

TiCl₂/nano- γ -Al₂O₃ as an efficient catalyst for synthesis of substituted pyrroles under solvent-free conditions at room temperature

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ABSTRACT

TiCl₂/nano- γ -Al₂O₃ as a new heterogeneous Lewis acid catalyst was synthesized and characterized by FE-SEM, XRD, FT-IR, EDS, XRF, BET and TGA. *N*-substituted pyrroles have been synthesized *via* Paal-Knorr reaction in the presence of TiCl₂/nano- γ -Al₂O₃ at room temperature under solvent-free conditions.

Keywords: TiCl₂/nano- γ -Al₂O₃, *N*-substituted pyrroles, Solvent-free conditions, Heterogeneous catalyst, Nano- γ -Al₂O₃.

1. Introduction

Pyrrole core serve as building block for many natural compounds [1], drugs [2] and electrically conducting materials [3]. Heme, chlorophyll and vitamin B12 as natural compound [1], porphyrines [3] as light emitting diode, amtolmetin, tolmetin [4] and atorvastatin (Fig. 1) [5] as drug have pyrrole moiety in their structures. The classic methods for the synthesis of pyrroles are Hantzsch reaction, [6], Knorr reaction [7], and Paal-Knorr reaction [8-11]. In Paal-Knorr reaction, 1,4-dicarbonyl compounds are condensed with primary amines (or ammonia) in the presence of a catalyst. Copper iodide on activated carbon (CuI/C) [12], montmorillonite KSF [9], polystyrenesulfonate [13], microwave irradiation [11], Sc(OTf)₃ [14], zirconium sulfophenyl phosphonate [15], vitamin B₁ [16], β -CD [17], silica sulfuric acid (SSA) [18], ZrCl₄ [19] and SbCl₅.SiO₂ [20] were used as catalyst for this reaction. Recently, synthesis of organic compounds using solid acid catalysts is more and more attention due to the numerous advantages such as cost-effectiveness, high catalytic activity, ease of product separation, recovery of the catalyst, repeated recycling potential and good stability. BF₃/ γ -Al₂O₃ is a solid acid catalyst that is previously synthesized, characterized and successfully used for alkylation reaction [21].

In continuation of our efforts toward the development of greener methodologies [22-25] we report herein, synthesis of TiCl₂/nano- γ -Al₂O₃ as a new nano-catalyst and application of it in synthesis of *N*-substituted pyrroles from 2,5-hexanedione and aromatic amines at room temperature under solvent-free conditions.

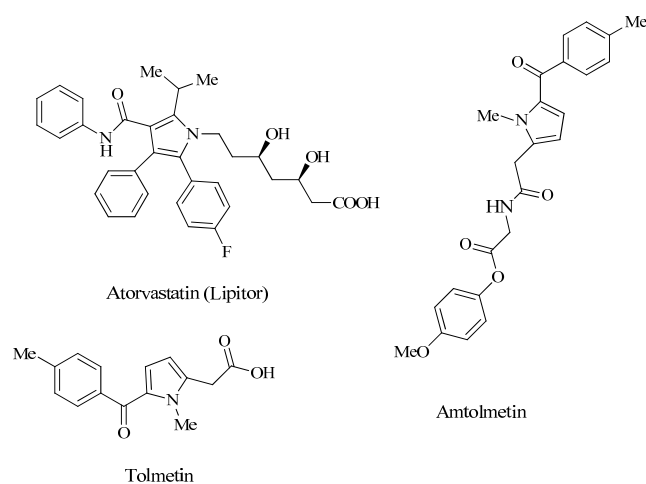


Fig. 1. Some pyrrole containing drugs.

