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Catalyst application of ZnO nanostructures in solvent free synthesis of polysubstituted pyrroles

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ABSTRACT

A simple, rapid, efficient, and environmentally benign procedure for synthesis of polysubstituted pyrroles has been achieved by the three-component reaction of amines, phenacyl bromide and dialkyl acetylenedicarboxylates under solvent free conditions using nano structures of ZnO as catalyst. Different morphologies such as nanorods and nanosheets of catalysis have been synthesized by simple reflux method using sodium dodecylsulfate (SDS) and applied in this reaction. Nanorod ZnO catalyst exhibited a significant enhancement in the yield of the desired product. The catalyst exhibited remarkable reusable activity.

1. Introduction

Pyrroles represent an important class of heterocyclic compounds [1–4]. They are commonly found as structural motifs in bio-active molecules such as porphyrins, alkaloids and co-enzymes [5]. Pyrrole derivatives have attracted particular attention in drug discovery due to their various pharmacological properties [6–10]. For example, anticancer drug candidate tallimustine and blockbuster cholesterol lowering drug atorvastatin (Lipitor) belong to this class. In view of their tremendous application in various research fields including biological science and medicinal chemistry, there is a continuing interest in developing versatile synthetic routes [11,12].

Various methodologies have been developed for polysubstituted pyrrole synthesis [13–15]. However there are disadvantages associated with some of the reported procedures such as the requirement of solvent, long reaction times, sensitive catalyst, *etc.*

In recent years, there has been an enhanced interest in catalysis by nano materials. These materials exhibit better catalytic activity compared to their bulk sized counterparts [16,17]. Zinc oxide nanostructure is a non-hygroscopic, inexpensive and non-toxic material, which was used as a catalyst in organic reactions [18–22]. On the other hand, the elimination of volatile organic solvents in organic syntheses is the most important goal in green chemistry [23–25]. Solvent-free organic reactions make syntheses simpler, save energy, and prevent solvent wastes, hazards and toxicity.

Herein we disclose a general, rapid, high yielding and green synthetic protocol for wide variety three-substituted pyrroles from amines, phenacyl bromide and dialkyl acetylenedicarboxylates by ZnO nanostructures with different morphologies.

2. Experimental

2.1. Material and instrument

All chemicals were obtained from Fluka or Merck and were used without further purification. Samples of nanoparticle, nanosheet and nanorod ZnO were synthesized in the labratory. The morphology of nanostructure ZnO was determined by using scanning electron microscopy (SEM) of a Holland Philips XL30 microscope. X-ray diffraction (XRD) analysis was carried out at room temperature using a Holland Philips Xpert X-ray powder diffractometer with Cu Ka radiation ($\lambda = 0.15406$ nm), over the 2θ collection range of 20–80°. Average crystallite sizes of products were calculated using Scherrer's formula: $D = 0.9\lambda/\beta \cos\theta$ [26], where D is the diameter of the nanoparticles, λ (Cu Kα) = 1.5406 Å and β is the full-width at half-maximum of the diffraction lines. In order to determine the structure of organic compounds: The IR spectra were recorded using a Shimadzu IR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker DRX-250 AVANCE instrument in $CDCl_3$ at 250 and 62.5 MHz, respectively δ in ppm, J in Hz. Mass spectra were obtained on a Finnigan MAT-8430 at 70 eV. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

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Table 1
The corresponding experimental conditions and morphologies of samples.

Entry	$Zn(OAc)_2.2H_2O$ (mol)	NaOH (mol)	Water (mL)	SDS (mol)	Morphology
1	0.003	0.01	75	–	nanoparticle
2	0.009	0.03	75	0.015	nanosheet
3	0.003	0.01	75	0.005	nanorod

2.2. General procedure for synthesis of catalysts

2.2.1. General procedure for the preparation of nanoparticle ZnO (NP-ZnO)

Sodium hydroxide (0.44 g) was disolved in distilled water (75 mL) at room temprature, zinc acetate dihydrate (0.6 g) was added to the mixture and the solution was refluxed for 1.5 h at 80 C. The solution was then cooled at room temperature, the precipitate was collected by filtration and washed with distilled water and ethanol (96%) several times. NP-ZnO was dried in the air at room temprature during 24 h [27].

2.2.2. General procedure for the preparation of nanosheet ZnO NS-ZnO

In a typical experiment, 1.32 g of NaOH was dissolved in 75 mL of distilled water under vigorous stirring. Then the template, sodium dodecylsulfate (SDS) (4.71 g) was added to the solution. Next $Zn(AcO)_2.2H_2O$ (1.8 g) was added to the mixture. The mixture was transferred to a round bottomed flask and was refluxed for 1.5 h (pH = 14). After cooling to room temperature, the precipitate was collected by filtration and washed with distilled water and ethanol (96%) several times. Finally, the ZnO sample was dried in the air at room temperature during 24 h.

