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Synthesis and characterization of substituted pyridones using isatoic anhydride

Pande G. B.[1] and Kendre K.L.[2]

[1]Department of Chemistry, Netaji Subhashchandra Bose College,Nanded

2.Yeshwant Mahavidyalaya,Nanded

ABSTRACT:

The reaction of dehydroacetic acid (I) (3-acetyl-4-hydroxy-6-methyl-2-pyrone) with amine give 4-pyridones (IV) has been known for a very long time (I). It has now been found that precursers to the pyridones are open-chain compounds 2,6-bis-(alky1amino)-2,5-heptadien-4-ones (III), which are isolable, stable compounds. The preparation of these compounds from 4-pyrones has been noted. The result showed that efficiency and yield of the reaction is high as compared to other conventional methods. This method offers advantage in terms of simple procedure and workup, mild reaction condition and excellent yields.

KEYWORDS: Dehydroacetic acid, Dihydropyridones, 4-pyrones.

INTRODUCTION:

Six-membered nitrogen heterocycles are key units in medicinal chemistry and versatile intermediates in organic synthesis[1,2] Dihydropyridones are important intermediates for the synthesis of natural products particularly alkaloids[3] and they have been extensively investigated as valuable building block for the construction of piperidines ,perhydroquinolens, indolizidines, quinolizidines and other alkaloid systems, with a wide range of a biological and pharmacological activities. These compounds known for their antiproliferative and antitubolin activities[4] and aspotential selective inhibitors of receptor tyrosyn kinase[5,6]. Their ability to induce leukaemic cell differentiation has been demonstarated[7]. In addition they have potent antimalarial activity [8]and good anticonvulsant activity against acutely elicited Seizures[9]

Pyridones represent a unique class of pharmacophore which are observed in various therapeutic agents[10] and antibiotics[11]. They are also versatile precursors for the construction of complex natural products[12], and larger pyridine systems such as those found in the nitroguanidine insecticide Imidadoprid[13] and subtype selective GABG receptor agonists[14]

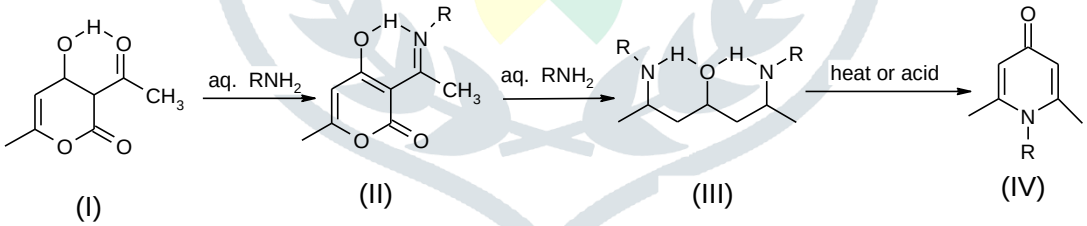
RESULTAND DISCUSSION:

Primary aliphatic amines react with 2,6-dimethyl-4-pyrone to give 2,6-dialkylamino-2,5-heptadien-4-one derivatives. When the alkyl group was methyl, the diamino derivative cyclized on warming to give 1, 2, 6-trimethyl-4-pyridone. The corresponding butylamino derivative did not thermally cyclize, but did give a pyridone on treatment with acid. The isopropylaminoketone did not cyclize. Several examples of 1, 2, 6-trisubstituted-4-pyridones formed ionic associates consisting of two parts of the pyridone and one part of perchloric acid. These associates are useful primary standards for nonaqueous titrations.

2, 6-Bis-(a1kylamino)-2,5-heptadien-4-ones have been prepared by the action of aqueous amines on (1) 3-acetyl-4-hydroxy-6-n1ethyl-2-pyrone (dehydroacetic acid). The reactions are facile and proceed smoothly at temperatures near, or slightly above, room temperature. In (1) the first products are 3-(1-alkyliminoalkyl)-4-hydroxy-6-methyls, followed by the 2, 6-his-(alkylamino)-2,5-heptadien-4-one. The other reactions yield only the latter product, but in all cases it decomposes to the 4-pyridone at higher temperature, or on prolonged reaction or by the action of acid.

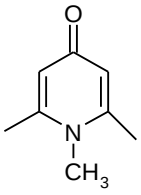
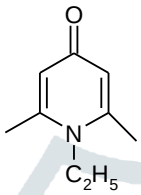
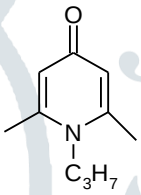
The reaction of dehydroacetic acid (I) (3-acetyl-4-hydroxy-6-methyl-2-pyrone) with amine give 4-pyridones (IV) has been known for a very long time (I). It has now been found that precursers to the pyridones are open-chain compounds 2, 6-bis-(alky1amino)-2, 5-heptadien-4-ones (III), which are isolable, stable compounds. The preparation of these compounds from 4-pyrones has been noted by Spooner, whose work has been confirmed.