2. Experimental

All compounds were purchased from Merck and Fluka chemical company and used without any additional purification. FT-IR (ATR, neat) spectra were obtained on a Bruker, Equinox 55 spectrometer. A Bruker

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(DRX-400 Avance) NMR was used to record the ^1H NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. XRD pattern using Philips Xpert MP diffractometer (Cu $K\alpha$, radiation, $k=0.154056$ nm) was achieved. FE-SEM was obtained on a Mira Tescan. Energy-Dispersive X-ray Spectroscopy (EDS) of $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ was measured by EDS instrument, Phenom pro X. BET surface area analysis of catalyst was done with Micromeritics, Tristar II 3020 analyzer. XRF analysis was done with Bruker, S4 Explorer instrument. The thermal gravimetric analysis (TGA) was done with "STA 504" instrument. The products were characterized by FT-IR, ^1H NMR, and a comparison of their physical properties with those reported in the literature.

2.1. Preparation of nano- $\gamma\text{-Al}_2\text{O}_3$

In a beaker containing $\text{Al}_2(\text{SO}_4)_3 \cdot 18 \text{H}_2\text{O}$ (66 g), we have added drop-wise with vigorous stirring, an aqueous solution of NaOH (1M, 600 ml) to dissolved of aluminium sulfate and then precipitated $\text{Al}(\text{OH})_3$ as a white solid. The solid was filtered and washed with distilled water to remove the sulfate ions and dried. In a beaker containing $\text{Al}(\text{OH})_3$ (20 g), aqueous solution of NaOH (1M, 100ml) was added to dissolved all of $\text{Al}(\text{OH})_3$ and converted it to soluble $\text{Na}(\text{Al}(\text{OH})_4)$. Then polyethylene glycole 4000 (0.3 % v/v) was added to resulted solution and converted it to Al_2O_3 by adding drop-wise aqueous solution of HCl (0.1 M) with vigorous mixing to reach pH=8. The obtained solid was isolated by centrifuge, washed with distilled water and then calcinated in 800°C for 3 hours.

2.2. General procedure for the preparation of $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$

To a mixture of nano- $\gamma\text{-Al}_2\text{O}_3$ (1 g) and CH_2Cl_2 (10 ml), TiCl_4 (0.5 ml) was added dropwise. The

resulting suspension was stirred for 1 hour at room temperature, filtered, washed with chloroform, and dried at room temperature.

2.3. General procedure for the synthesis of *N*-aryl-2,5-dimethyl pyrroles

In a mortar, a mixture of 2,5-hexanedione (1.2 mmol), aromatic amine (1 mmol), and $\text{TiCl}_4/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ (0.02 g) was grinding at room temperature. The progress of reaction was monitored by TLC (n-Hexane: EtOAc 8: 2). After completion of the reaction, 3 ml of ethanol was added and the heterogeneous catalyst was filtered. By adding crushed ice to filtrate, the pure product as a white solid was obtained.

Selected spectral data

N-(4-Ethyl phenyl)-2,5-dimethyl pyrrole

Brown solid. m.p.= $56\text{-}59^\circ\text{C}$. IR (ATR, neat): $\bar{\nu} = 2965, 1514, 1403, 1321, 1035, 999, 841, 747 \text{ cm}^{-1}$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 1.3$ (t, $J = 7.6$ Hz 3H), 2.1 (s, 6H), 2.7 (q, $J = 7.6$ Hz 2H), 5.92 (s, 2H), 7.13 (d, $J = 7.14$ Hz, 2H), 7.29 (d, $J = 7.3$ Hz, 2H) ppm.

3. Results and Discussion

In continuation of our research on the applications of solid acids in organic synthesis, we have synthesized $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ as a new heterogeneous nano-catalyst and investigated its efficiency in Paal-Knorr reaction at room temperature under grinding conditions.

For identification of the structure of $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$, we have studied FT-IR (ATR) spectra of TiCl_4 (aq), nano- $\gamma\text{-Al}_2\text{O}_3$ and $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ (Fig. 2). In TiCl_4 (aq) spectrum, a broad band at 3298 (H_2O), a middle band at 1619 (Ti-Cl) and a strong band at 850 cm^{-1} (Ti-O) were observed (Fig. 2a).