2.2.3. General procedure for the preparation of nanorod ZnO (NR-ZnO)

Sodium hydroxide (0.44 g) was dissolved in 75 mL of distilled water under vigorous stirring at room temperature. Afterwards, with the addition of SDS (1.57 g) and $Zn(AcO)_2.2H_2O$ (0.6 g) to the mixture, the solution was refluxed for 1.5 h at 80 C (pH = 14). The product was collected by filtration and washed with distilled water and ethanol (96%) several times [27].

2.3. General procedure for the preparation of polysubstituted pyrroles

To a stirred mixture of amine (2 mmol), phenacyl bromide (2 mmol) was added nanorod ZnO (15% mol). After 10 min dialkyl acetylenedicarboxylate was added at 70 C temperature. The mixture was stirred for about 60 min (TLC monitoring). The viscous residue was purified by column chromatography on silica gel (Merck 230–400 mesh) using n-hexane-EtOAc (9:1) as eluent.

Dimethyl 1-ethyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4a**). Brown oil. IR (KBr): ν = 1722, 1713, 1269 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.44 (3H, t, $^3J_{HH}$ = 7.0 Hz, Me), 3.83 (3H, s, Me), 3.84 (3H, s, Me), 4.35 (2H, q, $^3J_{HH}$ = 7.0 Hz, CH_2), 6.95 (1H, s, CH), 7.26–7.38 (5H, m, 5 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 16.9 (CH_3), 44.6 (CH_2N), 51.8 (CH_2O), 52.4 (CH_2O), 120.0 (C), 123.7 (CH), 124.8 (C), 126.9 (CH), 127.3 (2 CH), 128.7 (2 CH), 128.7)C),133.5 (C), 160.6 (C = O), 167.5 (C = O) [14].

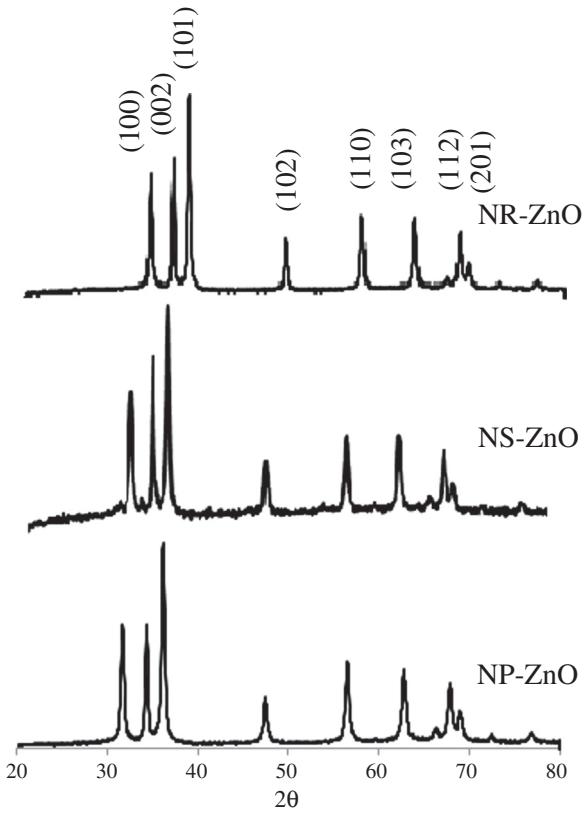


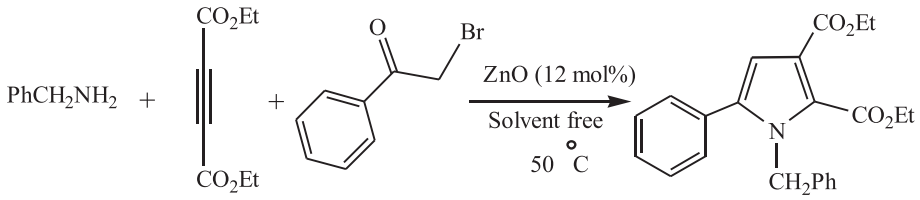
Fig. 2. XRD spectra of ZnO nanostructures.

