



MG(OTf)₂.SiO₂: A HETEROGENEOUS, RECYCLABLE CATALYST FOR THE SYNTHESIS OF ACETALS FROM ALDEHYDES OR KETONES

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ABSTRACT

Under mild circumstances, trialkyl orthoformate or ethylene glycol can be readily protects aldehydes and ketones, resulting in outstanding yields of the corresponding acetals in presence of a heterogeneous Mg(OTf)₂.SiO₂ catalyst. This approach works well with substrates that are sensitive to acid because of the mild reaction conditions. Catalytic amounts of Mg(OTf)₂.SiO₂ quantity required to convert aldehydes and ketones to acyclic or cyclic acetals at optimized reaction condition within short time. Utilized Mg(OTf)₂.SiO₂ as a heterogeneous catalyst is recyclable, thermally stable and can be reused multiple times without losing its activity.

Keywords: Acetals, Mg(OTf)₂.SiO₂, Ultrasound.

1. INTRODUCTION:

These days, a popular synthetic approach in the construction of many organic compounds is the protection of carbonyl groups as acetals ^[i, ii]. Thus, a significant issue in the production of acetals is the introduction of new techniques and the modification of current procedures of the acetalization techniques. The synthesis of acetals using catalysts such as CeCl₃.6H₂O ^[iii], Yt(III)(OTf)₃ ^[iv, v], In(III)(OTf)₃ ^[vi], Bi(III)(OTf)₃.4H₂O ^[vii], Ce(III)(OTf)₃ ^[viii], Ce(III)(OTf)₃.SiO₂ ^[ix], Antimony(V) ^[x], p-TSA ^[xi], Iron(III) tosylate ^[xii], Hydrochloric acid ^[xiii], Amberlyst 15 ^[xiv], Gallium triiodide ^[xv], N,N'-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea ^[xvi], cerium (III) trifluoromethanesulfonate ^[xvii], Sulfamic acid ^[xviii], ZrCl₄ ^[xix], have been reported in the recent years and literatures are available in public domain. All these catalysts have some drawbacks like harsh reaction condition, longer reaction time, low yield, unavailability of catalysts, cost of catalyst, requirement of stoichiometric quantity, non-recyclable etc. By considering all these facts we wish to disclose a simple process for the synthesis of acetals from parent aldehydes/ketones employing a catalytic quantity of Mg(OTf)₂.SiO₂.

2. RESULTS AND DISCUSSION:

Herein the present article we have evaluated $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ promoted protection of aldehydes or ketones using triethyl orthoformate or ethylene glycol respectively.

In case of diethyl acetals formation, stirring the carbonyl compounds (Aldehydes Ketones) and trimethyl orthoformate in ethanol with catalytic amount of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ under ultrasound irradiation. **Figure-01** presents a summary of the optimization that we have studied. Initially, for a model reaction benzaldehyde, triethyl orthoformate and $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ selected as a model substrate. We have studied the equivalents of triethyl orthoformate (**Entry-1-5, Figure-01**) initiated from 1.5 eq. (**Entry-1, Figure-01**) and observed that less than 3.0 eq. (**Entry-3, Figure-01**) lower the conversion of reaction while more than 3.0 eq. resulted no improvement in reaction conversion. In the similar way 0.1 eq. of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ (**Entry-6, Figure-01**) gives excellent yield while it drops significantly with low equivalents (**Entry-1-5, Figure-01**) of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$. Optimization of p-TsOH resulted that 1.0 eq. (**Entry-6, Figure-01**) is the minimum requirement of reaction. At the same time 5.0 relative volume of solvent (**Entry-6, Figure-01**) is required for the reaction for uniform steerable reaction and a reaction works well at ambient temperature. We also investigated higher temperature for reaction but the observed yield and time is comparable with standard condition and not much more impact on time-cycle of the reaction.

