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The studies on chemoselective promiscuous activity of hydrolases on acylals transformations

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ARTICLE INFO	A B S T R A C T
Keywords:	Chemoselective, mild and convenient protocol for the hydrolysis of the synthetically relevant acylals via pro-
Acylals	miscuous enzyme-catalyzed hydrolysis has been developed. It has been shown that promiscuous activity of the
Deprotection	used hydrolases dominates their native activity related with carboxylic esters hydrolysis. The main advantage of
Biotransformation	the present methodology is that it can be conducted under neutral conditions at room temperature. Moreover,
Promiscuity	complete deprotection of acylals takes place within 10–20 min. Developed protocol can be used with compounds
Chemoselectivity	having a variety of hydrolytic labile groups since the cleavage is proceeded under neutral conditions and occurs
	exclusively on acylal moiety. Further this protocol was extended by the tandem Passerini multicomponent re-
	action leading to the α -acetoxy amides using acylals as the surrogates of the carbonyl components to P-MCR.

1. Introduction

Recently, biocatalytic transformations have attracted significant attention due to their high selectivity and mild reaction conditions [1]. Moreover, a new frontier, refereed as a biocatalytic promiscuity, has largely extended the application of enzymes in organic synthesis [2]. Enzyme promiscuity is the ability of enzymes to catalyze alternative reactions that differ from their natural physiological activity [3]. Enzyme promiscuity started as being perceived as "associated with unwanted side effects, poor catalytic properties and errors in biological function" [4]. Nowadays, this marvel is increasingly being refereed as a phenomenon which dramatically enhance application of biocatalysis in organic synthesis. Furthermore, enzyme promiscuity provides environmentally sustainable protocols for organic synthesis. Hult and Berglund classified enzyme promiscuity into three major classes: condition, substrate and catalytic promiscuity [2d]. First two promiscuities of enzymes have been already communicated more than 100 years ago by Bourquelot and Bridel, who used a crude preparation of biocatalyst to obtain alkyl glucoside in dry alcohol [5]. If not all, several enzymes are promiscuous in nature. Among them, hydrolases (EC 3.1.1.x) undoubtedly play an important role due to their high stability, wide sources and broad range of substrates [6]. Several elegant examples regarding the significance of enzymatic promiscuity have been reported, such as multikomponent Ugi, Hantzsch or Mannich reactions [7], Canizzaro disproportionation [8], Henry reactions [9], Morita-Baylis-Hillman reaction [10], aldol condensation [11], or Michael additions [12]. Promiscuous activities are generally considerably less efficient than the primary functions of an enzyme [13]. Whereas most enzymes exhibit k_{cat}/K_M values in the order of $10^5-10^8 M^{-1} s^{-1}$ for their native substrates, the magnitude of promiscuous activities varies over more orders of magnitude. Although, the k_{cat}/K_M values for the promiscuous substrates are very low, the rate accelerations and catalytic proficiencies can be very high [14].

In our efforts to explore the application of this new area of enzyme promiscuity, we became interested in the selective deprotection of functional groups what is of great interest to organic chemists in the aspect of total synthesis of complex organic compounds both in academia and industry [15]. Recently, 1,1-diacetates (acylals) received increasing attention, since there are stable, easy to prepare and can be used as an alternative to acetals for the chemoselective protection of aldehydes in the presence of a ketone or other functional groups [16]. In this context, furfural (FUR) and 5-hydroxymethylfurfural (HMF) which are popularly referred as "sleeping-giants" have been emphasized as one of the top value-added aldehydes derived from a biomass [17]. The number of potential routes for transforming the furfural and its analogue 5-hydroxymethylfurfural (AMF), 5-dihydroxy-methyl-2-furanoic acid, furfuryl alcohol or levulinic acid is enormous (Fig. 1) [18].

