TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2019) 43: 435 – 451
© TÜBİTAK
doi:10.3906/kim-1807-58

Acid-activated clay as heterogeneous and reusable catalyst for the synthesis of bioactive cyclic ketal derivatives

Wided HAGUI[1,2,*], **Rym ESSID**[3], **Sondes AMRI**[1,2], **Nadia FERIS**[3], **Mohamed KHABBOUCHI**[1,2], **Olfa TABBENE**[3], **Ferid LIMAM**[3], **Ezzeddine SRASRA**[1], **Néji BESBES**[1]

[1]Laboratory of Composite Materials and Clay Minerals, Group of Green and Applied Organic Chemistry, National Center for Research in Materials Science, Technopole of Borj Cedria, Soliman, Tunisia
[2]Faculty of Sciences of Tunis, Tunis El-Manar University, El Manar Tunis, Tunisia
[3]Laboratory of Bioactive Substances, Biotechnology Center of Borj Cedria, Technopole of Borj Cedria, Soliman, Tunisia

Received: 13.07.2018 • **Accepted/Published Online:** 06.12.2018 • **Final Version:** 03.04.2019

Abstract: A new heterogeneous acid catalyst based on a natural resource, Tunisian clay (Clay-H0.5), has been prepared and characterized by FT-IR, FE-SEM, and powder X-ray diffraction (XRD), as well as chemical composition, cation exchange capacity, specific surface area, and pore volume. Acid treatment for 0.5 h enlarged the surface area from 78.24 to 186.10 m^2/g and pore volume (PV) from 0.186 to 0.281 cm^3/g. The catalytic activity of this material was investigated in ketalization reaction under mild solvent-free conditions. This achieved up to 92% isolated yield for only 10 wt.% of the catalyst. This environmentally friendly method has advantages such as simple work-up procedure, avoidance of organic solvents, and good performance in ketalization reactions. Importantly, the Clay-H0.5 catalyst showed good recyclability where insignificant activity loss was exhibited even after six runs. Synthesized cyclic ketals were tested for their possible antileishmanial and antibacterial activities as well as antifungal activity. Biological screening showed that compound **11** had important antileishmanial activity against both *L. major* and *L. infantum*, while compound **14** also had significant antibacterial activity against four gram-positive and two gram-negative bacteria, and antifungal activity against *Candida albicans*, with minimal inhibitory concentration values ranging from 15.62 µg/mL to 125 µg/mL.

Key words: Acid-activated clay, ketones, cyclic ketal, antibacterial activity, antileishmanial activity

1. Introduction

Cyclic ketals are of particular importance in organic synthesis as well as strongly implicated in several interesting fields including organic material sciences.[1−8] They are embedded in a plethora of molecules displaying very important pharmaceutical properties.[9,10] As an example, ketoconazole is a synthetic antifungal drug used to prevent and to treat fungal infections, especially in immunocompromised patients such as those with AIDS.[11−13] Dioxolane guanosine has exhibited potential anti-HIV activity[14,15] and O-ddc has proved to be an antitumor, anti-HIV, and anti-HBV agent[16,17] (Figure 1). Methods are available for the conversion of carbonyl groups in aldehydes and ketones to their corresponding cyclic ketals.[18] Yu and Zhang reported the synthesis of α-chloroketone acetals using iodobenzene dichloride in the presence of 4-Å molecular sieves.[19] Cerium(III) trifluoromethane sulfonate is also a suitable catalyst to convert hydroxyacetophenones into the corresponding

*Correspondence: wided-hagui@hotmail.fr

ethylene acetals in the presence of ethane-1,2-diol and tri-isopropyl orthoformate as a water scavenger.[20] The synthesis of cyclic acetals can be achieved efficiently via acetalization of an aldehyde under mild reaction conditions in the presence of trialkyl orthoformate and a catalytic amount of tetrabutylammonium tribromide.[21] Although these methods have been effective and have shown satisfactory results, they suffer from several drawbacks, such as corrosion, tedious work-up, environmental pollution, and nonrecoverability of catalysts.

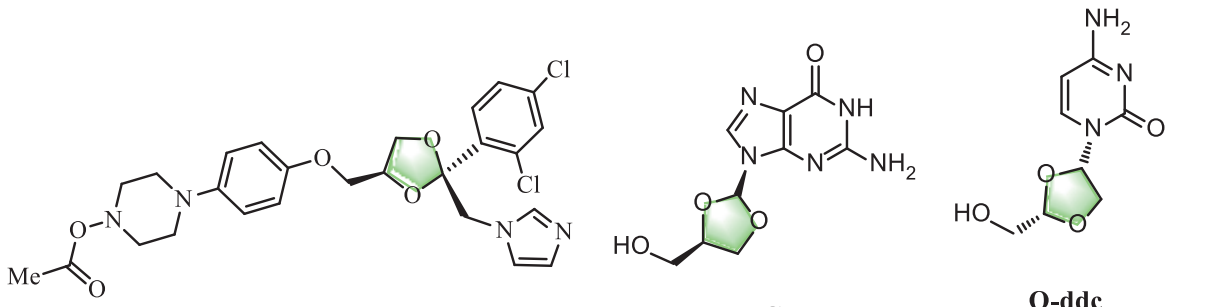


Figure 1. Relevant compounds containing 1,3-dioxolane motifs.

On the other hand, heterogeneous catalysts have emerged as a suitable alternative to green synthesis, as they are easily separated from products by simple filtration and they can be recovered and reused. Moreover, heterogeneous catalysts often avoid the contamination of the final product, which is essential for further implementation in the pharmaceutical market. Various heterogeneous catalysts have been used in acetalization reactions.[22–24] As an example, ester sulfate functionalized as ionic liquid is a highly effective catalyst for the acetalization of aldehydes and ketones with glycerol.[25] Ion exchange resins such as niobium phosphate have been evaluated in the acetalization of hexanal under mild reaction conditions.[26] The synthesis of dioxolanes catalyzed by tungstosilicic acid supported on activate carbon has also been reported.[27] Furthermore, mesoporous aluminosilicate can effectively catalyze the reaction between carbonyl compounds and methanol.[28,29]

The discovery of natural materials with high catalytic performance represents an alternative to pollutant and corrosive homogeneous catalysts.[30–33] Natural aluminosilicates such as zeolites and more particularly clays are economical, recyclable, nontoxic, noncorrosive, easy to handle, and effective catalysts in several chemical transformations.[34–37] The use of these materials as heterogeneous catalysts is a powerful and interesting method for the development of green protocols by minimizing the dangerous waste related to organic syntheses. Natural or modified clays are effectively used in a wide range of chemical reactions such as reduction of methylene blue,[38] esterification reactions,[39] hydroxylations of arylboronic acids,[40] cyclization reactions,[41] hydration of nitriles to amides,[42] allylsilylations of aromatic and aliphatic alkenes,[43] and synthesis of 1,3-oxazines.[44] In addition, these reactions are often carried out under mild conditions, providing high yields with good selectivities. In this context and based on our previous results,[45–47] we wish to report a safe, simple, and easy to handle protocol for the transformation of various ketones into their corresponding cyclic ketals such as 1,3-dioxolanes and 1,3-dioxanes under solvent-free conditions and without catalyst contamination using acid activated clay (Clay-H0.5) as a green and recoverable catalyst. In addition, selected 1,3-dioxolanes have been evaluated for possible biological activity as antileishmanial, antibacterial, and antifungal agents. We have also tested their cytotoxic activities.

2. Results and discussion

2.1. Catalyst characterization

Clay-H0.5 was prepared from crude clay (CC) collected from Djebel Haidoudi in southeastern Tunisia. For the introduction of acidic sites, the CC was treated with an HCl aqueous solution for 0.5 h. The X-ray diffraction (XRD) pattern of the original clay is given in Figure 2. This diffraction shows that the CC contains sharp and strong reflections, d_{001} = 14.02 Å ($2\theta = 7°$) and d_{002} = 4.25 Å ($2\theta = 24.89°$), which are typical characteristic peaks of smectite. The presence of quartz as a nonclay mineral is detected by the well-defined reflection at the 2θ value of 26.52° and it is in relation with the high contents of silica (Table 1). The low peak at the 2θ value of 12.35° is characteristic of the kaolinite phase in trace amounts, which is also confirmed by IR bands at 3693 cm^{-1} and 692 cm^{-1} (Figure 3). In addition, the presence of reflections at d_{060} = 1.49 Å ($2\theta = 62°$) and the two IR bands located at 3623 cm^{-1} and 924 cm^{-1} indicate that the smectite is dioctahedral. The XRD motifs obtained from Clay-H0.5 do not show a significant change.

