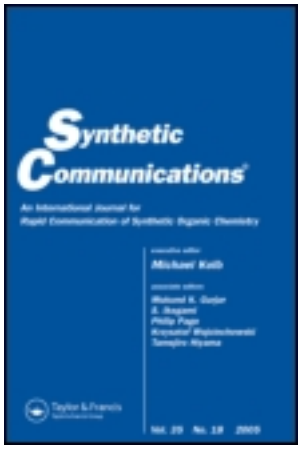

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PANI-HBF_4: A Reusable Polymer-Based Solid Acid Catalyst for Three-Component, One-Pot Synthesis of 3-Substituted Amino Methyl Indoles Under Solvent-Free Conditions

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PANI-HBF_4: A REUSABLE POLYMER-BASED SOLID ACID CATALYST FOR THREE-COMPONENT, ONE-POT SYNTHESIS OF 3-SUBSTITUTED AMINO METHYL INDOLES UNDER SOLVENT-FREE CONDITIONS

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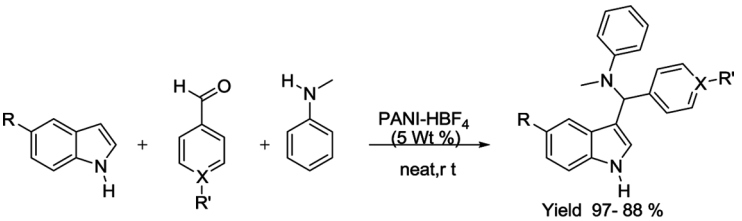
GRAPHICAL ABSTRACT



Where R = -H, -Br, $-OCH_3$
R' = -H, $-OCH_3$, $-CH_3$, $-NO_2$, -Cl, -Br
X = -C, -N

Abstract *A simple, fast, efficient, high-yielding, and green process is developed for one-pot, three-component synthesis of 3-substituted amino methyl indoles under solvent-free conditions using polyaniline salt as polymer-based reusable solid acid catalyst at room temperature. The advantages of polyaniline salt catalyst are ease of synthesis and handling, low cost, versatality, and recyclability.*

Keywords Multicomponent reaction; polyaniline salt catalyst; reusable catalyst; 3-substituted amino methyl indoles

INTRODUCTION

Multicomponent reactions have offered many fascinating and challenging transformations in organic synthesis.[1–7] The atom-economy, convergent character, operational simplicity, structural diversity, and complexity of the molecules are the

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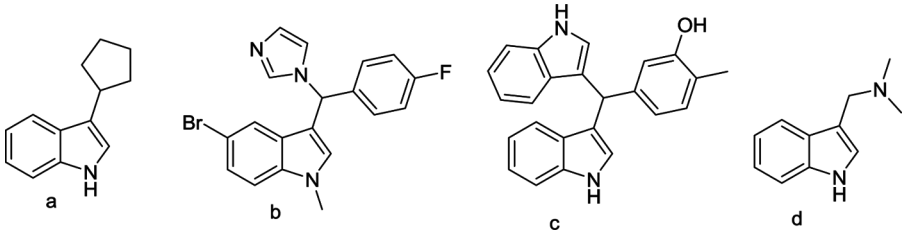


Figure 1. Biologically active 3-substituted indoles.

major advantages associated with multicomponent reactions. These multicomponent reactions are emerging as a powerful tool in the synthesis of biologically important compounds.[8,9]

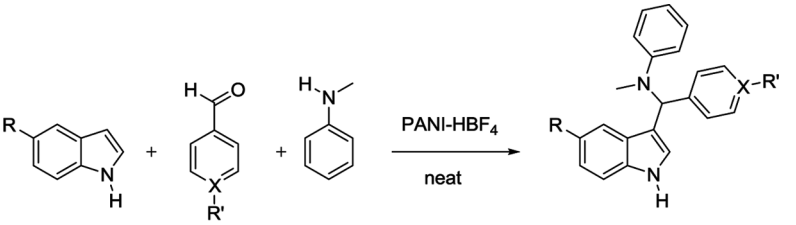
Indole derivatives have become increasingly useful and important in the field of pharmaceuticals.[10–13] Substituted 3-alkyl indole moieties are of much importance as they are widely distributed in nature and reveal a broad range of biological activity.[14,15] Indoles with substituents at the 3-position are considered as venerable pharmacophores[16–19] in drug discovery and are found in various natural products such as 5-HT1B/1D receptor agonist activities used in the treatment of migraines (Fig. 1a), aromatase inhibitors for breast cancer (Fig. 1b),[20] HIV-1 integrase inhibitor (Fig. 1c),[29] and Gramine (Fig. 1d).

