



## Titanium dioxide as an eco-friendly and recyclable catalyst for the synthesis of 1,1-diacetate under solvent-free conditions

Kiran F. Shelke<sup>1\*</sup>, Laxman S. Gadekar<sup>2</sup>

<sup>1</sup>Department of Chemistry, Late Pushpadevi Patil Arts and Science College, Risod, Dist. Washim-444 506 (MS INDIA)

<sup>2</sup>Padmabhushan Vasantdada patil College, Patoda, Dist. Beed-414 204 (MS- INDIA)

E-mail: kiranshelke82@gmail.com

### ABSTRACT

A simple, highly versatile and efficient method for the synthesis of 1,1-diacetates (acylals) is achieved from the various aliphatic, aromatic and heteroaryl aldehydes with acetic anhydride at room temperature under solvent-free conditions using titanium dioxide (TiO<sub>2</sub>) as catalyst. The key advantages of this process are mild condition, excellent chemoselectivity, easy work-up, excellent yields, very short time reactions and use of non-toxic, inexpensive, recyclable heterogeneous catalyst.

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### KEYWORDS

Aromatic and heteroaryl aldehyde;  
Titanium dioxide;  
1,1-Diacetate;  
Solvent-free.

### INTRODUCTION

Selective protection of carbonyl group plays an important role in the multistep organic synthesis of complex compounds and natural products. Acylal formation is one of the most useful methods to protect carbonyl groups due to the stability of the resulting acylals. They are stable in neutral and basic media<sup>[1]</sup>. Acylals are synthetically important precursors for the preparation of 1-acetoxydienes for Diels–Alder reaction<sup>[2]</sup>. Chiral allylic esters have been obtained using palladium catalysts by an asymmetric allylic alkylation of gem-diesters<sup>[3]</sup>. The preparation of homoallyl acetates by allylation of acylals has also been reported<sup>[4a]</sup>. Due to stability of acylals toward a variety of reaction conditions, geminal diacetates have been used as important build-

ing blocks for aldehydes and have played important roles in organic synthesis<sup>[4b]</sup>.

As per literature, a number of methods have already been developed for the synthesis of acylals from the reaction of aldehydes with acetic anhydride under different acid catalysts such as Saccharin sulfonic acid<sup>[5]</sup>, I<sub>2</sub><sup>[6]</sup>, InCl<sub>3</sub><sup>[7]</sup>, Cu(OTf)<sub>3</sub><sup>[8]</sup>, H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>.24H<sub>2</sub>O<sup>[9]</sup>, [Hmim]HSO<sub>4</sub><sup>[10]</sup>, SnCl<sub>4</sub>/SiO<sub>2</sub><sup>[11]</sup>, GaCl<sub>3</sub><sup>[12]</sup>, CAN<sup>[13]</sup>, Silica Phosphoric Acid<sup>[14]</sup>, melamine trisulphonic acid<sup>[15]</sup>, DBSA<sup>[16]</sup> and MCM-41<sup>[17]</sup>. Although these methods are an improvement most of them suffer from disadvantages such as long reaction times, harsh reaction conditions, low yields, use of corrosive, expensive or moisture-sensitive reagents, use of excess amounts of Ac<sub>2</sub>O, strictly reactive condition (N<sub>2</sub> atmosphere), special efforts required to prepare the catalyst and tedious

work-up procedure. Thus, the search for new reagents and methods is still of practical importance.

In recent years, solvent-free organic synthesis have offered more advantages as compared to their homogeneous counterparts due to the growing concern for the influence of organic solvents on the environment as well as on the human body, economical demands and simplicity in the processes<sup>[18]</sup>.

Titanium dioxide (TiO<sub>2</sub>) was found to be effective in certain organic transformations that include Biginelli reaction<sup>[19a]</sup> and Beckmann rearrangement<sup>[19b]</sup>. Very recently, effective synthesis of 2,4,5-triarylimidazole<sup>[19c]</sup> has also been reported. Titanium dioxide has been exploited in organic synthesis as an easy handling, green, mild, inexpensive, recyclable, commercially available and highly reactive heterogeneous Lewis acid catalyst. It was therefore decided to investigate titanium dioxide as a catalyst for the synthesis of acylals and found that it is an effective promoter in the synthesis of acylals from various aliphatic, aromatic and 4-oxo-(4*H*)-1-benzopyran-3-carbaldehydes and acetic anhydride.