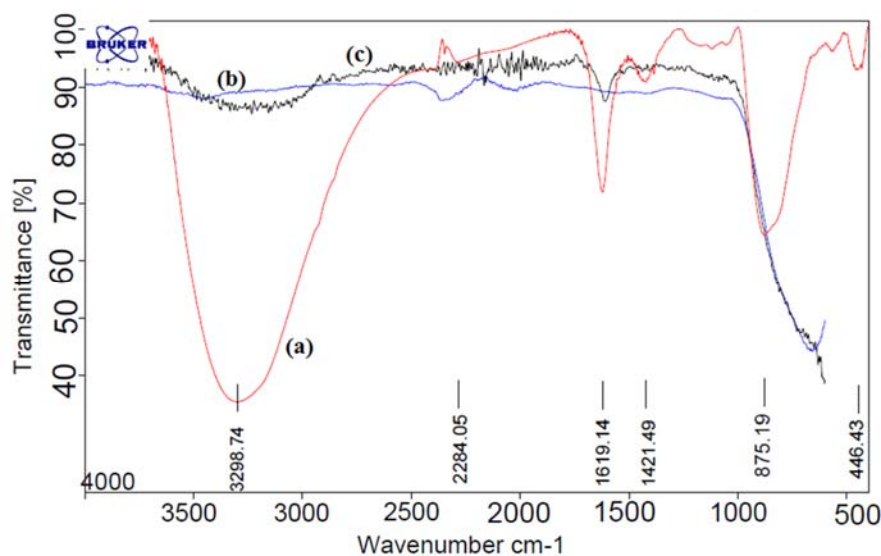


Fig. 2. FT-IR spectra of a) TiCl_4 (aq), b) nano- $\gamma\text{-Al}_2\text{O}_3$ and c) $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$.

In nano- γ -Al₂O₃ FT-IR spectrum, a very strong band at 600-1000 cm⁻¹ (Al-O) was observed (Fig. 2b). TiCl₂/nano- γ -Al₂O₃, in addition to γ -Al₂O₃ signal, two additional bands at 1619 and 3298 show binding of TiCl₂ to γ -Al₂O₃ (Fig. 2c).

The FE-SEM images of the TiCl₂/nano- γ -Al₂O₃ and nano- γ -Al₂O₃ nanoparticles are displayed in Fig. 3. They exhibit irregular spherical shape for nano particles below 50 nm.

Energy-Dispersive X-ray Spectroscopy (EDS) of TiCl₂/nano- γ -Al₂O₃ was measured by EDS instrument (Fig. 4) provided the presence of the expected elements in the structure of this catalyst and confirmed

supporting of TiCl₄ on nano- γ -Al₂O₃. The elemental compositions of TiCl₂/nano- γ -Al₂O₃ were found to be 58.5, 29.9 and 6.5% for O, Al and Ti, respectively.

To investigate the elemental component of TiCl₂/nano- γ -Al₂O₃, XRF analysis was performed. XRF analysis of catalyst was done by comparison of its Killo Counts per Seconds (KCPS) with pure samples.

In our catalyst, TiCl₂/nano- γ -Al₂O₃, the percentage of elements, Ti, Cl and Al, were determined via comparison with KCPS of pure TiO₂, NaCl and Al₂O₃ as can be seen in Table 1. 16.8 g of Ti and 23.8 g of Cl are equal to 0.35 mol and 0.67 mol, respectively, thus, the ratio of Ti:Cl is 1:2.

