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ARTICLE

Nanocatalytic one-pot, four-component synthesis of some new triheterocyclic compounds consisting of pyrazole, pyran, and pyrimidinone rings

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A new series of triheterocyclic compounds containing of pyrazole, pyran, and pyrimidinone rings was synthesized via a one-pot condensation of ethylacetoacetate, hydrazine hydrate, barbituric acid, and aromatic aldehydes in the presence of catalytic amounts of titanium dioxide nanowires. Various functional groups were well tolerated under the optimized reaction conditions.

Introduction

Knoevenagel reaction is one of the most important methods to construct C-C bonds in modern organic synthesis [1,2]. Knoevenagel products usually participate as active substrates in a Michael-type addition reaction. Over the past decade, many multicomponent strategies involving Knoevenagel condensation and Michael addition followed by intramolecular cyclizeation have been reported for the synthesis of new fused heterocycles [3-5]. Multipart heterocycles are widely present in natural compounds. Consequently, the development of strategies to synthesize such compounds is one of the important research areas in the field of biological science [6-8].

The synthesis of compounds incorporating both pyran and pyrazole rings [9-12] has attracted significant attention because of their pharmacological properties. In addition, some pyrimidines have found diverse biological activities [13-14]. Given the fact that the catalytic activity of some nanomaterials is often more than bulk cases, therefore, many elegant works on the nanocatalyzed organic synthesis have been reported in recent years. On the other hand, nanocatalysts have been considered to possess great potential as part of green technologies for organic synthesis [15]. Although a few preparative methods for the synthesis of pyrazolopyranopyrimidines using base catalysts such as Meglumine and DABCO have been recently reported in the literature [16,17], we are aware of no report on the four-component synthesis of pyrazolopyranopyrimidines using metal oxide nanoparticles as catalyst. Nano titanium dioxide has shown a good catalytic activity and recyclability for the successful synthesis of some organic compounds such as quinoxalines [18], pyrimidines [19], dicoumarols [20], and pyranochromens [21].

Experimental

Methods and Materials

All chemicals were purchased from Merck and Aldrich. The reaction progress was monitored by thin layer chromatography (TLC; silica-gel 60 F_{254}, *n*-hexane: AcOEt). IR spectra were recorded on a FT-IR JASCO-680 and the ^{1}H NMR spectra were obtained on a Bruker-Instrument DPX-400 MHz Avance 2 model. Mass spectra were recorded on a Shimadzu Gc-MS QP 100 Ex spectrometer. Scanning electron microscopy (SEM) studies of the nanostructures were carried out with a JEOL JEM 3010 instrument operating at an accelerating voltage of 300 kV. X-Ray diffraction (XRD, D8, Advance, Bruker, AXS) patterns were obtained for characterization of the heterogeneous catalyst. Melting points were measured on an electrothermal KSB1N apparatus.

General procedure for preparation of TiO_2 nanowires

In a typical synthesis, 0.115 g of commercial Degussa P25 powder was mixed with 3.5 mL of 10 M NaOH and 3.5 mL of EtOH. The mixed solution was then transferred into a 35 mL Teflon-lined stainless-steel autoclave. The autoclave was maintained at 180 °C under autogenous pressure for 24 h and then cooled to room temperature naturally. The sample so obtained was filtered off, washed several times with a dilute HCl aqueous solution and water until the pH value of the washing solution became about 7 [22].

Synthesis of 5 using TiO_2 nanowires

Ethylacetoacetate (0.13 ml, 1 mmol) and TiO_2 NWs (10 mol%) were added to a solution of hydrazine hydrate (96%, 0.05 ml, 1 mmol) in

H_2O/EtOH (5 ml, 50/50) over 20 min. Then, aromatic aldehyde (1 mmol) and barbituric acid (1 mmol) were added to the mixture and the mixture was heated under reflux for an appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and the precipitate was filtered, dried, and dissolved in hot EtOH to separate the catalyst. The pure product was obtained after recrystallization from EtOH.

