Article

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One-pot Solvent Free Synthesis of Some Tert-indolylmethane Amine Derivatives by $Fe(HSO_4)_3$ as a Recyclable Catalyst

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Solvent-free synthesis of 3-substituted indole derivatives by a one-pot three-component coupling reaction between aldehyde, N-alkyl aniline and indole by $Fe(HSO_4)_3$ catalyzed is described. The noticeable features of this protocol are the simplicity of the procedure, easy synthesized, recyclable and inexpensive catalyst, no organic solvent and high yields in relatively short reaction times.

Keywords: Multicomponent coupling reaction; $Fe(HSO_4)_3$; Solvent-free reaction; Tert-indolylmethane amine.

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, as high degrees of molecular diversity can be introduced by these reactions in a very fast, efficient, and time saving manner without the isolation of any intermediates.[1-7] Consequently, noticeable attention has been paid to the development of new and improved one-pot multicomponent reactions in recent years.[8-11]

Also significant interest has been devoted to the preparation of substituted indoles due to their varied biological activities[12-14] including antibiotics, insecticidal, and antioxidant.[15-17] They also act as inhibitors of tumor growth and colon cancer cell.[18]

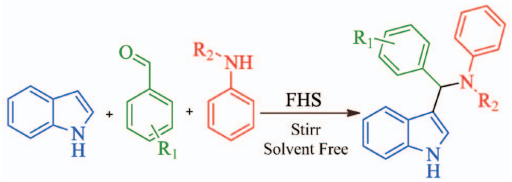
In spite of several methods available in the literature for the synthesis of substituted indoles,[19-25] there are only a few reports on production of substituted 3-aminoalkylated indoles using Multi Component Reactions (MCRs) protocols.[24,26]

In this work a three-component is reported reaction of indoles, N-alkylanilines and benzaldehydes in the presence of ferric hydrogen sulfate (FHS) as a recyclable, easy synthesized and inexpensive catalyst[27] and under solvent-free conditions is described.[28] (Scheme 1)

RESULTS AND DISCUSSION

Initially, we investigated the multicomponent reaction of benzaldehyde, aniline and indole in the absence or presence of FHS (10 mol %) as a catalyst. Unfortunately, the reaction did not proceed according to expectations and bis indolylmethane byproduct obtained as the major product instead of desired product. Surprisingly we find out that the reaction proceeded well when aniline was replaced with secondary amine such as N-methyl aniline.

Scheme 1 Catalytic synthesis of 3-aminoalkylated indoles



In order to obtain the best reaction condition for this catalytic transformation, the reaction was performed in different nonpolar, polar, protic and aprotic solvents such as ethanol, methanol, acetonitrile, DCM, THF and 1,4-dioxane in different temperatures. The results are summarized in Table 1. It appears solvents like EtOH and MeOH are not suitable for the reaction because of low yield of corrected product due to the formation of mentioned byproduct (Table 1, entries 1 and 2). The yield in DMF and DMSO were slightly better because of lower yield undesired bisindolylmethane byproduct (Table1, entries 7, 8, 18 and 19).

The best catalytic activity of FHS was found to be 10 mol % (Entry 10) and any excess of catalyst, beyond this proportion (10 mol %), did not show any further increase in the conversion and yield of the product (Entry 11) while de-

In the memory of Prof. Mohammad Rahimizadeh

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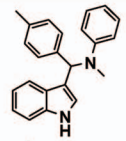
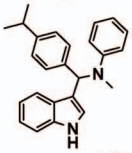
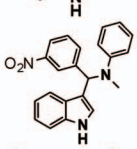
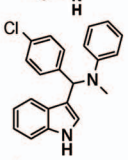
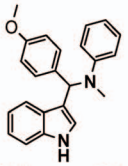
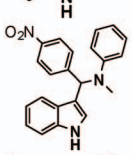
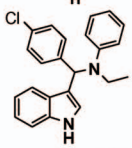
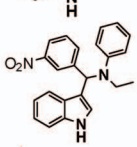
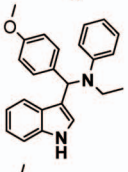
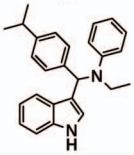
Table 1. Optimization conditions for reaction of N-methylaniline, *p*-methylbenzaldehyde, and indole