Diethyl 1-ethyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4b**). Brown oil, yield: IR (KBr): ν = 1718, 1690, 1262 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.28 (3H, t, $^3J_{HH}$ = 7.0 Hz, Me), 1.31 (3H, t, $^3J_{HH}$ = 7.1 Hz, Me), 1.46 (3H, t, $^3J_{HH}$ = 7.2 Hz, Me), 4.17–4.45 (6H, m, 3 CH_2), 6.96 (1H, s, CH), 7.29–7.51 (5H, m, 5 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 14.1 (CH_3), 14.2 (CH_3), 17.0 (CH_3), 44.5 (CH_2N), 60.6 (CH_2O), 61.1 (CH_2O), 120.5 (C), 123.1)C), 123.2 (C), 124.7 (CH), 126.8 (CH), 127.4 (2 CH), 128.7 (2 CH), 133.5 (C), 160.2 (C = O), 166.8 (C = O) [13].

Dimethyl-1-benzyl-4-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4c**). Brown oil, IR (KBr): ν = 1734, 1713, 1450 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 3.82 (3H, s, Me), 3.87 (3H, s, Me), 5.53 (2H, s, CH_2), 6.95 (1H, s, CH), 7.1–7.50 (10H, m, 10 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 51.9 (CH_2N), 52.4 (CH_3O), 54.2 (CH_3O), 119.1 (C), 124.1 (C), 125.7 (CH), 127.0 (CH), 127.3 (2 CH), 127.4 (2 CH), 127.9 (2 CH), 128.7 (CH), 128.8 (2 CH), 130.7 (C), 133.6 (C), 137.2 (C), 161.2 (C = O), 166.2 (C = O) [13].

Diethyl 1-benzyl-4-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4d**). Brown oil, IR (KBr): 1732, 1713, 1450, 1263 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.32 (3H, t, $^3J_{HH}$ = 7.0 Hz, Me), 1.37 (3H, t, $^3J_{HH}$ = 7.0 Hz, Me), 4.31 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 4.37 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 5.60 (2H, s, CH_2), 6.99 (1H, s, CH), 7.2–7.48 (10H, m, 10 CH). ^{13}C NMR

Fig. 1. SEM images of the samples obtained by the reflux method without template nanoparticle (NP-ZnO) or with using SDS template nanosheet (NS-ZnO) and nanorod (NR-ZnO).



Scheme 1. ZnO catalyzed synthesis of pyrrole.

(62.5 MHz, $CDCl_3$): 14.1 (CH_3), 14.2 (CH_3), 52.4 (CH_2N), 60.7 (CH_2O), 61.3 (CH_2O), 121.2 (C), 123.9 (C), 125.6 (CH), 126.9 (CH), 127.4 (2 CH), 127.5 (2 CH), 127.9 (CH), 128.6 (2 CH), 128.8 (2 CH), 130.1 (C), 134.0 (C), 137.1 (C), 160.3 (C = O), 166.9 (C = O). MS (EI, 70 eV): *m/z* (%) = 377 (M^+, 15), 291 (50), 287 (100), 215 (100), 226 (40), 125 (62), 66 (70), 57 (80). Anal. Calcd for $C_{23}H_{23}NO_4$ (377.43): C, 73.19; H, 6.14; N, 3.71. Found: C, 73.40; H, 6.12; N, 3.75%.

Diethyl 1-(4-chlorobenzyl)-4-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4e**). Brown oil, IR (KBr): 1740, 1732, 1484, 1257 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.28–1.33 (6H, m, 2 Me), 4.21–4.33 (4H, m, 2 CH_2), 5.50 (2H, s, CH_2), 6.94 (1H, s, CH), 7.2–7.48 (9H, m, 9 CH). ^{13}C NMR (75 MHz, $CDCl_3$): 13.9 (CH_3), 14.0 (CH_3), 51.7 (CH_2N), 60.7 (CH_2O), 61.3 (CH_2O), 120.9 (C), 122.8 (C), 124.1 (CH), 125.4 (CH), 126.9 (2 CH), 127.4 (2 CH), 127.9 (CH), 128.6 (2 CH), 128.6 (2 CH), 130.7 (C), 133.2 (C), 133.7 (C), 160.2 (C = O), 166.7 (C = O). MS (EI, 70 eV): *m/z* (%) = 413 (M^+, 15), 411 (M^+, 5), 357 (22), 355 (7), 269 (100), 267 (33), 157 (40), 143 (61), 67 (60), 42 (50). Anal. Calcd for $C_{23}H_{22}ClNO_4$ (411.12): C, 67.07; H, 5.38; N, 3.40. Found: C, 67.01; H, 5.22; N, 3.38%.

