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A new synthesis of 1,3-dioxan-5-one derivatives and their application in aldol condensation reactions

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Abstract: A facile synthesis of heterocyclic ketone **2** is reported in this work. The procedure takes place in one pot and gives a satisfactory yield. In comparison with other major reported procedures, the present method uses much easier conditions and inexpensive reagents. Ketone **2** is subsequently employed in aldol condensation reactions to give the respective bisarylmethylidene products under sonochemical conditions. Reactions proceed rapidly and products are obtained in relatively high yields. The efficiency of both reactions, use of inexpensive and commercially available reagents, and safe and mild conditions used for the reactions are amongthe advantages of this work.

Keywords: Ninhydrin, Primary amine, Arylisothiocyanates, Dialkyl acetylenedicarboxylates, Multi component reaction.

Introduction

One of the most important methods for the synthesis of conjugated enone systems is the aldol condensation reaction [1]. The reaction incorporates nucleophilic addition of enols to aldehydes, where elimination of water from □-hydroxy carbonyl intermediates leads to stable C═C bonds conjugated with carbonyl groups [2]. These enone fragments are important substructure of many synthetic and natural products with biological activities of interest [3-7]. Among these structures are bisaryl methylidene derivatives of ketones prepared via aldol condensations [8-11]. 1,3-Dioxan-5-one **2** is an important precursor for the synthesis of a variety of compounds of interest and is a synthetic equivalent to dihydroxyacetone (**1**, DHA, Scheme 1), an achiral ketotrioseserving as a C3 building block for the synthesis of various compounds with biological activities [12-15]. Enders has reviewed the synthesis of **2** and some of its derivatives[16,17], along with its applications in different important name reactions such as Mannich [18], Michael [19], and Diels-Alder [20] reactions to access several carbohydrate structures. Therefore, development of new methodologies for the preparation of derivatives of **2** has received lots of attention from organic chemists [21,22]. Because of interesting application of **2** in aldol reactions, we were persuaded to extend this chemistry, due to our ongoing program on aldol chemistry of analogous heterocyles [23-25]. In the present work, a new method is developed for easy synthesis of **2** starting from DHA. In addition, **2**is further subjected to aldol condensation reactions with aromatic aldehydes to access the respective bisarylmethylidene products. Conversion of **2** to **3** is assisted by ultrasonic irradiation, which can facilitate various organic transformations [26,27]. Thus aldol condensations proceed rapidly and high yields are obtained under relatively mild conditions (Scheme 1).

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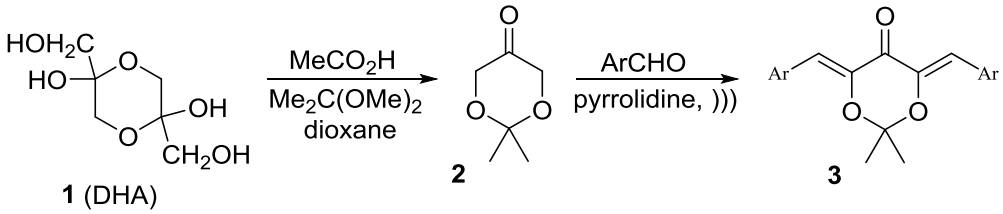


Scheme 1: Synthesis of derivatives of **2** and **3**.

Results and discussion

We first optimized the conditions for direct synthesis of **2** (Table 1). In the presence ofcatalyticquantities (20 mol%)ofcamphor-10-sulfonic acid(CSA), commercially available $Me_2C(OMe)_2$ reacted with dihydroxyacetone dimer to led to negligible amount of **2** (entry 1). Similar results were obtained with *p*-toluenesulfonic acid (PTSA) (entry 2). Results improved substantially when acetic acid was used as the catalyst (entry 3), while use of dioxane as the solvent proved to be crucial for the reaction to proceed efficiently (entry 4). In the presence of higher quantities of the catalyst (entry 5) or at a higher temperature (entry 6) no better outcomewas observed. The results did not improved either in the absence of the catalyst (entry 7) or with other carboxylic acids (entries 8-9).When compared to literature [21,22], this reaction presents one of the best procedures for one-pot synthesis of **2**.

