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Green synthesis of highly substituted pyridines via the one-pot multi-component reaction in 2,2,2-trifluoroethanol

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ABSTRACT

Highly substituted pyridine derivatives are synthesized from both electron-deficient and electron-rich substrates in a fast, high yielding, and operationally simple protocol in 2,2,2-trifluoroethanol (TFE). The solvent (TFE) can be readily separated from reaction products and reused in several reactions without any noticeable loss of activity.

1. Introduction

Pyridine derivatives have become increasingly important in the past few years because they are widely found in natural products with biological activity [1]. They have also found in many active pharmaceuticals and functional materials [2–4]. Among these compounds, indenopyridines (azafluorenes) have been reported to possess cytotoxic [5], phosphodiesterase inhibitory [6], adenosine A2a receptor antagonistic [7], anti-inflammatory/anti-allergic [8], coronary dilating [9] and calcium modulating activities [10]. They can cure the hyperlipoproteinemia and arteriosclerosis [11] as well as neurodegenerative diseases [12]. Several compounds of this type act as calcium antagonistic activators and herbicides [13]. Considering the above reports, the development of new synthetic methodologies for the construction of indenopyridine scaffolds is a beneficial and interesting challenge.

Researchers recently have developed several alternate and more efficient methods for the construction of this kind of fused heterocycles from suitable precursors [14–22]. Some new methods are available in the literature for the synthesis of these indenopyridine compounds from aldehydes, dimedone, and different anilines or ammonium acetate via the condensation of a aldehydes, 1,3-indandione or 1-indenone and aromatic ketones in the presence of ammonium acetate under microwave irradiation [23,24], by Pummerer reaction of imidosulfoxides [25], and Pd(0)-catalyzed cross-coupling reaction between arylboronic acids and 2-halopyridines [26]. In 2010, Mukhopadhyay et al. reported an elegant synthesis of indenopyridines from various aldehyde, 1,3-indandione, 2-acetylthiophene or 2-acetylfluorene and ammonium acetate using L-proline as a catalyst [27]. Recently, Alinezhad et al. have described an efficient method for the synthesis of substituted indenopyridines using aldehydes, 1,3-indandione, aromatic ketones, and ammonium acetate in the presence of Cu-doped ZnO nanocrystalline powder [28]. These methods show varying degrees of successes as well as limitations, such as multistep reaction processes, harsh reaction conditions, expensive reagents, cumbersome product isolation procedures, lower product yields, metal catalysts as well as more than stoichiometric amount of reagents. Therefore, a simple and efficient method for indenopyridine synthesis remains an attractive goal. In recent years, fluorinated alcohols have been introduced as new alternative sustainable solvents for organic transformations [29–31]. These solvents have been applied to oxidation reactions [32–38], aza-Diels–Alder [39], Hantzsch reaction [40], and Ferrier reaction [41]. The synthesis of pyrazoles [42], quinolines [43,44], and 2,3-dihydro-4(1H)-quinazolinones [45], has been reported by using 2,2,2-trifluoroethanol (TFE) and Hexafluoro-2-propanol (HFIP) as solvents. The peculiar physical and chemical properties of fluorinated alcohols, such as low nucleophilicity, high polarity, strong hydrogen bond donating ability and ability to solvate water, prompted us to extend their use as green solvents in organic synthesis. As part of our ongoing programme to develop highly efficient and environmentally benign synthetic processes [46–50], we turned our attention toward the four-component condensation of 1,3-indanedione, aldehyde, aromatic ketones and ammonium acetate in TFE as solvent. Herein, we describe a novel, efficient, and green procedure for the synthesis of indeno[1,2-*b*]pyridine derivative **5** via the four-component condensation (Scheme 1).

