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Copper oxide nanoparticles: Highly efficient heterogeneous catalyst for the synthesis of 3, 4-dihydropyrimidin-2 [1*H*] - ones

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ABSTRACT

An efficient multicomponent synthesis of 3,4-dihydropyrimidin-2[1*H*]-ones promoted by a heterogeneous copper oxide nanoparticles is presented herein. The copper oxide nanoparticles were synthesized by the electrochemical reduction method and their surface characterizations were examined using UV-Visible, FT-IR, XRD, SEM EDS and TEM techniques. This is the clean, efficient and green method for the synthesis of 3,4-dihydropyrimidin-2[1*H*]–ones derivatives using CuO nanoparticles. The copper oxide nanoparticles catalysts having promising features for the reaction response such as the shortest reaction time, simple work-up procedure, excellent product yields and minimum environmental effects.

KEYWORDS

CuO nanoparticles;
3,4-dihydropyrimidin-2[1*H*]-ones derivatives;
Multicomponent reaction;
Electrochemical reduction method.

INTRODUCTION

Biginelli reaction discovered in 1893, for the synthesis of multi-functionalized 3,4-dihydropyrimidin-2[1*H*]-one (DHPM) is an important milestone in the history of MCRs[1]. Dihydropyrimidin-2[1*H*]-ones (DHPMs) and their derivatives occupied an important place in medicinal and synthetic organic chemistry mainly due to their wide range of biological activities[2]. More recently DHPMs have emerged as the integral backbones of several calcium channel blockers[3]. The DHPM nucleus exhibits several medicinal applications which includes neuroprotectant[4], platelet antiaggregatory activity[5], chemo sensitizer acting in tumour therapy[6] and cerebral antischemic activity in the treatment of Alzheimer's disease[7]. Most notably among them are batezelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors[8-10]. These examples clearly demonstrate the remarkable potential applications of 3,4-dihydropyrimidin-2[1*H*]-one derivatives as a source of valuable drugs.

Many procedures have been reported for the preparation of these heterocyclic compounds[11], but only few methods exist for the synthesis of dihydropyrimidin-2[1*H*]–ones[12-14]. The harsh Bronsted acid catalytic conditions originally employed by Biginelli[15] for the synthesis of 3,4-dihydropyrimidin-2[1*H*]-ones, resulted frequently in yields. Due to this several synthetic improvements were developed, mainly those promoted by Lewis acid catalysts such as $BF_3.OEt_2$ [16a], $NiCl_2.6H_2O/H^+$ and $FeCl_3/H^+$ [16b], $CoCl_2.6H_2O/H^+$ [16c], $BiCl_3$ [16d], $InCl_3$ [16e], and $InBr_3$ [16f],

$CdCl_2$[16g], VCl_3[16h], $ZrCl_4$[16i], $NbCl_5$[16j], $Mn(OAC)_3.2H_2O$[16k], $CuCl_2$[16l] and lanthanide halides such as $LaCl_3.7H_2O$[16m] and $CeCl_3.7H_2O$[16n]. Metal triflates such as $Zn(OTf)_2$[17a], $Cu(OTf)_2$[17b], $Bi(OTf)_3$[17c] and $Sc(OTf)_3$[17d] or the lanthanides triflates eg. Yb $(OTf)_3$[17d] and La $(OTf)_3$[17e] also have been used successfully. Some of the above methods are plagued by one or more drawbacks such as longer reaction time, low yield and tedious work-up procedure. To overcome these problems, there is need to develop more efficient protocol at mild condition and environmentally begin catalyst. The heterogeneous catalysis has been increasingly used in organic synthesis and the main advantages of heterogeneous catalyst could be easily separated, simple handling and possible recycling[18].

