IRANIAN JOURNAL OF CATALYSIS

Use of 1,3-dioxan-5-one derivatives in organic synthesis

Compiled by Mohammad Javad Poursharifi

Mohammad Javad Poursharifi was born in 1971 in Ray City, Iran. He obtained his B.Sc. (1994) from Kharazmi University, Tehran. He then completed his M.Sc. studies in Organic Chemistry (2008) from Islamic Azad University, Saveh Branch, Iran. Currently, he is working towards his Ph.D. under the supervision of Professor Mohammad Majid Mojtahedi and Professor Mahmood M. Hashemi at Islamic Azad University, Science and Research Branch. His research involves synthetic applications of 1,3-dioxan-5-one derivatives.

Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran 1477893855, Iran.

Email: mojtahedi@ccerci.ac.ir

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

Introduction

Cyclohexanone and its heterocyclic and homocyclic analogues are important building blocks in synthetic organic chemistry. These molecules are used as versatile starting materials to react with various reagents and molecules to quickly construct more complex products. In addition, they can also be converted to other respective species such as enones, enols, enamines and so on to obtain more active synthetic precursors. Consequently, numerous reports can be found in the literature on synthetic applications of these cyclic reactants. As some illustrative examples we can point out participation of these starting materials in several important name reactions such as Mannich reaction [1], Diels-Alder cycloaddition [2], Baylis-Hillman reaction [3], Claisen-Schmidt condensation [4] and etc.

The smallest monosaccharide is triose which is important in biochemistry. Dihydroxy acetone (DHA) **1** is chemical equivalent to dihydroxyacetone phosphate (DHAP, **2**) which is the precursor for lactic acid and pyruvic acid. Compound **1**, which is the only achiral ketotriose, and its derivatives act as C3 building blocks in asymmetric synthesis of interesting target molecules [5]. However, DHA is not accessible in free form and dimerizes to inactive molecule **3**. Therefore, it is necessary to use DHA in its protected forms like 1,3-dioxan-5-one **4** or its derivatives and synthons (Scheme 1).

Molecules of type **4** are among the most important heterocyclic analogues of cyclohexanone and have received lots of attention by organic chemists in recent years [6]. In a pioneering work, Enders group designed a biomimetic procedure for synthesis of several carbohydrate structures through direct proline-catalyzed one-step aldol reactions [7]. In a parallel work, Majewski applied a similar approach in natural product synthesis [8]. In this report, several important examples on the preparation and synthetic applications of derivatives of **4** are presented.
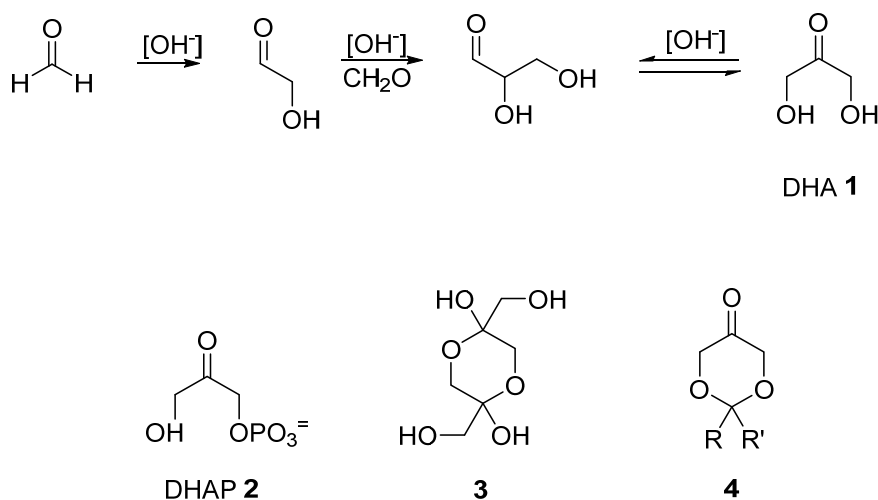
**Scheme 1.** Synthetic pathway to dihydroxyacetone equivalents.

Abstracts

(A) Masato Yasuda *et al.* reported a direct aldol reaction between a protected dihydroxyacetone and aromatic aldehydes. The reaction was catalyzed by a chiral zinc complex. The result of the reactions was the formation of *syn*-aldol products. These products were mainly obtained by the aldol reaction between acetonide form of dihydroxyacetone with benzaldehyde derivatives in amine/alcohol solvent mixtures leading to good yields of the products with high degrees of stereoselectivity [9].
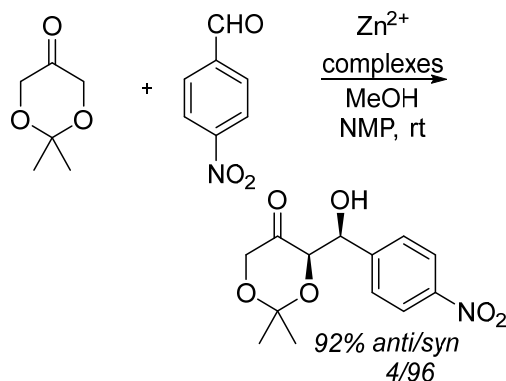