Entry [a]	Solvent [b]	Catalyst [c]	Time (h)	Temp (^{o}C)	Yield (%) [d,e]
1	Methanol	---	6	25	22
			2.5	45	25
2	Ethanol	---	6	25	22
			2.5	45	26
3	Acetonitrile	---	6	25	21
			2.5	45	25
4	DCM	---	6	25	12
			2.5	40	14
5	THF	---	6	25	15
			2.5	45	18
6	Dioxane	---	6	25	15
			2.5	45	17
7	DMF	---	6	25	25
			2.5	45	31
8	DMSO	---	6	25	22
			2.5	45	28
9	Solvent free	---	6	25	19
			2.5	45	29
10	Methanol	FHS (10 mol %)	6	25	51
			2.5	45	59
11	Methanol	FHS (20 mol %)	2.5	45	60
12	Methanol	FHS (5 mol %)	2.5	45	48
13	Ethanol	FHS (10 mol %)	6	25	52
			2.5	45	57
14	Acetonitrile	FHS (10 mol %)	6	25	45
			2.5	45	52
15	DCM	FHS (10 mol %)	6	25	30
			2.5	40	35
16	THF	FHS (10 mol %)	6	25	37
			2.5	45	45
17	Dioxane	FHS (10 mol %)	6	25	35
			2.5	45	37
18	DMF	FHS (10 mol %)	6	25	66
			2.5	45	75
19	DMSO	FHS (10 mol %)	6	25	54
			2.5	45	62
20	**Solvent free**	**FHS (10 mol %)**	6	25	83
		First Run	**2.5**	**45**	**95**
21[f]	Solvent free	FHS (10 mol %) Second Run	2.5	45	92
22[g]	Solvent free	FHS (10 mol %) Third Run	2.5	45	89
23[h]	Solvent free	FHS (10 mol %) forth Run	2.5	45	82
24[i]	Solvent free	FHS (10 mol %) fifth Run	2.5	45	78
25[j]	Solvent free	FHS (10 mol %) Sixth Run	2.5	45	73
26	Solvent free	$FeCl_2$	2.5	45	44
27	Solvent free	$FeCl_3$	2.5	45	36
28	Solvent free	$Fe(NO_3)_3.9H_2O$	2.5	45	57

[a] All reactions were performed using aldehyde 1 mmol, N-methylaniline 2 mmol and indole 1 mmol.
[b] 1.0 mL was used.
[c] The best catalytic activity of FHS was optimized to be 10 mol %.
[d] Yields are related to isolated pure products.
[e] Bisindolyl methane is the major byproduct.
[f-j] Efficiency of the reused catalyst in new runs (runs 2-6).

Table 2. Catalytic synthesis of 3-amino alkylated indoles under solvent-free conditions at 45 °C

No.	R_1	R_2	Product	Time (h)	Yield (%)[a]	mp found	Ref. (Reported)
1	p-Me	Me		2	95	158	**24** (160)
2	p-Isopropyl	Me		2.5	94	75-77	---
3	m-NO_2	Me		2	96	191	**25** (192)
4	p-Cl	Me		1.5	98	136	**24** (136)
5	p-MeO	Me		3	92	167	**24** (169)
6	p-NO_2	Me		1	98	65	**24** (66)
7	p-Cl	Et		2	95	105	---
8	m-NO_2	Et		2.5	92	87-90	---
9	p-MeO	Et		4	87	74	---
10	p-Isopropyl	Et		3	90	91	---

[a] Isolated yields

creasing the amount of catalyst from 10 to 5 mol % lowered the substrate conversion rate (Entry 12).

