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An eco-benign and highly efficient access to dihydro-1H-indeno[1,2-b] pyridines in 2,2,2-trifluoroethanol

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ABSTRACT

4-Aryl-4,5-dihydro-1H-indeno[1,2-b]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 recovered in excellent purity for direct reuse.

1. Introduction

Over the last years, fluorinated alcohols are attracting increasing attention as alternative solvents for a wide range of catalytic and organic reactions, because they display many advantages over common organic solvents, such as high hydrogen bonding donor ability, nonvolatility, nonflammability, polarity, high ionizing power, and low nucleophilicity [1–3]. In addition, highly fluorinated alcohols exhibit lower boiling points than do their parent alcohols. Based on these unique properties, these alcohols have met noteworthy applications in various domains. These alcohols display interesting properties, such as solvent, co-solvent, and additives in various catalytic processes: oxidation reactions with H_2O_2 (epoxidation of olefins, transformations of sulfides into sulfoxides, and Baeyer–Villiger oxidation) or sodium hypochlorite [4–9], aza-Michael reaction [10], protection and deprotection of amine groups [11,12], cyclopropanation of alkenes [13], and oxirane ring-opening without any catalyst [14,15]. Recently, we and others have demonstrated the usefulness of fluorous alcohols as a novel medium for the synthesis of heterocyclic compounds [16–27]. Dihydropyridines and related heterocyclic systems occur widely in natural products as well as in synthetic molecules, exhibiting a broad spectrum of biological activities such as vasodilators, bronchodilators, antiatherosclerotics, antitumor, hepatoprotective, and antidiabetic agents for the treatment of cardiovascular diseases including hypertension [28,29]. In recent years, indenopyridines (azafluorenes) have received more attention because of the wide range of useful pharmacological activities that include cytotoxic [30], phosphodiesterase inhibitory [31], adenosine A2a receptor antagonistic [32], antiinflammatory/antiallergic [33], coronary dilating [34] and calcium modulating activities [35]. Some of these compounds have been reported as cyclin-dependent kinase [36] and selective monoamine oxidase B (MAO-B) [37] inhibitors. As a result chemists and biologists alike have been attracted toward these compounds. According to the literature, several synthetic methods have been developed for the construction of this kind of fused heterocycles from suitable precursors [38–47]. In addition, they can also be accessed by the condensation of aldehydes, 1,3-indandione or 1-indenone and aromatic ketones in the presence of ammonium acetate under microwave irradiation [48], by Pummerer reaction of imidosulfoxides [49], and Pd(0)-catalyzed cross-coupling reaction between arylboronic acids and 2-halopyridines [50]. These methods show varying degrees of successes as well as limitations, such as harsh reaction conditions, expensive and detrimental metal reagents, tedious work-up, low product yields, long reaction times, and co-occurrence of several side products. Therefore, the development of novel methods for the synthesis of indenopyridines remains an attractive goal. In this article, we have presented a new, convenient, and highly efficient protocol for the synthesis of 4-aryl-4,5-dihydro-1H-indeno[1,2-b]pyridine derivatives via one-pot four-component cyclocondensation of 1,3-indanedione, aldehyde, alkyl acetoacetate and ammonium acetate in trifluoroethanol (TFE) (Scheme 1).

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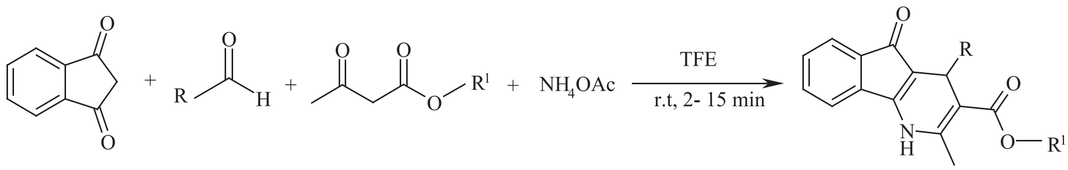


Scheme 1. Synthesis of 4-aryl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridines in TFE.

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.

Typical experimental procedure: A mixture of aldehyde (1 mmol), 1,3-indanedione (1 mmol), alkyl acetoacetate (1 mmol), and ammonium acetate (1.5 mmol) was stirred in one-pot in TFE (2 mL) at room temperature 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 4-aryl-4,5-dihydro-1H-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 [39]. Spectroscopic data for selected examples are shown below.

2-Methyl-4-(4-chlorophenyl)-5-oxo-4,5-dihydro-1H-indeno-[1,2-b] pyridine-3-carboxylic acid ethyl ester (5a): mp: 227–229 °C; FT-IR (KBr, cm^{-1}): 1640, 1705, 3270; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 4.05 (q, $J = 7.1$ Hz, 2H), 4.75 (s, 1H), 7.60-7.21 (m, 8H), 9.16 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.5$, 18.5, 36.3, 50.7, 106.1, 108.1, 118.9, 120.3, 128.2, 129.4, 130.2, 130.7, 132.1, 133.2, 135.9, 145.3, 145.7, 153.4, 167.2, 190.5.