Diethyl 1-(4-methylcyclohexa-1,5-dienyl methyl)-4-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4f**). Brown oil, IR (KBr): 1732, 1713, 1450, 1263 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.22–1.39 (6H, m, 2 Me), 2.33 (3H, s, Me) 4.18–4.35 (4H, m, 2 CH_2), 5.49 (2H, s, CH_2), 6.91 (1H, s, CH), 7.2–7.48 (9H, m, 9 CH). ^{13}C NMR (75 MHz, $CDCl_3$): 14.0 (CH_3), 21.1 (CH_3), 52.1 (CH_2N), 61.2 (CH_2O), 61.9 (CH_2O), 121.1 (C), 122.4 (C), 123.8 (CH), 125.4 (CH), 126.8 (2 CH), 127.4 (2 CH), 128.0 (CH), 128.5 (2 CH), 128.8 (2 CH), 129.4 (C), 130.1 (C), 133.5 (C), 133.9 (C), 160.3 (C = O), 166.9 (C = O). MS (EI, 70 eV): *m/z* (%) = 391 (M^+, 10), 363 (52), 291 (100), 247 (100), 171 (48), 125 (52), 66 (72), 57 (82). Anal. Calcd for $C_{24}H_{25}NO_4$ (391.16): C, 73.61; H, 6.38; N, 3.55. Found: C, 73.64; H, 6.44; N, 3.58%.

Dimethyl-1-hexyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4 g**). Brown oil, IR (KBr): ν = 1716, 1694, 1540, 1267 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 0.89 (3H, t, $^3J_{HH}$ = 7.8 Hz, Me), 1.26–1.42 (6H, m, 3 CH_2), 1.79 (2H, m, CH_2), 3.82 (3H, s, Me), 3.83 (3H, s, Me), 4.3 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 6.91 (1H, s, CH), 7.26–7.40 (5H, m, 5 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 14.1(CH_3), 22.6 (CH_2), 26.4 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 49.7 (CH_2N), 51.8 (CH_3O), 52.4 (CH_3O), 120.2 (C), 123.5 (CH), 125.5 (C), 126.9 (CH), 127.3 (2 CH), 128.7 (2 CH), 130.1 (C), 133.5 (C), 160.3 (C = O), 167.3 (C = O). MS (EI, 70 eV): *m/z* (%) = 343 (M^+, 25), 287 (68), 285 (100), 257 (100), 251 (40), 181 (62), 125 (68), 67 (70), 58 (35), 29 (44). Anal. Calcd for $C_{20}H_{25}NO_4$ (343.41): C, 69.95; H, 7.34; N, 4.08. Found: C, 66.89; H, 7.16; N, 4.18%.

Table 2
Optimization of reaction condition using different morphologies of ZnO (12 mol%) at 50 °C during 1 h.

Entry	Catalyst	Yield (%)
1	none	0
2	CM-ZnO	62
3	NS-ZnO	80
4	NP-ZnO	80
5	**NR-ZnO**	**85**

Diethyl-1-hexyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**4 h**). Brown oil, IR (KBr): ν = 1730, 1709, 1489, 1263 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 0.89 (3H, t, $^3J_{HH}$ = 7.8 Hz, Me), 1.25–1.37 (12H, m, 6 CH_2), 1.79 (2H, m, CH_2), 4.25–4.33 (6H, m, 3 CH_2), 6.91 (1H, s, CH), 7.3–7.42 (5H, m, 5 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 14.1 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 22.6 (CH_2), 26.4 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 49.7 (CH_2N), 60.6 (CH_2O), 61.3 (CH_2O), 120.5 (C), 123.3 (C), 125.4 (CH), 126.8 (CH), 127.4 (2 CH), 128.6 (2 CH), 128.9 (C), 133.6 (C), 160.2 (C = O), 167.1 (C = O). MS (EI, 70 eV): *m/z* (%) = 371 (M^+, 20), 299 (68), 251 (100), 227 (40), 165 (40), 86 (62), 86 (68), 58 (45), 57 (50), 29 (44). Anal. Calcd for $C_{22}H_{29}NO_4$ (371.47): C, 71.13; H, 7.87; N, 3.77. Found: C, 71.10; H, 7.81; N, 3.75%.

