Int. J. Bio-Inorg. Hybr. Nanomater., Vol. 4, No. 2 (2015), 73-78

ISSN Print: 2251-8533
ISSN Online: 2322-4142

International Journal of Bio-Inorganic Hybrid Nanomaterials

Catalytic Synthesis N-alkyl-3-acetyl-2-methylpyrroles using ZnO Nanostructure

Ashraf Sadat Shahvelayati[1*], Maryam Sabbaghan[2], Solmaz Banihashem[3]

[1, 3] Department of Chemistry, Yadegar-e-Imam Khomeini (RAH) Shahre-rey Branch, Islamic Azad University, Tehran, Iran

[2] Department of Chemistry, Faculty of Sciences, Shahid Rajaee Teacher Training University, Tehran, Iran

Received: 3 February 2015; Accepted: 6 April 2015

ABSTRACT

A simple, green synthesis of N-alkyl-3-acetyl-2-methylpyrrole derivatives using ZnO nanoparticles from the three component reaction of aliphatic amines, acetylacetone (as a 1,3-dicarbonyl compound) and α-haloketones under solvent-free condition is described.

Keywords: N-alkyl-3-acetyl-2-methylpyrroles; ZnO nanoparticles; Three component reactions; Solvent-free reactions; Acetylacetone

1. INTRODUCTION

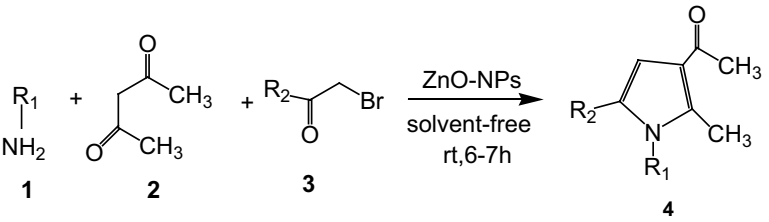
N-heterocyclic compounds received considerable attention in the literature as a consequence of their exciting biological properties and their role a pharmacophores [1]. Of these heterocycles, the synthesis, reactions, and biological activities of pyrrole derivatives stand as an area of research in heteroaromatic chemistry. A number of synthetic methods have been reported for the synthesis of both undecorated, and polysubstituted pyrroles [2].

However, some of these methods have some drawbacks, such as long reaction times, unsatisfactory yields and use of expensive catalysts. Therefore, it is necessary to develop a simple and green method for the synthesis of pyrrole derivatives without these problems.

In recent years multicomponent reactions (MCRs) have performed quantitative revolutions in nitrogen-containing heterocyclic compounds due to their application in biologically active pharmaceutical, agrochemicals and functional materials are becoming important [3-9].

Simple and green synthetic procedures constitute an important goal in organic synthesis. The goals of green chemistry are focused on four of the current demands of human kind which are minimizing waste and pollution, efficient exploitation of material and energy sources,

(*) Corresponding Author - e-mail: avelayati@yahoo.com



R_1= n-Bu, cy-Hexyl
R_2= 4-Br-C_6H_4, CO_2Et, 4-MeO-C_6H_4

Scheme 1: *Nano ZnO catalyzed synthsis of N-alkylpyrroles.*

minimizing hazard, and minimizing cost [10].

Therefore, with the development of industrialization, organic chemists have been confronted with a new challenge of finding novel methods in organic synthesis that can reduce and finally eliminate the impact of volatile organic solvents and hazardous toxic chemicals on the environment. So, use of non-toxic, environmentally, friendly, and inexpensive solid catalysts such as ZnO nanoparticle to perform organic reactions has attracted considerable interest [11-13]. In the continuation of our research on the application of MCRs in heterocyclic synthesis, herein, we report an efficient three-component synthesis for pyrrole derivatives using ZnO nanoparticles (NPs) as a green and reusable catalyst under solvent-free conditions (Scheme1) [14-17].