The immense potential of the indole nucleus as drug candidates prompted us to synthesize substituted 3-alkyl indoles based on multicomponent reactions. Literature reports[22–28] for the synthesis of 3-substituted amino methyl indole derivatives by various pathways are given in Table 1. Most of the methods have shortcomings such as use of strongly acidic conditions, long reaction times, poor yields, and solvents that are not acceptable in the context of green synthesis. Therefore, the discovery of facile, efficient, and environmentally benign approaches for the synthesis of indole derivatives is highly desirable.

Heterogeneous catalysts have gained much importance in organic synthesis. Recently, we have been establishing the use of polymer-based solid acid catalyst in various organic synthesis.[29] In this work, 3-substituted amino methyl indole derivatives were synthesized efficiently by multicomponent reaction of aldehydes,

Table 1. Literature reports on the synthesis of amino methyl inldoles

No.	Reactants; catalyst, solvent, condition	Time	Yield (%)	Ref.
1	Aldehyde, trimethyl silyl dialkyl amine, indole; $LiClO_4$; diethyl ether; rt	6 h	65–84	22
2	Aryl imine, indole; cinchona alkaloid; ethyl acetate; 50 °C	8–72 h	86–98	23
3	N-Sulfonyl aldemines, indole; $Cu(OTf)_2$; DCM; 20 °C	3–5 days	47–94	24
4	Immonium salts, indole (or) N-methyl indole; DCM, toluene; rt	2–15 h	73–92	25
5	Tosyl aldemine, 3-bromo indole; THF; rt	12–18 h	15–73	26
6	Aldemines, indole; $Dy(OTf)_3$; ionic liquid; rt	10–24 h	30–57	27
7	Aldehyde, amine, indole; PMA-SiO_2; rt CH_3CN; neat	3–4.5 h 1.75–2.75 h	65–85 85–95	28



Where R = -H, -Br, $-OCH_3$
R' = -H, $-OCH_3$, $-CH_3$, $-NO_2$, -Cl, -Br
X = -C, -N

Scheme 1. Synthesis of 3-substituted indoles catalyzed by PANI-HBF_4.

N-methyl aniline, and indoles under solvent-free conditions at room temperature using PANI-HBF_4 as polymer-based solid acid catalyst (Scheme 1).

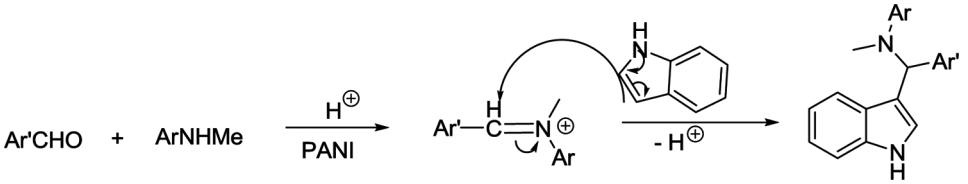
RESULTS AND DISCUSSION

Initially the reaction was conducted with benzaldehyde (0.01 mol), N-methyl aniline (0.013 mol), and indole (0.01 mol) under solvent-free conditions at room temperature for 30 min. The reaction gave 20% product of 3-substituted indole, 30% side product of bisindolylmethane, and remainders of starting material (Table 2). This reaction was carriedout with increasing amounts of PANI-HBF_4 catalyst with respect to the amount of benzaldehyde, and the results are included in Table 2. By

