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Nano *n*-propylsulfonated γ-Al_2O_3: a new, efficient and reusable catalyst for synthesis of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4] thiazepine]diones in aqueous media

Li Qiang Wu*

Nano *n*-propylsulfonated γ-Al_2O_3 is easily prepared by the reaction of nano γ-Al_2O_3 with 1,3-propanesultone. This reagent can be used as an efficient catalyst for the synthesis of spiro [indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine]diones in aqueous media. This new method consistently has the advantages of excellent yields and short reaction times. Further, the catalyst can be reused and recovered several times. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: nano *n*-propylsulfonated γ-Al_2O_3; 1,4-thiazepine; spirooxindole; heterogeneous catalysis; nanoparticles; multicomponent reactions

Introduction

Multicomponent reactions (MCRs) have attracted considerable attention since they are performed without the need to isolate any intermediate during their processes, may reduce time and save both energy and raw materials.[1–3] They have merits over two-component reactions in several aspects, including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules.

One aspect of MCRs that has received relatively little attention is their development using nanocatalysts which would lead to processes close to the ideal synthetic reaction.[4–7] Nanometer-sized particles are easily dispersible in solution by forming stable suspensions. Furthermore, nanoparticles as heterogeneous catalysts have high catalytic activities due to their larger surface area-to-volume ratio. For these reasons, the development of synthetically useful multicomponent reactions using nanocatalysts has gained considerable interest.

The 1,4-thiazepine ring is one of the important moieties in nitrogen- and sulfur-containing heterocycles, and aryl- and heteroaryl-fused derivatives of thiazepine represent an important group of compounds with interesting pharmaceutical properties. Some of these compounds exhibited angiotensin-converting enzyme inhibition,[8] leading to the development of temocapril,[9] a drug used for the treatment of hypertension.

The heterocyclic spirooxindole ring system is a widely distributed structural framework present in a number of pharmaceuticals and natural products,[10] including such cytostatic alkaloids as spirotryprostatins A[11] an B[12] and strychnophylline.[13] The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets.[14]

Recently, Chen *et al.*[15] and Karnakar *et al.*[16] reported respectively the three-component synthesis of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine]diones using *p*-TsOH or sulfonic acid-functionalized carbon as a catalyst in CH_3CN. However, the two methods are associated with one or more disadvantages such as prolonged reaction time, low yield and the use of toxic solvents. The recovery and reusability of the catalyst are also a problem. Therefore, it is still desirable to seek a green and eco-friendly protocol that uses a highly efficient and reusable catalyst for the preparation of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine]diones.

Organic reactions in water have become an important research area. Many reactions have been accomplished in aqueous medium.[17,18] Water has therefore become an attractive medium for many organic reactions, not only for the advantages concerning the avoidance of expensive drying reactants, catalysts and solvents, but also for some unique reactivity and selectivity. We now report a highly efficient procedure for the preparation of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine] diones via a one-pot, four-component reaction of 3-aminocrotononitrile, phenylhydrazine, isatins and thioacid using nano *n*-propylsulfonated γ-Al_2O_3 as an efficient and versatile catalyst in aqueous media (Scheme 1).

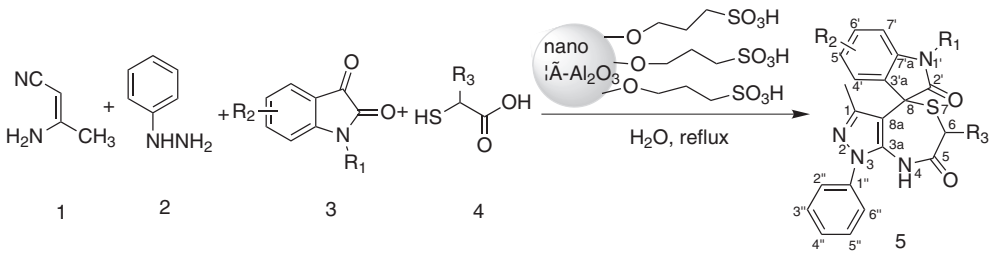
Experimental

Materials and Instrumentation

γ-Alumina powder with a particle size of about 20 nm was purchased from aladdin (Shanghai, China) and used without further purification. Other reagents and starting materials were purchased from commercial sources and used as received. All products were characterized by comparison of their spectral

* *Correspondence to: Li Qiang Wu, School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan 453003, China. E-mail: wliq1974@sohu.com*

School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan, 453003, China



Scheme 1. Synthesis of spiro[indoline-3,4-pyrazolo[3,4-e][1,4]thiazepine] diones using nano *n*-propylsulfonated γ-Al_2O_3.

and physical data with those previously reported. Progress of the reactions were monitored by thin-layer chromatography.

X-ray powder diffraction (XRD) patterns were recorded using a Cu Kα radiation source on a Bruker D8 Advance powder diffractometer. Scanning electron microscopy (SEM) studies were conducted on a JSM-6390LV instrument. Transmission electron microscopy (TEM) studies were performed using a JEM 2100 transmission electron microscope at an accelerating voltage of 150 kV. TGA curves were recorded using a DT-40 thermoanalyzer. IR spectra were determined on an FTS-40 infrared spectrometer. NMR spectra were determined on a Bruker AV-400 spectrometer at room temperature using tetramethylsilane (TMS) as an internal standard (DMSO-d_6 solution); coupling constants (*J*) were measured in Hz. Elemental analyses were performed by a Vario-III elemental analyzer. Melting points were determined on an XT-4 binocular microscope and were uncorrected.

