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A simple and convenient approach to the Friedländer synthesis of pyrano[2,3-*b*]pyridines

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ABSTRACT

$SnCl_2 \cdot 2H_2O$ mediated efficient synthesis of pyrano[2,3-*b*]pyridines was achieved by the Friedländer reaction of 2-amino-3-cyano-4*H*-pyrans with cyclopentanone/cyclohexanone under solvent-free condition.

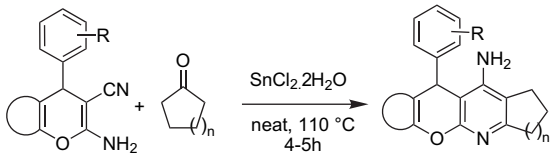
1. Introduction

The presence of pyranopyridine scaffold in the frame work of several biologically active naturally occurring alkaloids of plant origin[1] has enthused researchers to synthesize and study their potential biological activities. They are known to possess anti-allergic, anti-inflammatory, and estrogenic properties.[2] In addition, benzopyrano[2,3-*b*]pyridines exhibit anti-proliferative,[3] cancer chemopreventive,[4] anti-bacterial (including anti-tubercular),[5] anti-myopic,[6] anti-histamic,[7] hypotensive,[8] anti-rheumatic,[9] and anti-asthmatic activities.[10]

Despite numerous methods reported such as Skraup, Döbner-von Miller, and Combes,[11] the Friedländer annulation is the most simple and straightforward approach for the synthesis of poly-substituted pyridines and related azaheterocycles. Friedländer annulation is acid or base catalyzed annulation of *o*-aminoaryl ketones with carbonyl compounds containing a reactive α-methylene group. Among various Friedländer syntheses, cyclocondensation of *o*-aminobenzonitrile with various ketones has been less explored. Previous investigation[12,13] on condensation of these derivatives required prolonged reaction times, use of hazardous reagents and limits the large scale application. In view of its immense biological applications, the development of simple and convenient protocol is of considerable interest.

Over the past few years, organic reactions under solvent-free conditions have gained much popularity.[14] Solvent-free reactions are not only of interest from ecological point of view, but in many cases, also offer several synthetic advantages like higher yields, reduced pollution, low cost, improved selectivities, and simplicity in process and handling.[15]

Recently, $SnCl_2 \cdot 2H_2O$[16] has emerged both as the medium and catalyst in various organic transformations. In view of its inherent properties like reusability, greater selectivity, operational simplicity, non-corrosiveness, low cost, and ease of isolation, various synthetic transformations were accomplished. Previously, our group demonstrated the utility of $SnCl_2 \cdot 2H_2O$ as an alternative to ionic liquid[17d] and employed it as a reaction medium for carrying out various organic transformations. As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds,[17] we herein disclose a simple and convenient method for the synthesis of pyrano[2,3-*b*]pyridines by Friedländer reaction mediated by $SnCl_2 \cdot 2H_2O$ under solvent-free condition (Scheme 1).



Scheme 1.

2. Results and discussion

In our initial endeavor, we investigated the reaction of **1a** with cyclohexanone **2a** using various Lewis acid catalysts in different solvents (methanol, ethanol, and 1,2-dichloroethane) and neat at reflux or at 100 °C (Scheme 2 and Table 1). After systematic screening, we observed that tinchloride dihydrate gave moderate yield under solvent-free condition with equimolar amount of catalyst at 100 °C. Then, we optimized the reaction condition by increasing/decreasing the catalyst loading and temperature. The best result was obtained when the reaction was carried out with $SnCl_2 \cdot 2H_2O$ (also serving as reaction medium) under solvent-free condition at 110 °C. Further increase of temperature did not

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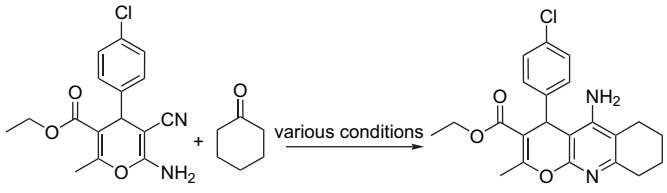

1a 2a 3a

Scheme 2.

improve the product yield or increase the reaction rate. We also studied the recyclability of $SnCl_2{\cdot}2H_2O$ as reaction medium. $SnCl_2{\cdot}2H_2O$ is insoluble in dichloromethane. This property was utilized in recycling the reaction medium. Since $SnCl_2{\cdot}2H_2O$ is insoluble in dichloromethane, it was used to bring out the organic part from the reaction mixture. Thus, dichloromethane leaves the $SnCl_2{\cdot}2H_2O$ in reaction vessel, which was recycled for further reactions (three times). The yield did not vary much while recycling the reaction medium and the yields were found to be 56, 55, and 53, respectively.

Table 1
Catalyst and solvent screening

Entry	Catalyst	Yield[a] (%)			
		MeOH	EtOH	DCE	Neat
1	$InCl_3$	—	—	5	—
2	$In(OTf)_3$	—	—	8	—
3	$SnCl_2.2H_2O$	—	—	45	54
4	NH_2SO_3H	—	—	—	Trace
5	CAN	—	—	—	—
6	$BiCl_3$	—	—	5	10
7	$Bi(OTf)_3$	—	—	10	12
8	$FeCl_3$	—	—	6	12

[a] All reactions were performed with 100 mol % catalyst at reflux or 100 °C for 5 h.

Table 2 summarizes our results on the Friedländer reaction of various 2-amino-3-cyano-4*H*-pyrans[18] with cyclohexanone/cyclopentanone under optimized condition (Scheme 3). The reaction was amenable to wide variations in 2-amino-3-cyano-4*H*-pyrans and afforded the corresponding highly substituted pyranopyridines **3a–l** in moderate yields.