The copper oxide nanoparticles have attracted much attention because of its applications in the field of catalysis. Thus the possibility of performing multicomponent reactions with heterogeneous catalysts like copper oxide nanoparticles could enhance their efficiency from an economic as well as a green point of view. The CuO nanoparticles has attracted much attention because of its applications such as high surface area, smaller size and heterogeneous nature. The CuO catalyst were used in diverse chemical processes, for example, the water gas shift reaction[19], the butanol dehydrogenation reaction[20] and the oxidation of carbon monoxide[21], copper based catalysts are used as a key intermediate in the industrial synthesis of methanol[22] which is promising as an environmentally friendly fuel for the power industry. In addition to this, it has applications as catalysts in traditional as well as new organic synthesis in Ullmann reaction[23], thermal cracking of plastics[24], synthesis of methyl amines[25] and many others. CuO has been also identified as a good catalyst for the combustion of methane[26].

EXPERIMENTAL

Materials and methods

All chemicals (up to 98.99% purity) are purchased from Aldrich and Rankem chemical suppliers and used as received.

Synthesis of copper oxide nanoparticles

The synthesis of CuO nanoparticles by the electrochemical reduction method originally reported by Reetz et al[27] for narrow size distributed metal nanoparticles. Cluster size was found to decrease with increase in current density[28]. The solid product exhibits electronic, paramagnetic, optical and better catalytic properties significantly different from those of bulk material due to its extremely small size and large surface area. In this work CuO nanoparticles were prepared[29] by using electrochemical reduction method[27]. The prepared CuO nanoparticles were characterized by the IR spectra recorded on FT-IR spectrophotometer [JASCO, FT-IR/4100] Japan. The X-ray powder diffraction were recorded on Bruker 8D advance X-ray diffractometer using CuKα radiation of wavelength = 1.54056 Å. To study the morphology of CuO nanoparticles the SEM analysis were carried out with JEOL; JSM- 6330 LA operated at 20.0kV and 1.0000 nA. The presence and elemental composition in CuO nanoparticles were examined using energy dispersive spectrophotometer (EDS). ^{1}H NMR spectra were recorded on 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

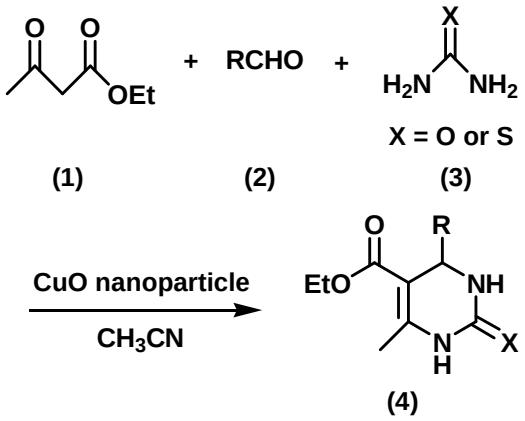
In the present work, attempt is made to optimize the reaction condition by using ethyl acetoacetate, aromatic aldehydes and urea or thiourea as a model reaction at different solvents and catalyst amount in the synthesis of DHPMs (TABLE 1). The use of water as a solvent in this reaction gave only moderate yield of product (54%). So we studied the effect of different solvents in the synthesis of synthesis of DHPMs derivatives **(5a-m)** and the results are summarized in TABLE 1. Among those examined, CH_3CN was found to be most efficient with respect to shorter reaction time and maximum yield of product. We hereby report a very simple green and highly efficient method for the synthesis of 3,4-dihydropyrimidin-2-[1*H*]-ones derivatives (Scheme 1). The reaction was carried out in CH_3CN and 200mg CuO nanoparticles catalyst. Multicomponent reactions are special type of synthetically useful organic reaction that gives complex product and attract the attention of chemists. Here we would like to report the use of copper oxide nanoparticles for the synthesis of DHPMs. through a three component reaction including ethyl acetoacetate **(1)** aromatic aldehydes **(2)** and urea or thiourea **(3)** in the presence of CuO nanoparticles

as a catalyst and acetonitrile as solvent to give compound **(4a-p)**.

TABLE 1 : Optimization of reaction conditions and wt% of CuO catalyst for the synthesis of 3,4-dihydropyrimidin-2[1*H*]one.