Synthesis of Nano *n*-Propylsulfonated γ-Al_2O_3

Nano γ-Al_2O_3 (6 g) was suspended in 600 ml of 0.1 M toluene solution of 1,3-propanesultone and the colloidal solution was refluxed for 48 h. The sulfonated nano γ-Al_2O_3 was isolated and purified by repeated washing and centrifugation.

General Procedure for the Synthesis of Spiro[indoline-3,4-pyrazolo[3,4-e][1,4]thiazepine]diones

A mixture of 3-aminocrotononitrile (1 mmol) and phenylhydrazine (1 mmol) was refluxed for 10 min in the presence of nano *n*-propylsulfonated γ-Al_2O_3 (100 mg) in water. Then, an equimolar mixture of isatins (1 mmol) and thioacid (1 mmol) was added, and the resulting reaction mixture heated under reflux for 5–10 h. After completion of the reaction (TLC), the resulting solid was collected by filtration. EtOAc (20 ml) was added, and the solid catalyst was removed by filtration, washed with EtOH, dried and reused for a consecutive run under the same reaction conditions. The solvent was evaporated and the crude product was purified by silica gel column chromatography using hexane and EtOAc (80:20) as eluent to give the title compound.

Spectral Data of the Unknown Compounds

6-Chloro-3′-methyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (***5m***; $R_1 = H$, $R_2 = 6\text{-Cl}$, $R_3 = H$)

M.p. 253–255°C; IR (KBr) *ν*: 3205 (NH), 3115 (NH), 2929, 1705 (C O), 1624 (C N), 1450, 1398, 1319, 1205, 1132, 1054, 958, 779, 682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 11.08 (s, 1H, NH), 9.88 (s, 1H, NH), 7.52–7.44 (m, 5H, H-2″-6″), 7.38 (d, $J = 7.6$ Hz, 1H, H-5′), 7.25 (d, $J = 7.6$ Hz, 1H, H-4′), 7.12 (s, 1H, H-7′), 4.53 (d, $J = 14.4$ Hz, 1H, CH_2), 3.22 (d, $J = 14.4$ Hz,1H, CH_2), 1.48 (s, 3H, CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): 179.2 (C_5), 170.9 ($C_{2'}$), 150.2 (C_{3a}), 144.3 (C_1), 137.8 ($C_{7'a}$), 136.9 ($C_{1''}$), 130.2 ($C_{6'}$), 128.5 ($C_{4'}$), 126.9 ($C_{3''}$), 126.0 ($C_{4''}$), 125.8 ($C_{3'a}$), 125.6 ($C_{5'}$) , 124.2 ($C_{7'}$), 114.5 ($C_{2''}$), 106.4 (C_{8a}), 47.9 (C_{spiro}), 31.6 (C_6), 11.8 (CH_3). Anal. calcd for $C_{20}H_{15}ClN_4O_2S$: C 58.46, H 3.68, N 13.64, S 7.80; found: C 58.57, H 3.70, N 13.53, S 7.78.

6-Chloro-3′,6′-dimethyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]- 2,7′(1′H)-dione (***5n***; $R_1 = H$, $R_2 = 6\text{-Cl}$, $R_3 = CH_3$)

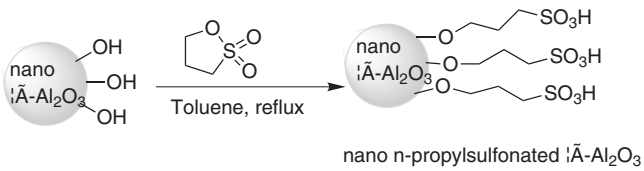
M.p. 276–278°C. IR (KBr) *ν*: 3366 (NH), 3244 (NH), 2925, 1718 (C O), 1655 (C N), 1462, 1382, 1243, 1199, 1056, 952, 915, 769, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 11.02 (s, 1H, NH), 9.90 (s, 1H, NH), 7.60–7.39 (m, 5H, H-2″-6″), 7.22 (d, $J = 7.6$ Hz, 1H, H-5′), 7.12 (s, 1H, s, 1H, H-7′), 7.10 (d, $J = 7.6$ Hz, 1H, H-4′), 4.77 (q, $J = 7.6$ Hz, 1H, CH), 1.52 (s, 3H, CH_3), 1.30 (d, $J = 7.6$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 178.9 (C_5), 174.2 ($C_{2'}$), 147.3(C_{3a}), 142.9 (C_1), 140.1 ($C_{7'a}$), 137.2 ($C_{1''}$), 130.1 ($C_{6'}$), 128.4 ($C_{4'}$), 128.0 ($C_{3''}$), 127.5 ($C_{4''}$), 125.9 ($C_{3'a}$), 125.5 ($C_{5'}$), 124.0 ($C_{7'}$), 114.2 ($C_{2''}$), 105.9 (C_{8a}), 49.3 (C_{spiro}), 34.5 (C_6), 16.3 (CH_3), 12.3 (CH_3). Anal. calcd for $C_{21}H_{17}ClN_4O_2S$: C 59.36, H 4.03, N 13.19, S 7.55; found: C 59.44, H 3.98, N 13.26, S 7.50.

Results and Discussion

Nano *n*-propylsulfonated γ-Al_2O_3 was easily prepared by the reaction of nano γ-Al_2O_3 with 1,3-propanesultone (Scheme 2), and was characterized by FT-IR, XRD, TGA, SEM and TEM. The amount of sulfonic acid loaded on the surface of nanoγ-Al_2O_3 was determined by TGA and confirmed by ion-exchange pH analysis.