2. RESULTS AND DISCUSSION

The reaction of aliphatic amines 1, acethylacetone 2, and α-bromoketones 3 under solvent-free condition and ZnO catalyst was studied to produce pyrroles 4 in good yields (Table 1), and it was compared with the situations without catalyst in different solvents (Table 2).

The structures of compounds 4a–4f were confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. For example, the 1HNMR spectrum of 4c in $CDCl_3$ exhibited characteristic signals in δ = 0.81-3.83 ppm for butyl group, together with one triplet and one quartet (δ = 1.35, 4.72 respectively) for the ethoxy group, one singlet in

Table 1: *Yield of pyrrole derivatives in the presence of ZnO catalyst.*

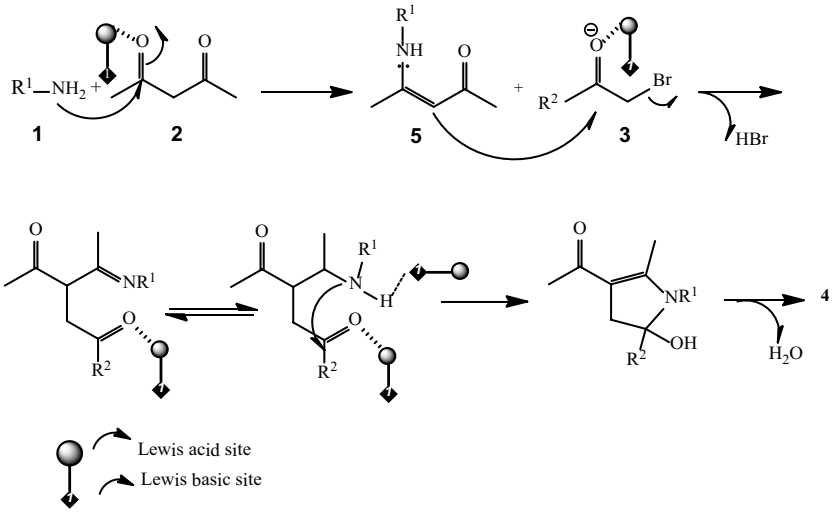
4	R_1	R_2	Yield (%)
a	n-Bu	4-Br-C_6H_4	90
b	n-Bu	CO_2Et	92
c	n-Bu	4-MeO-C_6H_4	95[a]
d	cy-Hexyl	CO_2Et	88
e	cy-Hexyl	4-MeO-C_6H_4	86
f	cy-Hexyl	4-Br-C_6H_4	75

[a]*4 c, yield 95% in the presence of ZnO catalyst for the first time, 93% in the second run, and 90% in the third run with recycled ZnO.*

δ = 2.66 ppm for methyl group, and one singlet in δ = 3.86 ppm for methoxy group. Moreover, it showed one singlet signal (δ = 6.49 ppm) for CH-pyrrole and two doublets (δ = 6.94, 7.26 ppm) for the aromatic protons. The ^{13}CNMR spectrum of 4c showed 19 signals in agreement with the proposed structure. Partial assignments of these resonances are given in Section 4. The ^{1}H and ^{13}CNMR spectra of the other products are similar to those of 4c.

A tentative mechanism for this transformation is proposed in Scheme 2. Enaminones were produced from reaction of 1,3-dicarbonyl compounds and amines. They are an important intermediate in the synthesis of pyrroles. Presumably, enaminone 5, formed by the initial reaction of amine 1 and 1,3- dicarbonyl 2, attacks α-bromoketones 3 and after cyclization of affords products 4.

To improve the yield of the target products, we carried out the test reaction in the presence of various solvents and the results are presented (Table 2). It was



Scheme 2: *Proposed mechanism for the synthesis of compounds 4.*

Table 2: *Effect of solvent on synthesis of 4a without catalyst.*

Solvent/catalyst		Time (h)	Yield (%)
a	THF/none catalyst	72	80
b	Ethanol/none	72	70
c	Methanol/none	72	70
d	CH_3CN/none	72	65
e	$CHCl_3$/none	72	65
f	ZnO NPs/ Solvent-free	6-7	95

observed that ZnO exhibited high activity and the corresponding product was performed in high yield.