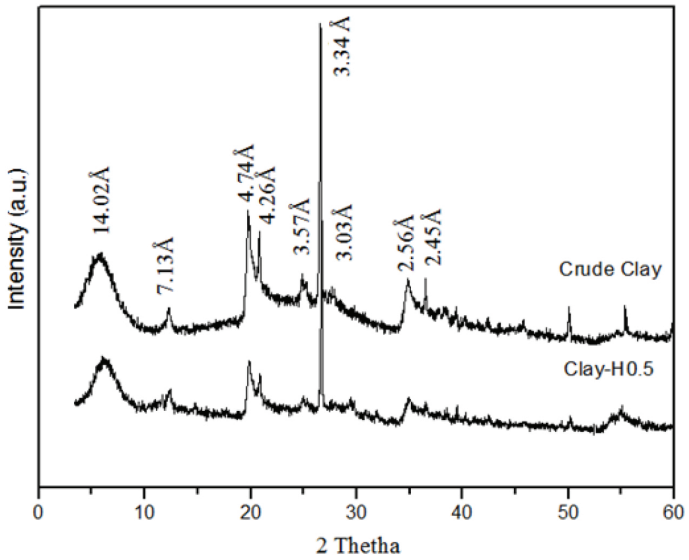


Figure 2. XRD of CC and Clay-H0.5.

Table 1. Textural properties and chemical composition of CC and Clay-H0.5.

Clays	Partial elementary analysis					CEC	S_{BET}	PV
	SiO_2 (%)	Al_2O_3 (%)	Fe_2O_3 (%)	MgO (%)	CaO (%)	(mEq/100 g)	(m^2/g)	(cm^3/g)
CC	49.06	16.05	9.06	3.02	0.55	75	78.24	0.186
C-$H_{0.5}$	58.12	14.11	6.29	2.14	-	35	186.1	0.281

CEC: Cation exchange capacity; BET: specific surface; PV: porous volume.

On the other hand, the IR spectrum of the parent smectite shows the typical bands of this material (Figure 3). A band assigned to the deformation and vibration valence of the O-H bond of water is found at 3447 cm^{-1}. The bands at 1041 cm^{-1} and 1100 cm^{-1} correspond to the Si-O groups. The band at 795 cm^{-1} indicates the presence of the quartz. The bands at 535 cm^{-1} and at 467 cm^{-1} are attributed to Si-O-Al and Si-O-Mg bending, respectively. After acid treatment, the IR spectrum of Clay-H0.5 shows a reduction in the

characteristic bands of Si-O-Al and Si-O-Mg. This decrease is explained by a partial dissolution of Al^{3+}, Fe^{2+}, and Mg^{2+} cations (≈15% of the Al^{3+} cations removed), which provoked a relative increase in the percentage of silica in the Clay-H0.5 sample (Table 1).

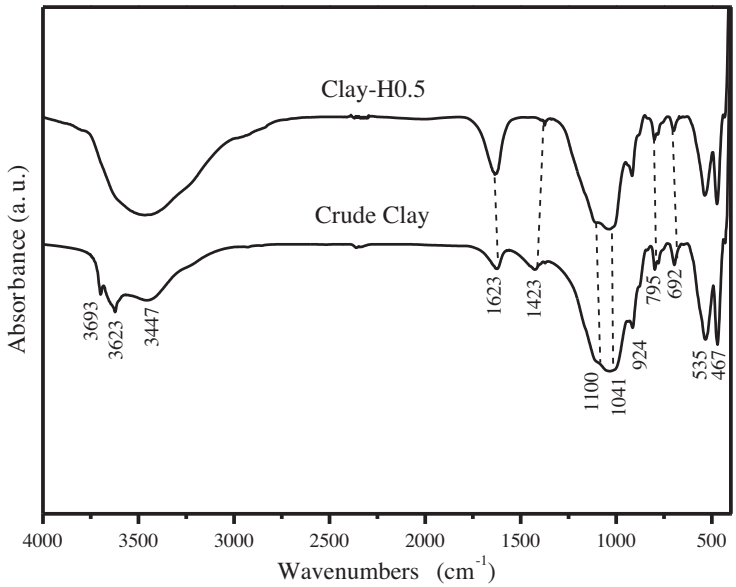


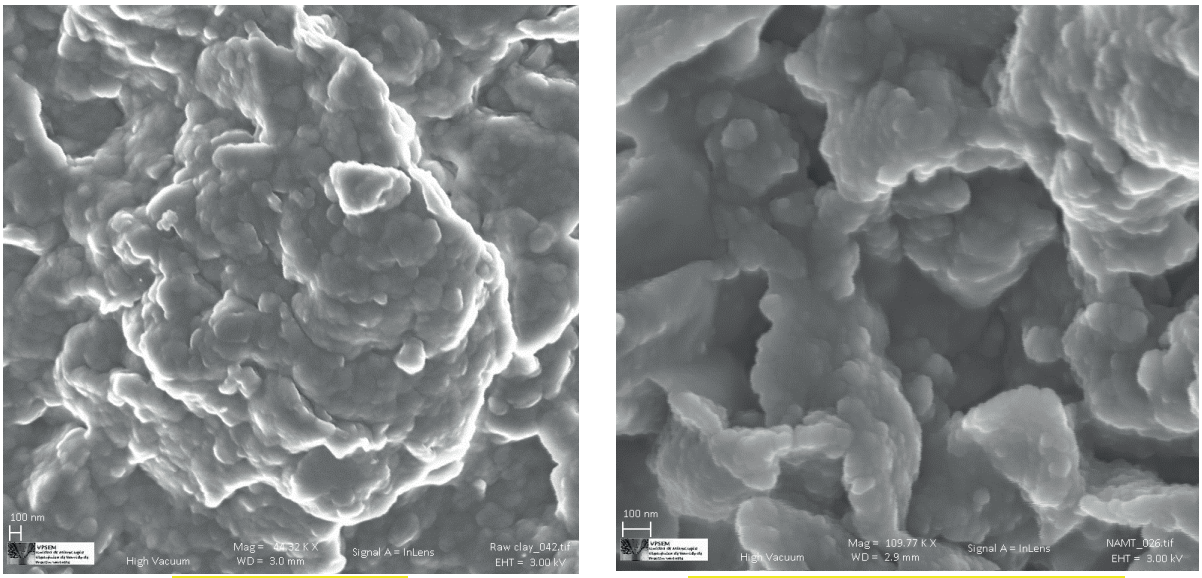
Figure 3. FT-IR of CC and Clay-H0.5.

The specific surface area (S_{BET}) and the cation exchange capacity (CEC) of Clay-H0.5 are also directly dependent on the dissolution of cations (Table 1). The CEC of the Clay-H0.5 sample decreases compared to the parent clay. The low value of CEC suggests the exchange of the residual interlayer cations. Furthermore, S_{BET} increases significantly after acid treatment from 78.24 to 186.10 m^2/g. This increase might be due to the decrease in the crystallite size and improvement in the microporous nature, increasing the nitrogen accessibility. The CC has low accessibility to N_2, which is due to the low size of the pores caused by the blocking of the interlayer spacing. The pore volume (PV) also increases from 0.186 to 0.281 cm^3/g. This increase of PV is essentially related to the creation of micropores, which is confirmed by FE-SEM micrographs. Figure 4 shows the scanning electron micrographs (SEMs) of CC (Figure 4a) and Clay-H0.5 (Figure 4b). The SEM micrographs clearly exhibit very different surface morphologies for CC and Clay-H0.5, especially the emergence of porosity.