FT-IR Analysis

Figure 1 presents the FT-IR spectra of nano γ-Al_2O_3 and nano *n*-propylsulfonated γ-Al_2O_3. As shown in this figure, the presence of an extra sulfonic acid group in the nano *n*-propylsulfonated γ-Al_2O_3 increases the number of vibrational modes and brings a completely different FT-IR spectrum. The FT-IR spectra of nano *n*-propylsulfonated γ-Al_2O_3 exhibits two characteristic peaks at 589 and 758 cm^{-1} due to the stretching vibrations of the Al-O



Scheme 2. Synthesis of nano *n*-propylsulfonated γ-Al_2O_3.

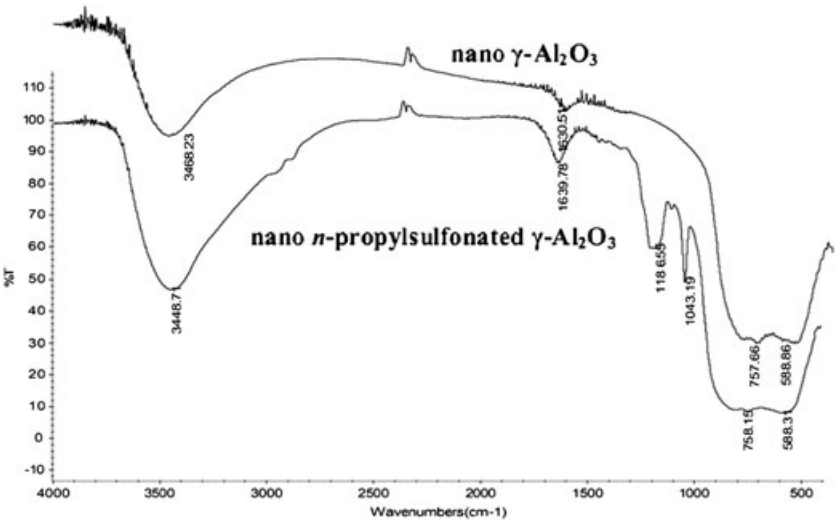


Figure 1. FT-IR spectra of nano γ-Al_2O_3 (top) and nano *n*-propylsulfonated γ-Al_2O_3 (bottom).

bond in γ-Al_2O_3. Moreover, two important peaks at 1043 and 1187 cm^{-1} are assigned to S-O stretching vibration. The broad peak at 3444 cm^{-1} belongs to the stretching of OH groups in SO_3H. These results indicate that reaction of nano γ-Al_2O_3 with 1,3-propanesultone succeed in incorporating sulfated groups in nano γ-Al_2O_3.

XRD Analysis

XRD measurements of nano γ-Al_2O_3 and nano *n*-propylsulfonated γ-Al_2O_3 exhibit diffraction peaks at around 19.5, 32.6, 36.6, 39.5, 45.8, 60.6 and 67.2, corresponding to the (111), (220), (311), (222), (400), (511) and (440) faces (Fig. 2). The observed diffraction peaks agree well with the cubic structure of γ-Al_2O_3 (JCPDS file no. 29-0063). It is clear that the ordered structure of nano γ-Al_2O_3 is retained after introducing the propylsulfonic acid group. The average crystallite sizes are calculated to be 14.9 nm using the Scherrer equation, which are in good accordance with TEM results.

TGA

The stability of the nano γ-Al_2O_3 and nano *n*-propylsulfonated γ-Al_2O_3 is determined by thermogravimetric analysis (Fig. 3). A significant decrease in the weight percentage of the nano γ-Al_2O_3 and nano *n*-propylsulfonated γ-Al_2O_3 at about 150°C is related to desorption of water molecules from the catalysts surface. In the TG curve of nano *n*-propylsulfonated γ-Al_2O_3, complete loss of all the covalently attached organic structure is seen in the temperature range of 230–960°C. The shouldering observed from 328°C onwards may be due to the decomposition of alkyl-sulfonic acid groups. According to the TGA, the amount of nano

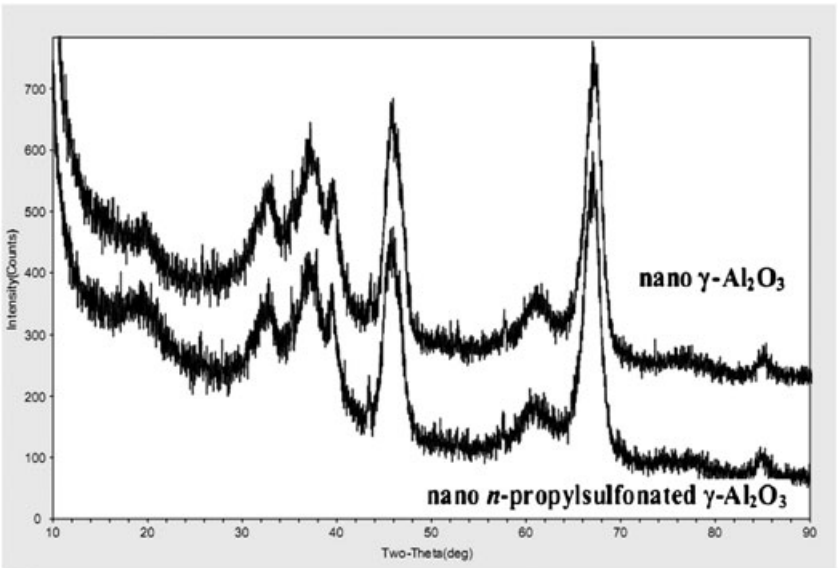


Figure 2. XRD patterns of nano γ-Al_2O_3 (top) and nano *n*-propylsulfonated γ-Al_2O_3 (bottom).