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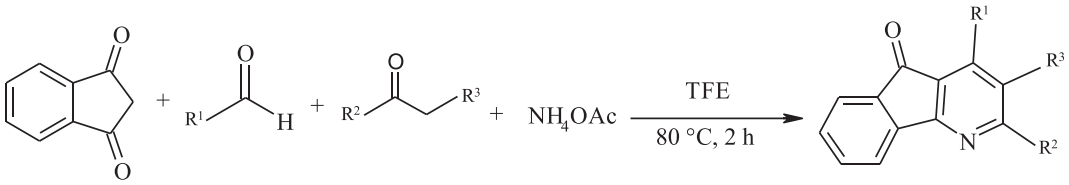

Scheme 1. Synthesis of highly substituted pyridines in TFE.

2. Experimental

2.1. Apparatus and analysis

NMR spectra were determined on an FT-NMR Bruker AV-400 spectrometer in $CDCl_3$ and are expressed in δ values relative to tetramethylsilane; coupling constants (J) are measured in Hertz.

Melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were recorded on a Rayleigh WQF-510 Fourier transform instrument. Commercially available reagents were used throughout without further purification.

2.2. Typical experimental procedure

A mixture of aldehyde (1 mmol), 1,3-indanedione (1 mmol), acetophenone (1 mmol), and ammonium acetate (1.5 mmol) was stirred in TFE (2 mL) at 80 °C for the stipulated time. The progress of the reaction is monitored by TLC. After completion of the reaction, the corresponding solid product **5** was obtained through simple filtering, and recrystallized from hot ethanol affording the highly pure indeno [1,2-*b*]pyridine derivatives. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature [23]. Spectroscopic data for selected examples are shown below.

4-(4-Chlorophenyl)-2-phenyl-indeno[1,2-b]pyridin-5-one (Table 1, entry 1), solid, mp 187–189 °C; IR (KBr): 3072, 1715, 1560, 1521, 1345 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.15 (s, 1H), 7.23–7.73 (m, 11H), 7.93–8.2 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.2, 117.5, 121.7, 123.8, 128.3, 128.9, 129.3, 129.7, 129.5, 131.3, 134.2, 135.1, 137.4, 140.1, 141.9, 143.1, 145.1, 147.4, 162.5, 194.1.

3-Methyl-4-(4-nitrophenyl)-2-phenyl-indeno[1,2-b]pyridin-5-one (Table 1, entry 10), solid, mp 248–250 °C; IR (KBr): 3070, 1717, 1560, 1520, 1347 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.06 (s, 3H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.43–7.73 (m, 9H), 7.93 (d, $J = 7.2$ Hz, 1H), 8.35 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.6, 121.2, 123.5, 123.7, 123.8, 128.3, 128.9, 129.2, 129.4, 129.5, 131.3, 135.2, 135.5, 140.1, 141.9, 142.8, 146.9, 147.6, 162.5, 163.8, 192.1.

Table 1
Synthesis of 5H-indeno[1,2-*b*]pyridin-5-ones in TFE.

Entry	R^1	R^2	R^3	Product	Yield (%)	mp °C[ref]
1	4-Cl-C_6H_4	C_6H_5	H	**5a**	95	187–189[24]
2	4-Cl-C_6H_4	4-OMe-C_6H_4	H	**5b**	92	201–202[29]
3	4-Br-C_6H_4	4-OMe-C_6H_4	H	**5c**	90	214–216[29]
4	4-NO_2-C_6H_4	4-OMe-C_6H_4	H	**5d**	88	223–225[24]
5	4-Cl-C_6H_4	4-Cl-C6H4	H	**5e**	85	227–229[24]
6	2-Cl-C_6H_4	4-OMe-C_6H_4	H	**5f**	92 (3 h)	265–266[24]
7	4-F-C_6H_4	4-OMe-C_6H_4	H	**5g**	95	193–194[24]
8	3-NO2-C_6H_4	4-OMe-C_6H_4	H	**5h**	88	220–221[24]
9	3-NO2-C_6H_4	C_6H_5	Me	**5i**	95	203–205[23]
10	4-NO2-C_6H_4	C_6H_5	Me	**5j**	90	248–250[23]
11	4-Cl-C_6H_4	C_6H_5	Me	**5k**	90	222–225[23]
12	4-Br-C_6H_4	C_6H_5	Me	**5l**	85	221–223[24]
13	4-Me-C_6H_4	4-OMe-C_6H_4	H	**5m**	90	162–164[29]
14	4-Me-C_6H_4	4-Cl-C_6H_4	H	**5n**	92	213–215[29]
15	4-Cl-C_6H_4	4-Cl-C_6H_4	H	**5o**	92	225–227[24]