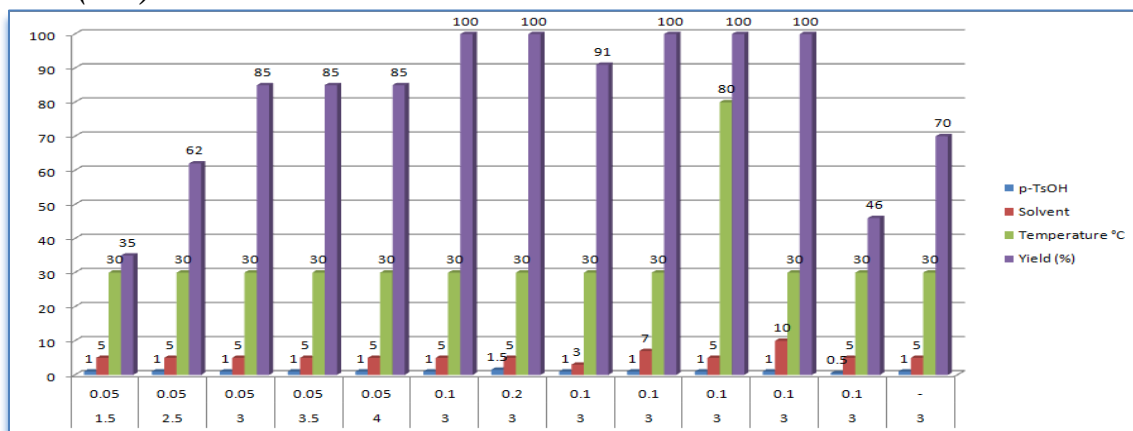
In case of cyclic acetals formation, removal of water molecule byproduct is necessary for the completion of reaction. Hence we have selected toluene as a solvent for reaction condition with temperature of boiling point of toluene i.e. 115°C . So in this situation stirring the carbonyl compounds (Aldehydes Ketones) and ethylene glycol in toluene along with catalytic amount of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ at 115°C . **Figure-02** presents a summary of the optimization that we have studied. Initially, for a model reaction Benzoylacetone, ethylene glycol and $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ selected as a model substrate. We have studied the equivalents of ethylene glycol (**Entry-1-5, Figure-02**) initiated from 1.0 eq. (**Entry-1, Figure-02**) and observed that less than 3.0 eq. (**Entry-5, Figure-02**) lower the conversion of reaction while with 3.0 eq. resulted into maximum reaction conversion. In the similar way 0.1 eq. $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ (**Entry-6, Figure-02**) gives excellent yield while conversion drops with low equivalents (**Entry-1-5, Figure-02**) of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$. Optimization of p-TsOH resulted that 1.0 eq. (**Entry-6, Figure-02**) is the minimum requirement of reaction. At the same time 10.0 relative volume of toluene (**Entry-6, Figure-02**) is required for the reaction and a reaction works well at 115°C . We also investigated lower temperature for reaction but the observed that reaction progress is too slow at lower reaction temperature.

Table-2.0 presents a summary of the outcomes that we have acquired. Selected substrate containing donating groups (**Entries 2-4, 14-15**) as well withdrawing groups (**Entries 5-7, 10-12**), electron deficient motif (**Entries 9-12, 16**), attached to carbonyl group, underwent smooth acetalization without any sign of by-products to yield the corresponding acetals in excellent yields within very short reaction times. Aldehydes that are aliphatic performed just as well (**Entries-8**).

The catalyst was recovered and recycled with standard optimized reaction condition using benzaldehyde, triethyl orthoformate and $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ as a reference substrates summarized in **Table-02**. Comparative yields were obtained by using recycled catalyst up to three cycles (**Entries-1-3, Figure-03**), while yield drop observed from next cycle i.e. from cycle 4 onwards.