Spectral data

Compound 5b: IR (KBr) ν = 3138, 3041, 2907, 1678, 1579, 1518, 1349; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.37 (br, 1H), 10.27 (s, 2H), 8.11 (d, 2H, *J*=8.0 Hz), 7.33 (d, 2H, *J*=8.0 Hz), 2.26 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.99, 151.20, 150.63, 145.54, 143.64, 131.78, 127.98, 123.12, 114.47, 104.86, 91.02, 31.04, 9.96.

Compound 5d: IR (KBr) ν = 3215, 3054, 1686, 1623, 1588, 1488, 1369, 836, 870; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.01 (br, 1H), 10.19 (s, 2H), 7.27 (d, 2H, *J*=8.0 Hz), 7.06 (d, 2H, *J*=8.0 Hz), 5.41 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.35, 150.57, 141.58, 134.64, 129.92, 128.59, 128.06, 127.71, 127.27, 89.45, 30.16, 9.96.

Compound 5e: IR (KBr) ν = 3077, 3003, 2951, 2228, 1671, 1624, 1602, 1378; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.30 (br, 1H), 102.40 (s, 2H), 7.69 (d, 2H, *J*=8.0 Hz),7.25 (d, 2H, *J*=8.0 Hz), 5.49 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.07, 150.61, 148.85, 143.70, 132.17, 131.83, 131.47, 127.80, 119.05, 108.22, 104.84, 89.73, 31.08, 9.95.

Compound 5f: IR (KBr) ν = 3212, 1689, 1606, 1511, 1426, 1249, 1177; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.96 (br, 1H), 10.15 (s, 2H), 6.96 (d, 2H, *J*=8.0 Hz), 6.77 (d, 2H, *J*=8.0 Hz), 5.37 (s, 1H), 3.69 (s, 3H), 2.22 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.57, 157.06, 154.89, 150.59, 137.46, 134.35, 128.10, 127.63, 125.12, 113.92, 113.18, 54.89, 9.99.

Compound 5g: IR (KBr) ν = 3221, 2962, 1690, 1622, 1462, 1388; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.12 (br, 1H), 10.18 (s, 2H), 7.08 (d, 2H, *J*=8.0 Hz), 6.97 (d, 2H, *J*=8.0 Hz), 5.40 (s, 1H), 2.81 (sep, 1H, *J*=8 Hz), 2.22 (s, 3H), 1.17 (s, 3H), 1.116 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.60, 150.60, 145.18, 143.50, 139.92, 129.43, 126.58, 126.49, 125.72, 105.91, 91.39, 32.89, 23.95, 23.90, 23.52, 9.98; MS (m/z): 339.3, 258.2, 243.1, 228.2, 213.1, 185.1, 128.1, 109.1.

Compound 5h: IR (KBr) ν = 3182, 3039, 1680, 1652, 1495, 1400, 1363, 1193; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.88 (br, 1H), 10.13 (s, 2H), 6.88 (d, 2H, *J*=8.0 Hz), 6.62 (d, 2H, *J*=8.0 Hz), 5.35 (s, 1H), 2.83 (s, 6H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.70, 154.12, 150.28, 146.09, 136.49, 127.20, 119.93, 112.61, 111.16, 109.47, 91.43, 40.58, 29.50, 10.01.

Compound 5i: IR (KBr) ν = 3200, 2937, 1686, 1625, 1592, 1506, 1462, 1129; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.16 (br, 1H), 10.17 (s, 2H), 6.37 (s, 2H), 5.39 (s, 1H), 3.65 (s, 6H), 3.62 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.46, 152.28, 150.54, 143.64, 138.41, 135.82, 112.42, 111.41, 106.68, 104.38, 91.03, 59.88, 56.02, 55.67, 30.35, 10.03.

Compound 5j: IR (KBr) ν = 3430, 3202, 3026, 1685, 1646, 1624, 1453, 1394, 1263; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.96 (br, 1H), 10.19 (s, 2H), 6.50 (d, 2H, *J*=8.0 Hz), 6.46 (d, 2H, *J*=8.0 Hz), 5.35 (s 1H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.64, 156.98, 150.59, 144.07, 143.59, 128.63, 124.76, 117.39, 113.71, 112.29, 89.35, 30.32, 9.97.

