

Nano-sawdust/Sn(IV) as an Efficient Bio-based Nano-catalyst for the Synthesis of Highly Substituted Dihydro-2-oxopyrroles

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Nano-sawdust/Sn(IV) was used as a readily available, inexpensive, biodegradable and environmentally benign solid acid bio-based nano-catalyst for the one pot cascade synthesis of highly functionalized dihydro-2-oxopyrroles. Four-component reactions (4CRs) of the dialkylacetylenedicarboxylates, amines and aldehydes were used for the synthesis of highly functionalized dihydro-2-oxopyrroles under thermal conditions.

Keywords: Nano-sawdust/Sn(IV), Dihydro-2-oxopyrrole, Multicomponent reaction, Solid acid nano-catalyst

INTRODUCTION

The performance of dihydro-2-oxopyrroles moieties in pharmaceuticals, agrochemicals, and natural products causes their synthesis remains an area of interest in synthetic chemistry. Therefore, a number of synthetic routes have been developed for the synthesis of highly functionalized dihydro-2-oxopyrroles, including ruthenium-catalyzed reaction of α,β -unsaturated imines with carbon monoxide and ethylene [1], reaction of isocyanides, dialkylacetylenedicarboxylates, and benzoyl chlorid [2], carboamination/oxidative cyclization of C-acylimines with alkenes [3], transannulation of 1-sulfonyl-1,2,3-triazole with ketene silylacetal [4], reaction of acetylene with imines and CO₂ [5], Pd-catalyzed cyclization of ethyl glyoxalate and amines [6] and reaction of α -cyanomethyl- β -ketoesters with alcohols [7]. Among these versatile synthetic methods, multicomponent reactions (MCRs) have attracted particular attention [8]. A few protocols have been reported for the synthesis of dihydro-2-oxopyrroles using a four-component reaction of dialkylacetylenedicarboxylates, aldehydes and amines.

This reaction has been catalyzed by TiO₂-nanopowder [9], I₂ [10], *p*-toluenesulfonic acid [11], Cu(OAc)₂·H₂O [12], AcOH [13], 1-methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO₄]) [14], InCl₃ [15], [n-Bu₄N][HSO₄] [16], Fe₃O₄@nano-cellulose-OPO₃H [17] and BF₃/nano-sawdust [18].

Development of new solid acids with numerous advantages such as cost effectiveness, environmentally benign, easy workup and good stability for one-pot multicomponent synthesis of highly substituted dihydrooxopyrrole scaffolds is still in demand. In this regard, our aim is developing low-cost and bio-based solid acid nano-catalysts for this multicomponent reaction.

Sawdust is a biodegradable, natural, cheap, renewable and readily available source of cellulose containing free OH groups with nucleophilic character. In this work, we have investigated the synthesis of sawdust based catalyst by bonding Lewis acids to OH groups of D-glucose units. For elimination of pectin, lignin, proteins and minerals in pine sawdust, it was treated respectively with NaOH, NaOCl and H₂O₂. For preparation of nano-sawdust, the sawdust has been treated with concentrated H₂SO₄ for partial hydrolysis of its cellulose. Then, the nano-sawdust was

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used to synthesize nano-sawdust/Sn(IV) as a new, biodegradable and green catalyst.

This study aims at preparation of nano-sawdust/Sn(IV) as a new carbon based solid Lewis acid. We evaluate the catalytic performance of nano-sawdust/Sn(IV) for the synthesis of highly functionalized dihydro-2-oxopyrroles *via* 4CRs of the dialkylacetylenedicarboxylates, amines and aldehydes under thermal conditions.