It seems that high surface area and better dispersion of nanoparticles in the reaction mixture are reason for better activities of ZnO NPs. The higher yield was obtained with increasing the amount of catalyst from 5% to 12.5%. Hence the optimum concentration of ZnO NPs was chosen 12.5% mol in the model reaction (Table 3).

As a result, solvent-free conditions accelerated the rate of reaction and also high yields were obtained for all products. So, in this research, we successfully prepared pyrroles derivatives in the presence of zinc oxide nanoparticles. As shown in Table1 phenacyl bromides with electron-donating groups such as methoxy group reacted faster than those with electron-withdrawing groups including Br.

Table 3: *Effect of increasing amount of ZnO on the reaction.*

Entry	ZnO (mmol)	Yield (%)
1	0.05	43
2	0.1	75
3	0.25	95

3. EXPERIMENTAL DETAIL

3.1. General

All used materials in laboratory are products of Merck, Aldrich, and Fluka companies. In order to detect products, TLC-Cards silicagel-G/UV has been employed. The catalyst was prepared and identified according to reference 18. Morphology and particle size of the catalyst were determined by the SEM and XRD images (Figures 1, 2). IR spectra were obtained using Shimadzu FTIR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-300 AVANCE instrument in $CDCl_3$ at 300.1 and 75.4 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.

3.2. Preparation of pyrrole derivatives

The reaction was carried out at 80°C with the mixture of 1,3-dicarbonyl (1 mmol) and amine (1 mmol) in

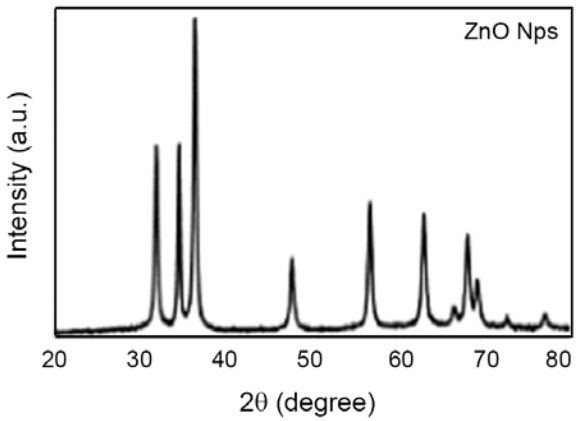


Figure 1: *XRD pattern of ZnO Nanoparticles.*

the presence of ZnO NPs as catalyst (12.5% mol), after 20 min, α-haloketone (0.5 mmol) was added to the mixture without solvent and was stirred for 6-7 h at r.t. After completion of the reaction (TLC monitoring), the products 4 were purified by column chromatography (n-hexane/AcOEt 5:1).

3.3. Preparation of ZnO nanoparticles

In a typical procedure, the definite amount of NaOH was dissolved in 30 mL of distilled water under vigorous stirring, followed by the addition of ionic liquid (IL) and 0.3 g $Zn(AcO)_2$.$2H_2O$ to the mixture. The mixture transfer to a round bottomed flask and was refluxed for 1.5 h. After cooling to room temperature, the precipitate was collected by filtration and washed with distilled water and ethanol (96%) several times [18].

Finally, The morphology of ZnO nanoparticles was determined by using scanning electron microscopy (SEM) and X-ray diffraction (XRD) (Figures 1, 2) [18].

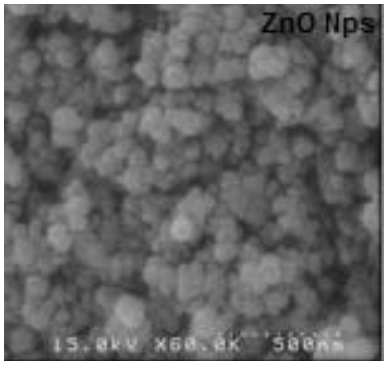


Figure 2: *SEM image of ZnO Nanoparticles.*

3.4. Reusability of catalyst

EtOAC (2 times) was added to the catalyst and the precipitate was centrifuged and filtered off. Nano ZnO regenerated by washing with hot EtOAc and then with acetone and drying of the precipitate at 300°C. The recyclability of ZnO NPs was examined in synthesis of 4c with no significant decreasing in reaction yields (Table 1).