The result showed that efficiency and yield of the reaction is high as compared to other conventional methods. Yields of all isolated product after purification found to be excellent as compare to the previously reported methods. This method offers advantage in terms of simple procedure and workup, mild reaction condition and excellent yields.



R = CH_3, C_2H_5, C_3H_7

Analytical and physical data of substituted 4-pyridones

Sr. No.	Product	M.F.	M.P. ^{0}C	Yield
1		$C_8H_{11}NO$	111	70%
2		$C_9H_{13}NO$	73	75%
3		$C_{10}H_{15}NO$	82	68%

5.4 EXPERIMENTAL:

All the chemicals used were of S.D. Fine chemicals. All the solvent used were distilled previously.

Melting points were measured in open glass capillaries on a Perfit Electrothermal melting-point apparatus and are uncorrected. The reactions were monitored by TLC using pre-coated plates (Merck). Column chromatography was performed using Acme silica gel (100–200 mesh). The products were also characterized by comparison of their melting point with literature values.

5.5 REPRESENTATIVE PROCEDURE:

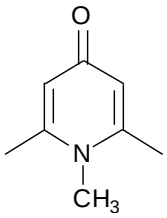
a) Dehydroacetic acid (I) (3.36 g, 0.02 mole) was dissolved in a small amount of $CHCl_3$ and excess ether. About 1.8 g anhydrous alkylamine (0.04 mole) was added, giving a white precipitate, alkylammonium dehydroacetate (X). When dry alkylammonium dehydroacetate was heated overnight on a steam bath (-50') the resulting product was -3-(l-alkylliminoalkyl)-4-hydroxy-6-methyl-2-pyridone.

b) N-(1-alkyliminoalkyl)-4-hydroxy-6-methyl-2-pyrone (4.5 g) was warmed on the steam bath (-50') for 0.2 hour with 12.5 ml 25% aqueous RNH_2 (0-1 mole), when the typical pale yellow, violet fluorescing solid precipitated. After the mixture was cooled and filtered, 2, 6-bis-(alkylaminoalkyl)-2,5-heptadien-4-one was obtained.

c) 2, 6-Bis-(alkylamino)-2,5-heptadien-4-one (1.33 g) and 20 g H_2O were boiled together for 0.5 hour.

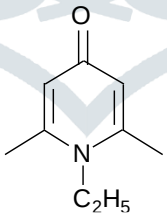
On cooling the solution and evaporation of excess water a white solid, recrystallized from water as long needles, 0.72 g, 52yO, proved, from its infrared-Spectrum, to be identical with 1-alkyl-2, 6-dimethyl-4-pyridone. $3H_2O$ prepared previously.

1, 2, 6-Trimethyl-1H-pyridin-4-one



Nature	White
Mp	111
1H-NMR (500 MHz, CDCl3)	5.1 S (2H), 1.5 S (6H), 3.8 S (3H)
13C-NMR (125 MHz,CD Cl_3)	22.4, 33.7, 103.2, 157.6, 187
IR (KBr)	1200, 1280, 1660, 1525, 2850, 3100.
Mass	(M+1) 138

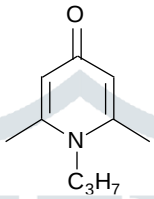
1-Ethyl-2,6-dimethyl-1H-pyridin-4-one



Nature	White
Mp	73
1H-NMR (500 MHz, CDCl3)	5.6 S (2H), 1.7 S (6H), 2.7 q (3H), 1.1 t (2H)

13C-NMR (125 MHz,CD Cl3)	14.4 , 20.4, 41.5, 104, 174, 188
IR (KBr)	1210,1300, 1670, 1525, 2900 3050
Mass	(M+1) 152

2,6-Dimethyl-1-propyl-1H-pyridin-4-one



Nature	Solid
Mp	82
1H-NMR (500 MHz, CDCl3)	5.5 S (2H), 1.7 S (6H), 2.7 t (2H), 1.6 q (3H),1.0 t(2H)
13C-NMR (125 MHz,CD Cl3)	12.2, 20.5, 22, 49, 104, 174, 186
IR (KBr)	1200,1290, 1665, 1525, 2850 3050
Mass	(M+1) 166

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