



SINCE 2013

NAAS SCORE : 4.32
(2017 to 2020)

Received on:
5th November 2021

Revised on:
24th December 2021

Accepted on:
26th December 2021

Published on:
1st January 2022

Volume No.
Online & Print

35

Page No.
01 to 08

IRJC is an international open access print & online journal, peer reviewed, worldwide abstract listed, published quarterly with ISSN, free-membership, downloads and access.

PRELIMINARY STUDIES ON PROTECTION OF CARBONYL COMPOUNDS USING ANHYDROUS SALT-SILICA MIXTURE

**YUSUF HASSAN¹, ABUBAKAR SIDDIQ SALIHU¹,
IDRIS ABIODUN OLASUPO², MESHACK RAPHAEL SUNDAY¹,
HAMIDAT KASIM¹ AND SHAMSUDDEEN SANI¹**

**¹DEPARTMENT OF CHEMISTRY, UMARU MUSA YAR'ADUA
UNIVERSITY, KATSINA, NIGERIA**

**²DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF LAGOS, AKOKA, LAGOS, NIGERIA.**

Corresponding author email: yusuf.hassan@umyu.edu.ng

ABSTRACT:

Some cheap, non-corrosive, and environmentally friendly inorganic salts were immobilised on silica to afford homogenous mixtures which were employed to mediate the protection of carbonyl functionality with ethylene glycol in the absence of solvent. The methodology proved to be feasible with the successful acetalisation and ketalisation of all the compounds albeit with fair to low yields.

KEYWORDS: *Anhydrous salts, Silica, Ethylene Glycol, Solvent-Free, Acetalisation, Ketalisation.*

INTRODUCTION:

Protection of carbonyl functionality in aldehydes or ketones is normally carried out via acetalisation or ketalisation reactions respectively. The strategy continues to be essential as it enables the carbonyl functionality to be protected from the effect of reagents such as Grignard reagents, metal hydrides, hydrogenation reagents, oxidants during organic synthesis^{1,2}. Besides the traditional methods of acetalisation or ketalisation reactions which involve the treatment of carbonyl compound with alcohol in the presence of protic acid³⁻⁶, many alternative methods have been reported. These includes the use of Lewis acids⁷⁻¹⁶, metal complexes¹⁷⁻²⁰, and other heterogenous catalysts²¹⁻²⁶.

Notwithstanding the aforementioned progress, there are still limitations that need to be addressed related to substrate scope, use of toxic and expensive reagents, high reaction temperature, long reaction time, low yields, and tedious work up²⁷. The potential of silica-supported reagents for the mediation of a number of transformations have been explored such as α -bromination of carbonyl compounds using *N*-bromosuccinimide²⁸, selective deprotection of phenolic methoxymethyl ethers²⁹, synthesis of bis- and tris(1H-indol-3-yl) methanes from indoles and carbonyl compounds³⁰, stereoselective synthesis of (Z)- and (E)-allyl halides³¹, chemoselective deprotection of trityl ethers³², synthesis of bis-(4-hydroxycoumarin-3-yl) methanes³³. In this work, some common anhydrous salts were immobilized on silica to afford powdered materials which were explored in the acetalisation and ketalisation of aldehydes and ketone respectively.

MATERIAL AND METHOD:

General

FTIR spectra were recorded on Agilent Cary 630, Chemicals were purchased from different manufacturers, vanillin, *p*-anisaldehyde, 4-bromobenzaldehyde, 4-hydroxybenzaldehyde (Sigma-Aldrich), 3-nitrobenzaldehyde (JN Chem., India). Benzophenone (Burgoyne Burbidges, India), ethylene glycol (Park Sci. Ltd, UK), silica gel 60-120 mesh (Sisco Research Laboratories Pvt. Ltd., India), anhydrous sodium sulphate, copper sulphate, and calcium chloride (Loba Chimie, India).

General Procedure for Preparation of Anhydrous Salt-Silica Mixture

Typically, Na₂SO₄-silica mixture (75% w/w) was prepared by grinding anhydrous Na₂SO₄ (0.285g) with silica (0.095g) using pestle and mortar until a homogenous, free-flowing powder was obtained³⁴. The appropriate ratios were varied to obtain the corresponding 50%, 55%, 60%, 65%, 70%, 75%, and 80% w/w.

General Procedure for Acetalisation/Ketalisation of Carbonyl Compounds

Carbonyl compound (0.3g, 2mmol), Na₂SO₄-silica [(75% w/w), 0.3g] were gently mixed, and ethylene glycol (130 μ l, 2.4mmol) was added. The mixture was ground using pestle and mortar in the absence of solvent. After the appropriate reaction time, the mixture was treated with diethyl ether (10ml) and filtered. The filtrate was allowed to dry and then washed with ethanol (10ml) followed by distilled water (5ml). After drying, different solid products were obtained. The FTIR spectra of the acetals and ketal were then recorded.