EXPERIMENTAL

Materials and Instruments

All chemicals and solvents were purchased from the Merck and Fluka chemical companies in high purity. The FT-IR spectra were recorded on an attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectrophotometer (Bruker, Equinox 55). The ¹H NMR and ¹³C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a BrukerDXR-400 spectrometer. Mass spectra (MS) were recorded on a FINNIGAN-MAT 8430 mass spectrometer, operating at an ionization potential of 70 eV. Melting points were obtained with a Buchi melting point B-540 B.V.CHI apparatus. Quantitative elemental information (EDS) of nano-sawdust/Sn(V) was measured by SEM/EDS instrument, Phenom pro X. The FESEM image was obtained on a Mira 3-XMU. The XRD pattern of catalyst was obtained by PAN analytical X'Pert Pro MPD, powered by a Philips PW3040/60 X-ray generator and fitted with an X'Celerator detector and a Cu K α anode ($\lambda = 1.5418 \text{ \AA}$) in the 2θ range from 5 to 80°.

Preparation of Nano-sawdust

Pine sawdust (8 g) was first treated with a solution of 17.5% w/v sodium hydroxide in water bath maintained at 100 °C for 12 h. The alkali treated fibres were washed repeatedly. The stock was then bleached with 200 ml of 1:1 diluted sodium hypochlorite solution (5% w/v) at 80 °C for 8 h. The resulting product was then treated with 20 ml of 20 % v/v hydrogen peroxide at 50 °C for 2 h. The resultant was hydrolyzed by refluxing with sulphuric acid (35% H₂SO₄ with fiber

to liquor ratio of 1:20) for 2 h at 60 °C with strong agitation. Resulting mixture was cooled to room temperature and diluted by adding an excess amount of distilled water. Then, the suspension was repeatedly centrifuged at 4000 rpm for 8 minutes. After each run, the nano-sawdust was washed with distilled water and centrifuged until the supernatant became neutral.

Preparation of Nano-sawdust/Sn(IV)

In a ventilated cabin, a 25 ml suction flask equipped with a constant-pressure dropping funnel containing SnCl₄ (1 ml) and gas inlet tube for conducting HCl, charged with 1 g nano-sawdust and chloroform, SnCl₄ was added drop wise over a period of 3 min at room temperature. The mixture was stirred for one hour at room temperature. The resulted mixture was filtered. The obtained white solid was washed with chloroform and dried at room temperature.

Typical Procedure for the Synthesis of Dihydro-2-oxopyrroles

In a round-bottom flask (50 ml) equipped with a reflux condenser, firstly, a mixture of primary amine (1 mmol) and dialkylacetylenedicarboxylate (1 mmol) in absolute ethanol (4 ml) was stirred for 15 min. Then, substituted aniline (1 mmol), formaldehyde 37% (3 mmol) or aromatic aldehydes (2 mmol) and nano-sawdust/Sn(IV) (0.07 g) in ethanol (3 ml) were added to the above mixture and refluxed. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was allowed to be cooled, filtered off and washed with EtOH (3 × 10 ml) to remove all unreacted substrates. For separation of catalyst from solid product, it was washed with chloroform (15 ml). The chloroform was evaporated and the crude solid product was recrystallized from ethanol to give the corresponding pure dihydro-2-oxopyrroles.

RESULTS AND DISCUSSION

In order to investigate the structure of catalyst, we studied the FT-IR (ATR) spectra of pine sawdust and nano-sawdust/Sn(IV) (Fig. 1). In both FT-IR spectra,