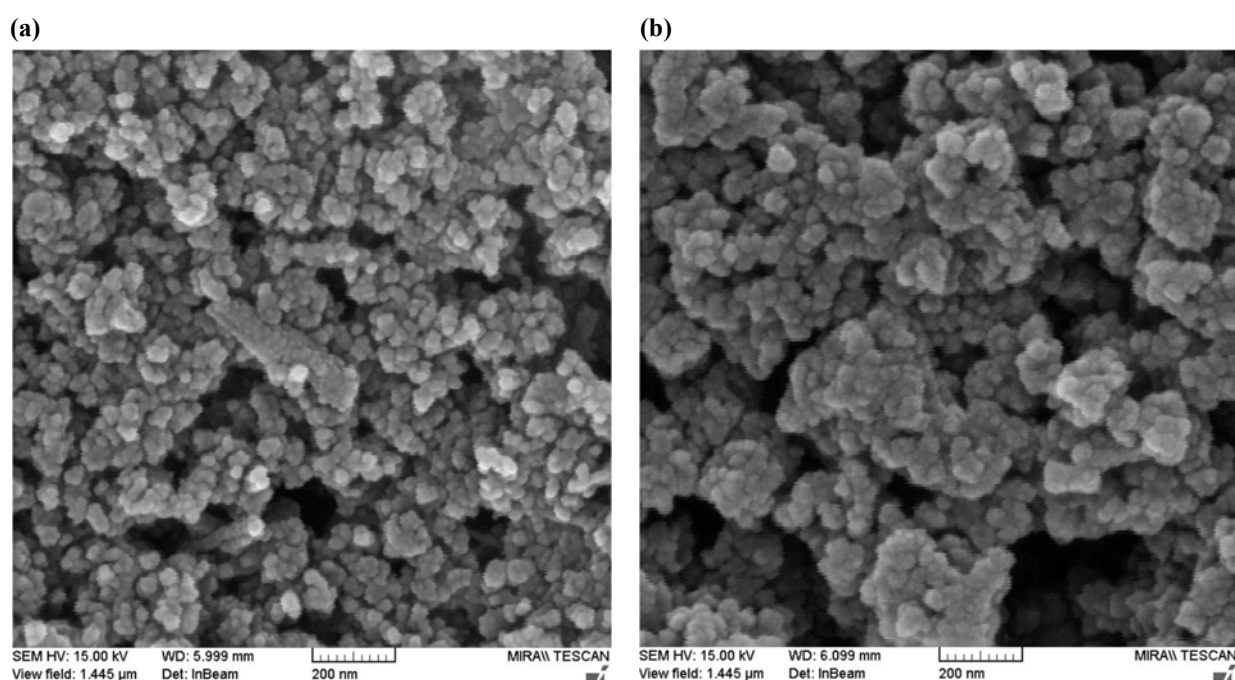


Fig. 3. The FE-SEM image of a) TiCl₂/nano- γ -Al₂O₃ and b) nano- γ -Al₂O₃.

The X-ray diffraction (XRD) pattern of TiCl₂/nano- γ -Al₂O₃ is shown in (Fig. 5). According to XRD pattern of catalyst, the values of 2 θ and FWHM are shown in Table 2.

The signals at 2 θ equal to 37 (b), 45 (c) and 67 (d) are shown nano- γ -Al₂O₃ structure. According to XRD pattern, the two additional signals at 2 θ equal to 32 (a) and 75 (e) with FWHM equal to 0.236 and 1.152 respectively, are shown the presence of bonded Ti to nano- γ -Al₂O₃ (Fig. 5).

The specific surface area of catalyst was measured by Brunauer–Emmett–Teller (BET) theory. Single point surface area at P/Po = 0.184317546 is 73.9645 m²/g and BET surface area is 75.5925 m²/g. The N₂ adsorption isotherm of catalyst is depicted in Fig. 6.

