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BRONSTED ACID CATALYST PROMOTED FOR BIOACTIVE SYNTHESIS OF 2, 4, 5-TRIPHENYL IMIDAZOLE DERIVATIVES

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ABSTRACT

The highly versatile and an efficient synthesis of 2,4,5-trisubstituted imidazoles is obtained by three component cyclocondensation of 1,2-dicarbonyl compounds, substituted aromatic aldehydes and ammonium acetate in thermal solvent free condition using Brønsted acidic methane sulfonic acid as catalyst. All the compounds were evaluated by advanced spectroscopic data (1H NMR, 13C NMR& LCMS) and the structural determination of the novel derivations was calculated by elemental analysis. The main focus of this process is cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short time reactions. Multicomponent reactions were encouraged an outstanding status in synthetic organic and medicinal chemistry for their high degree of atom economy and application in the diversity oriented convergent synthesis of complex organic moiety from simple and readily available substrates in a single vessel. In the present study, ten hybridized imidazoles derivatives were synthesized via cyclo condensation and evaluated for their invitro antimicrobial activity and antioxidant properties.

KEYWORDS: 2, 4, 5-triarylimidazoles, benzil, aromatic aldehydes, bioevluation.

1. INTRODUCTION

Imidazoles are a class of heterocyclic compounds that contain nitrogen atom and are currently under intensive focus due to their wide range of applications.[1] Synthetic study of imidazole units is very important due to their potent biological activity[2] and synthetic utility.[3] Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems. Compounds containing imidazole moiety have many pharmacological properties and play important roles in bio chemical processes.[4] The potency and wide applicability of the imidazole pharama cophores can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active sites 3b.[5,6]

Naturally occurring substituted imidazoles, as well as synthetic derivatives thereof, exhibit wide ranges of biological activities, making them attractive compounds for organic chemists. They act as inhibitors of p38 MAP kinase[7], B-Raf kinase[8], transforming growth factor b1 (TGF-b1) type 1 active in receptor-like kinase (ALK5)[9], cyclooxygenase-2 (COX-2)[10] and biosynthesis of interleukin-1 (IL-1).[11] Appropriately substituted imidazoles are extensively used as glucagon receptors[12] and CB1 cannabinoid receptor antagonists[13], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR)[14], antibacterial and antitumor agents[15] and also as pesticides.[16] Recent advances in green chemistry and organometallic catalysis has extended the application of imidazoles as ionic liquids[17] and Nheterocyclic carbenes.[18] Ionic liquid (IL) technology offers a new and environmentally benign approach toward modern synthetic chemistry. Ionic liquids have interesting advantages such as extremely low vapour pressure, excellent thermal stability, reusability, and talent to dissolve many organic and inorganic substrates. Ionic liquids have been successfully employed as solvents and catalyst for a variety of reactions which promise widespread applications in industry and organic syntheses.[19]

We report here a simple and efficient producers for the preparation of the 2, 4, 5-triarylimidazoles using methanesulphonic acid Brønsted acidic as catalyst that is considered as efficient catalyst. The methodology reported here in, consequently, the represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles derivatives.

2. METHODS AND MATERIALS

2.1. Experimental

All reagents, chemicals and solvents were procured from Aldrich and Merck and used without further purification. The newly synthesized derivatives of melting points that determined by open capillary method using a Galen Kamp melting point apparatus and is uncorrected. The desired products were characterized by spectroscopy data (FTIR, ^{1}H NMR and ^{13}C NMR spectra and Mass) and melting points. SHIMADZU FT-IR-8400s spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded by the compounds on a Bruker (400-MHz) Ultrasheild NMR and $CDCl_3$ was used as a solvent. The purity of the compounds and the progress of the reactions were monitored by use of TLC.