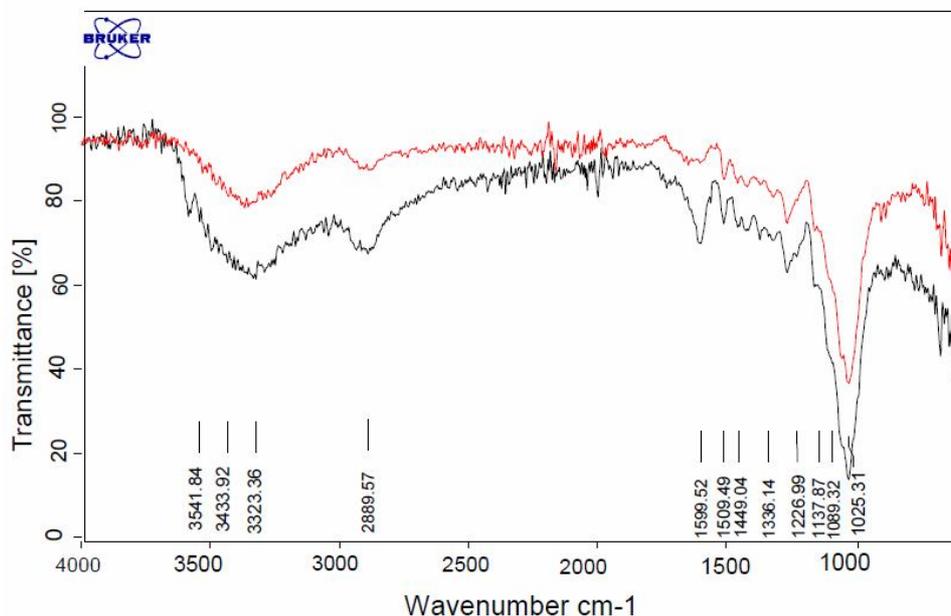
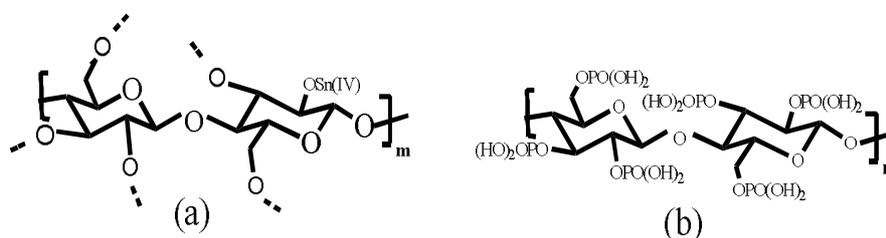


Fig. 1. FT-IR (ATR) spectra of (a) pine sawdust and (b) nano-sawdust/Sn(IV).



Scheme 1. Proposed structure for (a) nano-sawdust/Sn(IV) and (b) cellulose triphosphate

the bands at 3323, 2889 and 1226, 1137 and 1025 cm^{-1} were observed. In nano-sawdust/Sn(IV), in addition to the above mentioned bands, one band also appeared near 500 cm^{-1} which verifies the O-Sn bond in the catalyst. In fact, the exact characterization of this catalyst according to FTIR spectrum is not possible. The proposed structure containing possible model for acid sites formed on the catalyst is similar to the reported structure for cellulose triphosphate gels prepared by phosphorylation of trihydroxy groups of D-glucose units (Scheme 1).

The FESEM image of nano-sawdust/Sn(IV) is shown in Fig. 2. According to the FESEM data, the

particle size of catalyst is below 80 nm. Quantitative elemental information (EDS) of nano-sawdust/Sn(IV) was measured by SEM/EDS instrument (Fig. 3). According to this data, the weight percentages of Sn, Cl and C are 45.4, 41.0 and 13.5, respectively.

The XRD patterns in a range of 5-80° are shown in Fig. 4. The particle size of sawdust was determined with FESEM image and XRD pattern. The broad bands with high FWHM and using Scherrer equation showed that the particle size of sawdust is below 100 nm and it is a nanoparticle.

In this study, we have investigated the catalytic activity of nano-sawdust/Sn(IV) for the synthesis