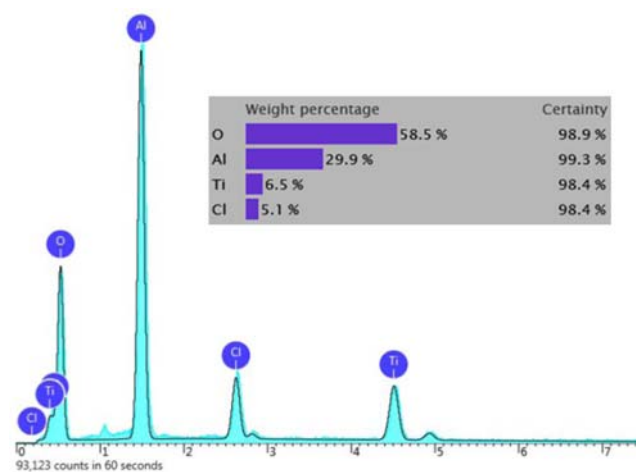


Fig. 4. EDS analysis diagram of TiCl₂/nano- γ -Al₂O₃.

Table 1. XRF analysis of TiCl₂/nano- γ -Al₂O₃

Sample	TiO ₂	NaCl	Al ₂ O ₃	Catalyst		
KCPS	2318.4 (TiO ₂)	516.5 (Cl)	498.2 (Al ₂ O ₃)	646.7 (TiO ₂)	204.6 (Cl)	296.2 (Al ₂ O ₃)
Amount of element (%)	60 (Ti)	60 (Cl)	53 (Al)	16.8 (Ti)	23.8 (Cl)	31.5 (Al)

Thermal gravimetric analysis (TG-DTA) pattern of TiCl₂/nano- γ -Al₂O₃ was detected by heating from 50°C to 400 °C and then cooling until 165°C (Fig. 7).

The catalyst is stable until 392 °C and only 10.5 % of its weight was reduced due to the removal of catalyst moisture. The char yield of the catalyst in 392°C is 89.5%. According to the TG-DTA diagram of TiCl₂/nano- γ -Al₂O₃ and our study, it was revealed that this catalyst is suitable for the promotion of organic reactions until 400°C. Based on these results, we have also suggested the following structure for TiCl₂/nano- γ -Al₂O₃ (Scheme 1). In our opinion, this heterogeneous catalyst can catalyze many organic reactions. In this work, we wish to report a simple method for the synthesis of pyrroles from 2,5-hexanedione and aromatic amines in the presence of TiCl₂/nano- γ -Al₂O₃ at room temperature under solvent-free conditions (Scheme 2).

Initially, we have decided to explore the role of TiCl₂/nano- γ -Al₂O₃ for the synthesis of *N*-phenyl-2,5-dimethyl-pyrrole as a model compound at room temperature using various solvents such as ethanol, water, methanol and petroleum ether (Table 3, entries 1–4). The results show that petroleum ether is an efficient solvent (yield 90%). In recent years, there has been an increasing interest in reactions that proceed in the absence of solvents due to the reduced pollution and low cost. Therefore, we have decided to test this reaction in solvent-free condition and in the presence of various catalyst ratios (Table 3, entries 5–8).

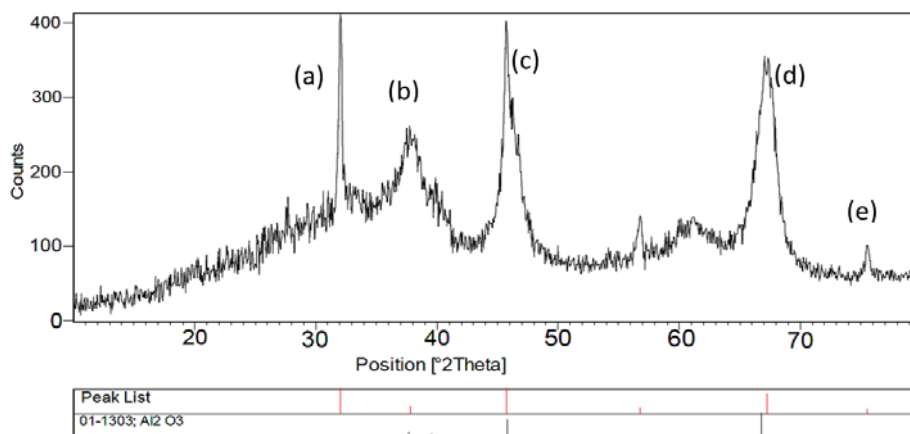
We have found that the reaction was catalyzed by TiCl₂/nano- γ -Al₂O₃ with good to excellent yield (Table 3, entry 7). In the absence of TiCl₂/nano- γ -Al₂O₃, low yield of product was obtained, which indicates that catalyst is obviously necessary for pyrrole synthesis (Table 3, entry 9).