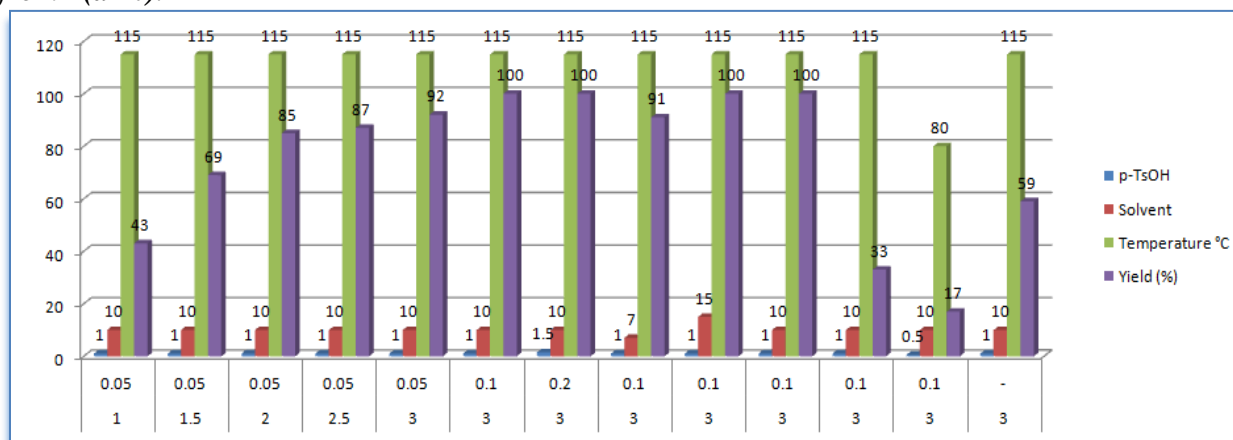
Finally, we have demonstrated a potent and incredibly effective technique for the acetalization of aldehydes and ketones using catalytic amount of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ as a recyclable catalyst. With only 10 mol% of $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$, this reaction proceeded without any problems and could be used with a variety of aldehydes and ketones.

Figure-01: Optimization of reaction conditions for the synthesis of diethyl acetals of 2(a-m) from 1(a-m).



* **Reaction conditions:** 1 (1.0eq.), Triethyl orthoformate (3.0 eq.) p-TSOH (1.0eq) , $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ (0.1eq) and EtOH (5.0 eq.) was maintained at 30°C for 30 min.

Figure-02: Optimization of reaction conditions for the synthesis of cyclic acetals of 2(a-m)' from 1(a-m).



* **Reaction conditions:** 1 (1.0eq.), Ethylene Glycol (2.0 eq.) p-TSOH (1.0eq) , $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ (0.1eq) and Toluene (10.0 eq.) was maintained at 30°C for 30 min.

Scheme-1: Synthesis of 2-chloro-3-formyl quinolines and 2-chloro-3-acetyl quinolines.