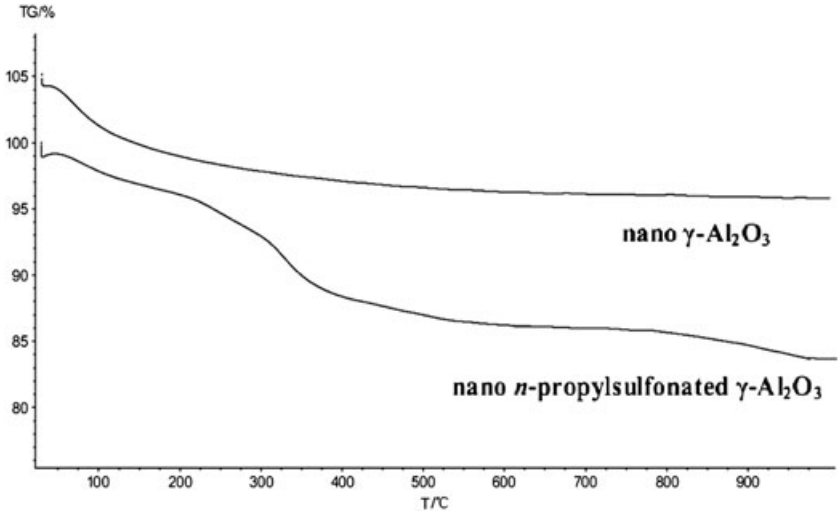


Figure 3. TG analyses of nano γ-Al_2O_3 (top) and nano *n*-propylsulfonated γ-Al_2O_3 (bottom).

n-propylsulfonated γ-Al_2O_3 is evaluated to be 0.78 mmol g^{-1}. This result is in agreement with that of ion-exchange pH analysis.

SEM and TEM Analysis

The morphology and size of the nano γ-Al_2O_3 and nano *n*-propylsulfonated γ-Al_2O_3 are analyzed by SEM and TEM as shown in Figs 4 and 5. The low-magnification SEM images (Fig. 4) show small nano-sized grains having spherical and quasi-spherical morphology with a narrow size distribution, which indicates the nano crystalline nature of γ-Al_2O_3 nano particles. The presence of

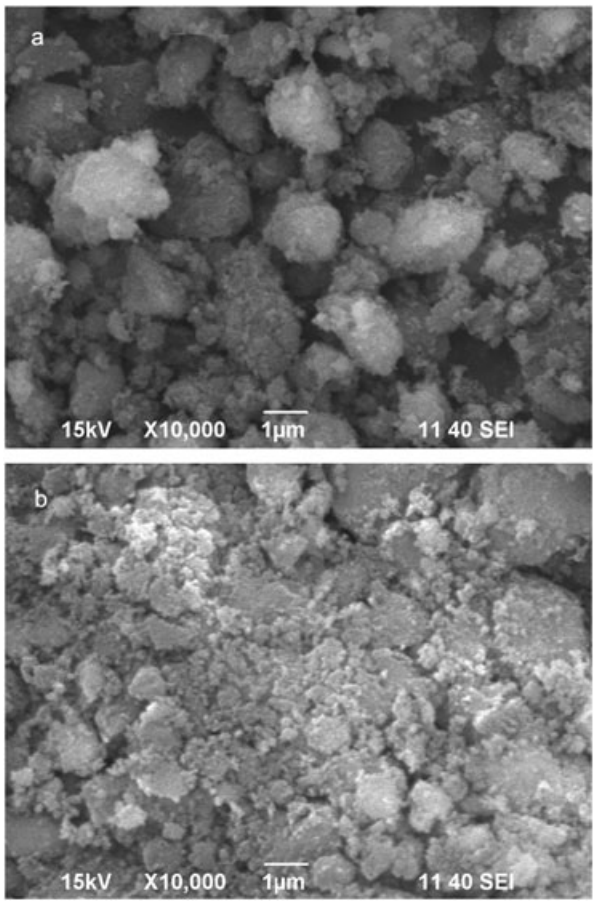


Figure 4. SEM images of (a) nano γ-Al_2O_3 and (b)nano *n*-propylsulfonated γ-Al_2O_3.

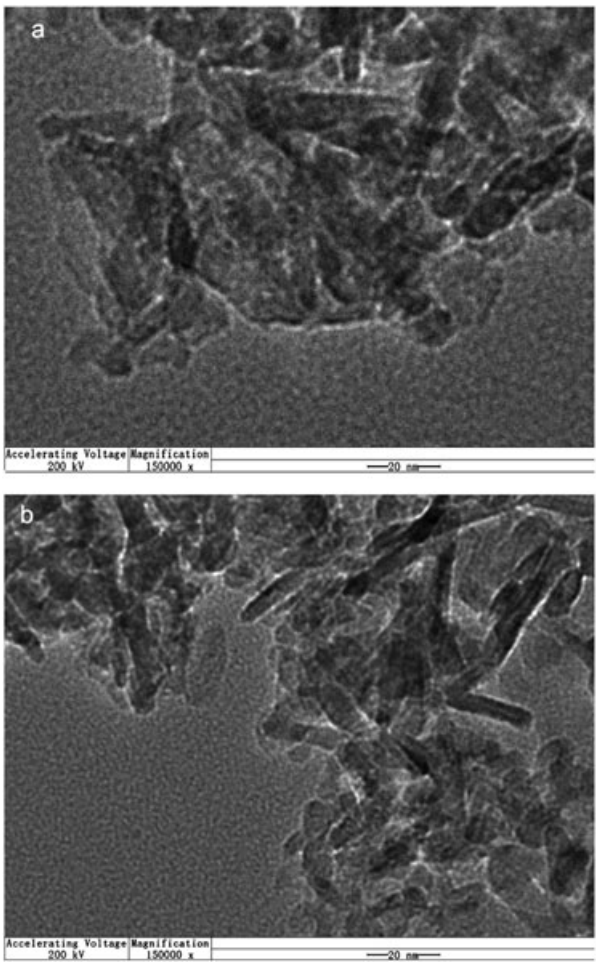


Figure 5. TEM images of (a) nano γ-Al_2O_3 and (b) nano *n*-propylsulfonated γ-Al_2O_3.