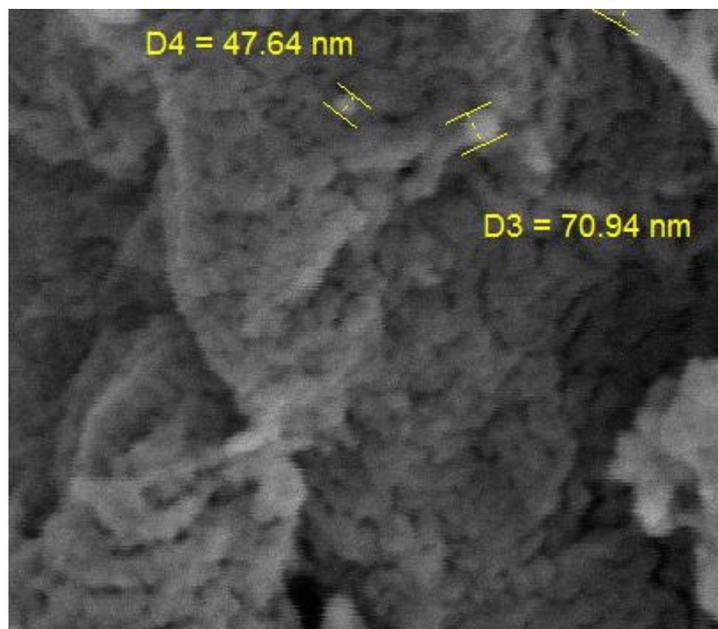


Fig. 2. The FESEM image of nano-sawdust/Sn(IV).

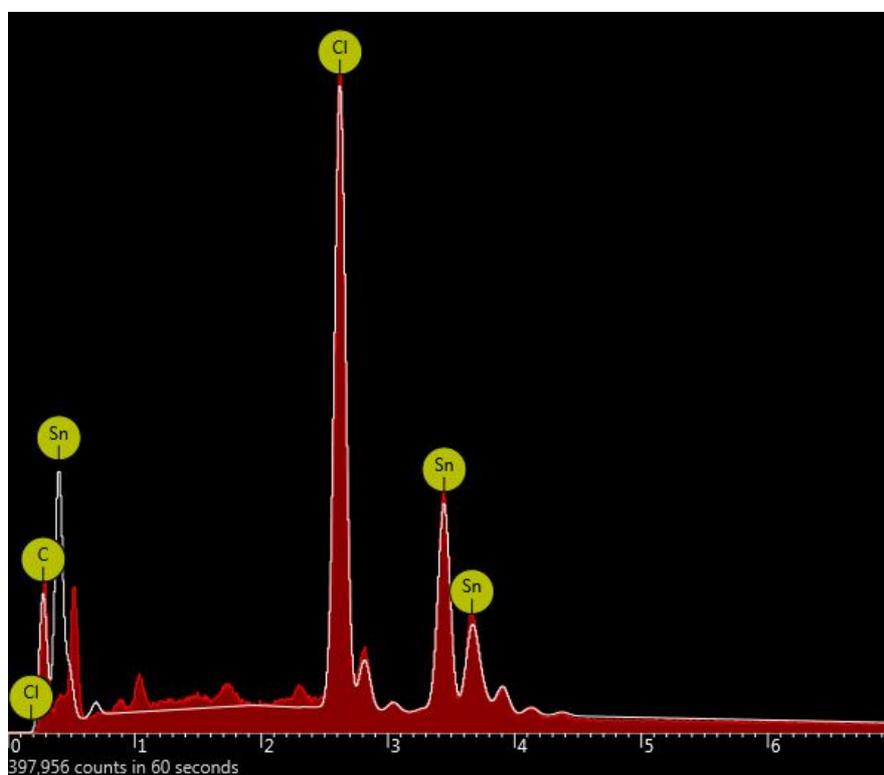


Fig. 3. EDS analysis diagram of nano-sawdust/Sn(IV).