2.2. Synthesis of cyclic ketals derivatives

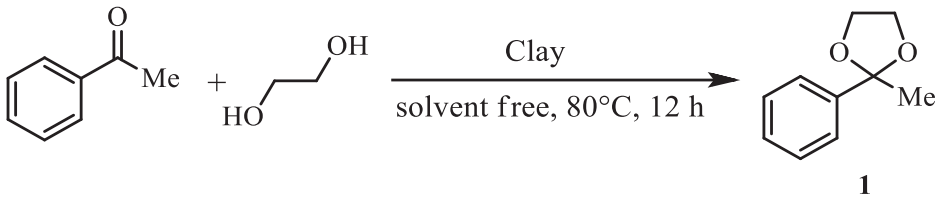
We have investigated the catalytic activities of CC and Clay-H0.5 in the acetalization of acetophenone under mild conditions (Scheme 1). The catalyst CC led to dioxolane **1** in only 29% yield. In contrast, Clay-H0.5 produced dioxolane **1** in higher yield (66%). This result suggests that Clay-H0.5 displays higher catalytic performance than CC due to the generation of a higher number of acidic sites and enhanced catalytic properties including surface area and PV.

Next we investigated the influence of some parameters (i.e. reaction temperature and reaction time) in acetalization of acetophenone with ethane-1,2-diol using Clay-H0.5 under solvent-free conditions (Table 2). First, a small conversion into the desired product was obtained at low temperatures in the presence of 10 wt.% Clay-H0.5 (Table 2, entries 1 and 2). It has been reported in the literature that aromatic ketones react only at high



(a) Crude clay CC **(b)** Acid activated clay Clay-H0.5

Figure 4. FE-SEM image of CC and Clay-H0.5



1

CC	29%
Clay-H0.5	66%

Scheme 1. Acetalization of acetophenone using CC and Clay-H0.5.

temperatures. Indeed, different solid acid catalysts, such as rare earth exchanged zeolites, K-10 montmorillonite clay, and cerium exchanged montmorillonite clay, have been used in the reaction between acetophenone and methanol.[29] These different catalysts have also exhibited low reactivity at ambient temperature for 10 h. In contrast, at 80 °C and even at 110 °C, higher yields of 66% and 70% were observed (Scheme 1 and Table 2, entry 3). However, a higher temperature of 140 °C resulted in a decrease in the yield of dioxolane **1** (Table 1, entry 4). A reduced reaction time of 6 h (or 3 h) provided similar yields in favor of the desired product **1** (Table 2, entries 5 and 6), but a reaction time of 1 h gave an incomplete reaction (Table 2, entry 7). In the presence of a low catalytic amount of catalyst, the formation of dioxolane **1** was obtained in 53% yield (Table 2, entry 8). Finally, due to ecofriendly concerns, we chose to perform the ketalization of ketones at 80 °C for 3 h in the presence of 10 wt.% Clay-H0.5. It should be noted that in all cases only the ketalization product was obtained.

We further investigated the recyclability and the durability performance of Clay-H0.5 in ketalization of acetophenone with ethane-1,2-diol under the optimized conditions. The immobilized catalyst could be recycled at least up to six times and without significant loss of its catalytic activity (Figure 5), which indicates that the

Table 2. Optimization of the reaction of acetophenone with ethane-1,2-diol under solvent-free conditions.

Entry	Catalyst amount (wt.%)	T (°C)	t (h)	Yield of **1** (%)
1	10	r.t	12	22
2	10	40	12	38
3	10	110	12	70
4	10	140	12	45
5	10	80	6	71
6	10	80	3	69
7	10	80	1	40
8	5	80	3	53

Clay-H0.5 has great potential to be a good catalyst for efficient industrial utilization. However, the recovered catalyst should be washed with water, THF, or CH_2Cl_2 and then dried at 80 °C for 6 h to facilitate its reuse.

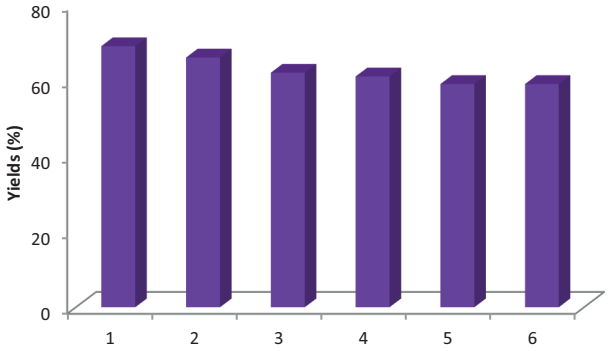
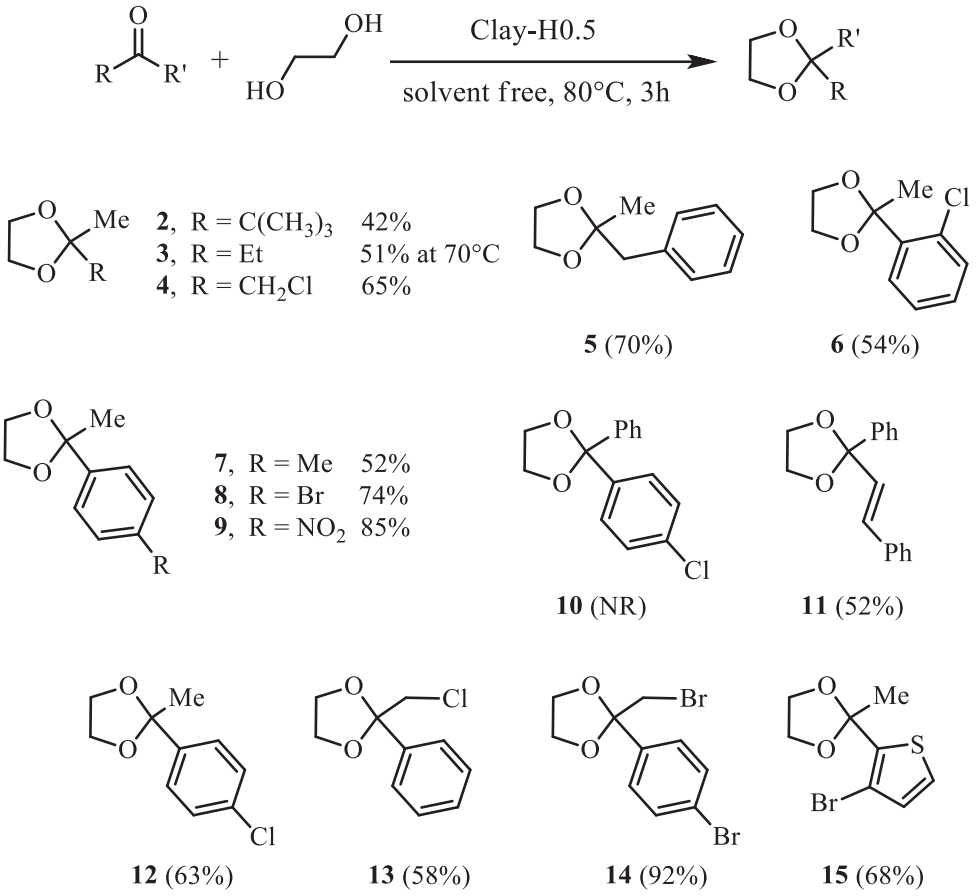


Figure 5. Recyclability of Clay-H0.5.

Having found the best reaction conditions, the scope of the reaction was examined using a variety of ketones and diols. Aliphatic ketones such as pinacolone, butanone, and chloroacetone were reacted with ethane-1,2-diol in the presence of Clay-$H_{0.5}$ (Scheme 2). Pinacolone showed a low reactivity in ketalization, affording dioxolane **2** in only 42% yield, which could be due to steric factors. The ketalization reaction was performed at 70 °C to afford dioxolane **3** in slightly better yield. 2-(Chloromethyl)-2-methyl-1,3-dioxolane **4** was isolated in 65% yield. Dioxolane **5** was prepared from phenylacetone and it was isolated in 70% yield. The reaction is slightly sensitive to the steric factor since dioxolane **6** was obtained in only 54% yield, using 2-chloroacetophenone as the starting product. Benzophenone, bearing an electron-donating group at *para*-positions such as Me, was smoothly reacted to give **7** in 52% yield, whereas benzophenones substituted by electron-withdrawing groups displayed higher reactivity to afford 1,3-dioxolanes **8** and **9** in 74% and 85% yields, respectively. 4-Chlorobenzophenone was found to be unreactive under these conditions, probably due to both steric and electronic factors. The less congested chalcone reacted with ethane-1,2-diol to give **11** in 52% yield. 4'-Chloroacetophenone was converted into the corresponding cyclic ketal **12** in 63% yield.