Diethyl 1-ethyl-5-(4-methoxyphenyl-1*H*-pyrrole-2,3-dicarboxylate (**4i**). Brown oil. IR (KBr): ν = 1729, 1713, 1579, 1297 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.26–1.35 (9H, m, 3 Me), 3.81 (3H, s, OMe), 4.24–4.32 (6H, m, 3 CH_2), 6.84 (1H, s, CH), 6.88 (2H, *d*, $^3J_{HH}$ = 6.4 Hz, 2 CH), 7.32 (2H, *d*, $^3J_{HH}$ = 6.4 Hz, 2 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 14.0 (CH_3), 14.1 (CH_3), 14.1 (CH_3), 49.5 (CH_2N), 55 (OMe), 60.5 (CH_2O), 61.1 (CH_2O), 113.9 (2 CH), 124.9 (C), 125.0)C), 126.0 (CH), 126.5 (C), 128.6 (2 CH), 133.0 (C), 153.0 (C), 158.5 (C = O), 160.2 (C = O). MS (EI, 70 eV): *m/z* (%) = 345 (M^+, 20), 328 (68), 282 (100), 256 (100), 226 (40), 133 (62), 85 (68), 71 (70), 57 (100). Anal. Calcd for $C_{19}H_{23}NO_5$ (345.38): C, 66.07; H, 6.71; N, 4.06. Found: C, 66.37; H, 6.04; N, 4.08%.

Dimethyl 1-ethyl-5-(4-chlorophenyl-1*H*-pyrrole-2,3-dicarboxylate (**4j**). Brown oil, IR (KBr): ν = 1709, 1697, 1400, 1263 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.40 (3H, *t*, $^3J_{HH}$ = 7.0 Hz, Me), 3.76 (3H, s, Me), 3.77 (3H, s, Me), 4.35 (2H, q, $^3J_{HH}$ = 7.2 Hz, Me), 6.43 (2H, d, $^3J_{HH}$ = 7.0 Hz, 2 CH), 6.92 (1H, s, CH), 7.25 (2H, d, $^3J_{HH}$ = 7.0 Hz, 2 CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 16.9 (CH_3), 44.6 (CH_2N), 51.9 (CH_3O), 52.5 (CH_3O), 119.1 (C), 122.5 (C), 124.7 (CH), 128.7 (2 CH), 128.8 (2 CH), 129.6 (C), 130.5)C),131.5 (C), 161.2 (C = O), 166.5 (C = O). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 32), 321 (M^+, 10), 265 (48), 235 (88), 178 (38), 165 (40), 183 (52), 197 (60), 86 (68), 56 (45). Anal. Calcd for $C_{16}H_{16}NO_4Cl$ (321.75): C, 59.73; H, 5.01; N, 4.35. Found: C, 59.65; H, 5.02; N, 4.15%.

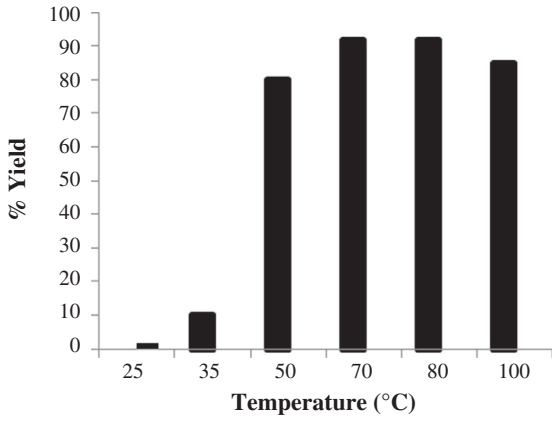


Fig. 3. Influence of reaction temperature on the synthesis of polysubstituted pyrroles.

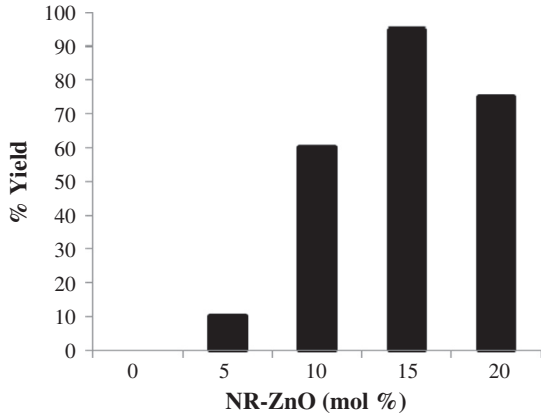


Fig. 4. Effect of catalyst loading on the synthesis of pyrrole, reaction conditions: Ethyl amine (1 mmol), DEAD (1 mmol), phenacyl bromide (1 mmol), solvent free, 70 °C, 1 h.

Table 3
One-pot synthesis of *N*-benzyl-2-[(2-oxoethyl-2-phenyl)amino] benzamide at different solvent during 1 h with NR-ZnO (12 mol%).

