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TsOH-SiO$_2$ as an efficient and eco-friendly catalyst for Knoevenagel condensation

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ABSTRACT

Tosic acid on silica gel (TsOH-SiO$_2$) was synthesized and characterized using microscopic and spectroscopic techniques such as powder X-ray diffraction (XRD), scanning electron microscopy (SEM) and FT-IR spectroscopy. Thermal behaviour of the catalyst was investigated by differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis. TsOH-SiO$_2$ showed excellent catalytic activity for the Knoevenagel condensation and was recyclable for six cycles.

The Knoevenagel reaction provides one of the most important potential alternatives in the synthesis of electrophilic olefin derivatives utilizing active methylene and carbonyl compounds.[1] Knoevenagel reactions are classically performed under homogeneous conditions using ammonia, amines, pyridine, piperidine and their salts as basic catalysts which cause complications in product separation, catalyst regeneration, etc.[2,3] To overcome these problems, several reaction conditions were tried which included the use of microwaves,[4] surfactants,[5] zeolites,[6] ionic liquids[7] and heterogeneous catalysts.[8] With regard to efficient methods for the synthesis of alkene derivatives by heterogeneous catalysis, a few reports are available in the literature including silica–HClO$_4$,[9] KF/NP and NaNO$_3$/NP,[10] hydrotalcite in ionic liquid medium,[11] CeCl$_3$/7H$_2$O–NaI,[12] ZnO,[13] silica-supported piperazine,[14] nickel nanoparticles,[15] borate zirconia,[16] silica–NH$_4$OAc[17] and silica–ZrCl$_4$.[18] Unfortunately, some of these methods have disadvantages such as use of expensive reagents and toxic solvents, low yields, prolonged reaction time, tedious procedure etc.

Knoevenagel reaction under heterogeneous conditions is a challenging task due to its high reaction rate, recyclability of catalytic system, formation of clean products and suppression of side product formation. Straightforward syntheses of heterogeneous catalysts were performed by supporting homogeneous mineral and organic acids on porous solids. Among the various supports, silica presents many advantages such as stability, reusability, no swelling and ease of handling.[19] In this context, perchloric,[20] sulfuric,[21] sulfamic,[22] phosphoric[23] acids and phosphorus pentoxide[24] are normally supported on silica by simple pore filling and/or by interacting with the surface of the solid. Although there are numerous reports on different acid catalysts supported on silica, relatively less work is available on tosic acid supported on silica gel as heterogeneous catalyst.[25–29] Thus, there is a lot of scope to further evaluate the catalyst for its application in various organic reactions.

Pyrazoles occupy a special role in the realm of synthetic organic chemistry. Members of this group display a broad range of pharmacological activities such as antimicrobial, anti-inflammatory, anticonvulsant, analgesic, herbicidal, antioxidant, cytotoxic and anticancer activities.[30] Numerous synthetic pyrazole derivatives have been used as valuable leads in photographic,[31] ultraviolet stabilizers[32] and energetic materials.[33] Such important pyrazole derivatives include natural products (*S*)-pyrazolylalanine, pyrazomycin and synthetic compounds sildenafil, ionazolac, difenamizole, mepirizole etc.

In the present investigation, the characterization of TsOH-SiO$_2$ using microscopic and spectroscopic methods has been described (Figs. 1, 2, 3, 4, 5 and 6, Supplementary data). The number of H$^+$ sites on the TsOH-SiO$_2$ was determined by acid–base titration and was found to be 0.54 meq/g. The catalytic activity of TsOH-SiO$_2$ was investigated for Knoevenagel condensation between different 5-aryloxy-3-methyl-1-phenylpyrazole-4-carbaldehydes and various cyclic active methylene compounds.[34]

To determine the best reaction conditions, we studied the influence of varying parameters such as catalysts, solvents, supporting materials, different amounts of loaded TsOH on supporting material

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Table 1
The influence of different catalysts on the model reaction under thermal solvent-free condition

Entry[a]	Catalyst	Time[b]	Yield[c] (%)
1	TsOH-SiO_2	5 min	94
2	TsOH	15 min	72
3	Silica sulfamic acid	10 min	Trace
4	Silica sulfuric acid	20 min	64
5	$NaHSO_4$–SiO_2	10 min	68
6	Cellulose sulfuric acid	1.2 h	Trace
7	Xanthan sulfuric acid	40 min	48
8	Sulfamic acid	15 min	44
9	Camphor sulfonic acid	25 min	44
10	Chlorosulfonic acid	1.5 h	38
11	Sulfanilic acid	2 h	32
12	Silica gel	3 h	42

[a] Reaction of 3-methyl-5-phenoxy-1-phenylpyrazole-4-carbaldehyde (1 mmol) with 1,3-dimethyl-2,4,6-pyrimidinetrione (1 mmol) in the presence of 30 mg of catalyst.
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

and amount of catalyst. The reaction of 3-methyl-5-phenoxy-1-phenylpyrazole-4-carbaldehyde (1 mmol) with 1,3-dimethyl-2,4,6-pyrimidinetrione (1 mmol) was selected as a model reaction for all catalytic studies.