Furthermore, 2-halo-1-arylethan-1-ones were found to be suitable starting products, as cyclic ketals **13** and **14** were isolated in 58% and 92% yields, respectively. The new 1,3-dioxolane **15** was also obtained in 68% yield. An efficient process that could directly prepare α-haloacetal of ketones from various ketones with

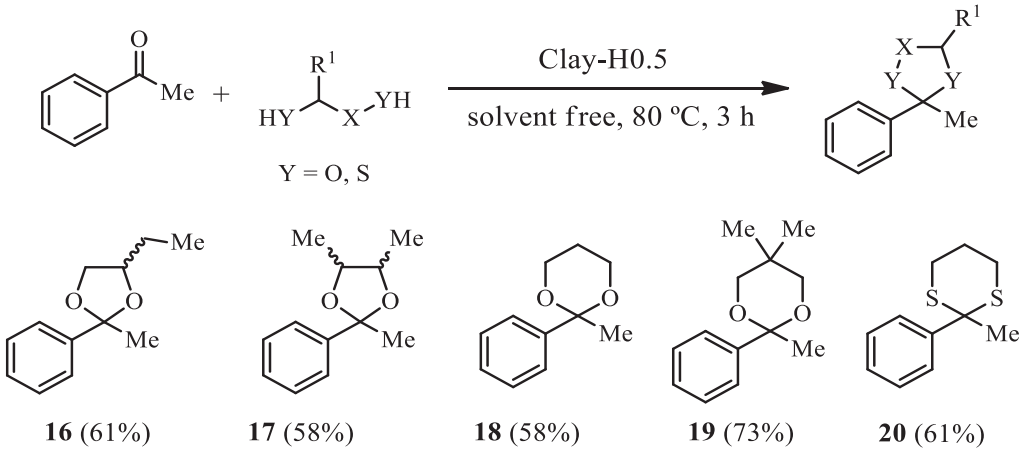


Scheme 2. Scope of ketones using Clay-H0.5.

N-halosuccinimide and ethylene glycol at room temperature for 24 h has been reported.[48] Herein, we have demonstrated that natural and recyclable aluminosilicate can also promote the ketalization reaction to offer respective α-haloacetal in high yields in reaction times as short as 3 h at 80 °C.

We next evaluated the reactivity of other diol derivatives in the acetalization of acetophenone (Scheme 3). The reaction with butane-1,2-diol and butane-2,3-diol allowed the formation of 1,3-dioxolanes **16** and **17** in 61% and 58% yields, respectively. It has been reported in the literature that ammonium triflate-functionalized silica is an efficient and recyclable catalyst for the synthesis of 1,3-dioxanes in the presence of triethyl orthoformate and propane-1,3-diol under mild conditions.[49] However, the acetophenone survived intact under these reaction conditions even after a long reaction time (48 h). In contrast, under our optimized condition, Clay-H0.5 efficiently catalyzed the acetalization of acetophenone with propane-1,3-diol, which gave the corresponding 1,3-dioxane **18** in 58% isolated yield.

Furthermore, a higher yield was observed when 2,2-dimethylpropane-1,3-diol was employed, as the corresponding cyclic ketal **19** was obtained in 73% yield. Finally, Clay-H0.5 was also operative with propane-1,3-dithiol, providing the formation of dithioacetal **20** in 61% yield. The Gold(I)/$AgBF_4$ system has been proven as an efficient catalyst in the transformation of alkynes into cyclic acetals and thioacetals, using toluene as solvent.[50] Moreover, efficient methods were also developed for the preparation of cyclic ketals and dithioacetals using transitional metal complexes such as InF_3 and $InCl_2$ as mild Lewis acid catalysts in aqueous organic



Scheme 3. Scope of alcohols using Clay-H0.5.

solvents (CH_2Cl_2, MeOH, and MeCN).[51–53] Despite the great advances in this realm, these methodologies are susceptible to expensive metal catalysts, high catalyst loading, uncommon reagents, and use of organic solvents. In contrast, Clay-H0.5 has both Brönsted and Lewis active sites, affording a synergistic catalyst in acetalization and thioacetalization without an additive under solvent-free conditions.

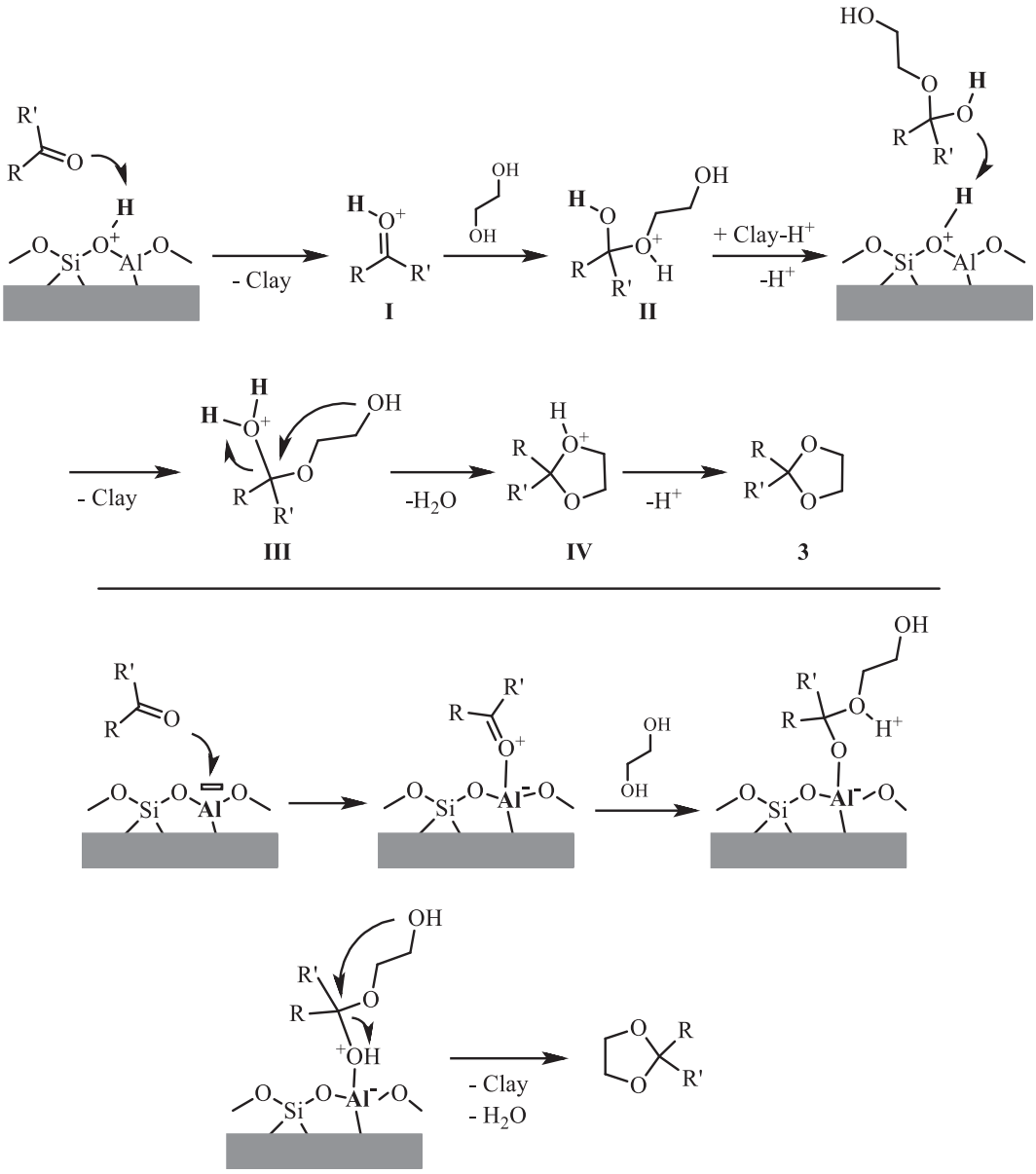
Clay-H0.5 has particularly interesting Brönsted acid sites where chemical reactions occur. The mechanism begins with a protonation of the ketone, as shown in Scheme 4. Then a nucleophilic addition by diol takes place to form oxonium ion **II**. After deprotonation, the hemiacetal intermediate also protonates to produce species **III**, which in turn reacts intramolecularly to give the desired dioxolane.[54–58] In addition, the clay exhibits weak Lewis acid sites on its surface, due to the presence of electron-deficient orbitals of the silicon and aluminum atoms.[59,60] Therefore, silicon and aluminum atoms could also enable the acetalization reaction.[45–47,61] As an example, aluminate intermediates are the key intermediates for the reaction (Scheme 4, bottom).