To expand the generality of this novel catalytic method, various aromatic primary amines were used under the optimized conditions and the results are presented in Table 4. Different kinds of aromatic amines bearing either electron-donating (Table 4, entries 2, 3, 8-11) or electron withdrawing (Table 4, entries 4-7) groups on aromatic rings were converted to the corresponding *N*-substituted pyrroles in the presence of TiCl₂/nano- γ -Al₂O₃. Moreover, we also examined the reactivity of less nucleophilic aromatic amines such as 1-aminonaphthalene in the presence of TiCl₂/nano- γ -Al₂O₃ (Table 4, entry 12).

The proposed mechanism for the formation of pyrrole in the presence of TiCl₂/nano- γ -Al₂O₃, which can act as Lewis acid catalyst is depicted in Scheme 3. Carbonyl groups is first activated by TiCl₂/nano- γ -Al₂O₃, and then amine attacks.

Table 2. XRD analysis of TiCl₂/nano- γ -Al₂O

No.	1	2	3	4	5
Pos. [2 θ]	31.900	37.676	45.666	67.253	75.537
FWHM [2 θ]	0.236	1.574	0.393	0.472	1.152

**Fig. 5.** XRD patterns of TiCl₂/nano- γ -Al₂O₃.

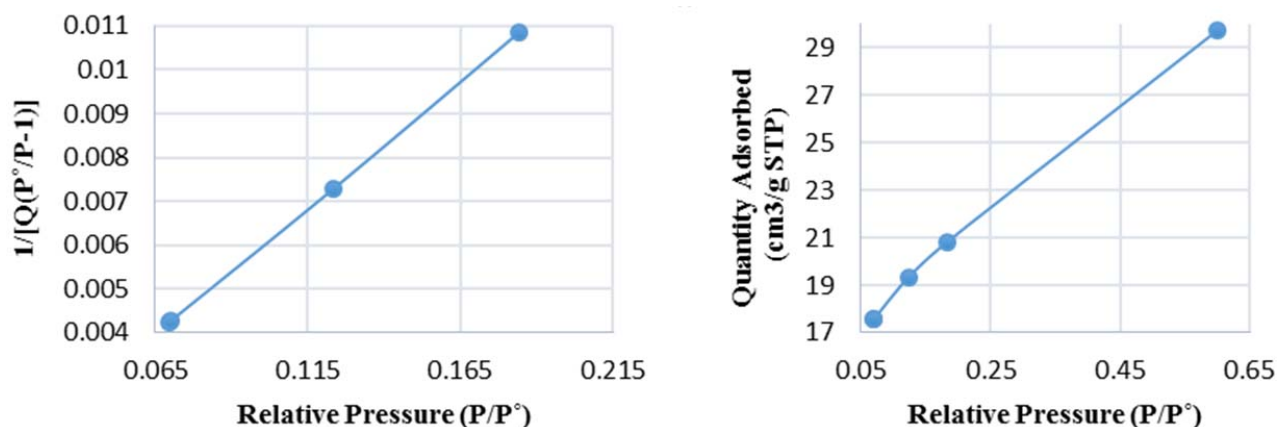


Fig. 6. Nitrogen adsorption isotherm at 77 K on TiCl₂/nano-γ-Al₂O₃.