The structures of all products **3a–l** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass, and elemental analysis. In the IR spectrum of **3a**, disappearance of –CN group and a peak at 1638 cm^{-1} (–C═N–) confirmed the formation of pyridine ring. Absorptions at 3435, 3349, and 1209 cm^{-1} indicated the presence of $-NH_2$ and –C–O–C-groups, respectively. Signals at δ 150.2 (–C═N), 154.2 ($-C-NH_2$), 22.3–32.4 ($-CH_2$ groups) in the ^{13}C NMR spectrum confirmed that cyclohexanone reacted with $-NH_2$ and –CN of 2-amino-3-cyano-4*H*-pyran. The ^{1}H NMR spectrum of **3a** displayed signals at δ 1.76, 2.20, and 2.71 ($-CH_2$ protons of cyclohexyl ring) and 4.03 ($-NH_2$ protons, D_2O exchangeable). Mass analysis also supported the structural assignment.

To further explore the potential of this protocol, we investigated the reaction of 2-amino-3-cyano chromenes with cyclohexanone/cyclopentanone and obtained the corresponding naphthopyranopyridines **5a–e** in moderate yields (Scheme 4 and Table 3).

The structures of all products **5a–e** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass, and elemental analysis. The IR spectrum of **5e** showed absorptions at 3483, 3397, and 1109 cm^{-1} indicating the presence of $-NH_2$ and –C–O–C-groups, respectively. Disappearance of –CN group and a peak at 1628 cm^{-1} (–C═N–) confirmed the formation of pyridine ring. In the ^{1}H NMR spectrum, $-NH_2$ protons appeared as a broad singlet at δ 4.19 (D_2O exchangeable) and the methylene protons ($-CH_2$) of cyclohexyl ring were seen as multiplets at δ 1.72, 2.26, and 2.83. Signals at δ 154.2 (–C═N), 160.4 ($-C-NH_2$), 22.3–32.4 ($-CH_2$ groups) in the ^{13}C NMR spectrum confirmed that cyclohexanone reacted with $-NH_2$ and –CN of pyran. Mass analysis also supported the structural assignment.

A mechanistic rationalization for the reaction is given in Scheme 5.

3. Conclusion

In summary, we have developed a simple and convenient method for the synthesis of highly substituted pyranopyridines from 2-amino-3-cyano-4*H*-pyrans and cyclohexanone/cyclopentanone using inexpensive and commercially available $SnCl_2{\cdot}2H_2O$ under solvent-free condition. The major advantage of this protocol is that $SnCl_2{\cdot}2H_2O$ (as reaction medium) can be recycled upto three times without much change in yield. The generality of the reaction was also extended to the synthesis of naphthopyranopyridines in moderate yields.

4. Experimental

4.1. Materials and methods

$SnCl_2{\cdot}2H_2O$, NH_2SO_3H, CAN, and $FeCl_3$ were obtained from S.D. Fine Chem. Ltd. $Bi(OTf)_3$, $In(OTf)_3$, $InCl_3$, and $BiCl_3$ were purchased from Aldrich and used as received. All melting points were uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on JEOL spectrometer at 500 MHz and 125 MHz and Bruker spectrometer at 300 MHz and 75 MHz, respectively. Mass spectra were recorded by electrospray ionization method on Thermo Finnegan Mass spectrometer. Elemental analyses were recorded using a Thermo Finnegan FLASH EA 1112 CHN analyzer. Column chromatography was performed on silica gel (100–200 mesh, SRL, India). Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

4.2. General procedure for the synthesis of pyranopyridines

To a two-neck round-bottomed flask fitted with a mechanical stirrer and oil bath, 2 g of $SnCl_2{\cdot}2H_2O$ was added and stirred at 50 °C. $SnCl_2{\cdot}2H_2O$ became viscous liquid. To this viscous liquid, 2-amino-3-cyano-4*H*-pyran **1** (1 mmol) and cyclohexanone **2a** (1.1 mmol) were added and stirred at same temperature for about 15 min. Then stirring was continued at 110 °C until the disappearance of starting materials, as indicated by TLC. After the completion of the reaction, the reaction mixture was allowed to cool to 40 °C and triturated with dichloromethane (3×15 mL) and stirred for 10 min. The organic layer thus obtained was washed twice with water and with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified through column chromatography (40% ethyl acetate in petroleum ether). The round-bottom flask, which contains the $SnCl_2{\cdot}2H_2O$ was again utilized for recycling the reaction medium (successfully recycled three times). The same procedure was followed for the synthesis of naphthopyranopyridines **5a–e**.

*4.2.1. Ethyl 5-amino-4-(4-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrano[2,3-b]quinoline-3-carboxylate (**3a**).* Off white solid; mp 138–140 °C; R_f 0.65 (40% EtOAc/petroleum ether); IR ν_{max} (KBr): 3435, 3349, 2928, 1685, 1638, 1571, 1447, 1295, 1209, 1057, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (t, 3H, J=6.9 Hz, $-OCH_2CH_3$), 1.76 (m, 4H, $-CH_2$), 2.20 (m, 2H, $-CH_2$), 2.42 (s, 3H, $-CH_3$), 2.71 (m, 2H, $-CH_2$), 4.03 (br s, 2H, D_2O exchangeable, $-NH_2$), 4.09 (m, 2H, $-OCH_2CH_3$), 4.80 (s, 1H, –*CH*), 7.18 (m, 4H, –Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 19.8, 22.3, 22.5, 22.9, 32.4, 37.9, 60.4, 99.2,