2.3. Biological activity

After having developed the synthesis of cyclic ketal derivatives over Clay-H0.5, we investigated the potential biological activities of 1,3-dioxolanes **7**–**9** and **11**–**15**. These compounds were tested for their antileishmanial activities against *L. major* and *L. infantum* (Table 3). Antileishmanial screening results indicate that *L. infantum* promastigotes are more sensitive than *L. major* towards cyclic ketals. Dioxolane **11** exhibited the best antileishmanial activity with an IC_{50} value of 24.16 ± 0.21 µg/mL and 18.25 ± 0.34 µg/mL for *L. major* and *L. infantum*, respectively (Table 3). Although dioxolane **14** showed significant antileishmanial activity against *L. infantum* with an IC_{50} value of 33.23 ± 0.11 µg/mL, it displayed moderate activity against *L. major* with a value of 65.67 ± 0.23 µg/mL. On the other hand, the 1,3-dioxolane derivatives **7**, **9**, **13**, and **15** displayed low antileishmanial activities against both *L. major* and *L. infantum* (100 µg/mL $<IC_{50}$ <500 µg/mL). In addition, compounds **8** and **12** were biologically inactive against *L. major* and *L. infantum*.

Although these 1,3-dioxolanes have shown satisfactory antileishmanial activities, they exhibited moderate cytotoxicities (SI <10). However, their external use as drugs against cutaneous leishmaniasis may avoid this toxicity. Moreover, further synergistic combinations with conventional drugs were needed to reduce toxicity effects and enhance the selective activity.

The antibacterial activities of cyclic ketals **7**–**9** and **11**–**15** have been also evaluated against gram-positive



Scheme 4. Mechanism of acetalization over Brönsted and Lewis acid sites of clay.

bacteria (*S. aureus* ATCC 29213, *S. aureus* clinical isolate (MRSA), *L. monocytogenes* ATCC 19115, and *E. faecalis* ATCC 29212) and gram-negative bacteria (*E. coli* ATCC 25922, *S. enteritidis* DMB560, and *P. aeruginosa* ATCC 27853) using the broth microdilution method for minimal inhibitory concentration (MIC) determination. The antifungal activity was tested against a yeast, *Candida albicans* ATCC 10231 (Table 4).

As shown in Table 4, only compound **14** showed a broad spectrum of activity against gram-positive and gram-negative bacteria and against *Candida albicans* with MIC values that ranged from 15.62 µg/mL to 125 µg/mL. This compound was the most effective synthetic compound having the lowest MIC value (15.62 µg/mL) against the methicillin-resistant *Staphylococcus aureus* clinical isolate (MRSA), *Enterococcus faecalis* ATCC 29212, and *Candida albicans* ATCC 10231. No antibacterial activities were recorded for the other synthesized

Table 3. Antileishmanial (IC_{50} ± SD) and cytotoxic activities (LC_{50} ± SD) of cyclic ketals.

Cyclic ketals	IC_{50} ± SD (µg/mL)		LC_{50} ± SD (µg/mL)	SI	
	L. major	*L. infantum*	Raw 264.7	*L. major*	*L. infantum*
7	326.9 ± 0.25	199.5 ± 0.34	>500	-	-
8	>500	>500	-	-	-
9	272.5 ± 0.51	170.01 ± 0.11	320.47 ± 0.78	1.17	1.88
11	24.16 ± 0.21	18.25 ± 0.34	31 ± 0.14	1.29	1.69
12	>500	>500	-	-	-
13	295 ± 0.46	169.5 ± 0.52	340.17 ± 0.27	1.15	2.00
14	65.67 ± 0.23	33.23 ± 0.11	68.12 ± 0.23	1.03	2.04
15	373.4 ± 0.68	245.5 ± 0.13	>500	-	-
Amphotericin B	0.48 ± 0.24	1.06 ± 0.08	10.76 ± 0.58	22.41	10.15

IC50: Inhibition concentration 50% (µg/mL). LC50: lethal concentration 50% (µg/mL). SI: Selectivity index. SD: Standard deviation.

Table 4. Antibacterial activities of synthetic compounds.

Microorganisms	MIC (µg/mL)	
	11	**14**
Gram-positive bacteria		
Staphylococcus aureus ATCC 29213	-	125
Methicillin-resistant *Staphylococcus aureus* clinical isolate (MRSA)	-	15.62
Listeria monocytogenes ATCC 19115	-	62.5
Enterococcus faecalis ATCC 29212	-	15.62
Gram-negative bacteria		
Escherichia coli ATCC 25922	-	125
Salmonella enteritidis DMB560	-	125
Pseudomonas aeruginosa ATCC 27853	-	-
Yeast		
Candida albicans ATCC 10231	2000	15.62

MIC: Minimal inhibitory concentration.

compounds, i.e. **7**–**9**, **12**, **13**, and **15**. However, compound **11** showed weak anti-*Candida* activity with MIC value of 2 mg/mL.

According to these results, while compound **8** is biologically inactive, its analog compound **14** exhibits potential antileishmanial and antibacterial activities. The comparative biological results of compounds **8** and **14** suggest that direct structural similarity does not always imply similarity in activity. Furthermore, the presence of a bromine atom linked to the methyl group significantly improves the biological activity. On the other hand, dioxolane **11**, which has the best resonance structures compared to the other synthesized cyclic ketals, has shown perfect antileishmanial activity with low anti-*Candida* activity.

2.4. Conclusion

We have reported a simple, efficient, and highly ecofriendly protocol for ketalization and thioacetalization reaction under solvent-free conditions at 80 °C for 3 h. Clay-H0.5 has been proposed as a cheap and renewable alternative to the commercial catalyst for the synthesis of cyclic ketals.[62] Moreover, the immobilized catalyst was easily recovered and reused without significant loss of its catalytic activity. This protocol was suitable for both aliphatic and aromatic ketones, proving the high activity of the catalyst. Under the optimized condition, most of the cyclic ketals were obtained in 60%–92% yields. Thus, the successful application of Clay-H0.5 provides the opportunity to simplify the reaction system. This will bring about significant reductions in production costs and eliminate environmental hazards.[50,63–65] Synthesized 1,3-dioxolanes were then evaluated for their antileishmanial and antibacterial activities as well as for their antifungal activities. Biological results suggest that compound **11** showed significant antileishmanial activity against both *L. major* and *L. infantum* and moderate antifungal activity against *Candida albicans*. Furthermore, compound **14** displayed moderate antileishmanial activity, excellent antibacterial activity against four gram-positive and two gram-negative bacteria, and important antifungal activity against *Candida albicans*. Further investigations on the development of acetalization and thioacetalization using new activated clays are ongoing in our laboratories, which could lead to the development of even more active derivatives than compounds **11** and **14**.

3. Experimental

3.1. Preparation of CC and Clay-H0.5

For preparation of the CC, the clay (50 g) was dispersed in 200 mL of distilled water and then subjected to vigorous stirring until complete homogenization. After separation of all organic matrixes, CC was dried and crushed in an agate mortar to obtain particles of 100 µm or less.

For preparation of Clay-H0.5, chemical activation was carried out by adding 10 g of the crude clay to 100 mL of HCl acid solution (3 M) and refluxing at 100 °C for 0.5 h. Then the suspension was centrifuged and the solid was washed with distilled water until no chloride anions could be detected (Ag+ test) and dried at 80 °C. The Clay-H0.5 was crushed and passed through a sieve in order to obtain fine particles with diameters of 75 µm.

3.2. Catalyst characterization

In XRD, CC and Clay-H0.5 were recorded between 3° and 60° 2θ at a scanning speed of 2°/min with a Panalytical diffractometer using monochromated CuKα radiation (30 mA and 40 kV).

For infrared spectroscopy, IR spectra were recorded on a PerkinElmer model 597 instrument in the 4000–400 cm^{-1} region. KBr pellets were prepared by mixing 2 mg of clay with 200 mg KBr.

