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3,5-Bis(trifluoromethyl) phenylammonium triflate: a new and green organocatalyst for the synthesis of indeno[1,2-b]pyridines

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A B S T R A C T

3,5-Bis(trifluoromethyl) phenyl ammonium triflate(BFPAT) catalyzed one-pot synthesis of indeno[1,2-b]pyridine compound derivatives by four-component condensation of aldehyde, aromatic ketones, 1,3-indanedione, and ammonium acetate in ethanol. Accessible starting materials, Simplicity of operation, green and practical catalyst, easy purification, and excellent yields are the key benefits of the current technique.

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1. Introduction

In the past 20 years, organocatalysis has emerged as an important area of research [1, 2]. Organocatalysts are easy and inexpensive to assemble, generate no waste, have simple purification, and have aspects of the high atomic economy thus encompassing the principles of Green Chemistry.[3-8] Organocatalytic reactions that afford achiral compounds have received considerable attention, since opening new pathways in organic synthesis as a cheap, non-toxic, readily available starting material providing the corresponding products with high yields [9-12].

Recently, Aryl ammonium triflate has gotten impressive consideration for numerous organic reactions, giving the corresponding products in high yields with great selectivity [13-19]. In proceeding with our studies on the utilization of new reagents or frameworks for organic transformations, [20-24] we present herein an effective strategy for the synthesis of indeno[1,2-b]pyridine derivatives utilizing 3,5-Bis(trifluoromethyl) phenylammonium triflate (BFPAT), as a new effective catalyst (Scheme 1).

Indenopyridines (azafluorenes) as a class of azaheterocycles are widely investigated for their assorted biological properties, such as cytotoxic [25], phosphodiesterase inhibitory [26], adenosine A2a receptor antagonistic [27], antiinflammatory/anti-allergic [28], coronary dilating [29] and calcium modulating activities [30]. Moreover, pyrimidine-related compounds are also used in the treatment of hyperlipoproteinemia and arteriosclerosis [31] as well as neurodegenerative diseases [32].

Consequently, there has been continuous interest in developing effective synthetic techniques for the synthesis of various Indenopyridines. Numerous synthetic strategies have been reported for the preparation of Indenopyridines and their analogues [33-39]. Some of these strategies are related with specific constraints, for example, the use of excess and expensive catalyst, long reaction time, numerous steps, low yields, toxic solvents, the use of harmful metal catalysts, and harsh reaction circumstance. Furthermore, most of the described methods lead to significant amounts of by-products resulting in poor overall yield. Consequently, there is still a need to find out greener catalyst to overcome these deficiencies and satisfy the criteria of a basic, proficient, and eco-friendly protocol for the synthesis of Indenopyridines.

2. Experimental

2.1. Preparation of 3,5-bis(trifluoromethyl) phenylammonium triflate (BFPAT)

CF_3SO_3H (7.50 g, 50 mmol) was added to a stirred solution of 3,5-bis(trifluoromethyl)aniline (11.45 g, 50 mmol) in toluene (50.0 ml) at 0-5 °C, and the mixture was stirred at the same temperature for 30 min. Evaporation of the solvent gave the crude product, which was washed with dry ether to give a pure BFPAT (15.8 g, 95%) as colourless crystals. ^{1}H NMR (acetone-d_6, 400 MHz) δ: 7.43–7.66 (brs, 3H); IR (KBr) 3416, 2965, 1532, 1250, 1179 cm^{-1}.

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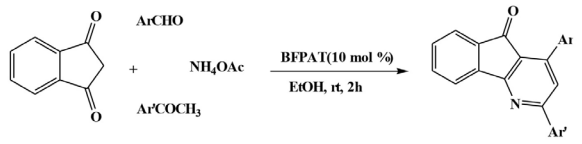


Scheme .1. Synthesis of indeno[1,2-b]pyridines using BFPAT organocatalyst.