RESULTS AND DISCUSSION:

The efficiency of Na₂SO₄-silica, CuSO₄-silica, and CaCl₂-silica mixtures was investigated in the acetalisation of 4-bromo benzaldehyde as a model reaction. Thus each of the reagents was used at seven different percentage weights for duration of five minutes. The percentage yields (Table 1) indicated that the highest yield for each reagent was recorded at 75% w/w. Apparently, Na₂SO₄-silica gave the highest yield (46%). An attempt to increase the percentage weight resulted in the reduction in the conversion. Perhaps the anhydrous salt which is responsible for removing the water by-product in order to drive the reaction forward is suppressing the acidity of the silica which is needed for the activation of the carbonyl group. At 50 % w/w and 55% w/w, the yields were found to be quite negligible.

Based on the performance of the reagents, Na₂SO₄-silica (75% w/w) was taken as optimum and the effect of duration was studied 30 minutes. However, the yields of the corresponding acetals at longer duration (Table 2) were less different from the shorter duration of 5 minutes.

To explore the substrate scope, some structurally different aldehydes and one aromatic ketone were subjected to the reaction condition. The corresponding products were isolated, and the disappearance of the C=O band along with the formation of the C-O ether band were confirmed by the FTIR spectroscopy (Table 3).

The yield of the products indicated that 4-hydroxy benzaldehyde formed the corresponding acetal with a moderate yield (41%) followed by 3-nitro benzaldehyde (37%) and 4-methoxy benzaldehyde (22%). Although both hydroxy- and methoxy- groups are ring activating, it was found that the nitro- substituent — ring deactivating group — gave higher yield than the methoxy substituent. Possibly the proximity of the nitro group (position 3) influenced the acetalisation reaction. In the case of 3-methoxy-4-hydroxy derivative and benzophenone, the yields recorded were quite low (14%).

CONCLUSION:

A preliminary investigation on the feasibility of anhydrous salt-silica mixture to mediate the acetalisation and ketalisation of some few carbonyl compounds was carried out in the absence of solvent. As a proof of concept, only aromatic systems were considered, and it turned out that the yields of the acetals and ketal were humbly low. But the methodology proved that the conversion of the carbonyl functionality to the corresponding acetal and ketal under the reaction condition was experimentally achievable.

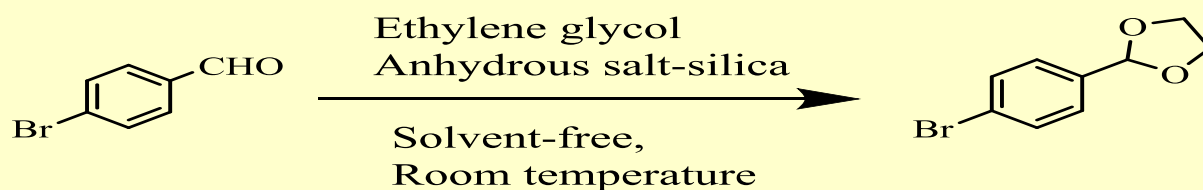
REFERENCES:

1. Clode, D. M. Carbohydrate Cyclic Acetal Formation and Migration. *Chem. Rev.* 1979, 79, 491–513.
2. Wuts, P. G. M.; Michigan, K. Protection for the Carbonyl Group. *Greene's Protective Groups in Organic Synthesis*, 5th ed.; Academic Press: New York, 2014; pp 554–558.
3. Butler, M. A. Photoelectrolysis and Physical Properties of the Semiconducting Electrode WO₂. *J. Appl. Phys.* 1977, 48, 1914–1920.
4. Gregg, B. T.; Golden, K. C.; Quinn, J. F. Indium(III) Trifluoromethanesulfonate as an Efficient Catalyst for the Deprotection of Acetals and Ketals. *J. Org. Chem.* 2007, 72, 5890–5893.
5. Hamada, N.; Kazahaya, K.; Shimizu, H.; Sato, T. An Efficient and Versatile Procedure for the Synthesis of Acetals from Aldehydes and Ketones Catalyzed by Lithium Tetrafluoroborate. *Synlett* 2004, 1074–1076.
6. Rudrawar, S.; Besra, R. C.; Chakraborti, A. K. Perchloric Acid Adsorbed on Silica Gel (HClO₄-SiO₂) as an Extremely Efficient and Reusable Catalyst for 1,3 dithiolane/dithiane Formation. *Synthesis* 2006, 2767–2771.
7. Greeves, C. N.; Stuart, W. Chemoselectivity and protecting groups. *Organic Chemistry*, 2nd ed.; Academic Press: Oxford University Press, 2012; pp 528–561.
8. Wuts, P. G. M.; Michigan, K. Protection for the Carbonyl Group. *Greene's Protective Groups in Organic Synthesis*, 5th ed.; Academic Press: New York, 2014; pp 559–643.
9. Cooks, R. G.; Chen, H.; Eberlin, M. N.; Zheng, X.; Tao, W. A. Polar Acetalization and Transacetalization in the Gas Phase: The Eberlin Reaction. *Chem. Rev.* 2006, 106, 188–211.
10. Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. A Simple and Versatile Method for the Synthesis of Acetals from Aldehydes and Ketones Using Bismuth Triflate. *J. Org. Chem.* 2002, 67, 5202–5207.
11. Smith, B. M.; Graham, A. E. Indium Triflate Mediated Tandem Acetalisation-acetal Exchange Reactions under Solvent-free Conditions. *Tetrahedron Lett.* 2011, 52, 6281–6283.
12. Smith, B. M.; Kubczyk, T. M.; Graham, A. E. Indium(III) Triflate Catalysed Transacetalisation Reactions of Diols and Triols under Solvent-free Conditions. *Tetrahedron* 2012, 68, 7775–7781.
13. Smith, A. B.; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. Phyllanthoside-Phyllanthostatin Synthetic Studies. 7. Total Synthesis of (+)-Phyllanthocin and (+)-Phyllanthocindiol. *J. Am. Chem. Soc.* 1991, 113, 2071–2092.
14. Gemal, A. L.; Luche, J. L. Lanthanoids in Organic Synthesis. 4.1 Selective Ketalization and Reduction of Carbonyl Groups. *J. Org. Chem.* 1979, 44, 4187–4189.

15. Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. Scandium Trifluoromethanesulphonamide and Scandium Trifluoromethanesulfonate as Extremely Active Acetalization Catalyst, *Synlett* 1996, 839.
16. Clerici, A.; Pastori, N.; Porta, O. Efficient Acetalisation of Aldehydes Catalyzed by Titanium Tetrachloride in a Basic Medium. *Tetrahedron* 1998, 54, 15679–15690.
17. Kocienski, P. J. *Protecting Groups*; Thieme, 1994, 156–170.
18. Zhu, Z.; Espenson, J. H. Organometallic Catalysis: Formation of 1,3-Dioxolanes and Their Analogs Catalyzed by Methylrhenium Trioxide (MTO). *Organometallics* 1997, 16, 3658–3663.
19. Wang, B.; Gu, Y.; Song, G.; Yang, T.; Yang, L.; Suo, J. An Efficient Procedure for Protection of Carbonyls Catalyzed by Sulfamic Acid. *J. Mol. Catal. A: Chem.* 2005, 233, 121–126.
20. Clerici, A.; Pastori, N.; Porta, O. Mild Acetalisation of Mono and Dicarbonyl Compounds Catalysed by Titanium Tetrachloride. Facile Synthesis of β -keto Enol Ethers. *Tetrahedron* 2001, 57, 217–225.
21. Kotke, M.; Schreiner, P. R. Acid-free, Organocatalytic Acetalization. *Tetrahedron* 2006, 62, 434–439.
22. Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. Application of Functional Ionic Liquids Possessing Two Adjacent Acid Sites for Acetalization of Aldehydes. *J. Org. Chem.* 2004, 69, 3582–3585.
23. Karimi, B.; Seradj, H.; Ebrahimian, G.-R. N-Bromosuccinimide (NBS) as a Powerful and Chemoselective Catalyst for Acetalization of Carbonyl Compounds under Almost Neutral Reaction Conditions. *Synlett* 1999, 1456–1458.
24. Karimi, B.; Hazarkhani, H.; Maleki, J. N-Bromosuccinimide (NBS) - Catalyzed Highly Chemoselective Acetalization of Carbonyl Compounds using Silylated Diols and Pentaerythritol under Neutral Aprotic Conditions. *Synthesis* 2005, 279–285.
25. Wu, H.-H.; Yang, F.; Cui, P.; Tang, J.; He, M.-Y. An Efficient Procedure for Protection of Carbonyls in Brønsted Acidic Ionic Liquid[Hmim]BF₄. *Tetrahedron Lett.* 2004, 45, 4963–4965.
26. Gopinath, R.; Haque, S. J.; Patel, B. K. Tetrabutylammonium Tribromide (TBATB) as an Efficient Generator of HBr for an Efficient Chemoselective Reagent for Acetalization of Carbonyl Compounds. *J. Org. Chem.* 2002, 67, 5842–5845.
27. Dong, J.L.; Yu, L.S.H.; and Xie, J.W. A simple and versatile method for the formation of acetals/ketals using trace conventional acids. 2018, *ACS Omega*, 3(5), 4974-4985.
28. Das, B.; Venkateswarlu, K.; Mahender, G.; Mahender I. A simple and efficient method for α -bromination of carbonyl compounds using N-bromosuccinimide in the presence of silica-supported sodium hydrogen sulfate as a heterogeneous catalyst. *Tetrahedron Lett.* 2005, 46(17), 3041-3044.
29. Ramesh, C.; Ravindranath, N.; Das, B. Simple, Efficient, and Selective Deprotection of Phenolic Methoxymethyl Ethers Using Silica-Supported Sodium Hydrogen Sulfate as a Heterogeneous Catalyst. *J. Org. Chem.* 2003, 68(18), 7101-7103.

30. Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. Silica supported sodium hydrogen sulfate and amberlyst-15: Two efficient heterogeneous catalysts for facile synthesis of bis- and tris (1H-indol-3-yl) methanes from indoles and carbonyl compounds. *Adv. Synth. Catal.* 2003, 345(5), 557-559.
31. Das, B.; Banerjee, J.; Ravindranath N. A simple and facile stereoselective synthesis of (Z)- and (E)-allyl halides catalyzed by silica supported sodium hydrogen sulfate: factors influencing the yields and stereochemistry of allyl halides. *Tetrahedron.* 2004, 60(38), 8357-8361.
32. Das B, Mahender G, Kumar VS, Chowdhury N. Chemoselective deprotection of trityl ethers using silica-supported sodium hydrogen sulfate. *Tetrahedron Lett.* 2004, 45(36), 6709-6711.
33. Padalkar V, Phatangare K, Takale S, Pisal R, Chaskar A. Silica supported sodium hydrogen sulfate and Indion 190 resin: An efficient and heterogeneous catalysts for facile synthesis of bis-(4-hydroxycoumarin-3-yl) methanes. *J. Saudi Chem. Soc.* 2015, 19(1), 42-45.
34. Hasaninejad, A., Zare, A., Sharghi, H., Niknam, K. and Shekouhy, M., 2007. P205/SiO₂ as an efficient, mild, and heterogeneous catalytic system for the condensation of indoles with carbonyl compounds under solvent-free conditions. *Arkivoc*, 14, 39-50.

Table 1. Acetalisation of 4-bromo benzaldehyde^a



Anhydrous salt-Silica	Yield (%) ^b						
	50% w/w	55% w/w	60% w/w	65% w/w	70% w/w	75% w/w	80% w/w
Na₂SO₄-Silica	Traces	12	18	20	26	46	44
CuSO₄-Silica	Traces	Traces	10	15	18	32	30
CaCl₂-Silica	Traces	Traces	14	17	20	33	28

^a Reaction mixture ground using pestle and mortar for 5 minutes

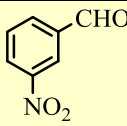
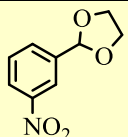
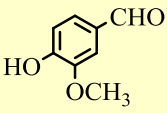
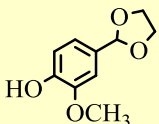
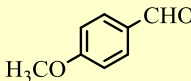
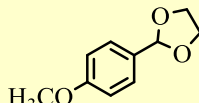
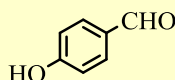
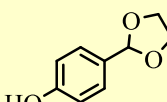
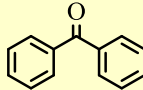
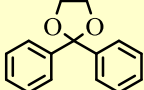
^b Isolated acetals as confirmed by the disappearance of C=O band and appearance of C-O band in the FTIR spectra

Table 2. Acetalisation of 4-bromo benzaldehyde using Na₂SO₄-silica, 75% w/w

Time (mins)	Yield (%) ^a
10	46
15	46
20	46
25	47
30	47

^a Isolated acetals as confirmed by the disappearance of C=O band and appearance of C-O band in the FTIR spectra

Table 3. Acetalisation and Ketalisation of Carbonyl compounds using Na₂SO₄-silica, 75% w/w^a

Carbonyl Compound	Product	Yield (%) ^b
		37
		14
		22
		41
		14

^a Reaction mixture ground using pestle and mortar for 5 minutes

^b Isolated acetals as confirmed by the disappearance of C=O band and appearance of C-O band in the FTIR spectra