The microstructure of the samples was investigated with a Philips XL 30 SEM microscope.

To determine chemical composition and structural formula, the clay was dissolved with three strong acids (HCl, H_2SO_4, HNO_3) at 3:1:1, respectively. The mixture was heated in a sand bath until everything went into solution except the silica. It was removed by filtration and dried. The silica content was then determined gravimetrically. Al^{3+} cations, Fe^{3+}, Mg^{2+}, and Ca^{2+} were determined by atomic absorption.

To determine cation exchange capacity, the CEC was determined by the Kjeldahl method. Accordingly, 200 mg of sample was exchanged with ammonium acetate (1 M) three times and then washed with anhydrous methanol; a final wash was performed with deionized water three times. The amount of ammonium retained was determined using a Kjeldahl unit. The CEC is expressed as milliequivalents per gram.

For Brunauer–Emmet–Teller (BET) surface and pore volume analysis, nitrogen adsorption measurements were performed at –196 °C with an Autosorb-1 tool (Quantachrome) for the determination of sample textural properties using the multipoint BET method. The samples were outgassed at 120 °C under a vacuum at 10^{-3} mmHg for 3.5 h.

3.3. Synthesis of cyclic ketal derivatives

Diol (4 equiv., 4 mmol), ketone (1 equiv., 1 mmol), and Clay-H0.5 (10 wt.%) were added successively into a 100-mL autoclave. The reaction mixture was carried out at 80 °C for 3 h under solvent-free conditions. After the reaction, the crude mixture was filtered to separate the catalyst. Distilled water (20 mL) was added to the mixture and the aqueous layer was extracted with CH_2Cl_2 (3 ×15 mL). The organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification via column chromatography (SiO_2) afforded the desired products.

3.4. Antileishmanial activity

Leishmania major (LC04) and *Leishmania infantum* (LV24) strains were cultured in RPMI 1640 medium (GIBCO-Invitrogen) supplemented with 10% heat-inactivated fetal calf serum, penicillin (100 U/mL), and streptomycin (100 µg/mL) and incubated at 27 °C in a humidified atmosphere with 5% CO_2.

Promastigotes at the stationary growth phase were seeded at 2 ×10^5 parasites per well in 100 µL of growth medium. Twofold serial dilutions of tested compounds were added and incubated at 27 °C for 72 h. The parasitic viability was measured using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) test. After 4 h of incubation, formazan crystals were solubilized with pure DMSO and estimated spectrophotometrically at 570 nm using a microplate reader (Bioteck). Antipromastigote activity was expressed as IC_{50} values, i.e. the concentration of the compound that inhibits the growth of promastigotes by 50%. Negative and positive control corresponding to untreated and amphotericin B-treated parasites respectively were added.[66] All tests were performed in triplicate.

Cytotoxicity of 1,3-dioxolanes was evaluated on murine macrophage cells (Raw 264.7). Macrophages were maintained in RPMI-1640 medium supplemented with 10% FBS, antibacterial solution, and antifungal solution (GIBCO, USA) and were incubated at 37 °C in a humidified 5% CO_2 atmosphere. Macrophage viability was controlled microscopically by counting cells after staining with 0.1% trypan blue solution. Macrophages were initially seeded in 96-well tissue culture plates at 10^5 cells/well and allowed to adhere overnight. The medium was then replaced with a fresh one containing different concentrations of 1,3-dioxolanes (from 0.48 µg/mL to 1 mg/mL). After 72 h of incubation at 37 °C, viability was estimated by MTT test as described above and selectivity index (SI) was determined as the ratio of IC_{50} macrophage/IC_{50} parasite.[67,68]

The results were expressed as mean ± standard deviation (SD) and statistically analyzed using Student's t-test by Microsoft Excel software. Differences were considered significant at $P < 0.05$. IC_{50} was calculated by a nonlinear regression equation in GraphPad Prism.

3.5. Antibacterial activity

For antibacterial activity, 1,3-dioxolanes were tested against gram-positive bacteria (including *Staphylococcus aureus* ATCC 29213, *Staphylococcus aureus* (MRSA), *Listeria monocytogenes* ATCC 19115, *Enterococcus faecalis*

ATCC 29212, and *Staphylococcus aureus* ATCC 25923) and gram-negative bacteria (*Escherichia coli* ATCC 25922, *Salmonella enteritidis* DMB560, and *Pseudomonas aeruginosa* ATCC 27853), and against *Candida albicans* ATCC 10231.

The antibacterial activity of 1,3-dioxolanes was evaluated using the disk diffusion method as described previously by Celiktas et al.[69] Briefly, bacterial suspensions were adjusted to 10^8 CFU/mL and were uniformly inoculated on Muller-Hinton agar plates. Different concentrations of 1,3-dioxolanes (ranging from 31.25 µg/mL to 1 mg/mL) were deposited on a filter paper disk and then applied on the agar surface. Plates were incubated for 24 h at 37 °C. Tetracycline (30 µg/disk) was used as a positive control. Clear inhibition zones around the disks indicated antibacterial activity. For a diameter zone inhibition over 10 mm, the MIC defined as the lowest concentration of the 1,3-dioxolanes showing total bacterial inhibition was calculated as recommended by Tay et al.[70] All experiments were conducted in triplicate.

2-Methyl-2-phenyl-1,3-dioxolane (**1**): 104 mg, 69%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.50 (m, 5H), 3.92–3.99 (m, 4H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 143.7 , 136.4 , 127.8 , 125.3 , 108.7 , 64.4 , 27.6.[71]

2-Methyl-2-tert-butyl-1,3-dioxolane (**2**): 42 mg, 42%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.95–3.82 (m, 4H), 1.27 (s, 3H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 112.95, 64.9, 37.9, 24.2, 18.2.[71]

2-Ethyl-2-methyl-1,3-dioxolane (**3**): 59 mg, 51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.10–3.85 (m, 4H), 1.61 (q, J = 7.4 Hz, 2H), 1.01 (s, 3H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 108.4, 64.5, 31.4, 22.7, 7.7.[72]

2-(Chloromethyl)-2-methyl-1,3-dioxolane (**4**): 88 mg, 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.10–3.85 (m, 4H), 3.49 (s, 2H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 108.0, 65.1, 53.2, 22.1.[73]

2-Benzyl-2-methyl-1,3-dioxolane (**5**): 124 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.12–7.29 (m, 5H), 3.64—3.86 (m, 4H), 2.85 (s, 2H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.9, 128.1, 127.7, 125.6, 109.4, 64.8, 44.9, 24.1.[71]

2-(2-Chlorophenyl)-2-methyl-1,3-dioxolane (**6**): 106 mg, 54%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34–7.28 (m, 2H), 7.18–7.13 (m, 2H), 4.05–3.91 (m, 2H), 3.75–3.66 (m, 2H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.5, 131.9, 131.3, 129.2, 127.6, 126.4, 108.3, 64.3, 25.2.[74]

2-Methyl-2-(*p*-tolyl)-1,3-dioxolane (**7**)**:** 92 mg, 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 4.11–3.99 (m, 2H), 3.85–3.74 (m, 2H), 2.38 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 129.2, 128.8, 128.4, 125.2, 108.8, 64.4, 27.6, 21.1.[75]

2-(4-Bromophenyl)-2-methyl-1,3-dioxolane (**8**): 179 mg, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44 (d, J = 8.1Hz, 2H), 7.12 (d, J = 7.9Hz, 2H), 4.09–4.00 (m, 2H), 3.81–3.72 (m, 2H), 1.65 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 142.4, 131.3, 127.1, 121.8, 108.4, 64.5, 27.5.[76]

2-Methyl-2-(4-nitrophenyl)-1,3-dioxolane (**9**): 177 mg, 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 7.9 Hz, 2H), 4.11–3.98 (m, 2H), 3.82–3.69 (m, 2H), 1.63 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.6, 147.6, 126.3, 123.4, 108.1, 64.7, 27.3.[77]

(*E*)-2-Phenyl-2-styryl-1,3-dioxolane (**11**): 131 mg, 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.61–7.56 (m, 2H), 7.43–7.23 (m, 8H), 6.72 (d, J = 16.0 Hz, 1H), 6.38 (d, J = 16.0 Hz, 1H), 4.19–4.11 (m,