4. SPECTRAL DATA

Ethyl 5-(4-bromophenyl)-1-butyl-2-methyl-1H-pyrrole-3-carboxylate (4a)

Pale yellow oil; 0.40 g (90%). IR: 1689, 1429, 1388, 1270 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, J = 7.3 Hz, Me), 1.14-1.17 (m, 2H, CH_2), 1.35 (t, 3H, J = 7.1 Hz, Me), 1.50-1.52 (m, 2H, CH_2), 2.61 (s, 3H, Me), 3.84 (t, 2H, J = 7.7 Hz, CH_2N), 4.28 (q, 2H, J = 7.1 Hz, CH_2O), 6.55 (s, 1H, CH), 7.22 (d, 2H, J = 7.7 Hz, 2CH), 7.53 (d, 2H, J = 7.7 Hz, 2CH). ^{13}CNMR (75 MHz, $CDCl_3$): δ 11.9 (Me), 13.9 (Me), 14.9 (Me), 20.1 (CH_2), 33.1 (CH_2), 44.3 (CH_2N), 59.7 (CH_2O), 110.5 (CH), 112.5 (C), 121.9 (C), 131.2 (2CH), 132.0 (2CH), 132.5 (C), 134.1 (C), 137.1 (C), 165.9 (CO). MS (EI, 70 eV): m/z (%) 365 (M+2, 10), 363 (M+, 9), 336 (100), 334 (98), 322 (20). Anal. Calcd. for $C_{18}H_{22}BrNO_2$ (364.28): C, 59.35; H, 6.09; N, 3.85%. Found: C, 59.68; H, 6.13; N, 3.69%.

Diethyl 1-butyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (4b)

Yellow oil; 0.30 g (92%). IR: 1691, 1401, 1393, 1289 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, J = 7.3 Hz, Me), 1.31-1.35 (m, 8H, 4 CH_2), 1.67-1.69 (m, 2H, CH_2), 2.38 (s, 3H, Me), 3.79 (t, 2H, J = 7.2 Hz, CH_2N), 4.28-4.32 (m, 4H, 2 CH_2O), 7.10 (s, 1H, CH). ^{13}CNMR (75 MHz, $CDCl_3$): δ 11.1 (Me), 14.0 (Me), 14.6 (Me), 14.7 (Me), 20.1 (CH_2), 33.0 (CH_2), 47.2 (CH_2N), 60.4 (CH_2O), 60.6 (CH_2O), 113.6 (C), 115.3 (C), 126.1 (CH), 134.9 (C), 164.6 (CO), 165.9 (CO). MS (EI, 70 eV): m/z (%) 281 (M+, 7), 252 (100), 238 (19). Anal. Calcd. for $C_{15}H_{23}NO_4$ (281.35): C, 64.03; H, 8.24; N, 4.98%. Found: C, 63.88; H, 8.11; N, 4.89%.

Ethyl 1-butyl-5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (4c)