3. Results and discussion

Initially, we carried out the four-component condensation of 4-chlorobenzaldehyde (1 mmol), 1,3-indanedione (1 mmol), acetophenone (1 mmol), and ammonium acetate (1.3 mmol) in trifluoroethanol at room temperature. After 24 h, only 60% of product **5a** was obtained after recrystallization of the crude product from ethanol. Much to our surprise, when we carried out the reaction in trifluoroethanol at 80 °C, the corresponding indeno[1,2-*b*]pyridine derivative **5a** (Table 1, entry 1) was obtained in high yield (95%) after 2 h.

The scope and generality of this four-component condensation were examined in more detail. Both the electron-rich and -deficient aldehydes worked well leading to good yields of product **5**.

Aromatic aldehydes with several functionalities such as Cl, F, Me, OMe, and NO_2 were found to be compatible under the optimized reaction condition. The electronic effect seemed to have a slight influence on the reaction since either the electron-withdrawing or the electron-donating groups on the different aromatic ring resulted in the hardly discriminate yields. In the case of ortho-substituted aldehydes the reaction time was longer and yields were somewhat lower than other aldehydes which were probably attributed to the steric hindrance (Table 1, entry 6). Satisfactorily, the reactions displayed high functional group tolerance and afforded the corresponding indenopyridines with great efficiency. To expand the scope of carbonyl substrates, propiophenone and acetophenone derivatives were applied to this protocol. In all cases, the desired reactions took place successfully to afford a series of indeno[1,2-*b*]pyridin-5-one (**5b**–**o**) in good yields (Table 1).

The structure of the products (**5a**–**o**) was established from their IR spectral data and comparison of their melting points with those of authentic samples. Also, the structure of some products was confirmed by ^1H NMR and ^{13}C NMR spectral data. Interestingly, the reaction did not proceed to completion when either ethanol or water alone was used as solvent.

A plausible mechanism for the formation of indeno[1,2-*b*]pyridines is shown in Scheme 2.

In this process, TFE can increase the electrophilic character of the electrophiles by virtue of its inherent Brønsted acidity which makes it capable of bonding with the carbonyl oxygen [51]. Moreover, the polar transition state of the reaction could be stabilized well by the high ionizing solvent TFE. Whereas, the hydrogen bond donating ability of these solvents drops as temperature rises owing to the fact that hydrogen-bond formation is exothermic, this ability has a slight influence on the reaction [52,53].

A possible mechanism for this reaction is shown in Scheme 2. A proton from TFE is donated to the oxygen atom of the aldehyde. Next, the carbonyl carbon is attacked by the nucleophilic 1,3-indanedione to form intermediate **I**. The second key intermediate is enamine **II**, which formed from acetophenone and ammonium acetate. Condensation of these two fragments gives intermediate **III**, followed by intramolecular cyclization to afford the final product. It may be assumed that the water exclusion of TFE may favor both imine and intermediate **I** formation.

After the reaction, TFE can be easily separated (by distillation) and reused without decrease in its activity. The possibility of recycling the trifluoroethanol was examined using the reaction of 4-chlorobenzaldehyde (**1a**), 1,3-indanedione (**2a**), acetophenone (**3a**) and ammonium acetate (**4a**) under the optimized conditions. Upon

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