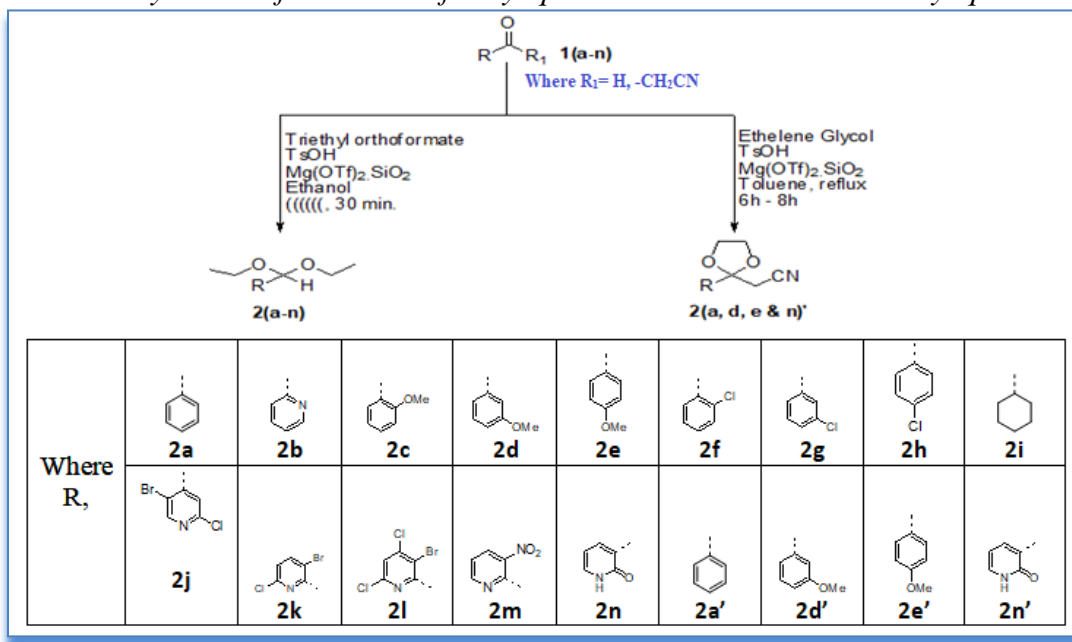







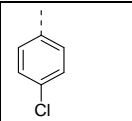
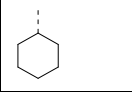
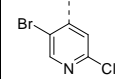
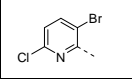
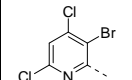
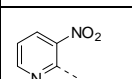
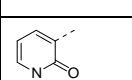
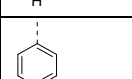
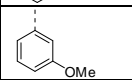
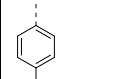
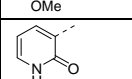
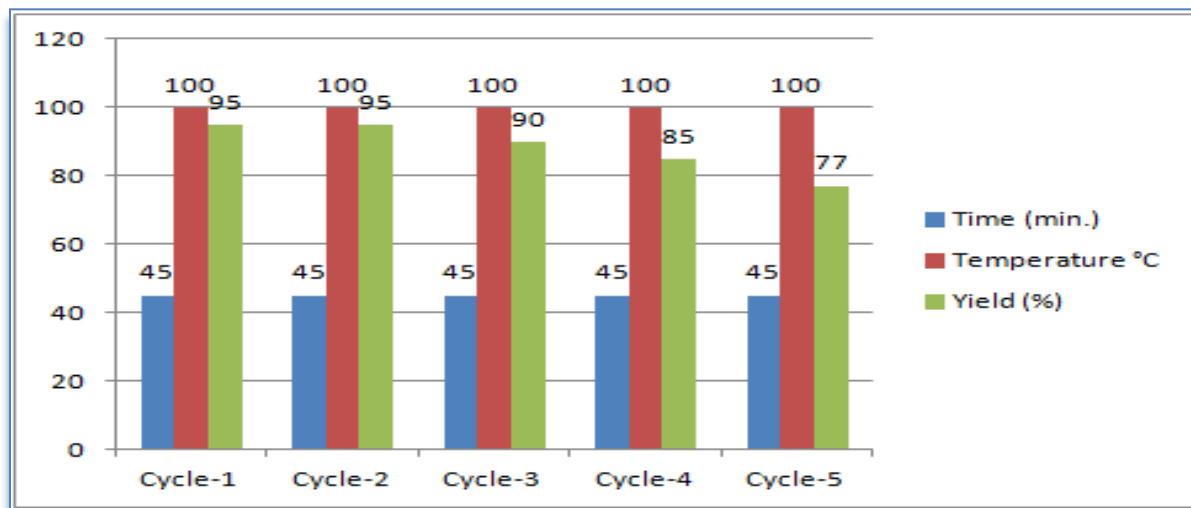


Table-02: Exploration of reaction conditions on a selected substrates **1(a-m)** to afford product **.2 (a-m) & 2(a, d, e & n)'**.

Entry	Products	2 (a-m)		Yield (%)
		R	R1	
1.	2a		H	98
2.	2b		H	95
3.	2c		H	97
4.	2d		H	94
5.	2e		H	98
6.	2f		H	99
7.	2g		H	93

8.	2h		H	94
9.	2i		H	92
10.	2j		H	89
11.	2k		H	93
12.	2l		H	88
13.	2m		H	85
14.	2n		H	82
15.	2a'		-CH ₂ CN	93
16.	2d'		-CH ₂ CN	83
17.	2e'		-CH ₂ CN	91
18.	2n'		-CH ₂ CN	78

* [Ref.]: References

Figure-03: Recycle of catalyst recovered from spent

3. Experimental Section

All chemicals and reagents were purchased from commercial resources like Avra, Spectrochem and Finar and utilized directly without purification. Reaction progress was monitored on TLC plate of silica-gel and visualized under UV light. Melting points were obtained by using Lab-India MR. Vis+ apparatus. The $^1\text{H-NMR}$ spectra were determined using Bruker 300/400 MHz instrument using TMS as the internal standard. Isolated compounds were purified using re-crystallization technique.