2.3. General Methods for Synthesis of 2,4,5-Trisubstituted Imidazoles

The mixture of Benzil (1mol), aldehyde (1mol), and ammonium acetate (2mol) were introduced in clean and dry 50mL four neck rounded bottom flask and Bronsted acid catalyst added in a above the mixture(3mmol) in an oil bath at room temperature as in Scheme-I. Then the reaction mixture was heated to 100°C for the appropriated period of time. After completion of the reaction, progress of the reaction was monitored by TLC; the mixture was cooled, poured in crushed ice and also neutralised with sodium carbonate solution. The mixture was taken in ethyl acetate and washed with water. The ethyl acetate layer was separated followed by distillation U/vacuumed and the solid product purified by recrystallization from ethanol. The entire desired product was characterized by comparison of their physical data with those of known compounds. Some characterization data for selected known products are given below**.**

3. SPECTRAL AND ANALYTICAL DATA

1). 2, 4, 5-Triphenyl-1H-imidazole (4a)

M.p. 269–271°C; FTIR (KBr, cm−1): 3436 (NH), 2989, 2479, 1638(C=C), 1510 (C=N); ^{1}HNMR (400 MHz, $CDCl_3$): 11.372 (s, 1H, NH, imidazole), 8.068 (d, J=7.6 Hz, 2H, aromatic), 7.845–7.287 (m, 13H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 149.08, 137.44, 135..54, 130..78, 130.66, 129.72, 128.83, 128.23, 127.65, 127.07, 125.88; LCMS (m/z); 297.41(M^{+}+H); Molecular formulae: $C_{21}H_{16}N_2$; Elemental analysis: Calculated: C- 85.11, H- 5.43, N- 9.44; Obtained: C- 85.05, H -5.41, N- 9.53.

2). 4-(4, 5-Diphenyl-1H-imidazol-2-yl)-phenol (4b)

M.p: 267–269°C. FTIR (KBr, cm^{-1}): 3590 (OH), 3454 (NH), 3284, 3064, 1701(C=C), 1283; 1HNMR (400 MHz, CDCl3): 11.742 (s, 1H, NH-imidazole), 9.158 (s, 1H, OH), 7.90 (d, J=7.6 Hz, 2H), 7.578–7.298 (m, 10H, Ar-H), 6.947 (d, J=8.8 Hz, 2H); ^{13}C NMR (400MHz, $CDCl_3$): 158.36, 147.61, 128.12, 126.74, 124.53, 121.89, 114.74, 114.85, 99.67, 95.46; LCMS (m/z); 313.17(M++H); Molecular formulae: C_{21} H_{16} N_2O; Elemental analysis: Calculated: C-80.74, H- 5.15, N- 8.97; Obtained: C-80.67,H – 5.14, N- 9.08.

3). 2-(2, 5-Dimethoxyphenyl)-4,5-diphenyl-1Himidazole (4c)

M.p-181-183°C. FTIR (KBr, cm-1):3333(NH), 3059(C-H), 2962, 2834, 1648(C=N), 1524, 1221, 1175, 1047, 742, 696. ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.690 (s, 1H, NH-imidazole),8.057-7.435(m,13H,Ar-H), 3.745(s,3H,OCH_3), 3.685(s. 3H,OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$):158.35, 152.66, 148.23, 144.21, 141.95, 138.46, 136.07, 134.19, 131.15, 130.83, 128.72, 128.61, 128.41, 128.13, 127.22, 126.35, 126.12, 119.71, 115.014, 115.38, 113.76, 55.91, 55.47; LCMS (m/z);357.44 (M+H); Molecular formulae : C_{23} H_{20} N_2 O_2; Elemental analysis: Calculated: C- 77.51, H-5.65, N-7.86; Obtained: C- 77.48, H – 5.64 , N- 7.92.