some larger particles attributes aggregating or overlapping of smaller particles. The sizes of nano γ-Al_2O_3 and nano *n*-propylsulfonated γ-Al_2O_3 are further analyzed by TEM and the results (Fig. 5) show that the nano particles have a nano dimension ranging from 10 to 20 nm. In TEM images, the shapes of γ- Al_2O_3 particles are relatively round, and those of treated *n*-propylsufonated γ-Al_2O_3 are rather rectangular, which is attributed to the presence of sulfonic acid groups covalently attached to the γ-Al_2O_3 surfaces.

Ion-Exchange pH Analysis

To an aqueous solution of NaCl (1 M, 25 ml) with a primary pH of 5.93, the catalyst (500 mg) was added and the resulting mixture was stirred for 2 h, after which the pH of the solution decreased to 1.81. This is equal to a loading of 0.78 mmol SO_3H g^{-1}.

Synthesis of Spiro[indoline-3,4-pyrazolo[3,4-e][1,4]thiazepine] diones Using Nano *n*- propylsulfonated γ-Al_2O_3

First, to achieve suitable conditions for the synthesis of spiro [indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine]diones, we tested the four-component condensation reaction of 3-aminocrotononitrile, phenylhydrazine, isatin and 2-mercaptoacetic acid as a simple model system in water at reflux temperature using various catalysts (Table 1). As can be seen in Table 1, the best result was obtained with 100 mg $mmol^{-1}$ of nano *n*-propylsulfonated γ-Al_2O_3 as the catalyst in water at reflux temperature (entry 3). Using less catalyst resulted in lower yields, whereas higher amounts of catalyst did not affect reaction times and yields. When this reaction was carried out without nano *n*-propylsulfonated γ-Al_2O_3 or with other catalysts such as $FeCl_3$, $AlCl_3$ or nano γ-Al_2O_3 the yield of the expected product was trace. In the presence of *p*-TsOH, Fe $(HSO_4)_3$, sulfamic acid or other nano *n*-propylsulfonated metal oxide such as nano *n*-propylsulfonated SiO_2 or nano *n*-propylsulfonated ZnO the product was obtained in low yield.

To find the optimal solvent for this reaction, the model reaction was carried out at 100°C or reflux temperature using EtOH, MeOH, H_2O, CH_2Cl_2, DMF and CH_3CN as solvent. It is shown in Table 2 that the reaction using H_2O (91%) or CH_3CN (89%) as the solvent gave the corresponding product **5a** in high yield (Table 2, entries 3 and 10). From the economical and environmental points of view, H_2O was chosen as the reaction medium for all further reactions. Furthermore, the relation between the yields of the model reaction and temperature was also studied. We carried out the reaction at temperatures ranging from 25°C to reflux temperature using water as the reaction medium (Table 2, entries 6–10), finding that the yields of desired product **5a** were improved as the temperature was increased. Therefore, the best reaction conditions were obtained in water under refluxed temperature.

The generality of this reaction was examined using several types of isatins. In all cases, the reactions gave the corresponding products in good to excellent yield (Table 3). This methodology offers significant improvements with regard to the scope of this transformation, simplicity of operation and green aspects by avoiding expensive or corrosive catalysts. In addition, when this reaction was carried out with 5-nitroisatin, TLC and ^1H NMR

Table 2. Solvent optimization for the synthesis **5a**[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	EtOH	Reflux	8	69
2	MeOH	Reflux	12	65
3	CH_3CN	Reflux	7	89
4	CH_2Cl_2	Reflux	12	49
5	DMF	100	8	68
6	H_2O	25	16	45
7	H_2O	40	16	51
8	H_2O	60	12	63
9	H_2O	80	8	79
10	H_2O	Reflux	5	91

[a]Reaction conditions: 3-aminocrotononitrile (1 mmol); phenylhydrazine (1 mmol); isatin (1 mmol); 2-mercaptoacetic acid (1 mmol); nano *n*-propylsulfonated γ-Al_2O_3 (100 mg).
[b]Isolated yield.

Table 1. Catalyst optimization for the synthesis **5a**[a]

Entry	Catalyst	mg $mmol^{-1}$	Time (h)	Yield (%)[b]
1	—	—	10	Trace
2	Nano *n*-propylsulfonated γ-Al_2O_3	50	7	70
3	Nano *n*-propylsulfonated γ-Al_2O_3	100	5	91
4	Nano *n*-propylsulfonated γ-Al_2O_3	150	5	91
5	Nano *n*-propylsulfonated γ-Al_2O_3	200	5	90
6	Nano *n*-propylsulfonated γ-Al_2O_3	250	5	90
7	*p*-TsOH	100	12	62
8	$Fe(HSO_4)_3$	100	12	49
9	Sulfamic acid	100	12	57
10	Nano *n*-propylsulfonated SiO_2	100	5	62
11	Nano *n*-propylsulfonated ZnO	100	5	69
12	$AlCl_3$	100	24	Trace
13	Nano γ-Al_2O_3	100	24	Trace
14	$FeCl_3$	100	24	Trace

[a]Reaction conditions: 3-aminocrotononitrile (1 mmol); phenylhydrazine (1 mmol); isatin (1 mmol); 2-mercaptoacetic acid (1 mmol); H_2O (10 ml); reflux.
[b]Isolated yield.