Table 2. Effect of catalyst amount on the product yield

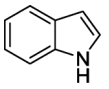
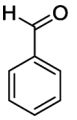
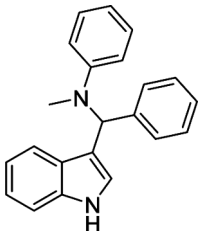
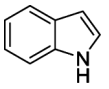
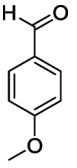
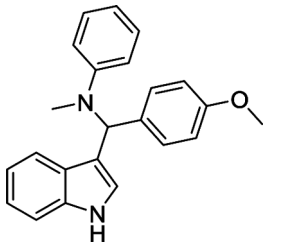
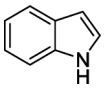
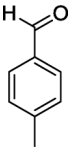
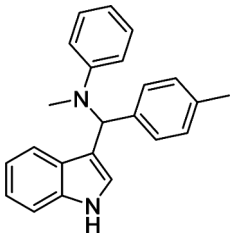
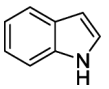
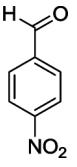
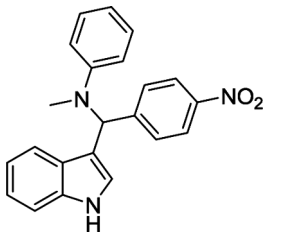
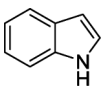
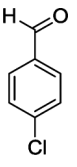
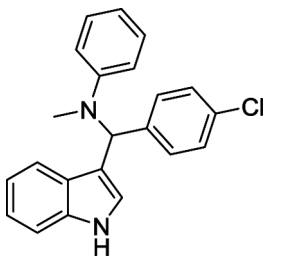
No.	Catalyst (wt%)[a]	Product yield (%)[b]	By-product (%)[b]
1	0	20	30
2	1	45	18
3	2	60	10
4	3	70	5
5	4	80	2
6	5	95	0

[a]With respect to aldehyde.
[b]Isolated yields.



Scheme 2. Possible mechanism for the formation of 3-substituted indoles.

Table 3. Three-component reaction of N-methyl aniline, indoles, and aldehydes catalyzed by PANI-HBF_4 for synthesis of 3-substituted amino methyl indoles

No.	Indole	Aldehyde	Product	Time (min)	Isolated yield (%)
1				30	95
2				30	97
3				30	94
4				45	90
5				40	92

(*Continued*)

Table 3. Continued

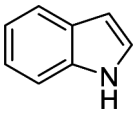
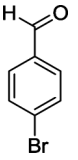
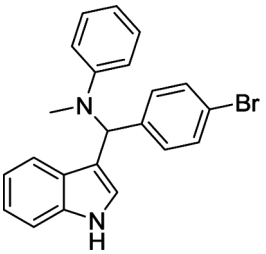
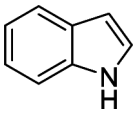
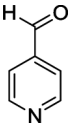
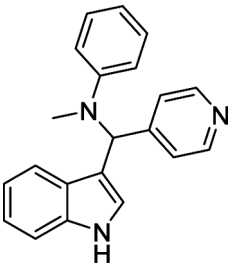
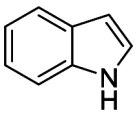
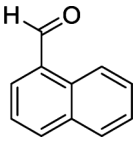
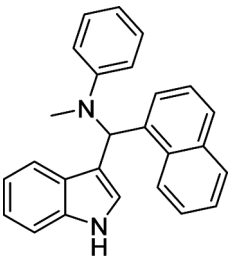
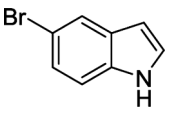
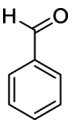
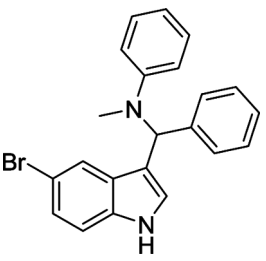
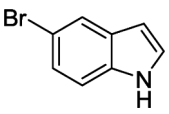
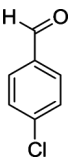
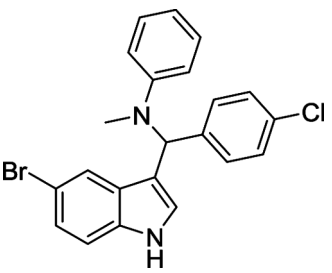
No.	Indole	Aldehyde	Product	Time (min)	Isolated yield (%)
6				40	92
7				45	93
8				45	90
9				50	92
10				50	88