Compound 5k: IR (KBr) ν = 3212, 3050, 1688, 1650, 1495, 1363, 1199; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.16 (br, 1H), 10.22 (s, 2H), 7.84-7.82 (m, 1H), 7.79-7.75 (m, 2H), 7.50 (s, 1H), 7.44-7.42 (m, 2H), 7.24 (d, 1H, *J*=8.0 Hz), 5.60 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.55, 150.55, 143.62, 140.12, 132.81, 131.45, 129.39, 127.50, 127.31, 127.19, 126.08, 125.77, 125.10, 124.29, 105.74, 81.06, 30.64, 10.05; MS (m/z): 346.1, 292.1, 351.1, 178.1, 152.0, 128.0, 109.0.

Compound 5l: IR (KBr) ν = 3021, 2954, 1694, 1610, 1479, 1391, 1303; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.29 (br, 1H), 11.14 (s, 2H), 7.34-7.27 (m, 4H), 5.37 (s, 1H), 2.19 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.76, 153.64, 151.65, 150.63, 143.12, 135.47, 131.86, 130.18, 128.04, 125.44, 89.19, 19.37, 16.91, 10.28.

Results and discussion

We herein present an efficient strategy for the one-pot synthesis of triheterocyclic compounds consisting of pyrazole, pyran, and pyrimidinone rings in the presence of catalytic amount of TiO_2 nanowires (NWs). Firstly, we prepared TiO_2 NWs from the commercial Degussa P25 powder.

Fig. 1 shows the X-ray diffraction pattern for the TiO_2 NWs. Seven diffraction peaks are well in agreement with the standard data for the TiO_2 NWs structure and all peaks can be also indexed to the pure anatase phase [22].

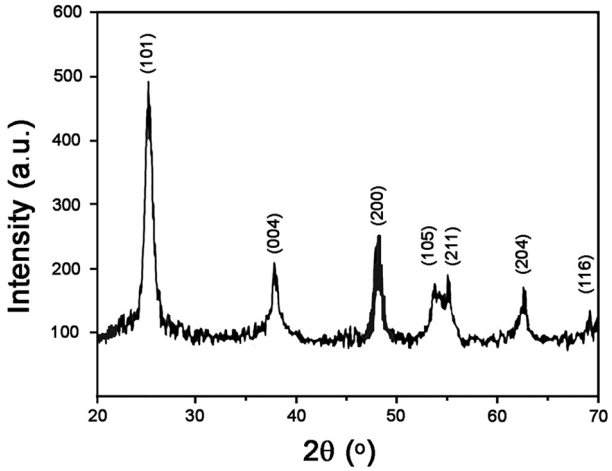


Fig. 1. X-ray diffraction pattern of TiO_2 NWs.

The morphology of the TiO_2 NWs was studied by scanning electron microscopy (SEM). Fig. 2 shows the SEM image for the as-synthesized TiO_2 NWs. The synthesized NWs are relatively uniform with a few microns in length and have diameters in the range of 50-100 nm.

In connection with our interest in the development of efficient metal oxide-catalyzed routes to heterocycles [23,24], as shown in Scheme 1, here, we describe the synthesis of triheterocyclic compounds **5** via a one-pot, four-component reaction of ethylacetoacetate (**1**), hydrazine hydrate (**2**), barbituric acid (**3**), and aromatic aldehydes (**4**) using TiO_2 NWs as efficient catalyst.

We began our study by examining the reaction of **1**, **2** with **3** and benzaldehyde (**4a**) in H_2O/EtOH under reflux by using TiO_2 NWs as catalyst.