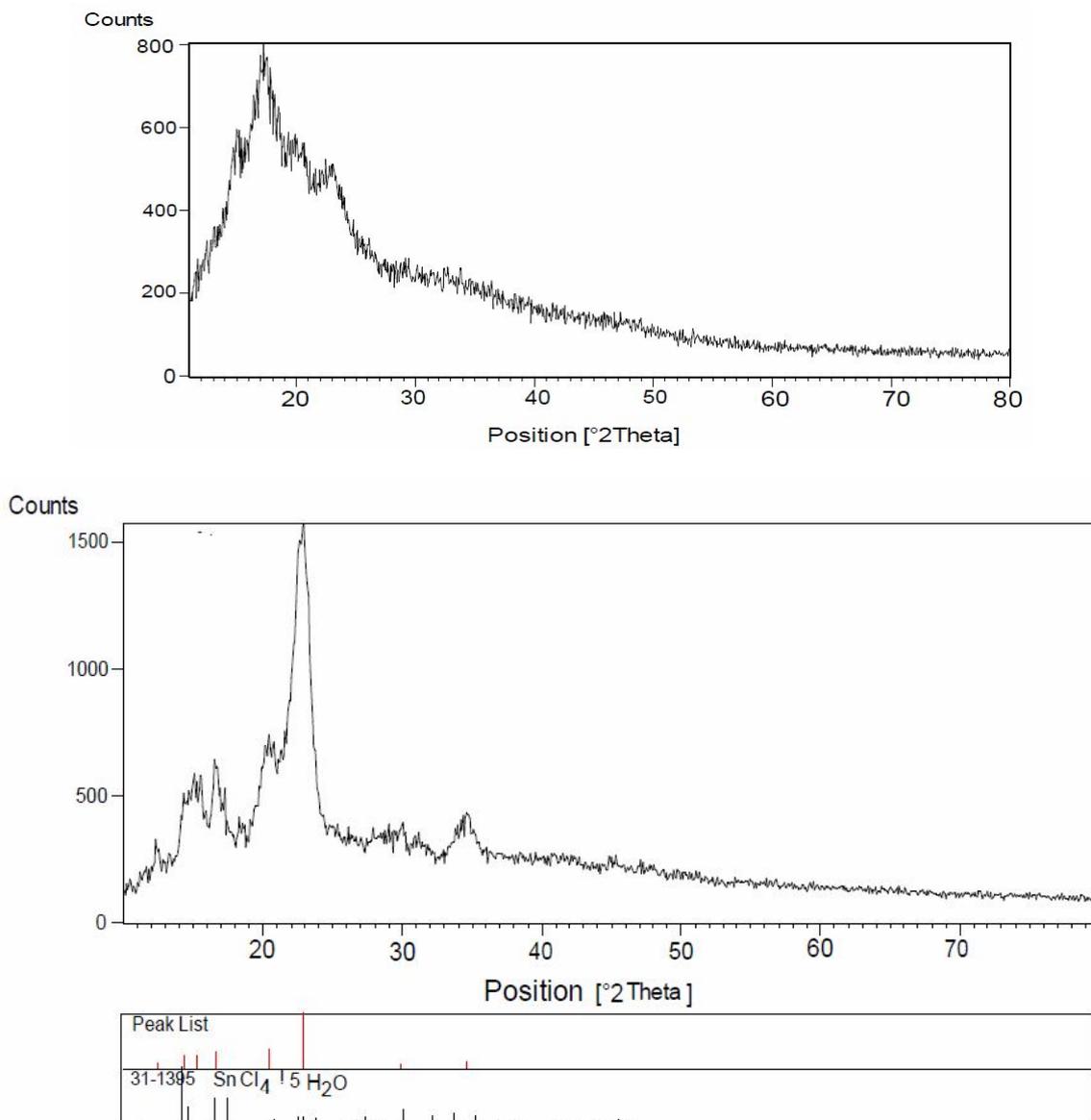
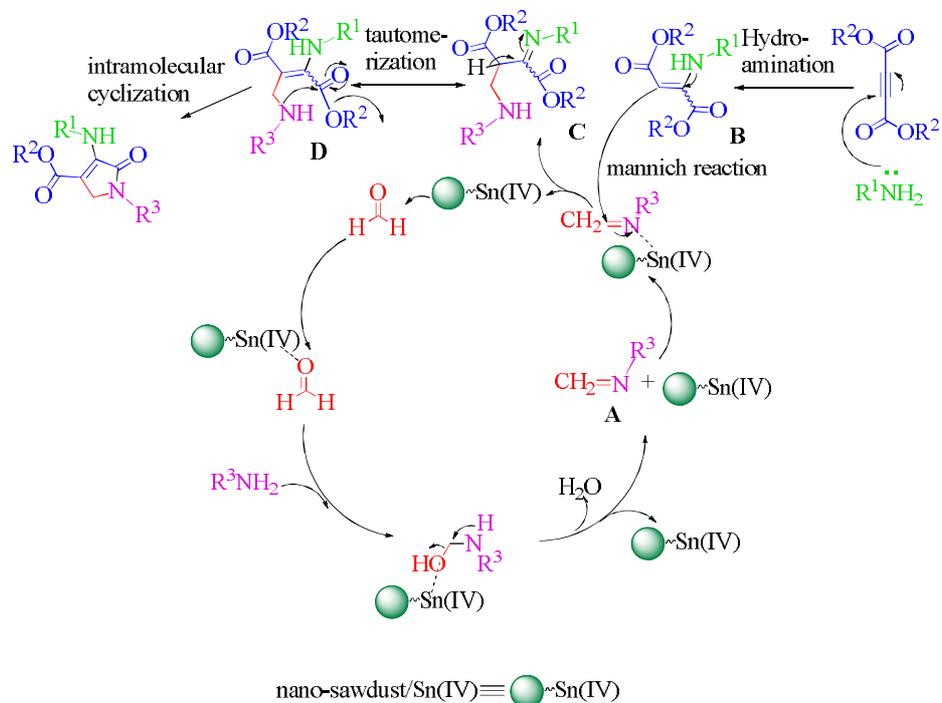