Deprotection of the 1,1-diacetates to their parent aldehydes is also of practical importance and several methods have been reported in the literature for this purpose [19]. However, many of these methods have drawbacks, such as harsh acidic conditions, high reaction temperature

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Fig. 1. Synthetically relevant aldehydes and examples of chemicals derived from furfural (FUR) and 5-hydroxymethylfurfural (HMF).

and long reaction times what makes them incompatible with chemically unstable compounds causing their decomposition [20]. Moreover, reported protocols are not chemoselective causing hydrolysis of other chemically labile groups present in the structure of the deprotected compounds [21]. In addition to this, the majority of the catalysts used for deprotection, especially the metal complexes are toxic, explosive or expensive and the products require complex purification procedures [22]. Due to the pharmacopoeia limits of heavy metal contaminations (below 5 ppm) reported methods cannot be used in the pharmaceutical and cosmetic industry. Therefore, development of a catalyst system that do not contain harmful components like transition metals, strong acids or bases seems highly desirable. As an alternative to the commonly employed deprotection protocols, a biocatalytic approach can be expected to be beneficial due to mild reaction conditions, thereby fulfilling the general principles of the sustainable chemistry. Enzymes are also important in another aspect as they often display high chemoselectivity what allows them to control the reaction pathways, prohibiting side-reactions [23]. Chemoselectivity is the existence of a preferential reaction of a chemical reagent with one functional group in the presence of the other functional groups [24]. This incredible feature makes enzymes a powerful tool in organic chemistry and is used more and more often in vitro studies.

As a part of an ongoing research to elaborate environmentally sustainable protocols, we wish to report a simple and efficient enzymatic method for chemoselective deprotection of aldehydes catalyzed under very mild reaction conditions. Additionally, we report our results on the novel approach to the synthesis of α -acetoxy amides via chemoenzyamatic tandem reaction in aqueous media.

2. Results

In the model reactions corresponding 1,1-diacetates **2a**-**j** were synthesized from their parent aldehydes **1a**-**j** using two different catalytic systems reported in literature [21]. Application of the domestically prepared catalyst, poly(4-vinylpyridine)-supported sulfuric acid and an acetic acid anhydride in DCM at ambient temperature (Method A) resulted in target products **2a**-**j** with excellent yields, up to 99% (Scheme 1). In case of the aldehydes **1h**-**j** the P4VP-H₂SO₄ catalyst turned out inactive and the used substrates **1h**-**j** were recovered. Application of a Lewis acid BF₃-OEt₂ with acetic acid anhydride under solvent free conditions at 0 °C (Method B) provided desired 1,1-diacetates **2h**-**j** with quantitative yields within few minutes (Supplementary data, Scheme

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R = Ar. 2-furfural. 2-thiophene. cinnamvl



Scheme 1. Synthesis of 1,1-diacetates 2a-j from the corresponding aldehydes 1a-j.

1).

The conventional deprotection of the 1,1-diacetates is achieved either under basic or acidic conditions by using e.g. sodium hydroxide or hydrochloric acid in organic solvents [25], the harsh reaction conditions make them inappropriate for the base- or acid-sensitive compounds like furfural or cinnamaldehyde. A variety of reagents for the removal of acylals have been developed to mend this inconvenience [26]. Recently, some action has been taken to replace organic solvents with environmentally benign water as a reaction medium [16e,16f,22a,27]. Although some of these methods have convenient protocols with good to high yields, they still suffer at least from one of the following disadvantages: long reaction time, require high temperature, lack of selectivity [28], the use of toxic metal catalysts and involve strongly acidic or oxidizing conditions. Therefore, replacement of these promoters with enzymes as a non-corrosive nature, and ecofriendly catalysts is an area of current interest and play a significant role in the development of clean technologies [29]. In 1997, Smonou et al. have shown only a rudimentary studies on enantioselective resolution of racemic 2-phenylpropionaldehyde via enzymatic hydrolysis of the corresponding acylal, with Candida rugosa lipase in aqueous media. Under reported conditions in a matter of hours optically active aldehydes were achieved with moderate enantiomeric excesses and low [30]. The obtained results can be explained by the fact that obtained chiral aldehydes are optically labile [31]. Inspired by this early reported data we have initiated detailed investigation on enzymatic acylals deprotection.