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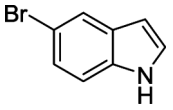
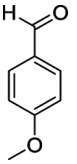
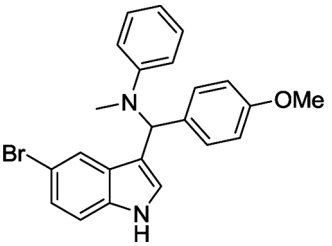
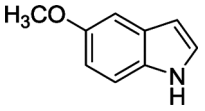
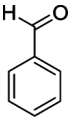
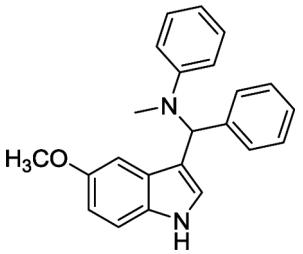
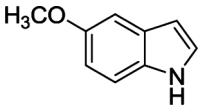
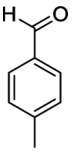
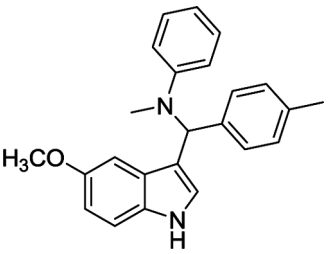
Table 3. Continued

No.	Indole	Aldehyde	Product	Time (min)	Isolated yield (%)
11				45	90
12				45	93
13				45	90

increasing the amount of catalyst from 1 to 4 wt%, the desired product formation was increased with decrease in by-product (bisindolylmethane formation) and starting material quantity. The reaction of benzaldehyde with N-methyl aniline in the presence of catalyst proceeds via the formation of immonium ion intermediate, which then reacts with indole and gives the product (3-substituted indole). Simultaneously, benzaldehyde reacts with indole to give the side product (bisindolylmethane formation) (Scheme 2). With the increase of catalyst amount of polyaniline salt (i.e, increasing the H^+ concentration in the catalyst), the formation of immonium ion increases and subsequently the desired product formation also increases. The product in 95% yield was obtained without side product with the use of 5 wt% of catalyst (Table 2). Increase in catalyst amount (>5 wt%), reaction time, and temperature of the reaction did not improve the product yield.

The amount of dopants, both fluoroboric acid and dodecylhydrogensulfate together, present in polyaniline salt was reported (47 wt%). However, it is difficult to find out the percentage of individual dopant present on polyaniline salt. The acid

groups such as fluoroboric acid and dodecyl hydrogen sulfate present in the polyaniline salt take part in organic transformation.

To evaluate the generality of this procedure, a variety of aromatic aldehydes (having electron-withdrawing and electron-donating groups) and heterocyclic aldehyde were reacted with a different indoles (indole, 5-bromo indole, 5-methoxy indole) and N-methyl aniline in the presence of a very low amount of PANI-HBF_4 catalyst (5 wt%) under solvent-free conditions and gave products in excellent yields. Results of these experiments are presented in Table 3. Electron-donating groups on the aromatic ring react faster than electron-withdrawing substituents and gave better yields. This indicates that the 3-substituted amino methyl indoles can be produced in greater yield in less reaction time when compared to the reported procedures.[22–28] All the synthesized compounds are well characterized by spectral data, and the characterization data for four new compounds (Table 3, entries 6, 7, 9, and 12) were reported in the experimental section.