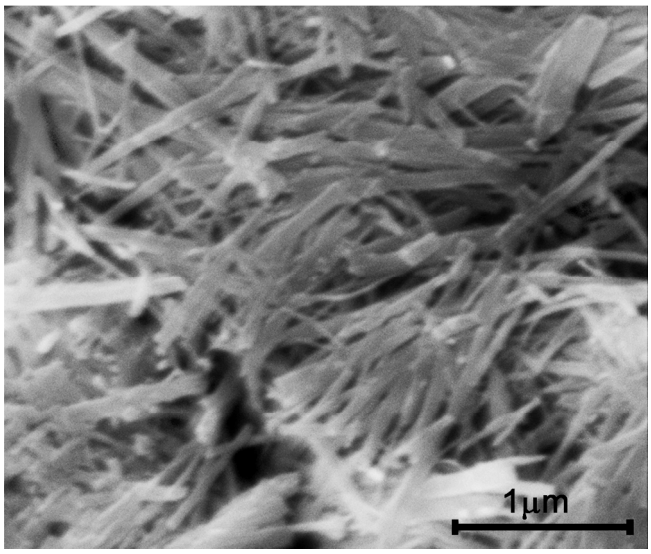
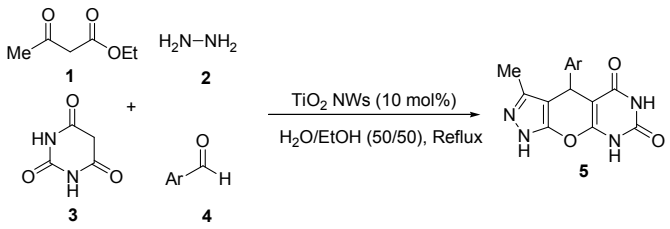


Fig. 2. SEM image of TiO_2 nanowires.

According to Fig. 3, the use of TiO_2 NWs (5 mol%) gave desired product in a moderate yield together with observable intermediates. Among the various amounts of TiO_2 NWs examined, 10 mol% was the most effective, and its use resulted in the formation of **5a** in 95% yield. Also, when substrates reacted in the absence of any catalyst, no desired product was obtained as determined by TLC method.



Scheme 1. Synthesis of pyrazolopyranopyrimidines using TiO_2 NWs.

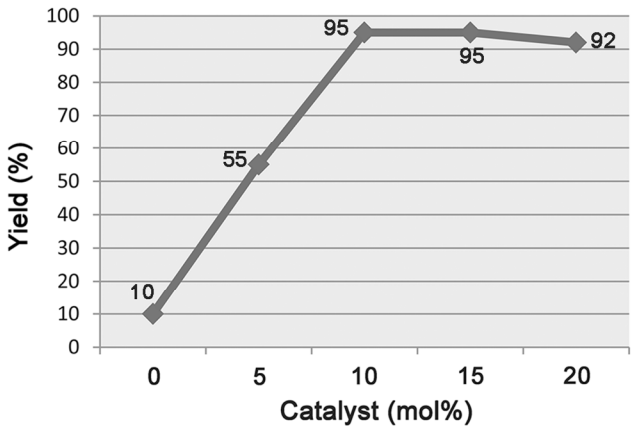


Fig. 3. Optimization of the amounts of TiO_2 NWs for the synthesis of **5a**. Reaction time: 60 min.

Furthermore, in order to compare the TiO_2 NWs with bulk case, an experiment was also investigated. However, it was found that the model reaction was completed in the presence of TiO_2 powder in a longer reaction time (about 100 min) than TiO_2 NWs.

Solvent choice is also an important factor in this reaction. After testing various solvents and solvent-free conditions, it was revealed that a combination of water and ethanol with a ratio of 1:1 leads to the best result.

Table 1. Various solvents in the one-pot synthesis of **5a.**

Entry	Solvent	Yield (%)
1	No	-
2	EtOH	70
3	Acetone	30
4	CH_2Cl_2	40
5	H_2O	55
6	H_2O/EtOH (1/1)	95

Under the optimized reaction conditions, the scope and generality of the reaction were subsequently explored (Table 2). The reactions with aromatic aldehydes bearing both electron-donating/withdrawing groups at the aromatic ring proceeded well to give the corresponding products in good to excellent yields.

Table 2. Synthesis of triheterocyclic compounds **5** using TiO_2 NWs (10 mol%) in EtOH/H_2O (1:1).