Table 3. Preparation of spiro[indoline-3,4- pyrazolo[3,4-*e*][1,4]thiazepine]diones[a]

Entry	R^1	R^2	R^3	Time (h)	Product	Yield (%)[b]
1	H	H	H	5	**5a**	91
2	H	H	CH_3	5	**5b**	92
3	H	5-Cl	CH_3	8	**5c**	88
4	H	5-Br	H	8	**5d**	87
5	H	5-F	H	5	**5e**	90
6	H	5-F	CH_3	5	**5f**	93
7	H	5-CH_3	H	7	**5g**	87
8	H	5-CH_3	CH_3	7	**5h**	86
9	CH_3	H	H	6	**5i**	90
10	CH_3	H	CH_3	6	**5j**	92
11	H	5-NO_2	H	10	**5k**	Trace[c]
12	H	5-NO_2	CH_3	10	**5l**	Trace[c]
13	H	6-Cl	H	7	**5m**	91
14	H	6-Cl	CH_3	8	**5n**	88
15	H	6-Br	H	7	**5o**	88
16	H	6-Br	CH_3	8	**5p**	90

[a]Reaction conditions: 3-aminocrotononitrile (1 mmol); phenylhydrazine (1 mmol); thioacid (1 mmol); isatins (1 mmol); nano *n*-propylsulfonated γ-Al_2O_3 (100 mg); H_2O (10 mL); reflux.

[b]Isolated yield.

[c]A combination of starting materials and numerous products.

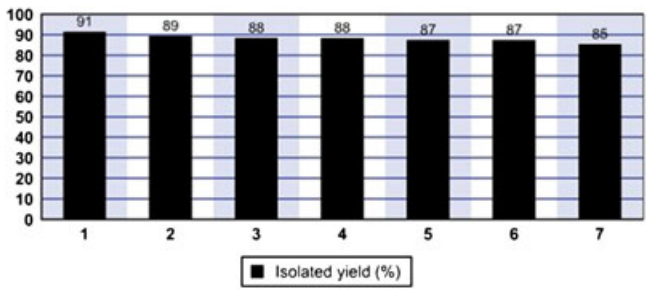
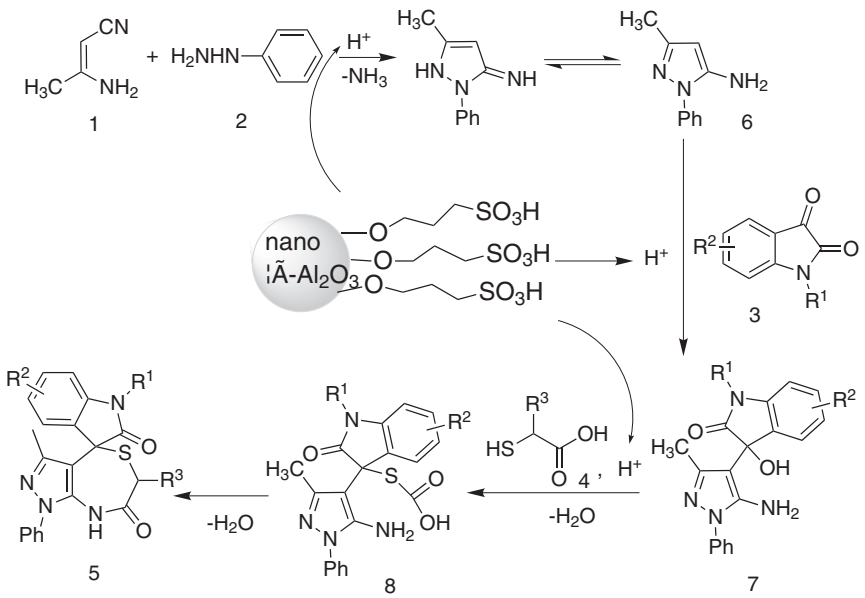


Figure 6. Reusability of nano *n*-propylsulfonated γ-Al_2O_3 synthesis of **5a**.

spectra of the reaction mixture showed a combination of starting materials and numerous products, and the yield of the expected product was very poor.

The reusability of the catalyst was tested in the synthesis of **5a**. The catalyst was recovered after each run, washed with EtOH, dried in an oven at 100°C for 30 min prior to use and tested for its activity in the subsequent run with no fresh catalyst added. The catalyst was tested for seven runs. It was seen that the catalyst displayed very good reusability (Fig. 6).

A plausible mechanism for the formation of the spiro-heterocycles is proposed in Scheme 3. The domino sequence of reactions is presumably triggered by the formation of 5-amino-



Scheme 3. A plausible mechanism for the spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine]diones.

3-methyl- 1-phenylpyrazole **6** from the acid-catalyzed reaction of phenylhydrazine with 3-aminocrotononitrile. Intermediate **6**, upon reaction with isatin **3**, affords intermediate **7**, which on further dehydration and upon reaction with the starting thioacid under acidic conditions presumably furnishes intermediate **8**, which subsequently undergoes dehydration leading to the final spiro-heterocycles.

Conclusion

We have successfully developed a novel and more environmentally friendly procedure for the preparation of spiro[indoline-3, 4-pyrazolo[3,4-*e*][1,4]thiazepine]diones of potential synthetic and pharmacological interest. The use of nano *n*-propylsulfonated γ-Al_2O_3 in water as a non-toxic and low loading of catalytic system with short reaction times and excellent product yields are the main advantages of this methodology, which appears to have a broad scope to represent a straightforward procedure for the synthesis of spiro[indoline-3,4-pyrazolo[3,4-*e*] [1,4]thiazepine]diones.