Table 1: Optimization of the synthesis of **2**.

Entry	Catalyst (20 mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	CSA	dioxane	60	24	< 5
2	PTSA	dioxane	60	24	< 5
3	$MeCO_2H$	dioxane	60	6	40
4	$MeCO_2H$	-	60	8	20
5	$MeCO_2H$[b]	dioxane	60	6	40
6	$MeCO_2H$	dioxane	80	8	35
7	-	dioxane	60	24	< 5
8	$H_2C_2O_4$	dioxane	60	8	< 5
9	$PhCO_2H$	dioxane	80	72	< 5

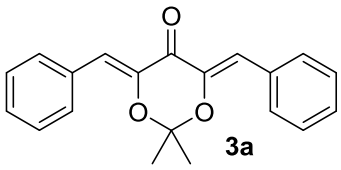
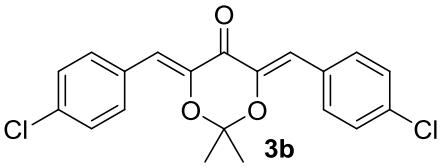
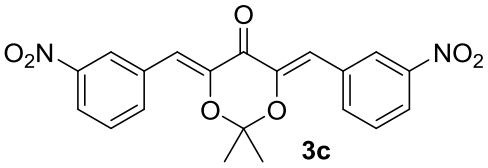
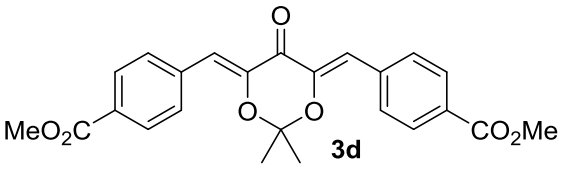
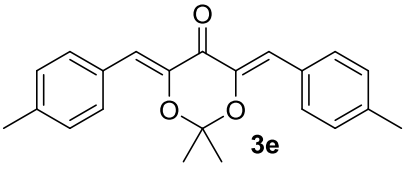
a) Isolated yield.
b) $MeCO_2H$ (40 mol%).

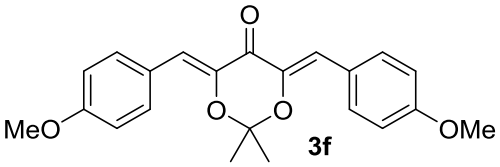
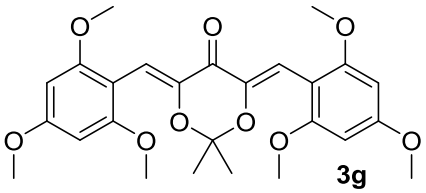
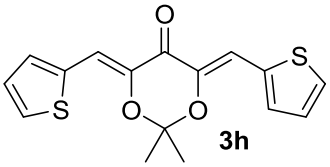
Next, the ketone **2** was used in further aldol condensation reactions to prepare various respective bisarylmethylidene derivatives (Table 2). In the presence of pyrrolidine (20 mol%), two equivalents of benzaldehyde reacted with **2** under ultrasonic conditions to give **3a** in 83% yield after 10 minutes

irradiation (entry 1). Equally well results were observed when aromatic aldehydes with electron-withdrawing substituents were used (entries 2-4). It was also the case with aldehydes bearing electron-releasing groups (entries 5-7) or a heteroaromatic substituent (entry 8). All reactions completed within 10-15 minutes irradiation in an ultrasonic bath and products were isolated in each case after working up the reactions with aqueous treatment.