Solvent	Wt. of catalyst. (mg)	Time (min)	Yield (%)[a]
H_2O	200	50	54
CH_3CN	200	25	98
CH_3CN : H_2O	200	40	79
EtOH	200	45	86
EtOH : H_2O	200	50	67
CH_3CN	150	30	93
CH_3CN	250	25	96

[a]**All yields refer to isolated products**



Scheme 1 : Copper oxide nanoparticle catalyzed synthesis of 3,4-dihydropyrimidin-2-[1*H*]-ones derivatives in acetonitrile

Typical experimental procedure for the preparation of 3,4-dihydropyrimidin-2[1H]-one

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and CuO nanoparticles (0.02g) was refluxed at 70°C in acetonitrile (10ml). The completion of the reaction was monitored by TLC. After cooling the reaction mixture was poured onto crushed ice (50g) and stirred for 5 min. The separated solid was filtered under suction, washed with cold water (50ml) and then recrystallized from ethanol to offer the pure product. The results are summarized in TABLE 2. All products were obtained in excellent yields (89-98%) The aqueous layer containing the catalyst was recovered by centrifuging and reutilized three times for the same reaction (TABLE 3)[30] as shown in scheme 1.

It is evident that aromatic aldehydes carrying either electron releasing or electron withdrawing substituents in the ortho, meta and para positions affored high yields of DHPMs. An important feature of this procedure is the survival of variety of functional groups such as nitro, bromo, chloro and ether under the reaction conditions. Thiourea also reacts under similar reaction conditions to form the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones in good to excellent yields. The structures of all the products were confirmed by comparing melting point and spectral data with those in the literature data (TABLE 2).

TABLE 2 : Synthesis of 3,4-dihydropyrimidin-2[1*H*]one using copper oxide nanoparticles in CH_3CN solvent

Products[a]	R	X	Rea. time (min)	Yield[b] (%)	M.p. (°C)	
					Found	Lit.
4a	C_6H_5	O	25	98	204-206	200-202[31a]
4b	4-MeC_6H_4	O	35	97	210-214	213[31a]
4c	4-ClC6H4	O	40	95	212-214	212-213[31b]
4d	3,4,5-$(MeO)_3$-C_6H_2	O	45	94	178-180	180-182[31b]
4e	3-$NO_2C_6H_4$	O	30	94	224-227	225-226[31b]
4f	4-$NO_2C_6H_4$	O	25	94	206-208	207-209[31b]
4g	4-$MeOC_6H_4$	O	25	98	202-204	200-201[31b]
4h	4-$NMe_2C_6H_4$	O	30	89	232-234	230-232[31b]
4i	2,4-$Cl_2C_6H_3$	O	30	94	250-252	248-250[34]
4j	$(CH_3)_2CH$	O	35	98	153-155	152-155[31c]
4k	$CH_3CH_2CH_2$	O	40	93	170-174	171-173[31c]
4l	3-$NO_2C_6H_4$	S	30	97	205-207	205-207[31a]
4m	3,4,5-$(MeO)_3C_6H_2$	S	30	94	190-193	193-195[31b]
4n	4$MeOC_6H_4$	S	40	92	152-154	154-155[34]
4o	4ClC_6H_4	S	30	97	182-185	184[34]
4p	C_6H_5	S	35	93	209-210	208-210[34]

[a]**All products were characterized from their spectroscopic (IR, ^{1}H NMR and MS) data and compared with authentic samples.** [b]**Isolated yields**

Herein, the series of DHPMs derivatives was presented by applying the method mentioned above.

The catalysts were recovered by a simple workup using the centrifugation method. The recovered catalyst was washed several times with THF and dried in vacuum. The separated catalyst was again reused for during three consecutive runs without significant loss of activity for the same reaction. It is noteworthy, that the yields of the product in the second and third uses were almost same as that in the first run (TABLE 3). We have compared our result with results obtained by some other reported procedures for the synthesis of DHPMs

derivatives **(5a)**. The data presented (TABLE 4) shows the promising features of this method in terms of reaction rate and the yield of product.

TABLE 3 : Reutilization of CuO nanoparticles in the synthesis of DHPMs.

Run	Fresh	1	2	3
Yield%	98	98	95	95

TABLE 4 : Comparisons of some other reported procedures with the present method for the synthesis of 3,4-dihydropyrimidin-2[1*H*]one.