Surprisingly omitting the solvent made the reaction faster and a much better yield of desired indolylmethane

amine products for secondary amine was obtained.

Reusability of catalyst was examined for 5 times under the conditions on entry 20. It shows suitable yields after each run (Entry 21 to 25).

We used some catalysts such as $FeCl_3$, $FeCl_2$ and $Fe(NO_3)_3$ but they had not results like $Fe(HSO_4)_3$, (Entry 26 to 28).

The scope and generality of this method is illustrated in Table 2.

Different aldehydes, including aromatic aldehydes with electron-donating and electron-withdrawing groups, and different N-alkylanilines such as N-methyl- and N-ethylanilines, afforded the desired products in good yields. Electron-withdrawing groups on aldehyde react rapidly and were good reagents in this reaction. N-methylaniline is also better in comparison with N-ethylaniline because of low steric effects. N-Alkylanilines were used in excess to avoid the formation of bis(indolyl)alkanes. (Table 2)

A plausible mechanism was shown in Figure 1. Accordingly, after benzaldehyde activation with catalyst, an iminium ion obtained from aldehyde and N-alkylaniline which readily reacted with electron reach indole ring in 3 position. [Figure 1] The by-product is water and the catalyst was regenerated after proton abstraction from indole ring.

Decreasing of reaction times, increasing of isolated yields, low percent of bis indolylmethane formation as by-product and solvent free conditions are the benefits of this method by means of FHS as catalyst.[29]

EXPERIMENTAL

All solvents and reagents were purchased from Merck and Fluka. NMR spectra were recorded on Bruker Aspect 3000 (100 MHz) spectrometers. All chemical shifts are reported as ppm and were referenced to residual solvent signals. IR spectra were recorded on a Thermo Nicolet Avatar-370-FTIR spectrometer. Mass spectra were recorded on Varian CH7A spectrometer.

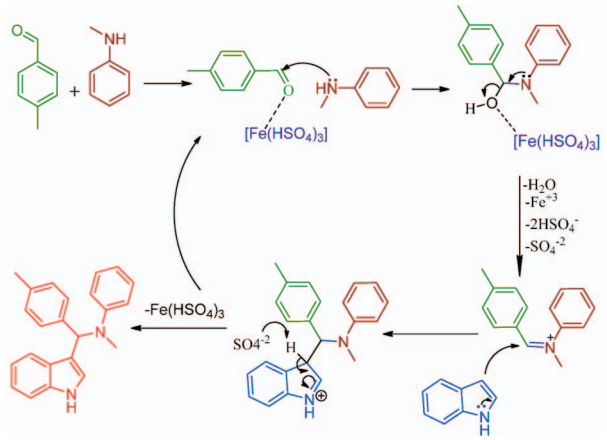


Fig. 1. A plausible mechanism for this reaction.

General procedure for the synthesis of 3-aminoalkylated indoles: A mixture of aldehyde (1 mmol), N-alkylaniline (2 mmol) and ferric hydrogensulfate (FHS) (10 mol %) was stirred at 45 °C for 3 min followed by addition of indole (1 mmol) and stirring is continued till the completion of the reaction as indicated by TLC (Table 2). The reaction mixture was diluted with diethyl ether (10 mL) and filtrate to recover the catalyst and extracted with (2 × 10 mL) HCl 5%. The organic phase washed with (2 × 10 mL) H_2O. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel, hexane–EtOAc, 3:1) to obtain analytically pure products. Some of the products are known compounds. (Table 2) and were characterized by comparison of their mp and spectral data with those of authentic samples.