Entry	Solvent	Temperature (°C)	Yield (%)
1	CH_3CN	Reflux	84
2	H_2O	Reflux	40
3	CH_2Cl_2	Reflux	45
4	n-Hexane	Reflux	60
5	**Solvent-free**	**70**	**94**

3. Results and discussion

3.1. Design, preparation and characterization of the catalysts

The method of synthesis of NR-ZnO and NP-ZnO was reported in our last article [27]. ZnO nanoparticles were obtained from the reaction between $Zn(AcO)_2 \cdot 2H_2O$ and NaOH by reflux method without adding template. Nanorod morphology was obtained using SDS [27]. Nanosheet ZnO (NS-ZnO) was synthesized by increasing the reactants and SDS to solvent ratio. This is reported in this article. SDS was employed as a directing agent to control ZnO nanostructure morphologies. The corresponding experimental condition and morphologies of samples are listed in Table 1. The morphologies of the products were examined by SEM. Fig. 1 shows the typical SEM images of the samples obtained by the reflux method. As shown in this figure, when only Zn^{+2} was used (without any template), ZnO nanoparticles were formed. Using SDS, ZnO nanorod was obtained in the same condition. The length and diameter of nanorods were 300–600 nm and 50–70 nm, respectively.

SEM image of NS-ZnO prepared in SDS clearly shows homogeneous samples with uniform nanosheet morphology. These nanosheets displayed a diameter of ~30 nm, length of ~700 nm and ~400 nm in width. Fig. 2 shows the XRD pattern of ZnO with typical morphologies synthesized by this method. All the prominent peaks in the pattern corresponded to the wurtzite structure of ZnO, which can be indexed on the basis of JCPDS file No. 36–1451. No other characteristic peaks of the impurities are observed, indicating the high purity of the catalysis. We observe that all samples exhibit highest relative intensities for the (1 0 1) peak revealing a preferred orientation of their corresponding products. While, comparing with other peaks, the samples show different relative intensities of the (0 0 2) peak. The average crystal sizes for NP-ZnO, NS-ZnO, NR-ZnO are about 30, 21, 30 nm respectively [26,27].

It seems that the formation of ZnO with different morphologies involves the interaction between "nucleus" and SDS to control the growth rate in a certain direction [27]. An explanation for the formation of nanosheet ZnO involves the role of precursor and the SDS to control the growth rate of various faces of the preformed nucleus. The SDS molecules firstly form bilayers in the precursor solution, that SDS molecules form bilayer-like micelles in concentrated solution. The head group regions of the formed micelles are occupied by coulombic force with precursor. At the moment, formation of $Zn(OH)_4^{2-}$ nuclei takes place in the head group regions of the micelles, resulting in uniform nano-sheets [28]. It seems that the NR-ZnO morphology results in cylindrical inverse micelles in aqueous solutions of SDS [29].

3.2. Catalytic activity of ZnO nanostructures in the synthesis of polysubstituted pyrroles

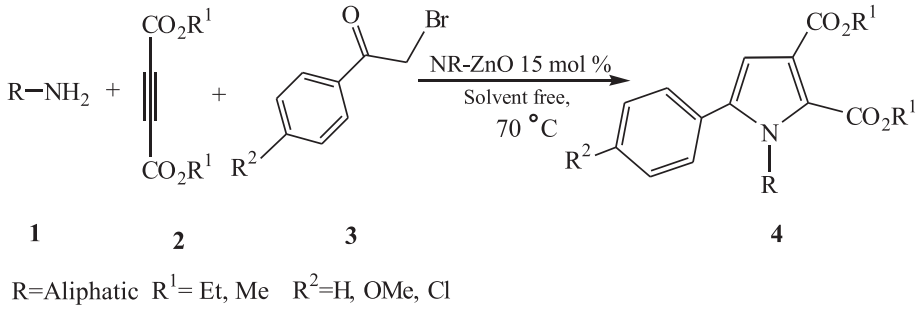
Initially, benzyl amine, phenacyl bromide and diethyl acetylenedicarboxylate (DEAD) were chosen as the model reaction (Scheme 1) and commercial zinc oxide (CM-ZnO) was used as the catalyst. It was found to give 62% yield of product at 50 °C under solvent free condition (Table 1, entry 2). Encouraged by this result, further optimization studies were carried out by nanostructures of ZnO with different morphologies including nanoparticle (NP-ZnO), nanorod (NR-ZnO) and nanosheet ZnO (NS-ZnO) as catalyst.

As shown in Table 2, the reaction did not take place without any catalyst (Table 2, entry 1) and the yield of the desired product was maximized when NR-ZnO was used (Table 2, entry 5).

The result of changing the reaction temperature is visualized in Fig. 3 when NR-ZnO was used. The best reaction temperature is between 70 and 80 °C. Thus, this reaction was carried out at the lower temperature, *i.e.*, at 70 °C.