Entry	Catalyst	Time (hr)	Yield (%)[a]	Literature
1	CuO NP	25 min	98	Present
2	$InBr_3$	7	98	[35]
3	TAFF	4	55	[36]
4	KSF Montmorillonite	8-10	92	[37]

Characterization of copper oxide nanoparticles

The prepared copper oxide nanoparticles were characterized by UV-Visible spectrophotometer, FT-IR spectrophotometer, XRD, SEM and EDS techniques. The UV-Visible spectrophotometer [Jasco 503] using a quartz cuvette with acetonitrile/ tetrahydrofuran as reference. The IR spectra were recorded on FT-IR spectrophotometer [Jasco, FT-IR/4100] Japan. Using dry KBr as standard reference in the range of 400-4000cm^{-1} The X-ray powder diffraction patterns of the copper oxide nanoparticles were recorded on Bruker 8D advance X-ray diffractometer using CuKα radiation of wavelength = 1.54056 Å. To study the morphology of CuO nanoparticles the SEM analysis were carried out with JEOL; JSM- 6330 LA operated at 20.0kV and 1.0000 nA. The presence and elemental composition in CuO nanoparticles were examined using energy dispersive spectrophotometer (EDS). TEM images were recorded on Tecnai $20G^2$ operated at 200kV.

Ethyl-1,2,3,4-tetrahydro-4-(4 methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (4g)

^{1}H NMR ($CDCl_3$, δppm): 1.19 (t, J = 9.6 Hz, 3H,CH_3), 2.31 (s, 3H, CH_3), 3.81(s, 3H, OCH_3),4.14 (q,J = 9.2 Hz, 2H, OCH_2), 5.37 (s, 1H, ArCH), 5.50 (s, 1H,H),6.85(d, J = 8.8 Hz, 2H, ArH), 7.24 (d, J = 8.8 Hz,2H, ArH), 7.54 (s, 1H, NH). IR (KBr, cm^{-1}): 3239, 3111, 2967, 2929, 2278, 1721,1784, 1647, 1514, 1459, 1272, 1219, 1166, 1087, 1030, 779.

Ethyl-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate (4n)

^{1}H NMR ($CDCl_3$, δ ppm): 1.17 (t, J = 9.2 Hz, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.14 (q, J = 9.6 Hz,2H, OCH_2), 5.34 (s, 1H, ArCH), 6.90 (d, J = 11.6 Hz, 2H,ArH), 7.20 (d, J = 9.2 Hz, 2H, ArH), 7.28 (s, 1H, NH), 7.90 (s, 1H, NH).

Ethyl-1,2,3,4-tetrahydro-4-(4-Chlorophenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate (4o)

^{1}H NMR ($CDCl_3$, δ ppm): 1.21 (t, J = 9.6 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.10 (q, J = 9.6 Hz, 2H, OCH_2), 5.35 (s, 1H,ArCH), 7.13 (s, 1H, NH), 7.25 (d, J = 8.4 Hz, 2H, ArH), 7.27 (d, J = 8.4 Hz, 2H, ArH), 7.67 (s, 1H, NH). IR (KBr, cm^{-1}): 3327, 3164, 3101, 2893, 2933, 2357, 1720, 1563, 1452, 1369, 1272, 1203, 1091, 806, 756.

RESULTS AND DISCUSSION

The reduction of copper ions was visibly evident from the color changes associated with it. UV-Visible absorption spectra during reduction of the precursor as they transformed into the copper oxide nanoparticles and after ageing times during its preservation under ambient conditions. The absorption bands for copper nanoparticles have been reported to be in the range of 550-600 nm[25,26a,b]. The copper particles showed a high about 570 nm which gradually changed to yellowish brown indicating copper being oxidized from zero to +2 oxidation state. The sharp peak at 570 nm can be attributed to a narrow size distribution of the particles formed in the solution. As an evident the particles showed hardly any change in the absorption spectra even after a month of ageing time, consistent with the highly stable nature of nanoparticles.