Yellow oil; 0.34 g (95%). IR: 1697, 1373, 1244, 1189 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.81 (t, 3H, J = 7.2 Hz, Me), 1.17-1.20 (m, 2H, CH_2), 1.35 (t, 3H, J = 7.1 Hz, Me), 1.51-1.53 (m, 2H, CH_2), 2.66 (s, 3H, Me), 3.81-3.84 (m, 2H,CH_2N), 3.86 (s, 3H, MeO), 4.72 (q, 2H, J = 7.1 Hz, CH_2O), 6.49 (s, 1H, CH), 6.94 (d, 2H, J = 8.6 Hz, 2CH), 7.26 (d, 2 H, J = 8.6 Hz, 2CH). ^{13}CNMR (75 MHz, $CDCl_3$): δ 11.9 (Me), 13.9 (Me), 14.9 (Me), 20.1 (CH_2), 33.1 (CH_2), 44.2 (CH_2N), 55.6 (MeO), 56.9 (CH_2O), 109.6 (CH), 112.0 (C), 114.2 (2CH), 126.0 (C), 131.1 (2CH), 133.5 (C), 136.3(C), 159.4 (C), 166.1 (CO). MS (EI, 70 eV): m/z (%) 315 (M+, 11), 286 (100), 272 (22). Anal. Calcd. for $C_{19}H_{25}NO_3$ (315.41): C,72.35; H, 7.99; N, 4.44%. Found: C, 71.88; H, 7.86; N, 4.39%.

Diethyl 1-cyclohexyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (4d)

Yellow oil; 0.34 g (88%). IR: 1681, 1311, 1265, 1209 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.33–1.35 (m, 6H, 2 Me), 1.27–2.00 (m, 10H, 5 CH_2), 2.04 (s, 3H, Me), 3.66 (m, 1H, CHN), 4.28–4.62 (m, 4 H, 2CH_2O), 7.28 (s. 1H, CH). ^{13}CNMR (75 MHz, $CDCl_3$): δ 11.9 (Me), 14.0 (Me), 14.3 (Me), 24.9 (CH_2), 29.3 (2CH_2), 31.1 (2CH_2), 54.4 (CH_2O), 55.1 (CH_2O), 57.8 (CHN), 112.2 (C), 115.9 (C), 126.1 (CH), 133.9 (C), 164.6 (CO), 165.9 (CO). MS (EI, 70 eV): m/z (%) 307 (M+, 12), 224 (100). Anal. Calcd. for $C_{17}H_{25}NO_4$ (307.38): C, 66.43; H, 8.20; N, 4.56%. Found: C, 66.88; H, 8.09; N, 4.51%.

Ethyl 1-cyclohexyl-5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (4e)

Yellow oil; 0.39 g (86%). IR: 1700, 1319, 1255, 1222 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.20–2.07 (m, 10H, 5 CH_2), 1.26 (t, 3H, J = 7.1 Hz, Me), 2.71 (s, 3H, Me), 3.72 (m, 1H, CHN), 3.91 (s, 3H, MeO), 4.12 (q, 2H, J = 7.1 Hz, CH_2O), 6.31 (s, 1H, CH), 6.98 (d, 2H, J = 8.8 Hz, 2CH), 7.23 (d, 2H, J = 8.8 Hz, 2CH). ^{13}CNMR (75 MHz, $CDCl_3$): δ 12.8 (Me), 14.4 (Me), 25.4 (CH_2), 26.5 (2CH_2), 32.4 (2CH_2), 55.0 (MeO), 57.7 (CH_2O), 58.8 (CHN), 110.1 (CH), 112.5 (C), 113.9 (2CH), 131.0 (C), 131.7 (2CH), 132.4 (C), 135.7 (C), 159.8 (C), 165.2 (CO). MS (EI, 70 eV): m/z (%) 341 (M+, 8), 258 (100). Anal. Calcd. for $C_{21}H_{27}NO_3$ (341.44): C, 73.87; H, 7.97; N, 4.10%. Found: C, 73.58; H, 8.09; N, 3.96%.

Ethyl 5-(4-bromophenyl)-1-cyclohexyl-2-methyl-1H-pyrrole-3-carboxylate (4f)