2H), 4.07–3.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 140.9, 136.1, 130.9, 129.3, 128.5, 128.2, 128.2, 128.0, 126.9, 126.0, 108.4, 64.8.[78]

2-(4-Chlorophenyl)-2-methyl-1,3-dioxolane (**12**): 132 mg, 63%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.08–3.94 (m, 2H), 3.80–3.71 (m, 2H), 1.90 (q, J = 7.4 Hz, 2H), 0.88 (t, J = 7.4 Hz, H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.1, 133.5, 128.1, 127.3, 108.3, 64.6, 28.3, 7.8.[71]

2-(Chloromethyl)-2-phenyl-1,3-dioxolane (**13**): 114 mg, 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.57–7.53 (m, 2H), 7.43–7.36 (m, 3H), 4.25–4.16 (m, 2H), 3.98–3.90 (m, 2H), 3.79 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.7, 128.8, 128.3, 126.0, 107.8, 65.8, 49.4.[19]

2-(Bromomethyl)-2-(4-bromophenyl)-1,3-dioxolane (**14**): 276 mg, 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 4.21–4.10 (m, 2H), 3.90–3.83 (m, 2H), 3.61 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.8, 131.4, 127.8, 123.0, 106.9, 65.9, 37.8.[48]

2-(3-Bromothiophen-2-yl)-2-methyl-1,3-dioxolane (**15**): 166 mg, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.17 (d, J = 5.3 Hz, 1H), 6.97 (d, J = 5.3 Hz, 1H), 4.14–3.89 (m, 4H), 1.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.1, 132.2, 124.5, 107.2, 106.2, 65.0, 25.5.

2-Methyl-2-phenyl-4-ethyl-1,3-dioxolane (**16**)**:** The reaction mixture was stirred for 3 h at 80 °C. Purification by flash column chromatography on silica gel afforded a mixture of regioisomers (116 mg, 61%).[71]

2-Methyl-2-phenyl-4,5-dimethyl-1,3-dioxolane (**17**)**:** The reaction mixture was stirred for 3 h at 80 °C. Purification by flash column chromatography on silica gel afforded a mixture of diastereoisomers (110 mg, 58%).[71]

2-Methyl-2-phenyl-1,3-dioxane (**18**)**:** 102 mg, 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41–7.26 (m, 5H), 3.80–3.7 (m, 4H), 2.02–1.12 (2H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.6, 129.1, 128.0, 127.2, 100.9, 61.6, 32.8, 25.9.[71]

5,5-Dimethyl-2-phenyl-2-methyl-1,3-dioxane (**19**)**:** 150 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50–7.30 (m, 5H), 3.55–3.30 (m, 4H), 1.55 (s, 3H), 1.25 (s, 3H), 0.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 141.1, 128.5, 127.4, 126.6, 100.9, 70.7, 31.9, 22.7, 21.7.[79]

2-Methyl-2-phenyl-1,3-dithiane (**20**)**:** 128 mg, 61%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.45–7.26 (m, 5H), 2.70–7.65 (m, 4H) 1.87 (q, J = 5.0 Hz, 2H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.2, 129.0, 128.2, 127.5, 54.4, 33.2, 28.5, 25.1.[50]

Acknowledgments

We are grateful to Tunis El-Manar University for providing financial support. The National Center for Research in Materials Science and the Biotechnology Center of Borj Cedria are also gratefully acknowledged.

References

1. Yokoyama, N.; Kanazawa, A.; Kanaoka, S.; Aoshima, S. *Macromolecules* **2018**, *51*, 884-894.
2. Tran, J.; Guégain, E.; Ibrahim, N.; Harrisson, S.; Nicolas, J. *Polym. Chem.* **2016**, *7*, 4427-4435.
3. Küçük, H. B.; Yusufoglu, A.; Matarac, E.; Dösler, S. *Molecules* **2011**, 16, 6806-6815.
4. Bera, S.; Malik, L.; Bhat, B.; Carroll, S. S.; MacCoss, M.; Olsen, D. B.; Tomassini, J. E.; Eldrup, A. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4455-4458.

5. Climent, M. J.; Velty, A.; Corma, A. *Green Chem.* **2002**, *4*, 565-569.
6. Genta, M. T.; Villa, C.; Mariani, E.; Loupy, A.; Petit, A.; Rizzetto, R.; Mascarotti, A.; Morini, F.; Ferro, M. *Int. J. Pharm.* **2002**, *231*, 11-20.
7. Delcourt, A.; Mathieu, G.; Baji, H.; Kimny, T.; Flammang, M.; Compagnon, P. L. *Mycopathologia* **1997**, *137*, 27-32.
8. Chen, H.; Boudinot, F. D.; Chu, C. K.; Mcclure, H. M.; Schinazi, R. F. *Antimicrob. Agents Chemother* **1996**, *40*, 2332-2336.
9. Liang, Y.; Sharon, A.; Grier, J. P.; Rapp, K. L.; Schinazi, R. F.; Chu, C. K. *Bioorg. Med. Chem.* **2009**, *17*, 1404-1409.
10. Feng, J. Y.; Parker, W. B.; Krajewski, M. L.; Deville-Bonne, D.; Veron, M.; Krishnan, P.; Cheng, Y C.; Borroto-Esoda, K. *Biochem. Pharmacol.* **2004**, *68*, 1879-1888.
11. Kumar, S.; Kaur, P.; Bernela, M.; Rani, R.; Thakur, R. *International Journal of Biological Macromolecules* **2016**, *93*, 988-994.
12. Das, B. C.; Madhukumar, A. V.; Anguiano, J.; Kim, S.; Sinz, M.; Zvyaga, T. A.; Power, E. C.; Ganellin, C. R.; Mani, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3974-3977.
13. Baji, H.; Flammang, M.; Kimny, T.; Gasquez, F.; Compagnon, P. L.; Delcourt, A. *Eur. J. Med. Chem.* **1995**, *30*, 617-626.
14. Narayanasamy, J.; Pullagurla, M. R.; Sharon, A.; Wang, J.; Schinazi, R. F.; Chu, C. K. *Antiviral Research* **2007**, *75*, 198-209.
15. Branalt, J.; Kvarnstrom, I. *J. Org. Chem.* **1996**, *61*, 3599-3603.
16. Grove, K. L.; Guo, X.; Liu, S. H.; Gao, Z.; Chu, C. K.; Cheng, Y. C. *Cancer Res.* **1995**, *55*, 3008-3011.
17. Kim, H. O.; Shanmuganathan, K.; Alves, A. J.; Jeong, L. S.; Beach, J. W.; Schinazi, R. F.; Chang, C. N.; Cheng, Y. C.; Chu, C. K. *Tetrahedron Lett.* **1992**, *33*, 6899-6902.
18. Krompiec, S.; Penkala, M.; Szczubiałka, K.; Kowalska, E. *Coordination Chemistry Reviews* **2012**, *256*, 2057-2095.
19. Yu, J.; Zhang, C. *Synthesis* **2009**, *14*, 2324-2328.
20. Ono, F.; Takenaka, H.; Fujikawa, T.; Mori, M.; Sato, T. *Synthesis* **2009**, *8*, 1318-1322.
21. Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842-5845.
22. Zong, Y.; Yang, L.; Tang, S.; Li, L.; Wang, W.; Yuan, B.; Yang, G. *Catalysts* **2018**, *8*, 48-58.
23. Fraile, J. M.; Saavedra, C. J. *Catalysts* **2017**, *7*, 393-407.
24. Silveira, C. C.; Mendes, S. R.; Ziembowicz, F. I.; Lenardão, E. J.; Perin, G. *J. Braz. Chem. Soc.* **2010**, *21*, 371-374.
25. Sun, S.; He, M.; Dai, Y.; Li, X.; Liu, Z.; Yao, L. *Catalysts* **2017**, *7*, 184-194.
26. Barros, A. O.; Faísca, A. T.; Lachter, E. R.; Nascimento, R. S. V.; San, Gil, R. A. S. *J. Braz. Chem. Soc.* **2011**, *22*, 359-363.
27. Shui-Jin, Y.; Xin-Xian, D.; Lan, H.; Ju-Tang, S. *J Zhejiang Univ. Sci.* **2005**, *6B*, 373-377.
28. Thomas, B.; Sugunan, S. *J. Porous Mater.* **2006**, *13*, 99-106.
29. Thomas, B.; Prathapan, S.; Sugunan, S. *Microporous and Mesoporous Materials* **2005**, *80*, 65-72.
30. Xia, W.; Wang, F.; Mu, X.; Chen, K.; Takahashi, A.; Nakamura, I.; Fujitani, T. *Catal. Commun.* **2017**, *90*, 10-13.
31. Lei, Z. Q.; Wei, L. L.; Wang, R. R.; Ma, G. F. *Catal. Commun.* **2008**, *9*, 2467-2469.
32. Gupta, N.; Sonu-Kad, G. L.; Singh, J. *Catal. Commun.* **2007**, *8*, 1323-1328.
33. Wang, B.; Gu, Y.; Song, G.; Yang, T.; Yang, L.; Suo, J. *J. Mol. Catal. A Chem.* **2005**, *233*, 121-126.
34. Wang, X.; Ma, K.; Guo, L.; Tian, Y.; Cheng, Q.; Bai, X.; Huang, J.; Ding, T.; Li, X. *Appl. Catal. A Gen.* **2017**, *540*, 37-46.