Fig. 4. XRD pattern of (a) nano-sawdust and (b) nano-sawdust/Sn(IV).

of dihydro-2-oxopyrroles *via* 4CRs of the dialkylacetylenedicarboxylates, amines and aldehydes. The synthesis of dihydro-2-oxopyrroles is an intermolecular nucleophilic addition reaction (Mannich reaction type) including several intermediates (Scheme 2).

Therefore, it is necessary to choose a suitable condition such as catalyst, solvent and temperature for

this reaction. As a model reaction, synthesis of methyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate was examined. Initially, the reaction was performed in the absence of catalyst and stirred for 3 h at room temperature in ethanol. After standard reaction workup, the desired compound was isolated in trace amount (Table 1). Therefore, different reaction conditions in the



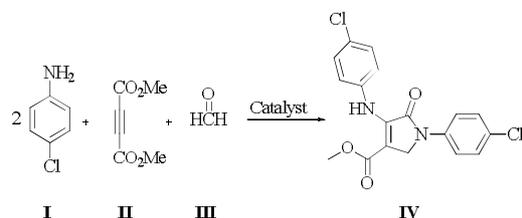
Scheme 2. Proposed mechanism for the synthesis of dihydro-2-oxopyrroles in the presence of nano-sawdust/Sn(IV)

presence of nano-sawdust/Sn(IV) was evaluated on the selected model reaction to develop a more robust and applicable protocol. As shown in Table 1, the most yield of reaction was acquired using 3 mmol of formaldehyde in ethanol and in the presence of 0.07 g nano-sawdust/Sn(IV) after 4 h of reflux (Table 1, Entry 10). The effect of different solvents on the reaction was investigated and revealed that ethanol gave the best results for this transformation. Reusability of catalyst was investigated for three cycles (Table 1, entries 16-18). For this purpose, after each run the reaction mixture was diluted with acetone or ethanol and subsequently centrifuged to obtain the catalyst. The obtained catalyst was then washed with chloroform followed by drying in oven at 100 °C for 4 h. The recovered catalyst was then used for the next run of the reactions. It was found that the reactivity of the catalyst decreases marginally for the next run (approximately, 4%). The FTIR spectrum of recovered catalyst shows that structure of catalyst is unchanged.

Finally, using the optimized reaction conditions obtained for the synthesis of methyl-1(4-chlorophenyl)-4-((4-chlorophenyl)amino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate, the scope of this transformation was explored in terms of the amounts of reactant, solvent, catalyst and reaction temperature. Accordingly, the synthesis of different dihydro-2-oxopyrrole derivatives were examined and high yields were noticed in most cases (Table 2).