Yellow oil; 0.52 g (75%). IR: 1717, 1345, 1258, 1227 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.14–2.07 (m, 10H, CH_2), 1.24 (t, 3H, J = 7.1 Hz, Me), 2.73 (s, 3H, Me), 4.10 (m, 1H, CHN), 4.21 (q, 2H, J = 7.1 Hz, CH_2O), 6.40 (s, 1H, CH), 7.31 (d, 2H, J = 8.3, 2CH), 7.63 (d, 2H, J = 8.3 Hz, 2CH). ^{13}CNMR (75 MHz, $CDCl_3$): δ 12.8 (Me), 14.3 (Me), 25.4 (CH_2), 26.4 (2CH_2), 32.4 (2CH_2), 58.0 (CH_2O), 58.9 (CHN), 110.8 (CH), 112.9 (C), 121.6 (C), 131.8 (2CH), 132.1 (2CH), 132.8 (C), 135.1 (C), 136.7 (C), 165.0 (CO). MS (EI, 70 eV): m/z (%) 391 (M+2, 10), 389 (M+, 9), 308 (100). Anal. Calcd. for $C_{20}H_{24}BrNO_2$ (390.31): C, 61.54; H, 6.20; N, 3.59%. Found: C, 62.05; H, 6.41; N, 3.64%.

5. CONCLUSIONS

We have efficiently synthesized some pyrrole derivatives in the presence of zinc oxide nanoparticles under solvent-free conditions in good yields. Zinc oxide nanoparticles as a green, mild and effective catalyst satisfactorily catalyzed the synthesis of these compounds. The catalyst was recyclable and has been reused for three successive runs with little loss of activities.

REFERENCES

1. Yavari I., Ghazvini M., Azad L., Sanaeishoar T., *Chin. Chem. Lett.*, **22** (2011), 1219.
2. Balme, G., *Angew. Chem., Int. Ed.*, **43** (2004), 6238.
3. Dhakshinamoorthy A., Garcia H., *Chem. Soc. Rev.*, **43** (2014), 5750.
4. Estevez V., Villacampa M., Menendez J.C., *Chem. Soc. Rev.*, **39** (2010), 4402.
5. Domling A.,Ugi I., *Angew. Chem. Int. Ed.*, **39** (2009), 3168.

6. Lichtenthaler F.W., *Acc. Chem. Res.*, **35** (2002), 728.
7. Litvinov V.P., *Russ. Chem. Rev.*, **72** (2003), 69.
8. Alinezhad H., Tajbakhsh M., *J. Chem. Soc.*, **55** (2011), 238.
9. Moss T.A., Nowak T., *Tetrahedron Lett.*, **53** (2012), 3056.
10. R.A. Sheldon, I. Arends, U. Hanefeld, 2007. *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, Germany.
11. Bhattacharyya P., Pradhan K., Paul S., Das A.R., *Tetrahedron Lett.*, **53** (2012), 4687.
12. Saeidian H., Abdoli M., Salimi R., *C. R. Chim.*, **16** (2013), 1063.
13. Bahrami K., Khodaei M.M., Farrokhi A., *Synth. Commun.*, **39** (2009), 1801.
14. Yavari I., Shahvelayati A.S., Malekafzali A., *J. Sulfur Chem.*, **31** (2010), 499.
15. Shahvelayati A.S., Issa Yavari I., Delbari A.S., *Chin. Chem. Lett.*, **25** (2014), 119.
16. Shahvelayati A.S., Adhami, F., Larijani, K., *Iranian J. Org. Chem.,* **3** (2011), 665.
17. Shahvelayati A.S., *Iranian J. Org. Chem.*, **4** (2012), 943.
18. Sabbaghan M., Shahvelayati A.S., Bashtani S.E., *Solid State Sci.*, **14** (2012), 1191.

AUTHOR (S) BIOSKETCHES

Ashraf Sadat Shahvelayati, *Assistant Professor, Department of Chemistry, Yadegar-e-Imam Khomeini (RAH) Shahre-e rey Branch, Islamic Azad University, Tehran, Iran*
Email: avelayati@yahoo.com

Maryam Sabbaghan, *Assistant Professor, Department of Chemistry, Faculty of Sciences, Shahid Rajaee Teacher Training University, Tehran, Iran*

Solmaz Banihashem, *M.Sc., Department of Chemistry, Yadegar-e-Imam Khomeini (RAH) Shahre-rey Branch, Islamic Azad University, Tehran, Iran*