35. Kaur, N.; Kishore, D. *J. Chem. Pharm. Res.* **2012**, *4*, 991.
36. Dasgupta, S.; Torok, B. *Organic Preparations and Procedures International* **2008**, *40*, 1-65.
37. Krstic, L. J.; Sukdolak, S.; Solujic, S. *J. Serb. Chem. Soc.* **2002**, *67*, 325-329.
38. Wang, N.; Hu, Y.; Zhang, Z. *Applied Clay Science* **2017**, *150*, 47-55.
39. do Nascimento, A. R.; Alves, J. A. B. L. R.; de Freitas-Melo, M. A.; de Araújo-Melo, D. M.; de Souza, M. J. B.; Pedrosa, A. M. G. *Materials Research* **2015**, *18*, 283-287.
40. Dar, B. A.; Bhatti, P.; Singh, A. P.; Lazar, A.; Sharma, P. R.; Sharma, M.; Singh, B. *Appl. Catal. A Gen.* **2013**, *466*, 60-67.
41. Suresh, D.; Dhakshinamoorthy, A.; Kanagaraj, K.; Pitchumani, K. *Tetrahedron Lett.* **2013**, *54*, 6479-6484.
42. Subramanian, T.; Pitchumani, K. *Catal. Commun.* **2012**, *29*, 109-113.
43. Motokura, K.; Matsunaga, S.; Miyaji, A.; Sakamoto, Y.; Baba, T. *Org. Lett.* **2010**, *12*, 1508-1511.
44. Kantevari, S.; Vuppalapati, S. V. N.; Bantu, R.; Nagarapu, L. *J. Heterocycl. Chem.* **2010**, *47*, 313-317.
45. Mnasri, S.; Besbes, N.; Srasra, N. F.; Srasra, E. *C. R. Chimie* **2012**, *15*, 437-443.
46. Besbes, N.; Jellali, H.; Pale, P.; Efrit, M. L.; Srasra, E. *Phosphorus, Sulfur and Silicon* **2010**, *185*, 883-889.
47. Besbes, N.; Jellali, H.; Pale, P.; Srasra, E.; Efrit, M. L. *C. R. Chimie* **2010**, *13*, 358-364.
48. Zheng, Z.; Han, B.; Wu, F.; Shi, T.; Liu, J.; Zhang, Y.; Hao, J. *Tetrahedron* **2016**, *72*, 7738-7743.
49. Karimi, B.; Ghoreishi, N. M. *Journal of Molecular Catalysis* **2007**, *277*, 262-265.
50. Santos, L. L.; Ruiz, V. R.; Sabater, M. J.; Corma, A. *Tetrahedron* **2008**, *64*, 7902-7909.
51. Madabhushi, S.; Mallu, K. K. R.; Chinthala, N.; Beeram, C. R.; Vangipuram, V. S. *Tetrahedron Lett.* **2012**, *53*, 697-701.
52. Smith, B. M.; Graha, A. E. *Tetrahedron Lett.* **2006**, *47*, 9317-9319.
53. Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Synth. Catal.* **2004**, *346*, 446-450.
54. Stawicka, K.; Díaz-A lvarez, A. E.; Calvino-Casilda, V.; Trejda, M.; Ban ares, M. A.; Ziolek, M. *J. Phys. Chem.* **2016**, *120*, 16699-16711.
55. Jin, Y.; Shi, J.; Zhang, F.; Zhong, Y.; Zhu, W. *J. Mol. Cat. A Chem.* **2014**, *383*, 167-171.
56. Miao, J.; Wan, H.; Shao, Y.; Guan, G.; Xu, B. *J. Mol. Catal. A Chem.* **2011**, *348*, 77-82.
57. Zhang, J.; Bao, S. H.; Yang, J. G. *Chin. Sci. Bull.* **2009**, *54*, 3958-3964.
58. Zhang, F.; Xu, D. Q.; Liu, B. Y.; Luo, S. P.; Yang, W. L.; Xu, Z. Y. *Chin. J. Catal.* **2005**, *26*, 815-818.
59. Hermida, L.; Amani, H.; Saeidi, S.; Abdullah, A. Z.; Mohamed, A. R. *Rev Chem Eng.* **2017**, *34*, 239-265.
60. Mnasri, S.; Srasra, N. F. *Infrared Physics & Technology* **2013**, *58*, 15-20.
61. Srasra, E.; Ayedi, M. T. *Applied Clay Science* **2000**, *17*, 71-84.
62. Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis, 4th Edition*; John Wiley and Sons: New York, NY, USA, 2007.
63. Wu, S. S.; Dai, W. L.; Yin, S. F.; Li, W. S.; Au, C. T. *Catal. Lett.* **2008**, *124*, 127-132.
64. Jermy, B. R.; Pandurangan, A. *Catal. Commun.* **2006**, *7*, 921-925.
65. Patel, S. M.; Chudasama, U. V.; Ganeshpure, P. A. *J. Mol. Catal. A Chem.* **2003**, *194*, 267-271.
66. Essid, R.; Rahali, F. Z.; Msaada, K.; Sghair, I.; Hammami, M.; Bouratbine, A.; Aoun, K.; Limam, F. *Industrial Crops and Products* **2015**, *77*, 795-802.
67. Ramdane, F.; Essid, R.; Mkadmini, K.; Hammami, M.; Fares, N.; Hadj-Mahammed, M.; El Ouassise, D.; Tabbene, O.; Limam, F.; Didi Ould Hadj, M. *Process Biochem.* **2017**, *56*, 186-192.
68. Weninger, B.; Robledo, S.; Arango, G. J.; Deharo, E.; Arango, R.; Munoz, V.; Callapa, J.; Lobstein, A.; Anton, R. *J. Ethnopharmacol.* **2001**, *78*, 193-200.

69. Celiktas, O. Y.; Kocabas, E. E. H.; Bedir, E.; Vardar Sukan, F.; Ozek, T.; Baser, K. H. C. *Food Chem.* **2007**, *100*, 553-559.
70. Tay, B.; Giday, M.; Animt, A.; Seid, J. *Asian Pac. J. Trop. Biomed.* **2011**, *1*, 370-375.
71. Santos, L. L.; Ruiz, V. R.; Sabater, M. J.; Corma, A. *Tetrahedron* **2008**, *64*, 7902-7909.
72. Fei, H.; Rogow, D. L.; Oliver, S. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 7202-7209.
73. Gallucci, R. R.; Going, R. *J. Org. Chem.* **1981**, *46*, 2532-2638.
74. Lukács, G.; Porcs-Makkay, M.; Komáromi, A.; Simig, G. *Arkivoc* **2008**, 3, 17-24.
75. McConville, M.; Blacker, J.; Xiao, J. *Synthesis* **2010**, *2*, 349-360.
76. Detty, M. R.; Murray, B. J.; Smith, D. L.; Zumbulyadis, N. *J. Am. Chem. Soc.* **1983**, *105*, 875-882.
77. Kondolff, I.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2006**, *2006*, 765-774.
78. Tanemura, K.; Suzuki, T. *Chem. Lett.* **2015**, *44*, 797-799.
79. Aoyama, T.; Suzuki, T.; Nagaoka, T.; Takido, T.; Kodomari, M. *Synth. Commun.* **2013**, *43*, 553-566.