Entry	Ar	Time (min)	Yield (%)[a]	M.p. (°C)
5a	C_6H_5	60	95	217-219
5b	4-NO_2-C_6H_4	55	91	232-234
5c	2,4-$(Cl)_2$-C_6H_3	70	93	230-232
5d	4-Cl-C_6H_4	60	91	221-223
5e	4-CN-C_6H_4	45	85	242-244
5f	4-MeO-C_6H_4	70	88	228-230

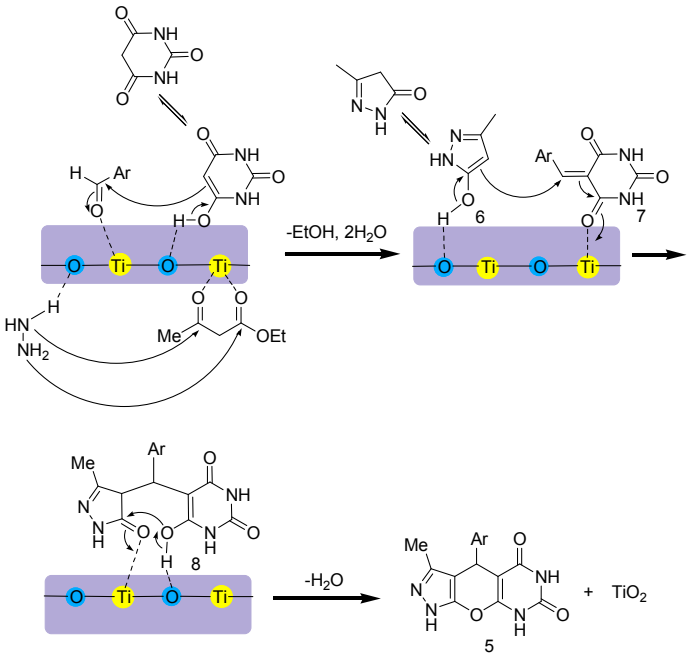
5g	4-Isopropyl-C_6H_4	85	87	218-220
5h	4-Dimethylamino-C_6H_4	90	84	260-262
5i	3,4,5-$(MeO)_3$-C_6H_2	85	88	252-254
5j	4-OH-C_6H_4	100	86	263-265
5k	2-Naphthyl	85	84	246-248
5l	2-Me-C_6H_4	75	83	262-263

[a]Isolated yields.

All the products were characterized by their spectral data such as NMR and FT-IR spectroscopy. As a representative example, the ^{1}H NMR spectrum of compound 5k showed two sharp singlets at 2.28 and 5.60 ppm as methyl and methine protons, respectively. Signals at 7.84–7.24 ppm corresponded to the aromatic protons. The amine protons appeared at 13.16 and 10.22 ppm. The ^{13}C NMR spectrum of compound **5k** also confirmed the suggested structure showing the expected signals.

A plausible mechanistic proposal which might be catalyzed by metal oxide species is shown in Scheme 2 for triheterocyclic compounds **5**. Initial addition of the hydrazine (**2**) to the ethylacetoacetate (**1**) promoted by titanium dioxide may generate an intermediate **6**. Simultaneously, the intermediate **7** is produced through the Knoevenagel condensation of barbituric acid (**3**) with aldehyde (**4**). In the next step, the intermediate **7** undergoes a Michael addition with the intermediate **6** and generates a new intermediate **8**. Finally, **8** undergoes an intramolecular cyclization reaction followed by H_2O elimination to afford the triheterocyclic product **5** and complete the catalytic cycle (Scheme 2).

TiO_2 nanowires as catalyst showed a good recyclability in the model reaction for the synthesis of **5a**. The catalyst could successfully be used for four runs during which loss of the catalytic activity was minimal.



Scheme 2. Suggested mechanism for the synthesis of triheterocyclic compounds **5** using TiO_2 NWs as the catalyst.

Conclusions

In summary, some triheterocyclic compounds containing pyrazole, pyran, and pyrimidinone rings were successfully synthesized via four-component reactions in the presence of TiO_2 NWs. The presented method has some advantages such as the use of a safe and recyclable catalyst, avoidance of toxic solvents, high product yields, short reaction times, and easy work-up procedure.

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Notes and references

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