To verify the recyclability of the PANI-HBF_4 catalyst, the reaction of benzaldehyde (0.01 mol), N-methyl aniline (0.013 mol), and indole (0.01 mol) was performed under solvent-free condition at room temperature for 30 min using 5 wt% of PANI-HBF_4 catalyst (with respect to the amount of benzaldehyde). After the reaction, ethyl acetate was added to the reaction mixture, and the catalyst was removed by filtration, washed thoroughly with ethyl acetate, dried in an oven, and reused for the next cycle. The reaction proceeded smoothly with yields of 95, 95, 94, 93, 91, and 93%. This result indicates that the activity of the catalyst was not affected by reusing the catalyst.

CONCLUSION

In conclusion, a simple, efficient, and green process was developed for the synthesis of 3-substituted amino methyl indoles using polyaniline salt. Easy synthesis of the catalyst, stability of catalyst, easy handling, convenient workup procedure, mild reaction conditions, versatility, low cost, reusability, and the eco-friendly nature of the catalyst make this method a valid contribution to the existing methods.

EXPERIMENTAL

Analytical thin-layer chromatography (TLC) was performed using Merck silica-gel 60 F glass plates. Flash chromatography was performed using Merck silica gel (60–120 mesh). Melting points were determined using a Mel-Temp II melting-point apparatus. NMR spectra were recorded using a Gemini 200-MHz Varian instrument and an Avance 300-MHz Bruker UX 300 Fourier transform (FT)NMR. NMR data were obtained in $CDCl_3$/DMSO-d_6 solution, and chemical shifts (δ) were given in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra were recorded using electrospray ionization (ESI) ion trap mass spectrometer (Thermofinnigan, Sanzox, CA, USA). High-resolution mass spectra (HRMS) were recorded using an Applied Biosystems QSTAR XL spectrometer. Infrared (IR) spectra were recorded using a Shimadzu 435 IR spectrophotometer.

Synthesis and Characterization of Polyaniline Salt Catalyst

A polyaniline salt, polyaniline-fluoroboricacid-dodecylhydrogensulfate salt (PANI-HBF_4), was synthesized via emulsion polymerization pathway and characterized in our earlier report.[30] Aniline was oxidized to polyaniline salt by benzoyl peroxide in the presence of sodium lauryl sulfate and fluoroboric acid. This polymerization pathway leads to incorporation of both acid and surfactant groups, into the polyaniline chain as dopants.

In a typical experiment, 3 g of benzoyl peroxide were dissolved in 30 ml chloroform in a 250-ml round-bottomed flask. Sodium lauryl sulfate (1 g) in 20 mL water was added to the solution. The mixture was stirred at 40 °C. Fluoroboric acid (5.5 ml) and aniline (1 mL) were dissolved in 50 ml water. This solution was added dropwise to the solution during 15–20 min under constant stirring, and the reaction was continued for 8 h. The chloroform layer containing polyaniline salt was separated from the aqueous layer and washed three times with distilled water. Polyaniline salt in the chloroform layer was precipitated by adding 300 ml of acetone. Polyaniline salt powder was filtered, washed with water followed by acetone, and dried at 70 °C until a constant mass.

Formation of polyaniline salt was confirmed from FTIR spectroscopy, electronic absorption spectroscopy, and x-ray diffraction studies. Polyaniline salt showed aggregated granular morphology with viscosity in dimethyformamide solvent (1.3 dL/g) and conductivity (0.03 S/cm).

General Experimental Procedure for the Synthesis of 3-Substitute Amino Methyl Indoles

In a typical experiment, benzaldehyde (0.01 mol, 1 mL) was added to N-methyl aniline (0.013 mol, 1.4 mL) in a 10-mL round-bottomed flask. PANI-HBF_4 (5 wt%) catalyst with respect to aldehyde (50 mg) was added, and the reaction mixture was stirred at room temperature for 5 min. Then indole (0.01 mol, 1.17 g) was added and stirred at room temperature. Completion of the reaction was monitored by TLC. After completion, ethyl acetate (2×10 mL) was added to the reaction mixture. The mixture was filtered, and the catalyst was removed. The solvent was evaporated under reduced pressure, and the crude product was purified by silica-gel column chromatography (eluent: n-hexane/EtOAc, 4/1) to furnish [(1H-indol-3-yl)-phenyl-methyl]-methyl-phenyl-amine (3.28 g, 95%). A similar procedure was adopted for the preparation of other 3-substituted amino methyl indoles. Authenticity of the products was confirmed from mp, ^{1}H NMR, and mass spectral data.