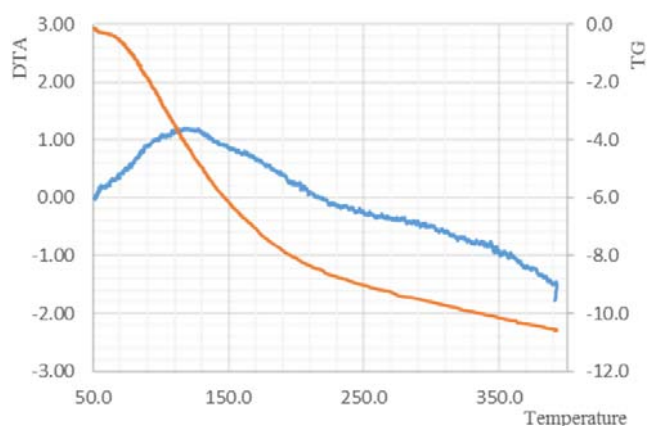
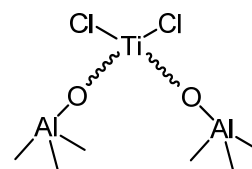
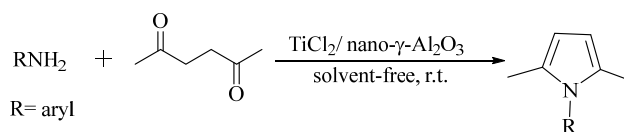


Fig. 7. Thermal gravimetric analysis (TG-DTG) pattern of TiCl₂/nano-γ-Al₂O₃.



Scheme 1. The proposed structure for TiCl₂/nano-γ-Al₂O₃.



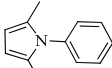
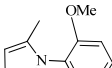
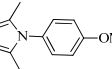
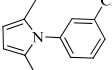
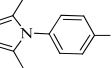
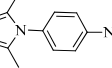
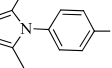
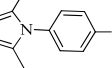
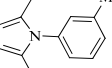
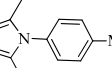
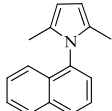
Scheme 2. Synthesis of pyrroles in the presence of TiCl₂/nano-γ-Al₂O₃.

Table 3. The condensation reaction of 2,5-hexanedione with aromatic amines under various conditions.

Entry	Temp. (°C)	Solvent	Catalyst (g)	Time (min)	Yield ^a (%)	Ref.
1	r.t.	Ethanol	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.02)	240	75	-
2	r.t.	Water	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.02)	60	40	-
3	r.t.	Methanol	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.02)	210	85	-
4	r.t.	Petroleum ether	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.02)	90	90	-
5	r.t. (grinding)	S.F.	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.005)	45	87	-
6	r.t. (grinding)	S.F.	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.01)	20	88	-
7	r.t. (grinding)	S.F.	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.02)	10	98	-
8	r.t. (grinding)	S.F.	TiCl ₂ /nano-γ-Al ₂ O ₃ (0.03)	20	80	-
9	r.t. (grinding)	S.F.	-	240	20	-
10	r.t.	Ethanol	Vitamin B ₁ (0.1)	60	90	[14]
11	60	Water	β-CD (0.15)	24 h	86	[15]
12	30	S.F.	Sc(OTf) ₃ (0.1)	25	93	[12]
13	r.t.	S.F.	SSA (0.15)	15	90	[16]
14	40	S.F.	ZrCl ₄ (0.1)	7	98	[17]
15	r.t.	Hexane	SbCl ₅ /SiO ₂ (0.3)	60	91	[18]

^aIsolated yield.