SPECTRA DATA

[(1H-Indol-3-yl)-(4-isopropyl-phenyl)-methyl]-methyl-phenyl-amine (2): Dark brown solid; mp = 75-77 °C ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.90 (br s, 1 H), 6.90–7.45 (m, 7H), 6.40–6.65 (d, J = 12.0 Hz, 2H), 5.50 (s, 1H), 2.70-3.05 (m, 1H), 2.80 (s, 3H), 1.15-1.40 (d, J = 12.0 Hz, 6H). IR (KBr): 3412, 2958, 2924, 1613, 1516, 1455, 741 cm^{-1}. MS: m/z = 355 $[M + H]^+$. Anal. Calcd. for $C_{25}H_{26}N_2$: C, 84.70; H, 7.39; N, 7.90. Found: C, 84.63; H, 7.35; N, 7.93. **[(1H-Indol-3-yl)-(4-chloro-phenyl)-methyl]-ethyl-phenyl-amine (7):** Brownish red solid; mp = 105 °C ^{1}H NMR (100 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.45–7.55 (m, 2H), 6.85–7.40 (m, 8H), 6.45–6.60 (d, J = 12.0 Hz, 2H), 5.60 (s, 1H), 3.15 (q, J = 17.0 Hz, 2H), 1.25 (t, J = 17.0 Hz, 3H). IR (KBr): 3412, 1613, 1516, 1488, 1455, 743 cm^{-1}. MS: m/z = 361 $[M + H]^+$. Anal. Calcd. for $C_{23}H_{21}ClN_2$: C, 76.55; H, 5.87; N, 7.76. Found: C, 76.49; H, 5.85; N, 7.79. **[(1H-Indol-3-yl)-(3-nitro-phenyl)-methyl]-ethyl-phenyl-amine (8):** Yellow solid; mp = 87-90 °C ^{1}H NMR (100 MHz, $CDCl_3$): δ 8.10 (d, J = 8.0 Hz, 2H), 8.00 (br s, 1H), 7.45-7.55 (m, 2H), 6.85-7.40 (m, 8H), 6.45-6.60 (d, J = 12.0 Hz, 2H), 5.65 (s, 1H), 3.15 (q, J = 17.0 Hz, 2H), 1.20 (t, J = 17.0 Hz, 3H). IR (KBr): 3412, 1613, 1524, 1349, 743 cm^{-1}. MS: m/z = 372 $[M + H]^+$. Anal. Calcd. for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.32; H, 5.71; N, 11.36. **[(1H-Indol-3-yl)-(4-methoxy-phenyl)-methyl]-ethyl-phenyl-amine (9):** Brown solid; mp = 74 °C ^{1}H NMR (100 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.25–7.65 (m, 8H), 6.90–7.20 (m, 4H), 6.70–6.80 (d, J = 4.0 Hz, 2H), 5.45 (s, 1H), 3.90 (s, 3H), 3.00 (q, J = 17.0 Hz, 2H), 1.10 (t, J

= 17.0 Hz, 3H). IR (KBr): 3412, 1613, 1521, 1349, 741 cm^{-1}. MS: *m/z* = 357 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.79; H, 6.75; N, 7.84. **[(1H-Indol-3-yl)-(4-isopropyl-phenyl)-methyl]-ethyl-phenyl-amine (10):** Brown solid; mp = 91 °C ^1H NMR (100 MHz, $CDCl_3$): δ 7.90 (s, 1H), 6.85–7.40 (m, 7H), 6.40–6.60 (d, *J* = 12.0 Hz, 2H), 5.55 (s, 1H), 2.85-3.15 (m, 3H), 0.90-1.20 (m, 3H), 1.00-1.10 (d, *J* = 12.0 Hz, 6H). IR (KBr): 3414, 3006, 2960, 2926, 2869, 1613, 1515, 1416, 741 cm^{-1}. MS: *m/z* = 368 $[M + H]^+$. Anal. Calcd. for $C_{26}H_{28}N_2$: C, 84.74; H, 7.66; N, 7.60. Found: C, 84.71; H, 7.65; N, 7.62.

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