The model studies under enzymatic deprotection were performed using benzylidene 1,1-diacetatein (**2a**) in phosphate buffer (50 Mm, pH 7.0) at 20 °C for 1 h. Initially, 10%v/v of acetone was used as a cosolvent [32]. To find the most convenient biocatalyst more than 20 different commercially available hydrolases and 3 domestic prepared liver acetone powders (Supplementary information) were screened (Scheme 2). The progress of the reaction was followed by GC analysis.

After completion, the reaction mixture was extracted with ethyl acetate and the crude product was purified by column chromatography (ethyl acetate/hexanes). Among the tested biocatalysts several lead to formation of benzaldehyde (**1a**) (Table 1, entries 3–16). Results are

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Scheme 2. Deprotection of the 1,1-diacetate 2a to its parent aldehyde 1a.

Table 1

Enzyme catalyzed deprotection of the benzylidene 1,1-diacetatein (2a) to the benzaldehyde (1a).^a

Entry	Catalyst	Conv. [%] ^b
1	_	< 1
2	BSA	< 1
3	P4VP-H ₂ SO ₄	7
4	Novozym 435	3
5	Candida cylindracea lipase	57
6	Candida rugosa lipase	15
7	Wheat germ lipase	53
8	Pseudomonas cepacia lipase	5
9	Pseudomonas fluorescence lipase	5
10	Hog pancreas lipase	20
11	Pig pancreas lipase	18
12	Rhizopus oryzae lipase	23
13	Aspergillus melleus acylase I	72
14	PLAP	> 99 (91%)
15	BLAP	> 99 (95%)
16	TLAP	> 99 (89%)
17	BLAP ^c	< 1

^a Reaction conditions: **2a** (1 mmol), acetone 10%v/v, PBS (50 mM, pH 7.4), 20 °C for 1 h, 200 rpm, enzyme (10 mg).

^b Determined by GC (Agilent VF-1701 ms). Isolated yields in brackets.

^c Thermally deactivated catalyst.

summarized in Table 1.

Following examples indicated that enzymes provided from the animal tissues and used as crude liver acetone powders (LAPs) from pig (PLAP), bovine (BLAP) and turkey (TLAP) were the most efficient biocatalyst resulted in quantitative deprotection of the acylal 2a and very high isolated yield of the corresponding aldehyde 1a, up to 95% (Table 1, entries 14-16). Recently, LAPs have been recognized as an inexpensive and accessible sources of the biocatalysts for chemo- end enantioselective transformations [33]. The control experiment without the enzyme proved that the non-enzymatic reaction does not occur (Table 1, entry 1). Furthermore, the denatured BLAP (denatured by heating) or BSA (Table 1, entries 2 and 17) was used as catalyst in this reaction and the result was similar to the control (Table 1, entry 1). P4VP-H₂SO₄ used initially for an aldehyde protection turned to be inefficient in reverse reaction under studied conditions providing 1a with very low conversion (Table 1, entry 3). Based on the preliminary results, BLAP was arbitrary selected and more efforts were taken to improve the overall procedure. Detailed analysis of the reaction progression revealed that the reaction proceeded smoothly and is complete within 15 min (Fig. 2).

The influence of the type of the water-miscible and immiscible cosolvent on the lipase-catalyzed reaction was widely reported in recent years, as it is one of the most easily altered factors in enzymatic reaction [34]. Simultaneously, the influence of various co-solvents; methyl *tert*butyl ether (TBME), acetonitrile (MeCN), THF and DMSO on the reaction of **2a** with BLAP was investigated (Table 2). Deprotection of the acylal **2a** was conducted in phosphate buffer (PBS, pH 7.4) with 10 %v/ v co-solvent at 20 °C for 20 min. Although, the substrate **2a** was hardly dissolve in water, enzymatic hydrolysis does take place without cosolvent providing product **1a** with high conversion (Table 2, entry 1). Adverse impact on the enzyme activity was noticed for acetonitrile (Table 2, entry 7). The application of methyl *tert*-butyl ether improved the enzyme activity and was similar to the result obtained for water-

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Fig. 2. Time profile of conversion of **1a** ($-\blacksquare$ -), butyl acetate ($-\bullet$ -) and benzyl acetate ($-\blacktriangle$ -) in reaction catalyzed by BLAP. Reaction conditions: substrate (1 mmol), acetone 10%v/v, PBS (50 mM, pH 7.4), 20 °C, 200 rpm, BLAP (10 mg).