2.2. Typical experimental procedure

A mixture of aldehyde (1 mmol), acetophenone (1 mmol), 1,3-indanedione (1 mmol), and ammonium acetate (1.2 mmol) dissolved in 3 mL toluene, and PFPAT (10 mol%) was stirred at r.t. 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 compound derivatives. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature. 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 186–188 °C; IR (KBr): 3070, 1712, 1560, 1520 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.14 (s, 1H), 7.22–7.72 (m, 11H), 7.92–8.2 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 111.5, 118.1, 121.7, 124.1, 128.3, 128.9, 129.4, 129.3, 129.7, 131.5, 134.2, 136.1, 137.2, 140.4, 142.1, 143.1, 145.2, 147.5, 163.5, 193.2.

3. Results and discussion

We initially explored the reaction of 4-Cl-benzaldehyde (1 mmol), acetophenone (1 mmol), 1,3-indanedione (1mmol), and ammonium acetate (1.2 mmol) in ethanol at room temperature in the presence of BFPAT(5 mol%), Which gave the expected product 5a in 80% yield. We subsequently examined the effect of catalyst loading and solvent on the yield of the product, and the results of these analyses are outlined in Table 1.

Various solvents have also been investigated (e.g., CH_2Cl_2, DMF, THF, toluene, and CH_3CN), and (Table 1, entries 4–8). Among them, ethanol gave the maximum yield at room temperature after 2 h (Table 1, entry 3). Moreover, in the absence of a catalyst, no conversion to the product was achieved even after 24 h (Table 1, entry 1). Using the same model reaction, we examined the optimal quantity of catalyst. While increasing the amount of catalyst to 10 mol %, the product of 5 was

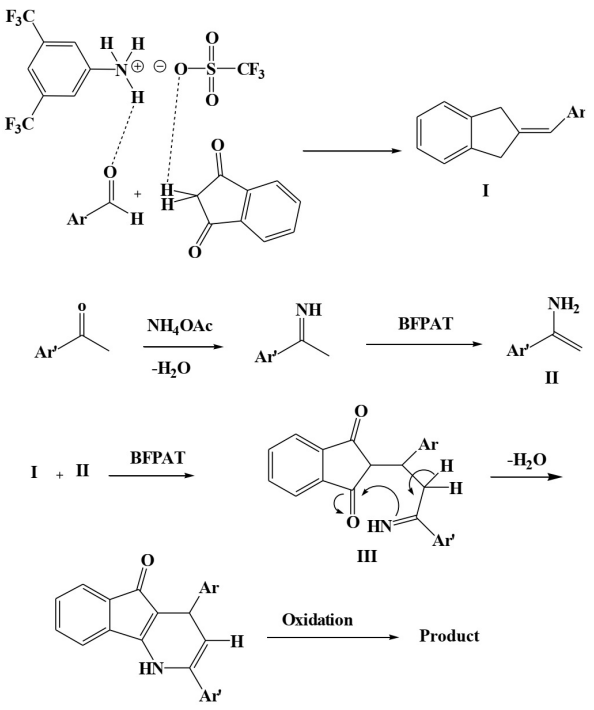
Table 1.

Effect of different BFPAT and solvent on the formation of 5a.

Entry	BFPAT amount (mol%)	Condition/solvent	Time (h)/ yield[b]
1	0	rt/Et OH	24/N.R
2	5	rt/Et OH	3/80
3	10	rt/Et OH	2/90
4	10	rt/DMF	5/60
5	10	rt/CH_3CN	5/70
6	10	rt/toluene	5/50
7	10	rt/THF	5/60
8	10	rt/CH_2Cl_2	5/50
9	15	rt/CH_2Cl_2	2/90

[a] Reaction condition: 4-Cl-benzaldehyde (1 mmol), acetophenone (1 mmo), 1,3-indanedione (1 mmol), and ammonium acetate (1.2 mmol) in ethanol at room temperature in the presence of BFPAT.

[b] Isolated yield



Scheme.2. Probable mechanism for BFPAT-catalyzed Synthesis of indeno[1,2-b] pyridines.

afforded in 90% yield, respectively (entry 3), which demonstrated the significant role of catalyst concentration in the reaction. Increasing either catalyst loading and/or increasing the reaction time did not raise the yield (Table 1, entry 9). Remarkably, when the reaction occurred in an ethanol medium, a solid product participated at the end of the reaction.