4). 2-(2, 4, 6-Trimethoxyphenyl)-4, 5-diphenyl-1Himidazole (4d)

M.p:180-182°C. FTIR (KBr, cm-1): 3392(NH), 3049(C-H), 2936, 2848, 1656 (C=N), 1525, 1222, 1196, 1039, 742, 693.^{1}HNMR (400MHz,$CDCl_3$) ppm: 11.455 (s, 1H, NH imidazole), 7.895-7.451 (m, 10H, Ar-H), 6.868-6.545(m, 2H, Ar-H), 3.690(s,3H, OCH_3), 3.612(s,6H,2.OCH_3);^{13}CNMR(400MHz,$CDCl_3$)ppm:153. 55,151.26,146.19,141.32, 136.71,131.66,130.95, 128.71, 128.54, 128.27, 128.01, 126.96,119.67,116.58,114.82, 112.76,55.55, 54.70. LCMS (m/z); 387.31 (M+H); Molecular formulae:
C_{24} H_{22} N_2 O_3; Elemental analysis: Calculated: C- 74.59, H- 5.73, N-7.25; Obtained: C- 74.52, H- 5.72, N- 7.35.

5). 2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4e)

M.p 262-264°C. FTIR (KBr, cm^{-1}): 3250 (NH), 3082 (C-H), 2914, 2902, 1601(C=N), 1520, 1156, 1087, 728, 692, 639. ^{1}HNMR (400MHz, CDCl3) ppm: 11.857 (s, 1H, NH-imidazole), 8.245 (d, J=8.4 Hz, 2H, Ar-H), 7. 874-7.562 (m, 12H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$):148.28, 138.96, 135.08, 131.74, 130.52, 129.20, 128.87, 128.56, 128.26, 128.12, 128.00, 127.85, 127.37, 126.83, 126.25; LCMS (m/z); 322.22 (M+2);: Molecular formulae: C_{21} $H_{15}Cl$ N_2; Elemental analysis: Calculated: C- 76.25 , H-4.56 , N- 8.46; Obtained: C- 76.17, H- 4.55, N- 8.54.

6). 2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (4f)

M.p: 249-252°C. FTIR (KBr, cm-1): 3420(NH), 3027(C-H), 2924, 2835, 16034(C=N), 1501, 1126, 1069, 826, 728, 715, 696. 1HNMR (CDCl3, 400MHz) ppm: 11.247(s, 1H, NH), 8.106(d, J= 8.0 Hz, 2H), 7.846 (d, J= 8.4 Hz, 2H), 7.720-7.274 (m, 10H, Ar-H); ^{13}C NMR (400MHz, $CDCl_3$): 145.59, 138.62, 135.19, 131.78, 130.88, 129.72, 129.13, 128.96, 128.51, 128.15, 127.88, 127.36, 127.09, 126.55, 121.63. LCMS (m/z); 376.18 (M+2); Molecular formulae: C_{21} $H_{15}Br$ N_2; Elemental analysis: Calculated: C- 67.21, H- 4.02, N-7.46; Obtained : C- 67.14, H -4.01, N- 7.53.

7). 2-(2-iodo-3,4-dimethoxyphenyl)-4,5-diphenyl-1H)-imidazole (4g)

M.p: 248-250°C. FTIR (KBr, cm-1):3333 (NH-imidazole), 3055(C-H), 2954, 1588 (C=N), 1691 (C=O), 1512, 1345, 874. ^{1}HNMR (400 MHz, $CDCl_3$) ppm:11.569 (s,1H,NH-imidazoles), 7.547 – 7.291 (m, 10H, Ar-H) 6.955(s,1H,Ar-H), 6.667(s,1H,Ar-H), 3.715 (s,6H,2OCH3); ^{13}C NMR (400 MHz, $CDCl_3$) ppm: 158.44, 153.65, 148.36, 136.19, 130.21, 129.53, 128.66, 127.74, 110.31, 108.47, 100.65, 50.95. LCMS (m/z); 484.28 (M+2); Molecular formulae: C23 H19 N2O2; Elemental analysis : Calculated : C- 57.28, H- 3.97, N-5.81; Obtained: C- 57.21, H – 3.95, N-5.89.