Table 2

Optimization of enzymatic deprotection of the benzylidene 1,1-diacetatein (2a) in PBS with various co-solvents catalyzed by BLAP.^{a.}

Entry	Co-solvent	Conv. [%] ^b
1	-	73
2	acetone 5%v/v	92
3	acetone 10%v/v	> 99
4	acetone 15%v/v	98
5	acetone 10%v/v	> 99 ^c
6	TBME	82
7	MeCN	69
8	DMSO	75
9	THF	85

 $^{\rm a}$ Reaction conditions: **2a** (1 mmol), co-solvent 10%v/v, PBS (50 mM, pH 7.4), 20 $^\circ$ C for 20 min, 200 rpm, BLAP (10 mg).

^b Determined by GC (Agilent VF-1701 ms).

^c Result after 12 min. at 30 °C.

miscible THF (Table 2, entries 6 and 9).

Only, slight increase in the conversion of **2a** comparable with this for neat buffer was observed for DMSO (Table 2, entry 8). The results indicated that the most suitable solvent for the enzymatic reaction was at first applied acetone, which offers the highest quantitative conversion to aldehyde **1a** at the concentrations of 10%v/v (Table 2, entry 3). Any variation in the concentration of this solvent resulted in the decrease of the reaction conversion (Table 2, entries 1 and 3). The elevation of the medium temperature to 30 °C manifested in higher reaction rate leading to the product **1a** with quantitative conversion within 12 min (GC and TLC analysis) (Table 2, entry 5). Finally, the enzymatic deprotection was carried on a preparative scale. Thus, **1** g (5 mmol) of the acylal **2a** was accomplished within 20 min with 92% yield of the isolated benzaldehyde **1a** (conv. > 99%).

Having established the preferred reaction conditions, the deprotection of several representative acylals **2** were also performed to demonstrate the versatility and uniqueness of the present protocol (Table 3). Aromatic acylals **2b-g** with various electron-withdrawing, and donating groups located at aromatic ring (Scheme 1) were converted to the parent aldehydes in an impressive conversion and high isolated yield of the target product **1** (Table 3, entries 1–6). (Furan-2-yl) methylene diacetate **2h** and 2-thiophenecarboxaldehyde diacetate **2i** were also efficiently converted to its corresponding aldehydes **1h** and **1i** without polymerization in the presence of BLAP (Table 3, entries 7 and 8). It is worthy of mention that the unsaturated acylals **2j** (Table 3, entry 9) were also proved amicable to this methodology.

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Table 3

Enzymatic deprotection of the various acylals $\mathbf{2}$ in PBS/acetone catalysed by BLAP.^a

Entry	Acylal 2	Conv.(%) ^b	Aldehyde 1	Yield (%) ^c
1	2b	> 99	1b	89
2	2c	> 99	1c	92
3	2d	> 99	1d	87
4	2e	> 99	1e	95
5	2f	> 99	1f	97
6	2g	> 99	1g	91
7	2h	> 99	1h	87
8	2i	> 99	1i	85
9	2j	> 99	1j	94

^a Reaction conditions: **2** (1 mmol), co-solvent 10%v/v, PBS (50 mM, pH 7.4), 20 °C for 20 min, 200 rpm, BLAP (10 mg).

^b Determined by GC (Agilent VF-1701 ms) or TLC.

^c Yield of isolated product.

Parallel, under the same reaction conditions used for deprotection of the acylals two different acetates were subjected to enzymatic hydrolysis with BLAP. As can be seen on Fig. 2 conversion of butyl acetate after 20 min did not exceed 8% and for benzyl acetate was negligible, less than 1%. Obtained results revealed that promiscuous activity of used biocatalyst in acylals transformation is noticeably higher than the expected one related with a carboxylic esters hydrolysis [35].