Product **3c** was new and its structure was elucidated based on ^{1}H and ^{13}C NMR spectra. Presence of aliphatic and olefinic protons with a ratio of 3:1 supports the formation of the central symmetrically substituteddioxane ring with vinilic attachments at positions 4 and 6, while aromatic protons pattern is in accordance with 1,3-substituted phenylene attachments. Similarly, presence of 11 signals in the ^{13}C NMR spectrum confirms the formation of **3c**. Additional confirmations were obtained with IR, mass, and elemental analyses. All other products which were known were confirmed by the comparison of their physical and spectral properties with those of authentic samples.

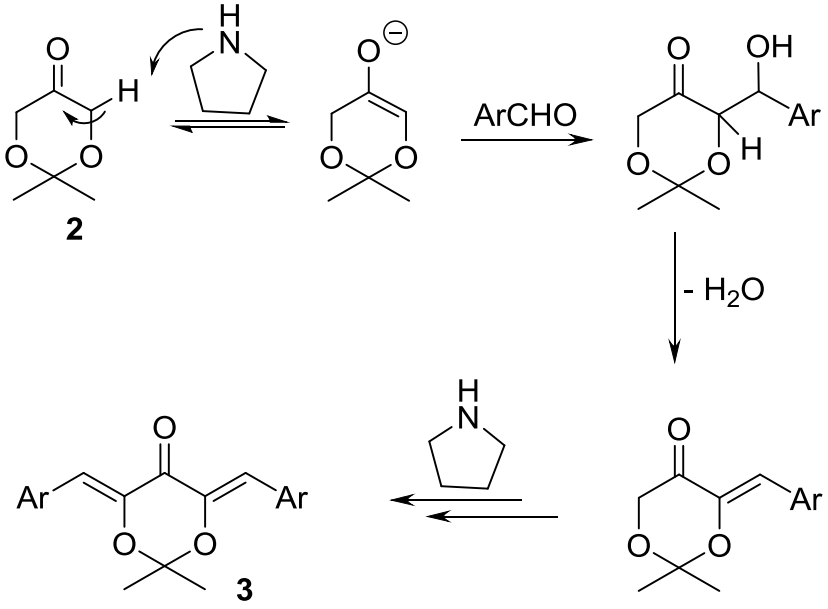
Table 2: One-pot synthesis of products **3**.

Entry	Aldehyde	Product	Mp (^{o}C)	Yield (%)[b]
1	C_6H_5CHO	 **3a**	104-105 [24]	83
2	4-ClC_6H_4CHO	 **3b**	137-138 [24]	90
3	4-$O_2NC_6H_4CHO$	 **3c**	202-204	80
4	4-$MeO_2CC_6H_4CHO$	 **3d**	223-225 [24]	87
5	4-MeC_6H_4CHO	 **3e**	128-129 [24]	71

6	4-$MeOC_6H_4CHO$	 **3f**	131-133 [24]	70
7	4-$(MeO)_3C_6H_2CHO$	 **3g**	240-241 [24]	95
8	2-thienyl-CHO	 **3h**	147-148 [24]	83

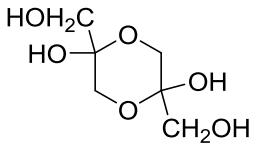
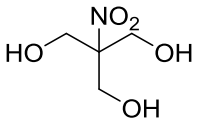
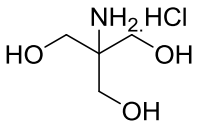
a) Isolated yield.

Based on these results, a mechanism can be proposed, as depicted in Scheme **2**. Initially, pyrrolidine facilitates deprotonation of a hydrogen and formation of the respective enolate of **2**. This enolate can then attack the starting aldehyde to form an aldol product, which upon facile dehydration gives the monoarylidene intermediate. Further repeat of these steps give the final product **3**. All steps are assisted by ultrasonic energy to proceed in short time periods.



Scheme 2: A possible mechanism.

Table 3: Literature comparison for the synthesis of **2**.