8).4-(4,5-diphenyl-1H-imidazol-2-yl)benzaldehyde (4h)

M.p: 221-223°C. FTIR (KBr, cm-1): 3300 (NH), 3052(C-H), 2980, 1593 (C=N), 1696 (C=O), 1504, 1345, 876. 1H NMR (400 MHz, $CDCl_3$) ppm: 11.779 (s, 1H, NH-imidazoles) 10.548 (s, 1H, Aldehyde), 8.214 – 7.287 (m, 14H, Ar-H). 13C NMR (400 MHz, $CDCl_3$) ppm: 195.07, 138.58, 134.55, 132.47, 130.15, 129.67, 129.17, 128.95, 128.76, 128.51, 128.39, 128.78, 128.16, 128.08, 127.48. LCMS (m/z); 325.07; Molecular formulae: C22 H16 N2O; Elemental analysis : Calculated : C- 81.45, H-4.96, N-8.64; Obtained: C- 81.38, H – 4.95, N- 8.74.

9). 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzonitrile (4i)

M.p:234-236°C. FTIR (KBr, cm-1): 3365 (NH), 3048(C-H), 2976, 1585 (C=N), 1694 (C=O), 1515, 1342, 873. ^{1}H NMR (400 MHz, $CDCl_3$): 11.845 (s, 1H, NH-imidazoles) 8.014 – 7.295 (m, 14H, Ar-H). 13C NMR (400 MHz, CDCl3) ppm: 147.07, 137.79, 135.15, 130.36, 129.75, 129.18, 128.96, 128.57, 128.19, 127.64,119.09,114.76; LCMS (m/z); 322.34; Molecular formulae: C22 H15 N3; Elemental analysis: Calculated: C- 82.22, H-4.70, N-13.08; Obtained: C- 82.14, H – 4.68, N- 13.17.

10). 2-(4-Nitrophenyl)-4.5-diphenyl-1H-imidazole (4j)

MP 199-201 ºC (lit. [24] 199-201,ºC). IR spectrum, , cm-1: 3421 (NH), 2928, 1596 (C=N), 1515 (NO2), 1345 (NO2), 856. 1H NMR (400MHz, CDCl3) ppm : 11.754 (s,NH-imidazole,1H),8.218-7.347 (m, 14H, Ar-H). 13C NMR (400MHz, CDCl3) ppm: 118.5, 122.0, 124.0, 125.4, 126.1, 126.9, 127.0, 128.4, 129.7, 130.6, 136.1, 141.0, 147.0. Calculated: C 73.89, H 4.43; N 12.31. LCMS (m/z); 342.37(M+H); Molecular formulae: C_{21} H_{15} N_2O_3; Elemental analysis : Calculated: C- 73.89, H-4.43, N- 12.31; Obtained : C- 73.81, H -4.41, N- 12.39.

BIOLOGICAL ACTIVITY

Anti-Bacterial Activity

The anti-bacterial activities of newly desired compounds are examined against four pathogenic bacteria strains (24, 25). The results of this bacterial activity were observed for tested compounds. The gram negative bacteria were examined against E.coli, P. aeruginosa. The gram positive bacteria screened were examined against S-aureas and Bacillus. The target compounds were used at the different concentration and average value calculated and using DMSO as a solvent the amoxylin 10 µg/ml discs were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

Anti-Fungal Activity

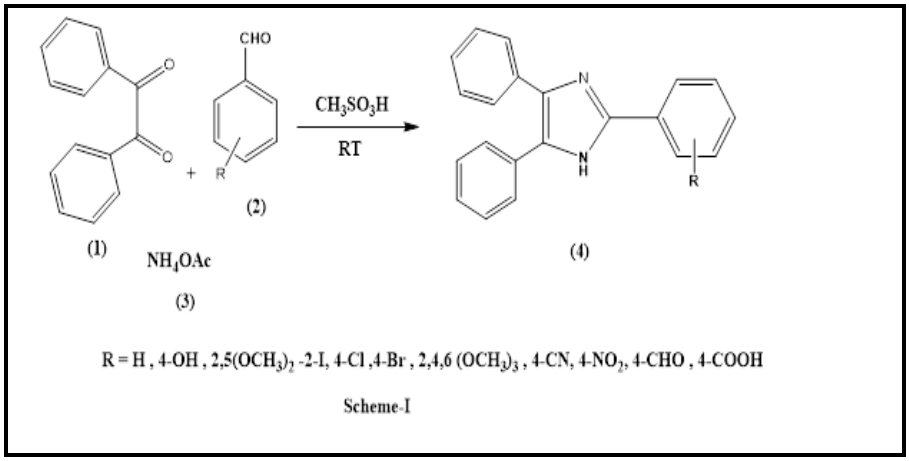
Anti-fungal activities of new synthesized compounds were examined by disc diffusion method against the organism of A.Ngier and C.albicans. The target compounds were used at the different concentration and average value and using DMSO as a solvent. The standard drug was used as ketoconazole 50 µg/ml against both organisms.