Encouraged by these results we were wondering if the deprotection may occur selectively in the presence of other label functional groups existing in the same molecule (Scheme 3).

A series of the various *O*-acetyl 1,1-diacetates 2 k-p were obtained with the yields up to 99% from their parent aldehydes according to the general Method B with BF₃-OEt₂ as a catalyst (Supplementary information). Although the salicylaldehyde is a simple molecule, its *O*acetylated homologous are important and versatile precursors for a variety of useful compounds, particularly for the complex heterocyclic systems which exhibit desirable biological activity [36]. Due to this fact several acylals provided from the 2-acetoxybenzaldehyde 2k and its three analogues 2l-n were tested under developed enzymatic conditions (Table 4, entries 1–4).

The obtained results reveal that enzyme catalyzed deprotection generally results in high yields with acylals **2k-1** and **2n** including those carrying hindered *O*-acetylated groups (Table 4, entries 1, 2 and 4). It is noteworthy that deprotection of an aryl aldehyde diacetates occurs selectively without cleavage of the phenolic acetate function (Table 4, entries 1–4). The formation of the products **3** was not observed (Scheme 3). With the advantages of the mild reaction conditions and tremendous



Scheme 3. Chemoselective deprotection of the O-acetyl 1,1-diacetates 2a.

Table 4

Enzymatic deprotection of varie	ous acylals 2 in PBS/acetone	catalysed by BLAP. ^a
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Entry	Acylal 2	Conv.(%) ^b	Aldehyde 1	Yield (%) ^d
1	2k	79 (95) ^c	1k	84
2	21	81 (> 99) ^c	11	85
3	2 m	92 (> 99) ^c	1m	91
4	2 n	75 (93) ^c	1 n	81
5	20	> 99	1o	85
6	2p	> 99	1p	83

^a Reaction conditions: **2** (1 mmol), co-solvent 10%v/v, PBS (50 mM, pH 7.4), 20 °C for 20 min, 200 rpm, BLAP (10 mg).

^b Determined by GC (Agilent VF-1701 ms) or TLC.

Result after 30 min at 20 $^\circ\text{C}.$

¹ Yield of isolated product.

enzyme chemoselectivity, the 1,1-diacetates obtained from the aliphatic or heterocyclic aldehydes possessing hydrolytically labile functional groups **2o** and **2p** were converted to their parent aldehydes **1o** and **1p** without affecting those sensitive moieties in short time with full conversion and high yields (Table 4, entries 5 and 6). 4-Oxobutyl benzoate **1o** and 5-acetoxymethyl-2-furaldehyde **1p** are the progenitors for the furano-epothilone D and halichondrins, which exhibit anti-cancer activity [37] as well as a ranitidine also known as Zantac, a drug commonly used in treatment of peptic ulcer disease, gastroesophageal reflux disease, and the Zollinger–Ellison syndrome [38].

In addition, the 1,1-diacetates were additionally recognized as an important starting materials for Diels-Alder reactions [39], moreover they can be converted into the other useful functional groups by the reaction with appropriate nucleophiles [40] or used as the carbonyl surrogates for asymmetric synthesis [41]. Recently, we have shown that vinyl acetate provides components for the promiscuous enzyme-promoted Passerini reaction (P-MCR) and the Knoevenagel condensation [42]. As a consequence we extend our studies to verify if the acylals **2** can be used as the substrates for P-MCR providing both carbonyl components, aldehyde and carboxylic acid (Scheme 4). It is well recognized that multicomponent reaction can be carried on under aqueous conditions [43].

According to these literature data we set up an experiment with the benzylidene 1,1-diacetatein (2a) and 1.0 equiv. of an 1-(iso-cyanomethyl)-4-methoxybenzene (4) in neat buffer what resulted after 24 h in the α -acetoxy amides 5 with 32% yield. The acetone was excluded from the reaction medium as a co-solvent, due to its competitive character towards the aldehyde in P-MCR [44]. The moderate yield of the conducted reaction can be justified by the fact that isocyanides have low stability and undergo spontaneous hydrolysis in an aqueous



Scheme 4. Chemoenzymatic tandem synthesis of the α -acetoxy amides 5 from 1,1-diacetate 2a.