Entry	Conditions	Reactants	Yield (%)	Reference
1	$MeCO_2H$, dioxane, 60 ^oC.		40	This work
2	i) PTSA, benzene, refluxed overnight, molecular sieves, $NaHCO_3$, EtOAc; ii) $HgCl_2$, Al, THF, 0 ^oC, 30 min; iii) KH_2PO_4, 0 ^oC, $NaIO_4$, 5 min, $CHCl_3$, EtOAc; iv) $TiCl_3$, NH_4OAc, dioxane, 0 ^oC, 45 min, Et_2O.			[22]
3	i) 2,2-DMP, CSA, DMF, r.t., 40 h, Et_3N, EtOAc; ii) $NaIO_4$, KH_2PO_4, H_2O, 5-10 °C, 3 h, to r.t. over 15 h.		58	[21]

Conclusion

In summary, we have presented a new method which can be used for efficient synthesis of ketone **2**. We have also showed that this ketone can be further employed for the preparation of the respective bisarylmethylidenes derivatives using inexpensive and mild conditions. Both reactions take place using catalytic quantities of a simple reagent. Table **3** summarizes the results of two of the most relevant procedures for the synthesis of **2** with the outcome of the present work.

Experimental

Melting points are uncorrected. IR spectra are recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. NMR spectra are obtained on a FT-NMR Bruker Ultra Shield^{TM} (500 MHz) as $CDCl_3$ solutions using TMS as internal standard reference. Elemental analyses are performed using a ThermoFinnigan Flash EA 1112 instrument. MS spectra are obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments are carried out on pre-coated silica gel plates using petroleum ether/EtOAc (5:1) as the eluent. All other chemicals are commercially available. Aldehydes are redistilled or recrystallized prior to being used.

*Typical procedure for the synthesis of **2***

Acetic acid (125 µl, 20 mol%) was added dropwise to a mixture of dihydroxyacetone dimer **1** (1.01 g, 5.6 mmol) in dioxane (2 mL), while being heated at 60 °C under argon atmosphere. After 5 minutes, 2,2-dimethoxypropane (7.0 ml, 57 mmol) was added to the mixture and the mixture was stirred for 6 h at 60 °C. The mixture was concentrated under reduced pressure and the residue was distilled (120 °C/200 torr) to obtain 0.58 g of **2** as a clear and colorless liquid.

General procedure for the synthesis of 3:

A mixture of an aldehyde (4.0 mmol), ketone **2** (2.0 mmol), and pyrrolidine (33 µl, 20 mol%) was sonicated for 10-15 min. The progress of the reaction was monitored by TLC using silica gel coated plates and petroleum ether/EtOAc (9:1). At the end, water (5 mL) was added to the mixture and the product was extracted with Et_2O (2×5 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent led to a solid residue which was purified by either column chromatography (using silica gel and petroleum ether/EtOAc (9:1) as the eluent) or recrystallization from EtOH. The identity of known compounds was confirmed by the comparison of their spectral and physical data with those available in the literature. The structure of the new product was determined by

physical and spectroscopic specifications and their purity was confirmed by elemental analyses.

(4Z,6Z)-2,2-Dimethyl-4,6-bis(3-nitrobenzylidene)-1,3-dioxan-5-one (3c):

Yellow solid was obtained in 70% yield. Mp 202-206 ^{o}C;^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (s, 6H), 6.95 (s, 2H), 7.56 (dd, *J* = 8.0, 7.5 Hz, 2H), 7.98 (d, *J*= 7.5 Hz, 2H), 8.17 (d, *J*=8.0 Hz, 2H), 8.71 (s, 2H) ppm;^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 102.7, 114.0, 123.8, 125.4, 129.9, 135.2, 136.6, 146.8, 148.9, 177.3 ppm; IR (neat) ν1687, 1598, 1527, 1352 cm^{-1}; MS (70 eV) m/z 396 (M^+), 356, 175, 163, 89; Anal Calcd for $C_{20}H_{16}N_2O_7$: C, 61.61; H, 4.07; N, 7.07. Found: C, 61.58; H, 4.15; N, 6.85.

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