Spectral Data for New Compounds

[(4-Bromo-phenyl)-(1H-indol-3-yl)-methyl]-methyl-phenyl-amine (6). Brick red solid; mp = 126–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H), 5.5 (s, 1H), 6.58–6.60 (m, 3H), 7.00 (d, 2H), 7.18–7.22 (m, 4H), 7.24–7.28 (m, 3H), 7.36 (s, 1H), 7.98 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 30.75, 47.43, 111.13, 112.41, 119.45, 119.67, 122.19, 123.68, 123.98, 124.27, 126.70, 129.64, 130.81, 133.90, 136.72, 148.02, 149.49, 153.82. IR (KBr): 423, 517, 741, 1009, 1177, 1452, 1515,

1613, 2854, 2879, 3036, 3377 cm^{-1}. ESIMS: m/z 391 ($M^+ + H$). HRMS calcd. for $C_{22}H_{20}N_2Br$, 391.0809. Found 391.0794.

[(1H-Indol-3-yl)-pyridin-4-yl-methyl]-methyl-phenyl-amine (7). Light brick red solid; mp = 95–98 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H), 5.48 (s, 1H), 6.47–6.49 (d, 2H), 6.53 (s, 1H), 6.93–6.98 (m, 3H), 7.10–7.15 (m, 4H), 7.30 (d, 1H), 8.0 (s 1H), 8.46 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 30.82, 47.36, 111.00, 112.35, 119.34, 119.75, 119.89, 122.07, 123.93, 126.82, 129.58, 130.66, 131.19, 132.14, 136.67, 143.74, 147.74. IR (KBr): 425, 606, 743, 1004, 1183, 1454, 1518, 1599, 2870, 2920, 3038, 3406 cm^{-1}. ESIMS: m/z 314 ($M^+ + H$). HRMS calcd. for $C_{21}H_{20}N_3$, 314.1657. Found 314.1667.

[(5-Bromo-1H-indol-3-yl)-phenyl-methyl]-methyl-phenyl-amine (9). Brick red solid; mp = 140–145 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H), 5.5 (s, 1H), 6.57–6.60 (q, 3H), 7.00 (d, 2H), 7.18–7.22 (m, 4H), 7.24–7.28 (q, 3H), 7.36 (s, 1H), 7.98 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 30.75, 47.43, 111.15, 112.44, 119.41, 119.76, 122.24, 123.76, 123.98, 124.32, 126.87, 129.70, 130.85, 133.96, 136.78, 148.12, 149.54, 153.92. IR (KBr): 477, 525, 748, 1009, 1103, 1450, 1514, 1611, 2879, 3022, 3061, 3380 cm^{-1}. ESIMS: m/z 391 ($M^+ + H$). HRMS calcd. for $C_{22}H_{20}N_2Br$, 391.0801. Found 391.0796.

[(5-Methoxy-1H-indol-3-yl)-phenyl-methyl]-methyl-phenyl-amine (12). Brick red solid; mp = 186–190 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H), 3.78 (s, 3 H), 5.48 (s, 1H), 6.48–6.50 d, 2H), 6.76–6.79 (t, 2H), 6.92–7.00 (m, 3H), 7.09–7.13 (m, 3H), 7.18–7.22 (q, 1H), 7.25–7.28 (q, 1H), 7.33–7.35 (d, 1H), 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 31.04, 47.10, 55.22, 111.1, 112.41, 113.57, 119.19, 119.25, 120.00, 120.12, 121.89, 123.51, 123.87, 129.63, 129.84, 133.30, 136.24, 136.96. IR (KBr): 428, 480, 719, 1023, 1171, 1208, 1485, 1584, 1621, 2829, 2934, 3001, 3391 cm^{-1}. ESIMS: m/z 343 ($M^+ + H$). HRMS calcd. for $C_{23}H_{23}N_2O$, 343.1810. Found 343.1818.

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