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solution [45,46]. Nevertheless, the target α -acetoxy amide **5** was provided with substantially higher yield than analogously obtained under similar reaction conditions in classical three component P-MCR (32% *vs* 19%) [43]. It is important to notice that again the promiscuous activity of enzymes in acylals **2** deprotection is predominant and the product **6** which arises from the enzymatic hydrolysis [47] of α -acetoxy amide **5** was not observed under studied reaction conditions (Scheme 4).

3. Conclusions

In conclusion, we have developed a practical and efficient protocol for the selective enzyme catalyzed hydrolysis of the acylals in the presence of the ester groups leading to the parent aldehydes in an aqueous media. The hydrolysis reaction catalyzed by hydrolases occurs quantitatively in neutral pH at room temperature within minutes. This interesting and predominantly promiscuous role of an enzyme activity in the acylals hydrolysis dominates the native activity of BLAP hydrolase. This is the first example showing the dominant role of promiscuous enzymes activity over the native one. After a careful optimization of the reaction condition, target products were obtained with the yields up to 97% and with excellent chemoselectivity. It is important to note that all described enzymatic transformations were catalyzed by the catalyst prepared from animal tissues, easy accessible from the local butcher store. The advantage of the present protocol is the simplicity in operation, low cost of used catalysts, high yields and chemoselectivity in respect to the functional groups. Moreover, developed protocol is compatible with the sensitive functionalities such as OMe, Bz, OAc, and double bonds which upon deprotection of the acylals remain untouched. Simple experimental procedure is important with regard to the economic and sustainable consideration and allows us to believe that elaborated method may represent a valuable alternative to the existing reagents reported in the literature. In addition this protocol can be applied for compounds possessing synthetically relevant protecting groups like carboxybenzyl group (Cbz) or tert-butoxycarbonyl (Boc) which remain unaffected under enzymatic transformation [29a,29c,48].

In order to expand this protocol toward synthesis of peptidomimetics, additional experiments were performed. Developed protocol was extended by the multicomponent reaction providing target α acetoxy amides under one-pot one step procedure. These experiments revealed that acylals can be used as the surrogates of the carbonyl components and carboxylic acids for the multicomponent reactions leading to the pharmaceutically relevant peptidomimetic molecules. This cascade process is characterized by very high atom economy and can be enlarged for the synthesis of biologically active compounds. Conducted experiments showed the advantage of an enzyme catalysed reaction conducted in water over classical chemical methods fulfilling the requirements of green chemistry.

4. Materials and methods

4.1. General methods

All the chemicals were obtained from commercial sources and the solvents were of an analytical grade. ¹H- and ¹³C NMR spectra were recorded in CDCl₃ solution. Chemical shifts are expressed in parts per million using TMS as an internal standard. The conversion of amine was measured by gas chromatography using PerkinElmer Gas Chromatograph Clarus 680that was equipped with a coating DB-1701 ms 0.25 column (30 m × 0.25 mm). TLC analyses were done on Kieselgel 60 F254 aluminum sheets. Lipases from hog pancreas, *Pseudomonas cepacia, Pseudomonas fluorescens, Candida rugosa, Candida cylindracea*, wheat germ, *Rhizopus oryzae*, and acylase I from *Aspergillus melleus* were purchased from Sigma-Aldrich. Immobilized lipase from Candida antarctica B (Novozyme 435) was purchased from Sigma-

Aldrich. Column chromatographies were performed on Merck silica gel 60/230–400 mesh. Enzymatic reactions were performed in a vortex (Heidolph Promax 1020) equipped with incubator (Heidolph Inkubator 1000). To prove the ability of the established protocol each reaction was repeated at least three times.

4.2. Preparation of crude liver powders (LAPs)

Freshly purchased liver (200 g) is homogenized twice in a cold (-20 °C) acetone using the kitchen stand blender (24 000 rpm) equipped with a glass jar. The mass obtained after filtration was further homogenized twice in a cold (-20 °C) DCM and filtrated. The residue obtained was dried under the vacuum at room temperature for 2 h. Light brown powder (50 g) was stored in a refrigerator before used.