The result of our optimization studies in catalyst loading is presented in Fig. 4. The yield increased smoothly with catalyst load up to 15% but further increase led to the decrease of product conversion. The results indicate the significant role of NR-ZnO as a catalyst for the reaction.

To understand the role of solvent, we screened various solvent systems, such as CH_3CN, H_2O, CH_2Cl_2 and n-hexane (Table 3). The results showed that polar solvents such as CH_3CN gave higher yields comparing to another solvents. However, the amount of desired product was found to be greater in solvent-free condition.



Scheme 2. NR-ZnO catalyzed synthesis of pyrrole in optimum condition.

Table 4
Substrate scope, reaction conditions: phenacyl bromide (1.0 mmol), amine (1 mmol), dialkyl acetylenedicarboxylate (1.0 mmol), NR-ZnO (15%), Solvent free, 70 C.

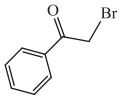
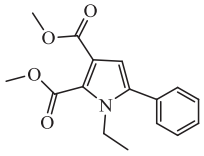
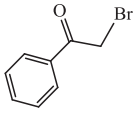
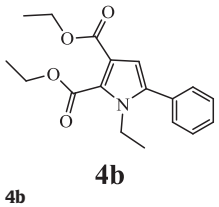
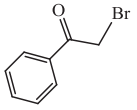
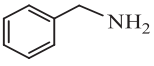
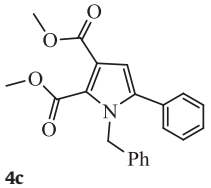
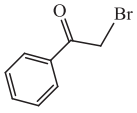
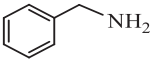
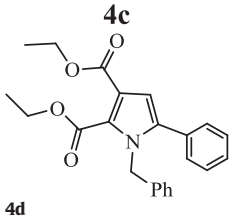
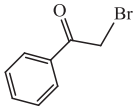
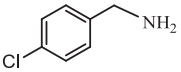
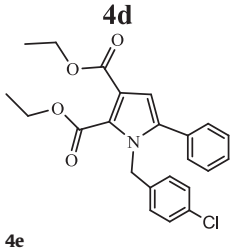
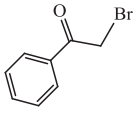
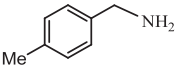
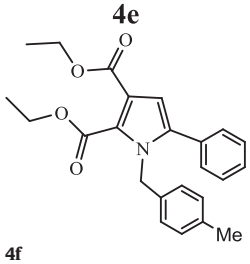
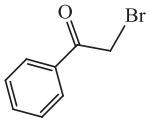
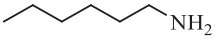
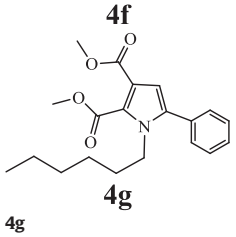
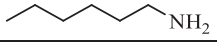
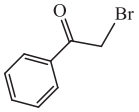
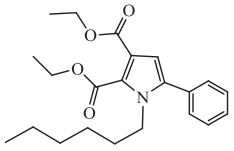
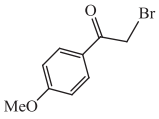
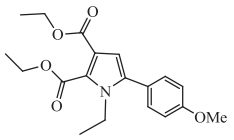
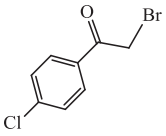
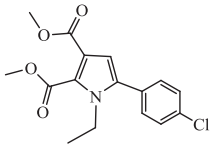
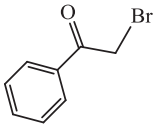
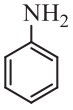
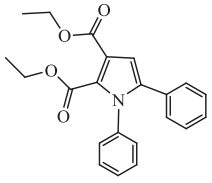
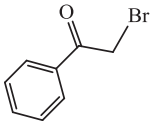
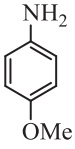
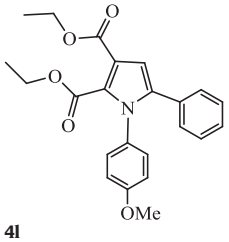
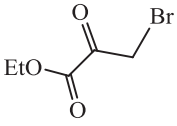
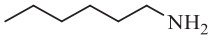
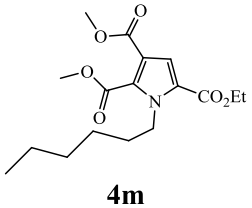
Entry	α-Bromo ketone	Amines	Acetylene dicarboxylate	Product	Time (min)	Yield[a] (%)
1				 **4a**	45	90
2				 **4b**	45	88[b]
3				 **4c**	50	90
4				 **4d**	50	94
5				 **4e**	60	82
6				 **4f**	60	86
7				 **4g**	45	92
8					45	86