With the optimal reaction conditions in hand, the scope and efficiency of this approach were explored for the synthesis of a wide variety of substituted indeno[1,2-b]pyridines and results are summarized in Table 2.

A wide range of aldehydes with both electron-donating and electron-withdrawing substituents were also converted to the corresponding indeno[1,2-b]pyridines in excellent yield and purity as outlined in table 2.

It has been shown that the electronic characteristics of the substituents have little impact on the efficiency of this reaction. For example, Aromatic aldehydes bearing an electron-withdrawing group (e.g., 4-Cl, 3-NO_2, 4-NO_2, 4-Br, or 4-F) group reacted efficiently to afford the corresponding products in good to excellent yields (85−93%). For ketone substrates carrying an electron-donating group on the benzene ring, satisfactory high yields were also noted. Notably, electron-sterically hindered (2-Cl and 2,4-di-Cl) substrates reacted well to give the expected products in good yields (80−85%, 5c-5e).

A possible mechanism for the formation of indeno[1,2-b]pyridines is figured in Scheme 2.

In this process, BFPAT can improve the electrophilic character of the electrophiles by virtue of its intrinsic Brønsted acidity which makes it able of bonding with the carbonyl oxygen. Moreover, the highly hydrophobic wall of a moiety of BFPAT effectively repels H_2O produced by condensation. The superiority of BFPAT to similar catalysts such as pentafluorophenylammonium triflate (PFPAT) [13] and diphenylammonium triflate (DPAT) [40], is ascribed to the lower basicity of the $(CF_3)_2C_6H_3NH_2$ counter amine compared to $C_6F_5NH_2$ and Ph_2NH.

It was suggested that the product 5 may form via the initial formation of intermediate I, which was obtained from the nucleophilic attack of 1,3-indanedione to the aldehyde. The second key intermediate is

Table 2.
Synthesis of indeno[1,2-b]pyridines in the presence of BFPAT

Entry	Ar	Ar′	Product	Yield	Mp[ref]
1	4-Cl-C_6H_4	C_6H_5	**5a**	90	186-188[29]
2	4-NO_2-C_6H_4	4-CH_3O-C_6H_4	**5b**	91	217-218[29]
3	3-NO_2-C_6H_4	2,4-$Cl_2C_6H_3$	**5c**	85	262-263[30]
4	4-Cl-C_6H_4	4-Cl-C_6H_4	**5d**	88	226-227[15]
5	2-Cl-C_6H_4	4-OMe-C_6H_4	**5e**	80	265-267[29]
6	4-F- C_6H_4	4-OMe-C_6H_4	**5f**	93	196-197[15]
7	4-NO_2- C_6H_4	4-OMe-C_6H_4	**5g**	92	223-225[29]
8	3- NO_2- C_6H_4	4-OMe-C_6H_4	**5h**	90	220-222[30]
9	4-Me- C_6H_4	4-OMe-C_6H_4	**5k**	92	160-161[15]
10	4-Br- C_6H_4	4-OMe-C_6H_4	**5l**	90	216-218[29]
11	4-Cl- C_6H_4	4-OMe-C_6H_4	**5m**	92	200-202[29]
12	4-Br- C_6H_4	2-pyridyl	**5n**	85	177-179[29]

enamine II, which is formed from acetophenone and ammonium acetate. Condensation of these two parts gives intermediate III, followed by intramolecular cyclization and air oxidation produces the final product.

It can be supposed that the water exclusion of BFPAT may favor both imine and intermediate I formation. In addition, $(CF_3)_2C_6H_3NH_2$ easily separated from the reaction mixture after workup with distillation under reduced pressure ($(CF_3)_2C_6H_3NH_2$: 85 °C/15 mmHg(lit.)).

4. Conclusion

In summary, we have demonstrated an efficient and practical process for the synthesis of some indeno[1,2-b]pyridine derivatives in ethanol using BFPAT as a green, inexpensive, and powerful organocatalyst. The advantages offered by this method are: simple reaction condition, operational simplicity, a green and cost-effective catalyst, easy purification, and excellent yields. We would like to say that this strategy is environmentally friendly, and is a new effective procedure for the synthesis of indeno[1,2-b]pyridine derivatives.

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