RESULTS AND DISCUSSION

As a result of the versatile biological potent activities of substituted imidazoles of different conventional process for the synthesis of these derivatives have been reported (20,21).[28,29] In typical methods, benzil, different functional group aromatic aldehydes and ammonium acetate are condensed in the presence of strong Bronsted acid methane sulphonic acid under RT conditions. These Bronsted acid catalysts present limitations due to the use of corrosive reagents and the necessity of neutralization of the base media. In addition, the synthesis of these heterocycles in polar organic solvents such as ethanol, methanol, acetic acid, DMF and DMSO lead to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed of. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in large amounts for organic reactions have posed a serious threat to the environment. Thus, design of solvent-free catalytic reaction has attracted tremendous attention in recent times in the area of green synthesis (22).[33] 2,4,5-Trisubstituted imidazole were synthesised in excellent yield by condensing benzil (10mmol), ammonium acetate with substituted aromatic aldehyde derivatives (10mmol), in the presence of Brønsted acid catalyst methane sulphonic acid (3mmol), as a catalyst in solvent free condition at RT. The stoichiometric amount of ammonium acetate in the preparation of 2, 4, 5-trisubstituted imidazoles is two. We can synthesised 2,4,5-trisubstituted imidazoles using two equivalents of ammonium acetate but we observed in our experiment and other published papers, if we use inexpensive and available ammonium acetate having more than two equivalents, the reaction will show better results. Thus, small amount of the ammonium acetate was found to be advantageous and hence the molar ratio of benzil to ammonium acetate was kept at 1:2. The efficiency and versatility of the methane sulphonic acid as a catalyst for the preparation of 2,4,5-trisubstituted imidazoles were demonstrated by the broad range of substituted and structurally diverse substituted aromatic aldehydes to synthesize the corresponding products in high to excellent yields (Table 2).

Table 2: Comparison between our catalyst methane sulfonic acid and the other used catalyst about 2-(2-iodo-3, 4-dimethoxyphenyl)-4, 5-diphenyl-1H)-imidazole.

S.NO	Catalyst	Conditions	Time (min)	Yield (%)
1	PTSA	RT	150	74
2	Sulphanilic acid	RT	180	70
3	Silica sulphuric acid	RT	150	75
4	Camphor sulphonic acid	RT	120	84
5	Silica per sulphuric acid	RT	150	78
6	Methane sulfonic acid	RT	60	95



Scheme-I

In Vitro Antioxidant Activity Assay

2.3.1. 1, 1-Diphenyl-2-Picrylhydrazyl (DPPH) Radical-Scavenging Assay

For the determination of the radical-scavenging potent activity newly synthesized derivatives, we used our implementation of the Salazar-Aranda et al.[20] method. A set of serial dilutions in methanol were prepared for each test sample. Then, 0.5 mL aliquots of each dilution were mixed with a solution of 1, 1-diphenyl-2-picryl hydrazyl (DPPH) in methanol(0.5 mL, 76 µM). The resulting mixtures were kept in the dark at room temperature for 30 min. The absorbance of each sample was measured at 517 nm (A517) and methanol was used as the blank. To calculate the radical-scavenging activity as DPPH decolouration percentage, the formula below was used.

$$\text{DPPH (\%)} = [1 - (B/A)] \times 100$$

Where A indicates the absorbance value of the DPPH solution (used as control) and B is the absorbance of the DPPH solution with the sample. Results were expressed as EC50, which represents the required concentration to diminish the absorbance of DPPH by 50%. Quercetin was employed as the reference compound.