4.3. Preparation of acylals 2a-g. General Method A

P4VP-H₂SO₄ was prepared according to the literature procedure [48,49]. Catalyst (20 mg) was added to a stirred solution of an aldehyde (1 mmol) and acetic anhydride (3 mmol) in dry DCM at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the mixture was diluted with dichloromethane and filtered to remove the catalyst. The organic solution was washed with an aqueous solution of NaHCO₃ and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure, and the crude product was purified by the crystallization from ethyl ether/hexane. Benzylidene 1,1-diacetatein (**2a**): white crystals, 99% yield (206 mg, 0.99 mmol); ¹H NMR (400 MHz, CDCl₃) δ 7.68 (s, 1H), 7.59–7.47 (m, 2H), 7.41 (dd, *J* = 4.0, 2.6 Hz, 3H), 2.12 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 168.75, 135.51, 129.74, 128.59, 126.67, 89.73, 20.84. The ¹H and ¹³C NMR data were in accordance with those reported in the literature [50].

4.4. Preparation of acylals 2 h-p. General Method B

Acetic acid anhydride (2 mmol) and BF3-OEt2 (2 drops) were cooled down to 0 °C. Aldehyde (1 mmol) was added slowly with stirring, and the mixture was stirred at room temperature for 30 min. The product mixture was poured into a 10% aqueous solution of NaOAc (20 mL) and stirred rapidly for 10 min. The product was extracted with ethyl ether $(3 \times 15 \text{ mL})$, the extracts were combined, and washed with aqueous NaHCO₃ followed by water. After drying over anhydrous sodium sulfate the crude product was concentrated under vacuum and isolated by recrystallization from ethyl ether/hexane or silica gel chromatography (ethyl acetate/hexane). (Furan-2-yl)methylene diacetate (2 h): white crystals, 98% yield (194 mg, 0.98 mmol); 1 H NMR (400 MHz, CDCl₃) δ 7.70 (s, 1H), 7.44 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.52 (dd, *J* = 3.3, 0.5 Hz, 1H), 6.38 (dd, J = 3.3, 1.8 Hz, 1H), 2.12 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) & 168.36, 147.93, 143.62, 110.35, 109.67, 83.49, 20.64. ¹H and ¹³C NMR data were in accordance with those reported in the literature [50].

4.5. General deprotection protocol

A solution of diacetate **2** (1 mmol) and BLAP (10 mg) in phosphate buffer (50 mM, pH 7.4) was stirred in a vortex (200 rpm) at 20 °C for for an appropriate time as required to complete the reaction. After complete conversion, as indicated by GC or TLC, the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum to give the corresponding aldehyde **1**.

4.6. General GC methods for conversion determination

GC program parameters; injector 250 °C; flow 1 mL/min;

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temperature program 70 °C; 140 °C/rate 10 °C per min./hold 3 min; 250 °C/rate 10 °C per min./hold 3 min.

4.7. Preparation of α -acetoxy amide 5 using benzylidene 1,1-diacetatein (2a)

Isocyanide 4 (147 mg, 1 mmol) was added to the suspension of acylal 2a (208 mg, 1 mmol) in phosphate buffer (50 mM, pH 7.4) at room temperature. The BLAP (bovine liver acetone powder) catalyst (10 mg) was added. The reaction mixture was stirred at ambient temperature for 24 h. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the corresponding semi-solid product 5 with 32% yield (100 mg, 0.32 mmol). ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.30 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.37 (s, 1H), 6.09 (s, 1H), 4.39 (qd, J = 14.6, 5.7 Hz, 2H), 3.79 (s, 3H), 2.14 (s, 3H); 13 C NMR (100 MHz, CDCl₃) δ 169.17, 168.14, 159.16, 135.59, 129.80, 129.06, 129.00, 128.76, 127.39, 114.16, 75.58, 55.29, 42.88, 20.99. The ¹H and ¹³C NMR data were in accordance with those reported in the literature [43].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https:// doi.org/10.1016/j.bioorg.2019.02.050.

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