Acknowledgment

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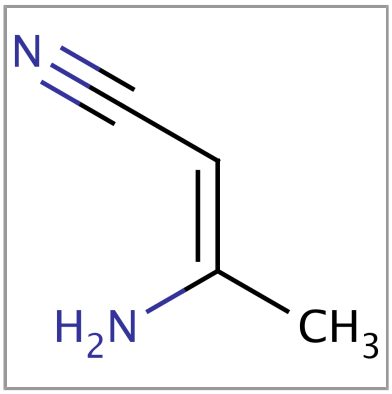

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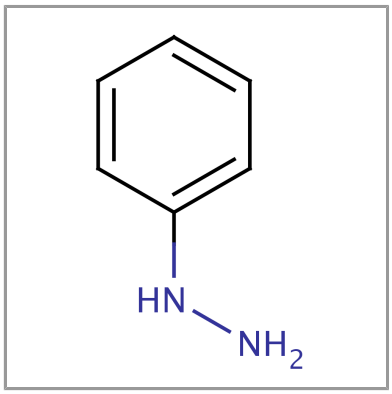

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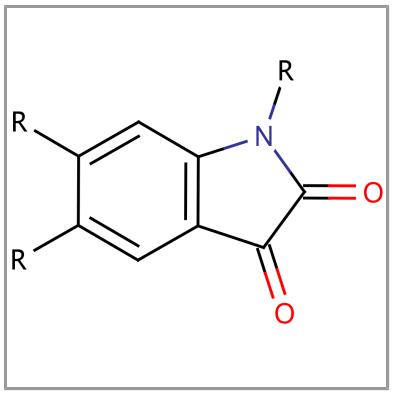

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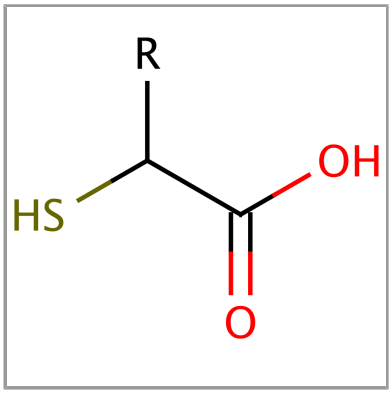

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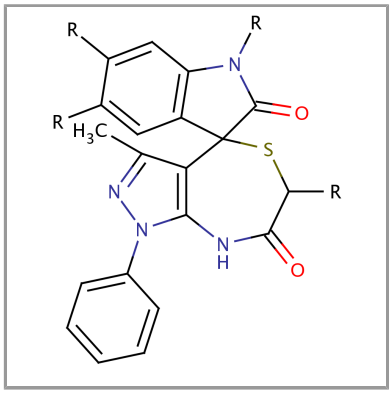

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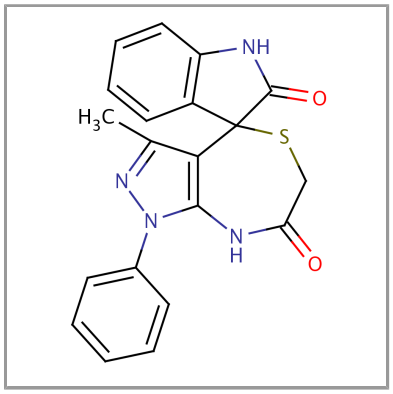

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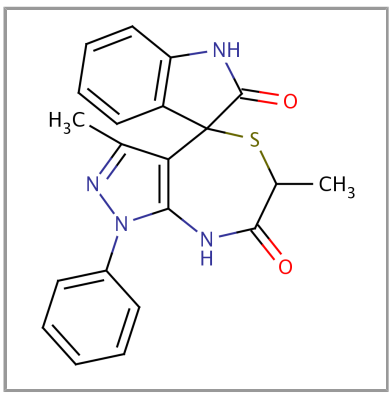

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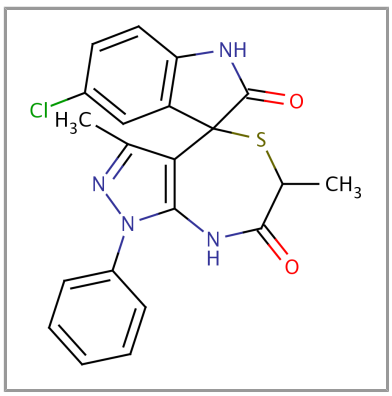

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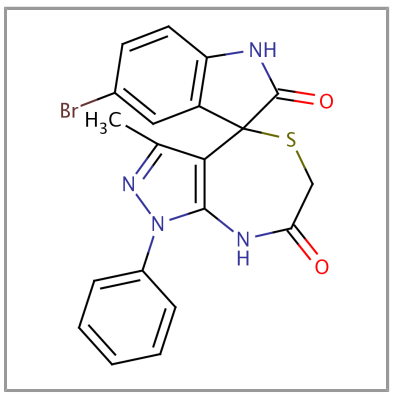

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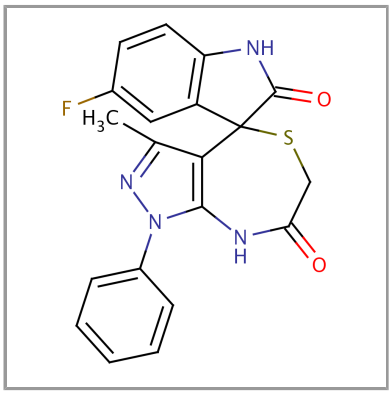

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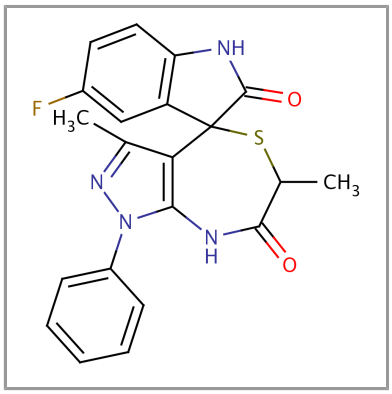