## EXPERIMENTAL

The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. <sup>1</sup>H NMR spectra were recorded on an 300 MHz FT-NMR spectrometer in CDCl<sub>3</sub> as a solvent and chemical shift values are recorded in units  $\delta$  (ppm) relative to tetramethylsilane (Me<sub>4</sub>Si) as an internal standard.

### GENERAL PROCEDURE FOR PREPARATION OF 2 (A-P)

1 (a-p) (1 mmol), acetic anhydride (2 mmol) and titanium dioxide (1 mol%) were taken in a round bottom flask and stirred at room temperature. The time required for each reaction is indicated in TABLE 1. The reaction was followed by TLC (*n*-Hexane: EtOAc, 9:1). After completion of the reaction, the mixture was diluted with ethyl acetate (15 mL) and shaken well to dissolve the organic components, then filtered to separate out titanium diox-

ide and washed with ethyl acetate. The solid residue of titanium dioxide was further washed with hot 10 ml acetone and then dried up; this recovered titanium dioxide reusable. The organic layer was washed with 10% NaHCO<sub>3</sub> solution and water and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure to give pure 2 (a-p) in excellent yields without further purification. The products 2(a-p) were confirmed by comparisons with authentic samples, IR, <sup>1</sup>H NMR and melting points.

### SPECTRAL DATA OF REPRESENTATIVE COMPOUND

#### Compound (2a)

IR (KBr, cm<sup>-1</sup>): 3060, 1755, 1605, 1470, 1375, 1245, 1205, 1065, 1010, 760, 700. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 7.6 (s, 1H), 7.4–7.2 (m, 5H), 1.92 (s, 6H).

#### Compound (2d)

IR (KBr, cm<sup>-1</sup>): 3124, 1762, 1610, 1529, 1345, 1210, 1200, 1090, 1000, 960, 850. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 8.07 (d, J = 8.4 Hz, 2H), 7.54 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 1.96 (s, 6H).

#### Compound (2j)

IR (KBr, cm<sup>-1</sup>): 3070 (ArC-H), 1656 (C=O, chromone), 1768 (OCOCH<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.13 (s, 6H), 7.4 (s, 1H), 8.2 (s, 1H), 7.5–7.8.2 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 175.47, 168.77, 154.88, 153.77, 135.68, 130.90, 126.88, 124.27, 119.79, 118.22, 85.64, 21.37.

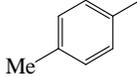
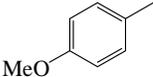
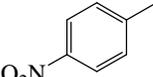
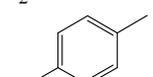
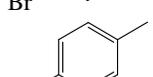
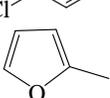
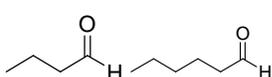
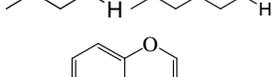
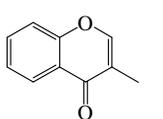
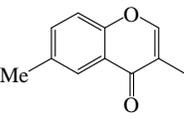
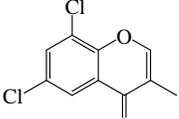
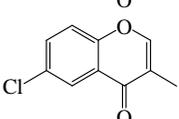
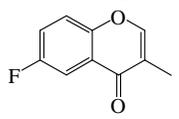
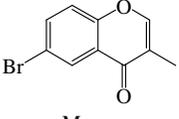
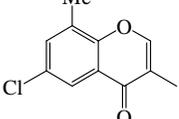
#### Compound (2l)

IR (KBr, cm<sup>-1</sup>): 3080 (ArC-H), 1657 (C=O, chromone), 1776 (OCOCH<sub>3</sub>), 990 (C-Cl). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.13 (s, 6H), 7.77 (s, 1H), 7.72 (d, 1H, J = 2.20 Hz), 8.06 (d, 1H, J = 2.20 Hz), 8.18 (s, 1H), <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 173.58, 168.59, 155.31, 150.95, 134.68, 131.90, 126.31, 124.94, 124.45, 120.60, 84.91, 21.08.