3.2. Antioxidant Activity

The DPPH assays of newly prepared imidazole presented EC50 of >16 and >10 mg/mL, respectively **(Table 1**), which compared to most of the results shown by its derivatives, suggests that the 2, 4, 5-triphenylsubstitution in the imidazole heterocyclic is relevant for the antioxidant activity of these compounds, where the effect of their substitutions on their ring is further developed below.

The DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging method is widely used to examined antioxidant activities in a relatively short period of time compared to other methods. The results of this assay are shown in Table 1, comparing the synthesized products with the standard quercetin, where the most active synthesized imidazole derivatives were 4d, 4e and 4f with excellent values. These results exhibited that the presence of halogen substituted on an aromatic ring bonded to imidazole are essential in the antioxidant activity. The consulted literature showed that this could be due to the free pair of electrons in nitrogen in imidazole, which can react with free radicals, being favoured due to their aromatic ring stabilization.[23]

Table 1: Antioxidant activity (EC50) of synthesized compounds 1–10.

Compounds	DPPH
4a	3.227 ± 0.135
4b	1.379 ± 0.629
4c	0.1391 ± 0.092
4d	16.68 ± 0.003
4e	16.78 ± 0.634
4f	7.14 ± 1.908
4g	0.339 ± 0.101
4h	12.227± 3.041
4i	0.172 ± 0.039
4j	4.00 ± 0.133
* Quercetin	0.051 ± 0.036

* Served as the reference compound. Values are mean ± SD, DPPH n = 2, ABTS n = 3. EC_{50} = Concentration required to decrease the absorbance by 50%.

Table I: Antimicrobial activity screening activity synthesized scaffold.

Entry	Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
4a	05	07	05	08	04	06
4b	12	11	14	16	12	14
4c	10	14	12	15	11	12
4d	14	13	11	15	12	13
4e	14	15	18	17	14	17
4f	15	15	17	16	16	15
4g	12	14	18	20	12	14
4h	10	08	11	09	10	08
4i	08	09	07	10	09	08
4j	10	08	11	10	05	06
Amoxicillin	22	22	25	25	-	-
Ketoconazole					20	20
DMSO	-	-	-	-	-	-

Biological Activity

All the synthesized derivatives were evaluated by anti-oxidant properties. The compounds containing halogen derivatives exhibited good active potent against Quercetin. All the synthesized derivatives were evaluated by anti-bacterial activity as well as antifungal Activity. The electron attracting group of compounds and electron donating group compounds showed different activity against the all bacterial and fungal strains. Therefore, electron withdrawing group of derivatives exhibited poor biological activity compared with electron releasing groups. All halogen compounds exhibited good to excellent activity even though, these are electron attracting groups but also having lephoplic nature. The compound which possess electron donating group showed moderate activity as shown in Table-I. The compound containing chloro aldehydes, which exhitbited maximums at S-aureus, E-coli and B.substill at 21, 19,18. S. typhi showed "13'. The compound possesses Br-aldehydes, which is exhibited at E.coli as well as S.typhi at 20 and 21. Whereas S.aureus and B.substill showed at 18,18. Derivatives of these compounds exhibited antifungal activity at '17' of A.Ngier and '20' of C.albicans whereas electron donating group of substituents showed low potent activity against fungal strains.

4. CONCLUSION

Multicomponent reactions encouraged an outstanding status in organic synthesis and medicinal chemistry for their high degree of atom economy and application in the diversity-oriented convergent synthesis of complex organic molecules from simple and readily available substrates in a single vessel. A simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazoles is acquired by three component cyclocondensation of benzil, substituted aromatic aldehydes and ammonium acetate as ammonia source in solvent free condition using Brønsted acidic catalyst methane sulphonic acid as catalyst. The key advantages of this process are cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, excellent yields and very short time reactions.

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