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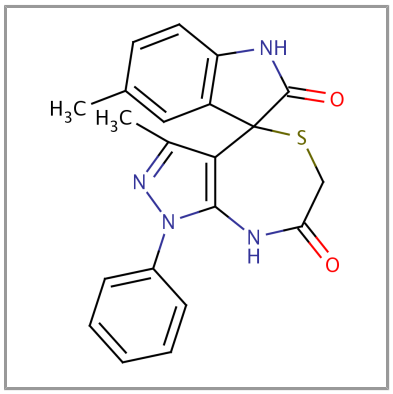

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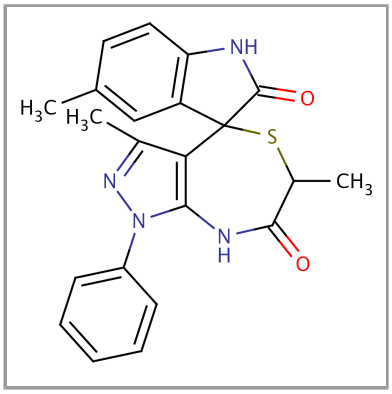

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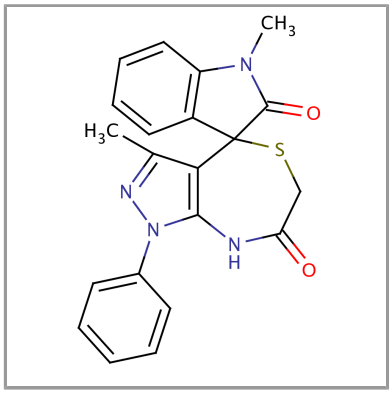

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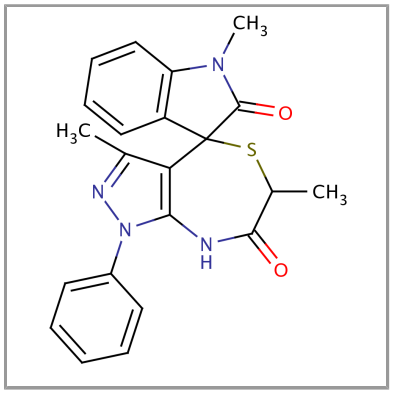

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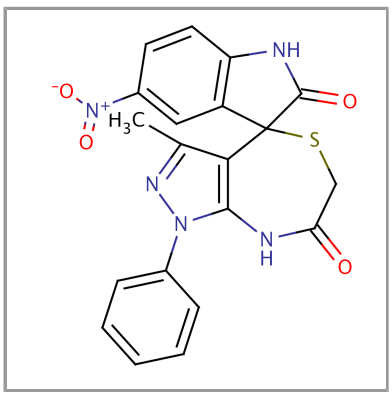

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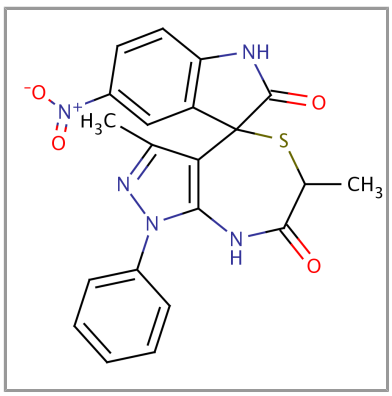

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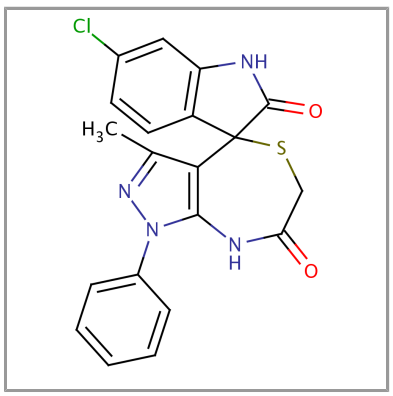

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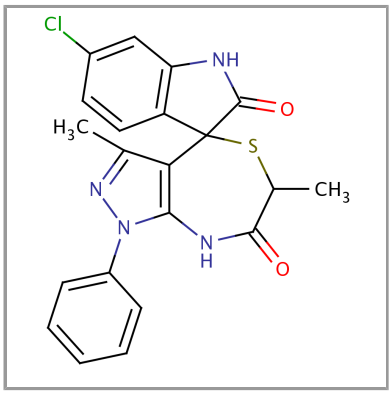

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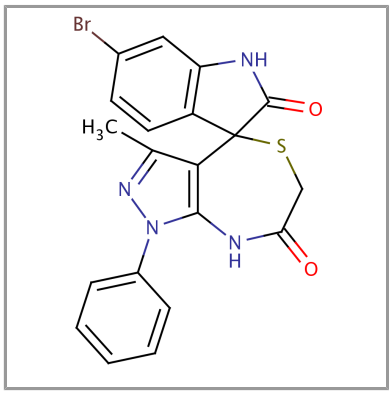

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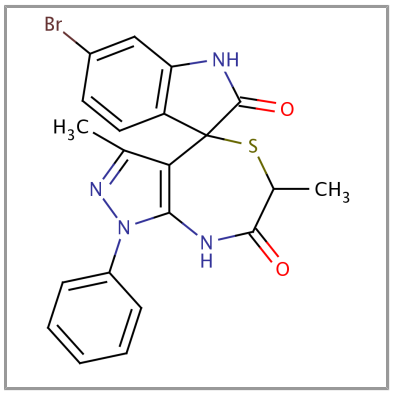

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