CONCLUSIONS

In summary, nano-sawdust/Sn(IV) as a green, inexpensive, natural, biodegradable and readily available bio-based solid acid nano-catalyst was introduced. It was shown that various substituted dihydro-2-oxopyrrole derivatives can be successfully synthesized by a simple and high efficient one-pot four-component procedure using nano-sawdust/Sn(IV). This approach has many advantages including high conversions, low-cost and easy workup, making this method more attractive.

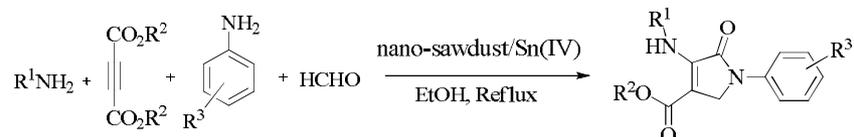
Table 1. Preparation of Methyl-1(4-chlorophenyl)-4-((4-chlorophenyl)amino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate under Various Conditions^a

Entry	Solvent	Catalyst	Reactant I: II:III	Condition	Time (h)	Yield (%) ^b
1	EtOH	-	2:1:1.5	R.T.	3	Trace
2	EtOH	Nano-sawdust/Sn(IV)(0.02)	2:1:1.5	R.T.	3	14%
3	EtOH	Nano-sawdust/Sn(IV)(0.02)	2:1:1.5	Reflux	3	30%
4	EtOH	Nano-sawdust/Sn(IV)(0.02)	2:1:2	Reflux	3	36%
5	EtOH	Nano-sawdust/Sn(IV)(0.02)	2:1:2.5	Reflux	3	44%
6	EtOH	Nano-sawdust/Sn(IV)(0.02)	2:1:3	Reflux	3	49%
7	EtOH	Nano-sawdust/Sn(IV)(0.04)	2:1:3	Reflux	3	61%
8	EtOH	Nano-sawdust/Sn(IV)(0.06)	2:1:3	Reflux	3	73%
9	EtOH	Nano-sawdust/Sn(IV)(0.07)	2:1:3	Reflux	3	78%
10	EtOH	Nano-sawdust/Sn(IV)(0.07)	2:1:3	Reflux	4	91%
11	EtOH	-	2:1:3	Reflux	4	26%
12	MeOH	Nano-sawdust/Sn(IV)(0.07)	2:1:3	Reflux	4	63%
13	EtOH/MeOH	Nano-sawdust/Sn(IV)(0.07)	2:1:3	Reflux	4	67%
14	CHCl ₃	Nano-sawdust/Sn(IV)(0.07)	2:1:3	Reflux	4	42%
15	<i>n</i> -Hexane	Nano-sawdust/Sn(IV)(0.07)	2:1:3	Reflux	4	38%
16	EtOH	Nano-sawdust/Sn(IV)(0.07), 2 nd run	2:1:3	Reflux	4	88%
17	EtOH	Nano-sawdust/Sn(IV)(0.07), 3 rd run	2:1:3	Reflux	4	87%
18	EtOH	Nano-sawdust/Sn(IV)(0.07), 4 th run	2:1:3	Reflux	4	82%
19	MeOH	I ₂ (10 mol%)	2.1:1:1.2	R.T.	1	81% ¹⁰
20	MeOH	Cu(OAc) ₂ ·H ₂ O (0.4 eq)	2.6:1:1.4	R.T.	3	86% ¹²
21	MeOH	[<i>n</i> -Bu ₄ N][HSO ₄] (10 mol%)	2:1:1	R.T.	4	86% ¹⁶
22	MeOH	InCl ₃ (20 mol%)	2:1:1.5[c]	R.T.	3	79% ¹⁵
23	EtOH	AcOH	3:1:1.5[d]	Reflux	4	89% ¹³

^aReactions were run with the following steps: in the first step, dimethylacetylenedicarboxylate (1 mmol) and 4-chloroaniline (1 mmol) were added into 4 ml solvent and kept at room temperature for 15 min. Then, 4-chloroaniline (1 mmol), and formaldehyde catalyst were added to the above mixture respectively, and then stirred at rt or under reflux condition for desired time. ^bIsolated yield after recrystallization in ethanol.