#### Compound (2n)

IR (KBr, cm<sup>-1</sup>): 3055 (ArC-H), 1660 (C=O, chromone), 1770 (OCOCH<sub>3</sub>), 900 (C-F). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.13 (s, 6H), 7.30 (d, 1H, J = 8.78 Hz), 7.79 (dd, 2H, J = 2.30 & 8.70 Hz), 8.20 (s, 1H), 8.5

TABLE 1 : Titanium dioxide catalysed preparation of acylals<sup>a</sup>

Compound	R	Time (min)	Yield % <sup>b</sup>	M.p.(°C)	
				Found	Reported
2a		5	96	45-46	44-46 <sup>[11]</sup>
2b		10	95	82-83	81-82 <sup>[11]</sup>
2c		5	94	65-65	64-65 <sup>[11]</sup>
2d		5	96	124-126	125-126 <sup>[11]</sup>
2e		5	95	93-94	93-95 <sup>[11]</sup>
2f		5	92	81-82	79-81 <sup>[11]</sup>
2g		10	89	52-54	52-53 <sup>[10]</sup>
2h		10	91	oil	oil <sup>[16]</sup>
2i		10	93	oil	oil <sup>[16]</sup>
2j		10	95	130-132	131-132 <sup>[12]</sup>
2k		15	92	148-150	150 <sup>[13]</sup>
2l		10	92	190-191	189 <sup>[13]</sup>
2m		10	89	170-171	170 <sup>[13]</sup>
2n		10	90	155-156	156 <sup>[13]</sup>
2o		10	91	170-172	171 <sup>[13]</sup>
2p		20	90	161-162	162 <sup>[13]</sup>

<sup>a</sup>Reaction condition: aliphatic, aromatic and heteroaryl aldehydes (1 mmol), acetic anhydride (2 mmol), titanium dioxide (1 mol%) at RT under solvent-free conditions. <sup>b</sup>Isolated yield based upon starting aldehyde.

(s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 173.58, 168.23, 154.85, 137.25, 128.65, 125.30, 120.15, 119.90, 84.88, 77.55, 76.32, 20.63.

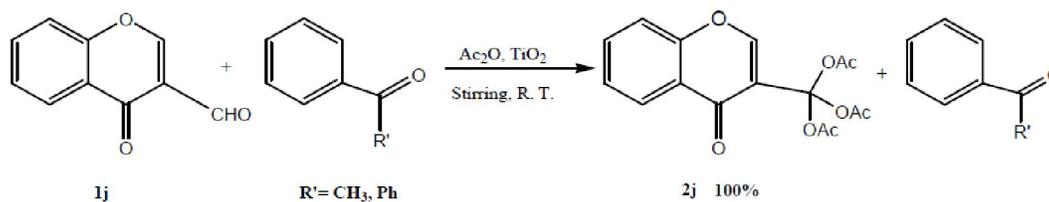
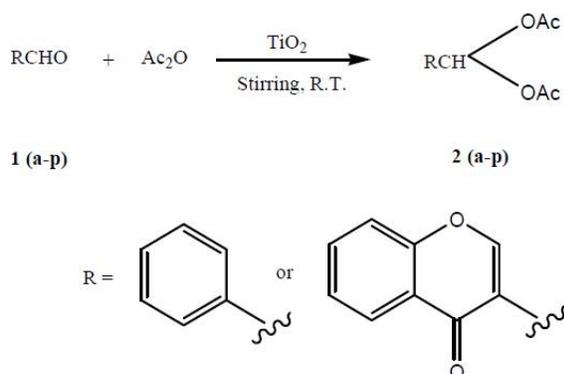
### Compound (2o)

IR (KBr,  $\text{cm}^{-1}$ ): 3060 (ArC-H), 1650 (C=O, chromone), 1750 ( $\text{OCOCH}_3$ ), 1016 (C-Br).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.14 (s, 6H), 7.40 (d, 1H,  $J = 8.78$  Hz), 7.80 (dd, 2H,  $J = 2.30$  & 8.70 Hz), 8.19 (s, 1H), 8.4 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 173.56, 168.17, 154.93, 137.09, 128.53, 125.38, 120.07, 119.84, 77.63, 76.36, 20.68.

## RESULTS AND DISCUSSION

In continuation of our work on the protection of aldehydes and ketones<sup>[13,20]</sup>, the study of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehydes<sup>[21]</sup> and as a part of an ongoing research project to develop reactions novel synthetic methodology<sup>[22]</sup>, herein, we report a convenient, mild, efficient and rapid method for the preparation of acylals from a variety of aliphatic, aromatic and heteroaryl aldehydes with acetic anhydride in the presence of a catalytic amount of titanium dioxide at room temperature under solvent-free conditions (Scheme 1).

In an initial endeavor, we tried to the reaction of benzaldehyde 1a and acetic anhydride was selected



as model to investigate the effects of different amounts of catalyst on the yield. The best result was obtained by carrying out the reaction with 1:2 mol ratios of benzaldehyde: acetic anhydride and 1 mol% of titanium dioxide at room temperature under solvent-free conditions and under this conditions 2a was obtained in 97% yield after 5 min (TABLE 1, compound 2a). To determine the role of titanium dioxide, the model reaction was carried out in the absence of catalyst at room temperature under solvent-free conditions; the desired product was not obtained after 120 min. This result indicates that titanium dioxide exhibit a high catalytic activity in this transformation.