Figure 1 represents IR spectra of copper oxide nanoparticles. In the IR spectrum the peaks appear exactly at the 3298 cm^{-1} may or is due to N-H stretching or hydroxyl group adsorbed on CuO nanoparticles. 1603 cm^{-1} is due to deformation of OH group and 2870 cm^{-1} is due to C-H stretching. Some of the peaks reflects in the range of 706-912 cm^{-1} that might be due to bending mode of vibrations M-O-M bending (M = Cu). In order to understand the phase symmetry of the prepared copper oxide nanoparticles a systematic study

on the XRD was undertaken. Figure 2 shows XRD pattern for CuO nanoparticles. The lattice parameter observed a = 4.653, b = 3.410, c = 5.108. Sharp peaks were obtained at corresponding to the planes (111), (201), (211) and (312) indicates the FCC structure of CuO nanoparticles and which was found to be highly crystalline in nature. The diffraction is in good co-ordination with ASTM card no. 74-1021. The average particle size was calculated to be 9.56 nm using Debye Scherer formula[27,28].

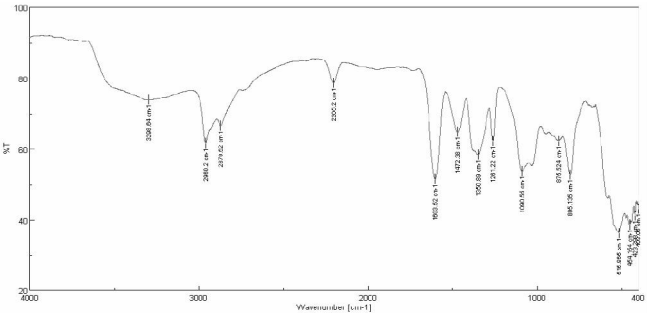


Figure 1 : IR spectra of CuO nanoparticles using 0.01 M TBAB

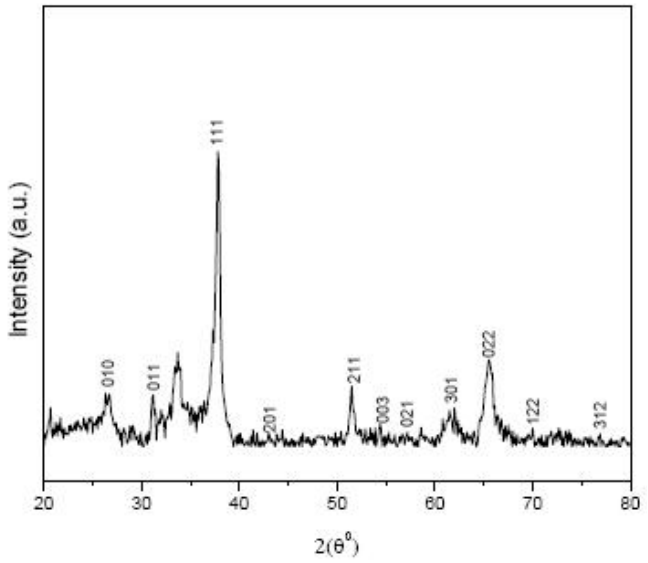


Figure 2 : X-ray diffraction pattern of copper oxide nanoparticles capped with TBAB at room temperature

To evaluate morphology of CuO nanoparticles as shown in Figure 3 (a) and (b) SEM microstructure of the electrochemical reduction derived copper oxide nanoparticles reveals the presence of dense agglomerations Figure 3 (a) Shows these particles have irregular shape and their distribution is not uniform. This is probably due to the partial solubility of the surfactant in the solvent under the given experimental conditions. Figure 3 (b) shows the presence of porous nanoparticles that are agglomerated irregularly. Energy dispersive pattern of copper oxide nanoparticles in Figure 4 shows the % of elements, presence of bromine is due to the use of TBAB. Figure 5 TEM images shows agglomeration of CuO nanoparticles with particles size distribution 4nm-8nm. The nanoparticles were stable in air and water and did not convert into any other associated compounds.