^cDiethylacetylenedicarboxylate instead of dimethylacetylenedicarboxylate was used. ^d4-Bromoaniline instead of 4-chloroaniline was used.

Table 2. Synthesis of Dihydro-2-oxopyrrole Derivatives in the Presence of Nano-sawdust/Sn(IV) under Reflux Condition^a



Entry	R ¹ (R ³)	R ²	Product	Time (h)	Yield (%) ^b	M.P. [Ref]
1	4-Me-C ₆ H ₄	Me		3	84%	175-176 [12]
2	4-Me-C ₆ H ₄	Et		4	88%	128-130 [13]
3	4-Et-C ₆ H ₄	Me		4	81%	125-126 [10]
4	4-Et-C ₆ H ₄	Et		4	80%	98-100 [16]
5	4-OMe-C ₆ H ₄	Me		4	83%	160-162 [10]

Table 2. Continued

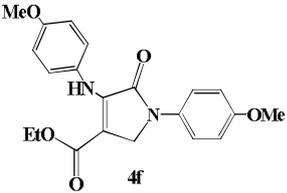
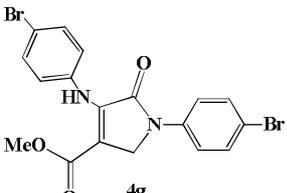
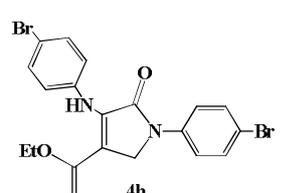
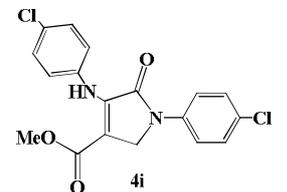
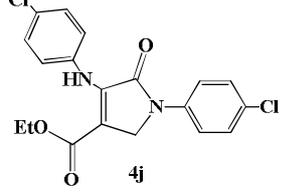
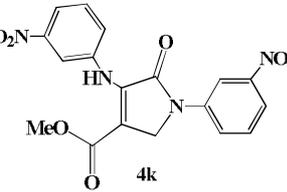
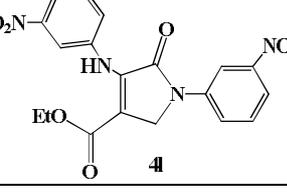
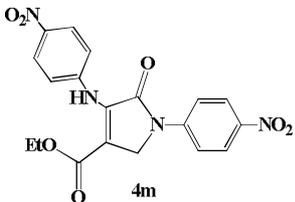
6	4-OMe-C ₆ H ₄	Et	 4f	5	85%	152-154 [15]
7	4-Br-C ₆ H ₄	Me	 4g	2	90%	181-182 [12]
8	4-Br-C ₆ H ₄	Et	 4h	2.5	91%	165-166 [12]
9	4-Cl-C ₆ H ₄	Me	 4i	4	91%	173-174 [12]
10	4-Cl-C ₆ H ₄	Et	 4j	4	95%	165-167 [16]
11	3-NO ₂ -C ₆ H ₄	Me	 4k	3	79%	204-206 [16]
12	3-NO ₂ -C ₆ H ₄	Et	 4l	3	85%	191-192 [16]

Table 2. Continued

13	4-NO ₂ -C ₆ H ₄	Et		5	75%	206-208 [16]
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^aFor entries of 1-13 and 18, the amounts of amine (mmol): dialkylacetylenedicarboxylate (mmol): formaldehyde (mmol): nano-sawdust/Sn(IV) (g) are equal to 2:1:3:0.07. For entries of 14-17, the amounts of amine (mmol): dialkylacetylenedicarboxylate (mmol): aldehyde (mmol): nano-sawdust/Sn(IV) (g) are equal to 2:1:2:0.07. ^bIsolated yields after recrystallization in ethanol.

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