The substrate, 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde has three active centers such as an  $\alpha,\beta$ -unsaturated carbonyl group, a carbon-carbon double bond and a formyl group. Of these three reactive centers, the reaction chemoselectively occurs at the formyl group. TABLE 1 shows that aromatic and heteroaryl aldehydes, having different substituents such as chloro, nitro, methoxy, methyl, bromo, fluoro, etc. are converted to the corresponding acylal derivatives with high yields.

The acylals are prepared at room temperature and isolated by simple quenching in water and neutralization with  $\text{NaHCO}_3$ . All the reactions are completed within 5-20 min with excellent yields (89-97%). This methodology avoids the use of corrosive acids, solvents and requires only a catalytic amount of the titanium dioxide to promote the reaction. The identities of compounds 2 (a-p) were established by comparison of their physical and spectroscopic properties with those reported earlier<sup>[11,13]</sup>.

In order to demonstrate the high selectivity of the procedure, we investigated competitive reactions for the preparation of the acylals from 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde in the presence of acetophenone or benzophenone using a catalytic

TABLE 2: Comparison of some other procedure with the present method for acylal synthesis<sup>a</sup>.

4-Nitrobenzaldehyde (1d)					
Entry	Catalyst	mol %	Time	Yield %	Reference
1	I <sub>2</sub>	10	2 h	99	6
2	InCl <sub>3</sub>	10	4 h	88	7
3	Cu(OTf) <sub>3</sub>	2.5	4 h	94	8
4	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> ·24H <sub>2</sub> O	1	30 min	92	9
5	[Hmim]HSO <sub>4</sub>	3.8	40 min	89	10
6	DBSA	0.2 mmol	7 min	90	16
7	TiO <sub>2</sub>	1	5 min	96	Present work
4-Oxo-(4H)-1-benzopyran-3-carbaldehyde (1j)					
1	GaCl <sub>3</sub>	5	12 min	92	12
2	CAN	6	2 h	89	13
3	TiO <sub>2</sub>	1	10 min	95	Present work

<sup>a</sup>Reaction condition: aldehydes (1 mmol), acetic anhydride (2 mmol), titanium dioxide (1 mol%) at room temperature.

TABLE 3 : Recycling of titanium dioxide for the synthesis acylal<sup>a</sup> [TABLE 1, compound 1d]

Entry	1	2	3	4	5
Cycle <sup>b</sup>	Fresh	First reuse	Second reuse	Third reuse	Fourth reuse
Yield (%) <sup>c</sup>	96	94	92	91	91

<sup>a</sup>Reaction condition: 4-nitrobenzaldehyde (1 mmol), acetic anhydride (2 mmol), titanium dioxide (1 mol%) at room temperature.

<sup>b</sup>Reaction time-5 min; <sup>c</sup> Isolated yield.

amount of titanium dioxide at room temperature under solvent-free conditions. It was found that ketones did not produce any acylals under the optimized reaction condition. This result suggested that chemoselective protection of aliphatic, aromatic and heteroaryl aldehydes in the presence of ketones could be achieved with this procedure (Scheme 2).

The data presented in TABLE 2 show the promising features of this method in terms of molar ratio of the catalyst, reaction rate and yield of the product compared with those reported in the literature for the synthesis of compounds 2d and 2j.

Further investigation was the reusability of catalyst is important for the large-scale operation and industrial point of view. Therefore, the recovery and reusability of titanium dioxide was examined. The reusability of the catalyst was investigated in the model reaction. The results illustrated in TABLE 3 showed that the catalyst could be used four times without significant loss of activity.

## CONCLUSION

In conclusion, we have described a facile and

solvent-free efficient method for the preparation of acylals from a variety of aliphatic, aromatic and heteroaryl aldehydes with acetic anhydride in the presence of a catalytic amount of titanium dioxide at room temperature under solvent-free conditions. Ketone was found not to react with acetic anhydride to yield corresponding product under the same conditions. The notable merits of the present method are short reaction times, mild reaction conditions, excellent chemoselectivity, green method, simple work-up procedure, excellent yield of products and easy recovery and reusability of catalyst. It is thus a rapid, convenient and environmentally benign method for the preparation of compounds of type 2 (a-p).

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