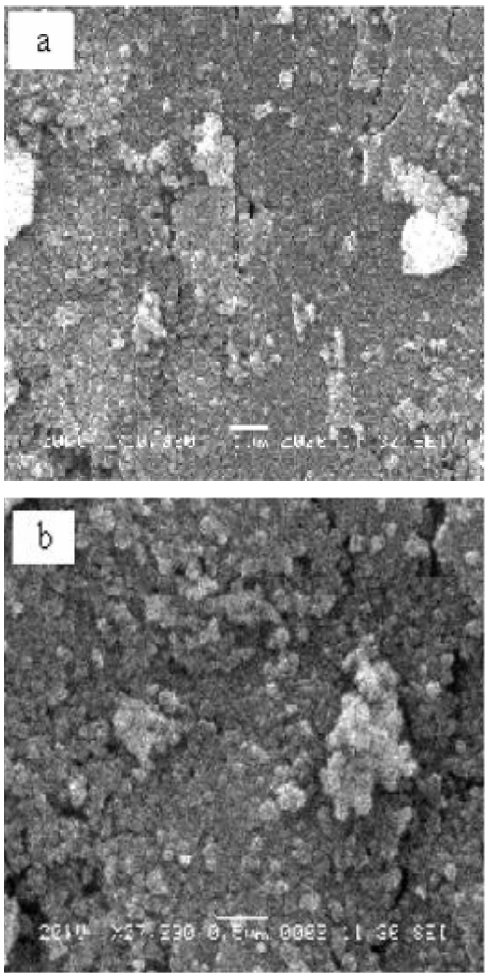


Figure 3 : (a) and (b) SEM of as prepared copper oxide nanoparticles capped with 0.01M TBAB (current density 6 mA/cm^2)

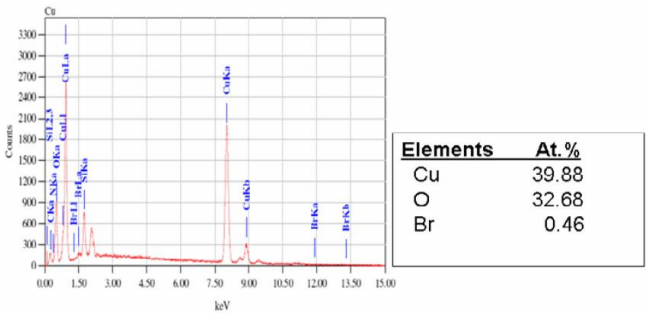


Figure 4 : Shows an energy dispersive spectrum indicating the chemical composition of freshly prepared CuO nanoparticles

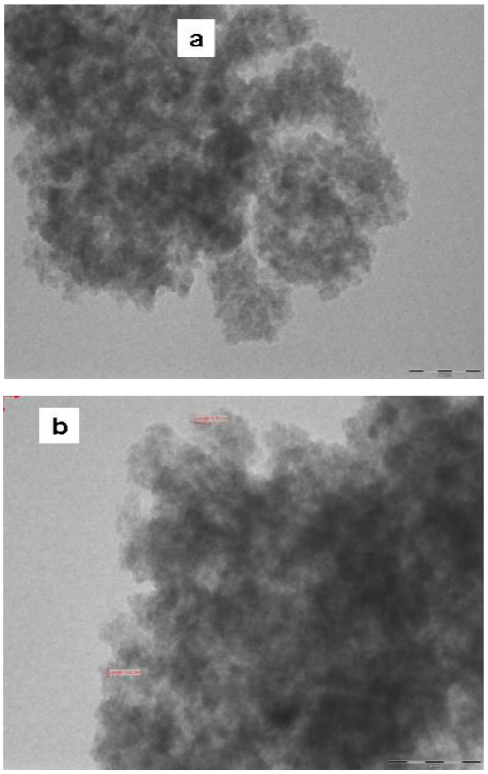


Figure 5 : TEM images of copper oxide nanoparticles capped with 0.01M TBAB (current density 6 mA/cm^2)

CONCLUSION

In conclusion, we have demonstrated the efficiency of CuO nanoparticles as a new heterogeneous catalyst for the multicomponent Biginelli reaction. The recovered solid catalyst can be reused at least three times without a significant loss of activity. This catalyst is expected to contribute the development of more environment begin methods and forms part of nanometal chemistry. Several milder conditions, short reaction times, excellent yields and reusability of the catalyst makes this procedure more attractive in synthesizing a variety of these derivatives.

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