In order to evaluate the superiority of TsOH-SiO_2, the model reaction was performed with various sulfur containing catalysts. The order of reactivity of various catalysts was TsOH-SiO_2 > TsOH > $NaHSO_4$–SiO_2 > silica sulfuric acid > xanthan sulfuric acid > sulfamic acid > camphor sulfonic acid > chlorosulfonic acid > sulfanilic acid > silica sulfamic acid > cellulose sulfuric acid (Table 1). The results revealed that TsOH-SiO_2 was the most effective for the said reaction as it catalysed the reaction at a much faster rate (5 min) with excellent yield of the product (94%) (entry 1). Adsorption of TsOH on solid surface (silica) increases surface area of the catalyst. The increased surface area provides more active sites for the interaction of reactants enhancing rate of the reaction. TsOH is also moisture sensitive and may affect rate of the reaction (entry 2) giving product in 72% yield only as compared to TsOH-SiO_2 (product yield 94%). Knoevenagel condensation using freshly synthesized TsOH-SiO_2 and TsOH-SiO_2 after keeping it in ambient atmosphere for 5 days produced same results. This showed that there was no obvious deteriorating effect of atmospheric oxygen or moisture towards the activity of the supported catalyst. After doing the controlled experiments it was found that the supported catalyst was more efficient and less moisture sensitive than the unsupported catalyst. In a comparative study, the model reaction was also performed in the presence of silica gel under same reaction condition, it was observed that the reaction was completed in 3 h but only 42% product could be isolated (entry 12).

In order to evaluate the influence of various solvents, the model reaction was carried out in different organic solvents such as CH_3OH, CH_3CH_2OH, $(CH_3)_2CHOH$, CH_3COOH, $CHCl_3$, CH_3CN and polyethylene glycols (Table 2). When CH_3OH, CH_3CH_2OH and $(CH_3)_2CHOH$ were employed as solvents, moderate yield of the product was obtained after a long period of time (entries 3–5). Relatively less polar solvents like $CHCl_3$ and CH_3CN gave only trace amount of the product (entries 6 and 7). When the reaction was performed in PEG-200, PEG-400 and CH_3COOH, the reaction went to completion in a relatively shorter time period giving a mixture of products (entries 8–10). In order to examine the specific effect of temperature on product formation, the model reaction was also carried out at room temperature under grinding condition. It was observed that the reaction was completed in same time period as that of thermal solvent-free condition but product yield was moderate (entry 1).

Table 2
Effect of various solvents for the synthesis of **5a** using solution conditions versus the solvent-free method in the presence of TsOH-SiO_2

Entry[a]	Solvent	Temperature	Time[b]	Yield[c] (%)
1	—/Grinding	rt	5 min	62
2	—	70 °C	5 min	94
3	CH_3OH	Reflux	4 h	62
4	CH_3CH_2OH	Reflux	3.5 h	68
5	$(CH_3)_2CHOH$	Reflux	7 h	56
6	$CHCl_3$	Reflux	16 h	Trace
7	CH_3CN	Reflux	17.5 h	Trace
8	PEG-200	Reflux	3 h	Mixture
9	PEG-400	Reflux	3.5 h	Mixture
10	CH_3COOH	Reflux	4 h	Mixture

[a] Reaction of 3-methyl-5-phenoxy-1-phenylpyrazole-4-carbaldehyde (1 mmol) with 1,3-dimethyl-2,4,6-pyrimidinetrione (1 mmol) in the presence of 30 mg of catalyst.
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

Table 3
Effect of different supports on the synthesis of **5a** under thermal solvent-free condition

Entry[a]	Supports	Time[b] (min)	Yield[c] (%)
1	Silica gel	5	94
2	Zirconia	15	Trace
3	Acidic alumina	30	72
4	Basic alumina	35	64
5	Neutral alumina	35	60
6	Titania	40	45

[a] Reaction of 3-methyl-5-phenoxy-1-phenylpyrazole-4-carbaldehyde (1 mmol) with 1,3-dimethyl-2,4,6-pyrimidinetrione (1 mmol) in the presence of 30 mg of catalyst.
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

Table 4
Effect of TsOH loading on the support for the synthesis of **5a** under thermal solvent-free condition

Entry[a]	TsOH-SiO_2 (%w/w)	Time[b] (min)	Yield[c] (%)
1	10	35	64
2	12	20	76
3	15	15	82
4	20	5	94
5	25	5	94

[a] Reaction of 3-methyl-5-phenoxy-1-phenylpyrazole-4-carbaldehyde (1 mmol) with 1,3-dimethyl-2,4,6-pyrimidinetrione (1 mmol) in the presence of 30 mg of catalyst.
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

Table 5
Effect of amount of catalyst on the synthesis of **5a** under thermal solvent-free condition

Entry	TsOH-SiO_2 (mg)	Time[a] (min)	Yield[b]
1	10	50	54
2	20	35	68
3	30	5	94
4	40	5	94

[a] Reaction progress monitored by TLC.
[b] Isolated yield.

The effect of different supports over the catalytic performance was also examined using the model reaction (Table 3). Among the various supports the maximum conversion was obtained when tosic acid was supported on silica (entry 1). When zirconia (ZrO_2) was used as support, the product was obtained in trace amount