-pyran-3-carboxylate, ethyl-6-amino-5-cyano-4-(4-bromophenyl)-2-methyl-4*H*-pyran-3-carboxylate and ethyl-6-amino-



Scheme 1. Iodine catalyzed simple and efficient synthesis of 2-pyridones.