Table 4. Synthesis of 1,2,5-trisubstituted pyrroles in the presence of $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$.^a

Entry	Ar	Product	Time (min)	Yield (%) ^b	m.p. (°C)		Ref.
					Found	Reported	
1	Ph		10	98	48-51	48-50	[26]
2	<i>o</i> -OMe-C ₆ H ₄		25	80	62-64	61-63	[16]
3	<i>p</i> -OMe-C ₆ H ₄		15	85	55-58	56-57	[16]
4	<i>m</i> -Cl-C ₆ H ₄		15	95	43-45	41-42	[27]
5	<i>p</i> -Cl-C ₆ H ₄		10	97	46-48	48-49	[26]
6	<i>p</i> -NO ₂ -C ₆ H ₄		90	66	128-130	144-146	[26]
7	<i>p</i> -Br-C ₆ H ₄		10	96	70-72	56-58	[25]
8	<i>p</i> -Et-C ₆ H ₄		10	98	56-59 ^c	-	-
9	<i>m</i> -Me-C ₆ H ₄		20	85	51-52	55-57	[25]
10	<i>p</i> -Me-C ₆ H ₄		30	80	46-48	47-50	[25]
11	1-Naphtyl		60	60	115-118	120-122	[25]

^aConditions: amine (1 mmol) and 2,5-hexanedione (1.2 mmol), catalyst (0.02 g), r.t., grinding.

^bIsolated yield

^cThe spectroscopic data was shown in experimental section.

Cyclization and dehydration of intermediate afford the final product together with two H₂O molecules and release of $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ for the next catalytic cycle.

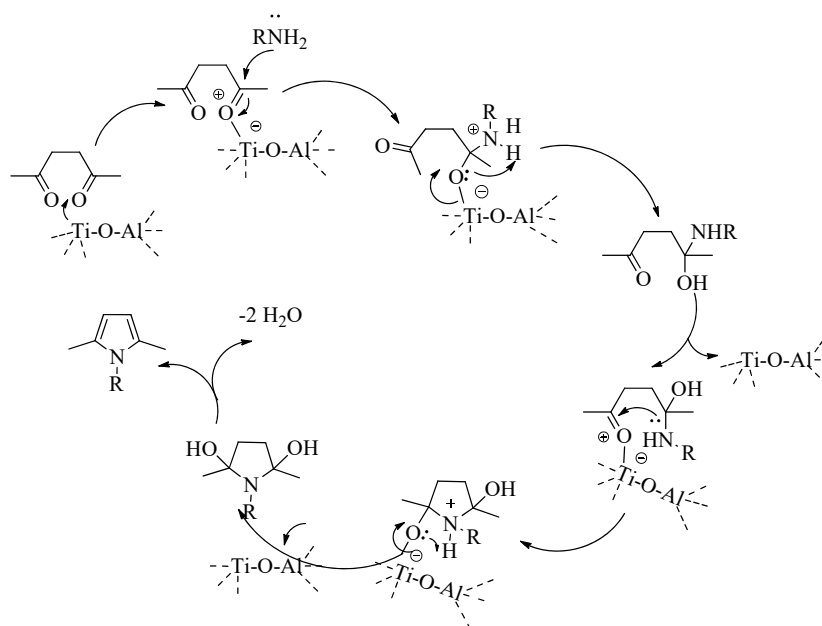
The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus, after the completion of the reaction, the catalyst was separated. The recovered catalyst was washed with ethanol (20 mL) and dried at room temperature without further purification to use for the next run in current reaction under identical condition. As can be seen, the catalyst could be reused for third times without any appreciable loss of its activity. The yields were 98, 95 and 94%, respectively.

4. Conclusions

In summary, we have developed a simple, efficient, and green protocol for synthesis of *N*-substituted pyrroles using $\text{TiCl}_2/\text{nano-}\gamma\text{-Al}_2\text{O}_3$ as a novel heterogeneous solid acid catalyst under solvent-free conditions at room temperature. The short reaction times, simple workup, good to excellent yields, mild reaction conditions, and use of nontoxic and noncorrosive catalyst are important features of this new method. In addition, recyclability of the catalyst caused that this methodology be a valid contribution to the existing processes in the field of Paal-Knorr reaction.

Acknowledgment

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Scheme 3. Proposed mechanism for the synthesis of pyrrole.

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