2-Methyl-4-(4-nitrophenyl)-5-oxo-4,5-dihydro-1H-indeno-[1,2-b] pyridine-3-carboxylic acid ethyl ester (5d): mp: 216-218 °C; FT-IR (KBr, cm^{-1}): 1595, 1640, 1704, 3290; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (t, $J = 7.1$ Hz, 3H), 2.55 (s, 3H), 4.05 (q, $J = 7.1$ Hz, 2H), 5.13 (s, 1H), 6.55 (s, 1H, NH), 7.09-7.29 (m, 4H), 7.52 (d, $J = 8.2$ Hz, 2H), 8.13 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 20.2, 37.5, 60.2, 106.7, 109.5, 116.9, 122.1, 123.6, 128.5, 130.8, 132.1, 133.5, 135.1, 143.2, 145.5, 153.0, 153.2, 167.5, 191.6.

2-Methyl-4-(4-bromophenyl)-5-oxo-4,5-dihydro-1H-indeno-[1,2-b] pyridine-3-carboxylic acid ethyl ester (5f): mp: 176-178 °C; FT-IR (KBr, cm^{-1}): 1640, 1703, 3280; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.3$ Hz, 3H), 2.42 (s, 3H), 3.99 (q, $J = 7.3$ Hz, 2H), 4.95 (s, 1H) 6.75 (s, 1H, NH), 6.98 (d, $J = 6.40$ Hz, 2H), 7.14-7.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.2$, 18.5, 36.1, 56.4, 105.1, 109.2, 112.22, 123.1, 123.6, 128.5, 129.6, 131.5, 133.2, 134.5, 142.4, 145.8, 153.1, 153.3, 166.1, 191.4.

2-Methyl-4-(4-phenyl)-5-oxo-4,5-dihydro-1H-indeno-[1,2-b]pyridine-3-carboxylic acid ethyl ester (5 g): mp: 220-221 °C; FT-IR (KBr, cm^{-1}): 1580, 1630, 1705, 2975, 3260; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (t, $J = 7.3$ Hz, 3H), 2.48 (s, 1H), 4.03 (q, $J = 7.3$ Hz, 2H), 5.02(s, 1H, CH), 7.11 (s, 1H, NH), 7.65-6.81 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 13.4, 18.2, 42.1, 61.5, 102.4, 109.6, 113.5, 123.4, 125.7, 128.7, 128.9, 133.9, 136.5, 141.3, 142.2, 145.7, 150.1, 168.1, 167.3, 192.3.

2-Methyl-4-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-indeno-[1,2-b] pyridine-3-carboxylic acid ethyl ester (5i): mp: 213-214 °C; FT-IR (KBr, cm^{-1}): 1633, 1700, 3260; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (t, $J = 7.2$ Hz, 3H), 2.45 (s, 3H), 3.67 (s, 3H), 4.01 (q, $J = 7.2$ Hz, 2H), 4.87 (s, 1H), 6.54 (s, 1H, NH), 6.96–7.30 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 16.5, 41.1, 55.3, 58.9, 101.9, 103.5, 121.7, 126.7, 128.6, 134.4, 135.9, 139.5, 142.2, 143.5, 145.8, 150.1, 156.5, 166.2, 192.2.

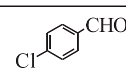
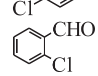
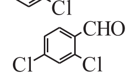
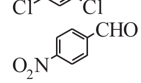
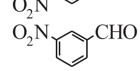
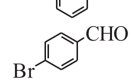
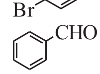
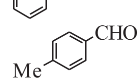
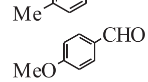
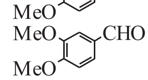
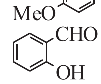
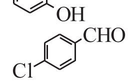
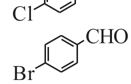
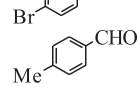
3. Results and discussion

Initially, we carried out the four-component condensation of 4-chlorobenzaldehyde (1 mmol), 1,3-indanedione (1 mmol), alkyl acetoacetate (1 mmol), and ammonium acetate (1.5 mmol) in trifluoroethanol at room temperature. The reaction was remarkably fast (2 min) and, after distilling off the HFIP, the 4-aryl-4,5-dihydro-1H-indeno[1,2-b]pyridine **5a** was obtained in high yield (95%) (Table 1, entry 1). At the beginning of the reaction, the reagents itself were dissolved completely in the medium to form a homogeneous mixture (Fig. 1a), but near the completion of the reaction, the system became a suspension, and the product precipitated at the end of the reaction (Fig. 1b).

Encouraged by this success, we extended this reaction to a range of aldehydes **1a-m** under similar conditions to furnish the respective substituted 4,5-dihydro-1H-indeno[1,2-b]pyridine **5a-m** in good yields. The results are summarized in Table 1.

Both the electron-rich and -deficient aldehydes worked well leading to good yields of products **5**. Aromatic aldehydes with several functionalities such as Cl, Br, Me, OMe, OH and NO_2 were found to be compatible

Table 1
Synthesis of indenopyridines (azafluorenes) in TFE.

Entry	Aldehyde	^{1}R	Time (min)	Product	Yield[ref]%
1		Et	2	**5a**	95[39]
2		Et	8	**5b**	90[39]
3		Et	5	**5c**	92[40]
4		Et	3	**5d**	95[39]
5		Et	7	**5e**	95[42]
6		Et	5	**5f**	95[42]
7		Et	8	**5 g**	90[40]
8		Et	10	**5 h**	92[39]
9		Et	15	**5i**	90[41]
10		Et	15	**5j**	90[42]
11		Et	10	**5 k**	85[42]
12		Me	2	**5 l**	95[39]
13		Me	5	**5 k**	92[40]
14		Me	10	**5 m**	90[42]