Table 4 (*continued*)

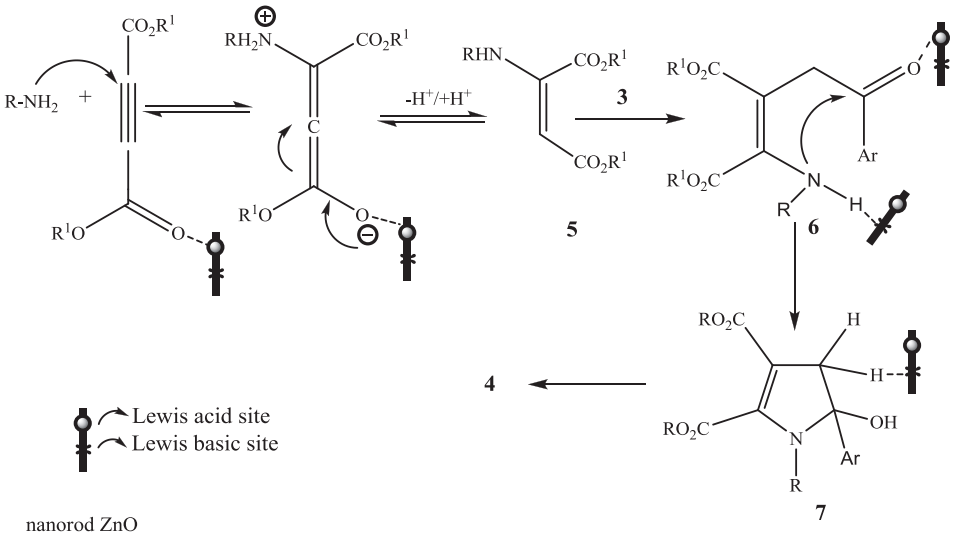
Entry	α-Bromo ketone	Amines	Acetylene dicarboxylate	Product	Time (min)	Yield[a] (%)
				 **4h**		
9				 **4i**	60	75
10				 **4j**	60	78
11				 **4k**	360	0
12				 **4l**	360	0
13				 **4m**	60	0

[a] Isolated yield. **4a–c** are known compounds [13–14].
[b] Yield obtained after 3 catalytic cycles.

To extend the scope, NR-ZnO was tested with various amines, phenacyl bromide with dialkyl acetylenedicarboxylate and the resulting products were formed in high yield (Scheme 2, Table 4). All the products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The yields of products were in the range of 75–94% and the reaction time varies depending upon the nature of the substrate. Aromatic amines didn't give the desired products (Table 4, entries11 and 12). Also the reaction with ethyl bromopyruvate was not successful (Table 4, entry 13).

The catalyst can be resolved three times without significant loss of activity. The reusability of the catalyst was checked for the synthesis of diethyl 1-ethyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (Table 4, entry 2). The catalyst was filtered off after each run and washed thoroughly with ethylacetate; it was then dried at room temperature for 24 h and used for the next catalytic cycle.

Mechanistically, it is conceivable that the reaction involves the initial formation **5** between the amine and the electron-deficient acetylenic compound, which reacts with the phenacyl bromide to generate **6** [13]. Cyclization of this intermediate followed dehydration, which affords 1,2,3,5-substituted pyrroles. NR-ZnO has Lewis acid sites (Zn^{2+}) and Lewis basic sites (O^{2-}) [24,30]. In this reaction, the Zn^{2+} sites are interacting with carbonyl groups in acetylenic compound and phenacyl



Scheme 3. Proposed mechanism of formation of three-substituted pyrroles catalyzed by ZnO nanostructures.

bromide and O^{2-} site of ZnO nanostructures taking up a proton of **7** to generate **4** (Scheme 3) [30]. The detailed formation mechanism of product needs to be further investigated.

4. Conclusions

Herein, we disclose a general, rapid, high yielding and green synthetic protocol for synthesis of three-substituted pyrrole derivatives via the one-pot three-component reactions of amine, phenacyl bromide and dialkyl acetylenedicarboxylates under solvent free conditions using nanorod ZnO. The efficiency of the catalytic activity is dependent on the particle size and morphology of ZnO. Low temperature in catalyst synthesis and pyrrole preparation is interesting from an economic point of view. Development of such catalysts has resulted in more economical and environmentally friendly chemistry replacing unstable or toxic catalysts.

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