3.1 Preparation of (diethoxymethyl)benzene 2a:

A mixture of aromatic aldehyde 1 (1.0 eq.), Triethyl orthoformates (3.0eq.), p-TsOH (1.0 eq.) and 0.1 mol % $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ in Ethanol (5.0 rel vol) was irradiated under ultrasound at an ambient temperature for 30 min. Progress of the reaction monitored by TLC. After completion of reaction, reaction mass concentrated to get residue which was dissolved in MTBE and solid catalyst separated by filtration. Filtrate ml diluted with Aq. NaHCO_3 (1.0 eq.) solution, stirred for a few minutes. After that layers were separated and organic layer on concentration provided crude product. The isolated crude product on column purification over silica gel using hexane–ethyl acetate to afford colorless oil. Isolated product was analyzed by their physical properties (Boiling points), $^1\text{H-NMR}$ and verified by comparison with authentic commercially available data.

Similar optimized protocol used for the preparation of **2(b-m)**.

Spectral data of some representative molecules

(Diethoxymethyl)benzene (2a): $^1\text{H-NMR}$, 400 MHz, CDCl_3 : δ = 7.36-7.52(m, 5H), 5.54(s, 1H), 3.54-3.66(quartet, 4H), 1.25-1.29(t, 6H).

3-bromo-6-chloro-2-(diethoxymethyl)pyridine (2k): $^1\text{H-NMR}$, 400 MHz, CDCl_3 : δ = 8.13-8.15(d, 1H), 7.49-7.51(d, 1H), 5.63(s, 1H), 3.52-3.75(quartet, 4H), 1.13-1.17(t, 6H).

3-bromo-4,6-dichloro-2-(diethoxymethyl)pyridine (2l): $^1\text{H-NMR}$, 400 MHz, CDCl_3 : δ = 7.17(s, 1H), 5.83(s, 1H), 3.63-3.91(quartet, 4H), 1.26-1.36(t, 6H).

2-(diethoxymethyl)-3-nitropyridine (2m): $^1\text{H-NMR}$, 400 MHz, CDCl_3 : δ = 8.32-8.84(d, 1H), 8.30-8.33(d, 1H), 7.66-7.70(dd, 1H), 5.78(s, 1H), 3.51-3.75(quartet, 4H), 1.11(t, 6H)

3.2 Preparation of 2-(2-phenyl-1,3-dioxolan-2-yl)acetonitrile 2a':

A mixture of aromatic ketones 1 (1.0 eq.), Ethylene glycol (3.0eq.), p-TsOH (1.0 eq.) and 0.1 mol % $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ in toluene (10.0 rel vol) was heated to 115°C and maintained for 6-8h. Progress of the reaction monitored by TLC. After completion of reaction, reaction mass cooled to RT and solid catalyst separated by filtration. Filtrate ml diluted with Aq. NaHCO_3 (1.0 eq.) solution, stirred for a few minutes. After that layers were separated and organic layer on concentration provided crude product. The isolated crude product dissolved in ethyl acetate and precipitated using hexane which on filtration provided off white solid. Isolated product was analyzed by their physical properties (Melting points), $^1\text{H-NMR}$ and verified by comparison with authentic commercially available data.

2-(2-phenyl-1,3-dioxolan-2-yl)acetonitrile (2a'): $^1\text{H-NMR}$, 400 MHz, CDCl_3 : δ = 7.35-7.54(m, 5H), 4.24-4.25(t, 2H), 3.92-3.93(t, 2H), 2.96(s, 2H).

Similar optimized protocol used for the preparation of 2(c-d and n)'.

4. CONCLUSION

In summary, in the present work we have first time employed an efficient, effective and mild heterogeneous $\text{Mg}(\text{OTf})_2 \cdot \text{SiO}_2$ catalyst for the synthesis of acetals from corresponding aldehydes and ketones. The reactions afforded very good to excellent yields of under ultrasound irradiation at ambient temperature for diethyl acetals while under conventional condition at 115°C for cyclic acetals. Developed methodology is scalable, commercial, environmentally benign, ecofriendly. Used heterogeneous catalyst is recyclable and can be used multiple times without losing its efficiency. All synthesized compounds were characterized by their Melting points, $^1\text{H-NMR}$.

5. ACKNOWLEDGMENT

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