(B) Several derivatives of 1,3-dioxan-5-one were synthesized in situ from DHA in the presence of catalytic amounts of acetic acid and trialkoxyalkanes in dioxane at 60 °C. The products were then subjected to aldol condensation with aromatic aldehydes to form the respective bischalcones in high yields. Reactions were completed in short times using pyrrolidine catalyst [10].
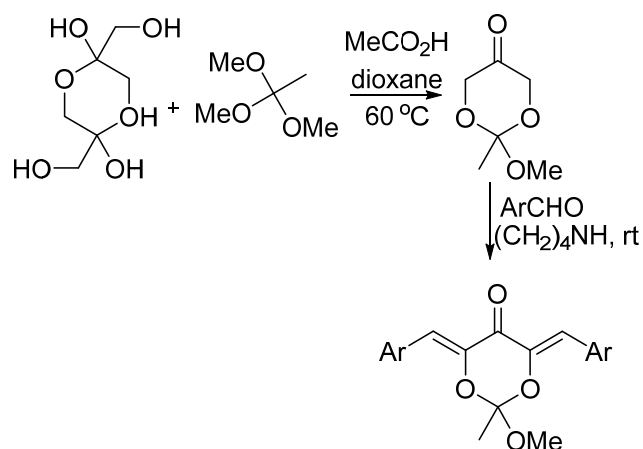
(C) (β)-Aza-galacto-fagomine (AGF) has very important role in pharmacological chaperone therapy of Krabbe disease. This molecule was stereoselectively synthesized in six steps and 14% overall yield. The key steps of the work are based on organocatalyzed aldolization and reductive hydrazination reactions. Therefore, stereoselective synthesis of AGF was accomplished from a commercially available alcohol. This made the final product readily accessible for further studies [11].
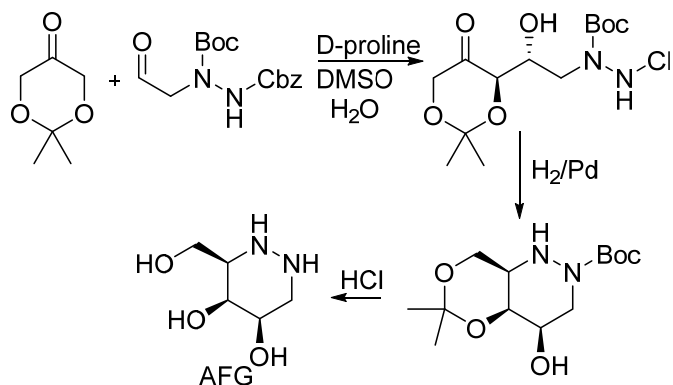

(D) 1,3-Dioxane-5-one was reacted with aromatic aldehydes and malononitrile under ultrasonic conditions to get the pyrano[3,2-*d*][1,3]dioxin derivatives by using aqueous sodium hydroxide solutions. Reactions were completed after a few minutes. Products precipitated in the reaction vessels and were purified by simple crystallization from ethanol without chromatographic separations. A similar reaction was also conducted with ethyl cyanoacetate instead of malononitrile to give the respective ester, as opposed to nitrile, products in high yields [12].
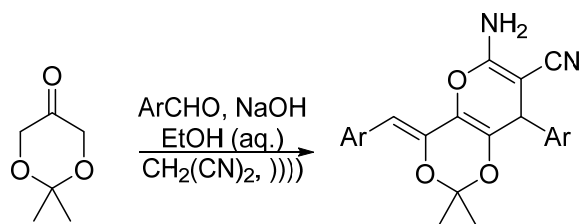

(E) Synthesis of a novel series of bisarylmethylidenes of 2-methoxy-2-methyl-1,3-dioxan-5-one was reported. Products were obtained quickly and in high yields at room temperature via the reaction of the starting ketone with various aromatic aldehydes by using pyrrolidine as the catalyst in ethanol. When reactions finished, products precipitated in the reaction vessels. This saved the time and avoided usual cumbersome chromatographic separations. Structural elucidation of the products was accomplished by proton and carbon NMR spectroscopic methods. The *Z* stereochemistry for the olefinic C=C bonds was confirmed by X-ray crystallography. Interestingly, products showed different colors in solid and solution states. Thus, these products were studied for their photophysical properties as well [13].
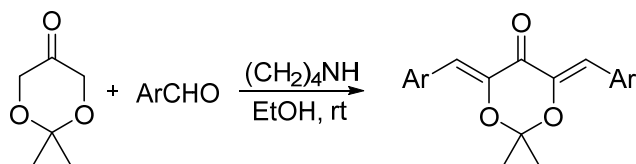
(F) 2,2-Dimethyl-1,3-dioxane-5-one was reacted with a chiral aldehyde under a stereo-controlled proline-catalyzed aldol reaction. The results showed that products would form with very good diastereoselectivity when acyclic chiral α-oxy and α-amino aldehydes are used. The reaction was used as a key step to synthesize medicinally relevant azasugars for the treatment of Fabry's disease [14].
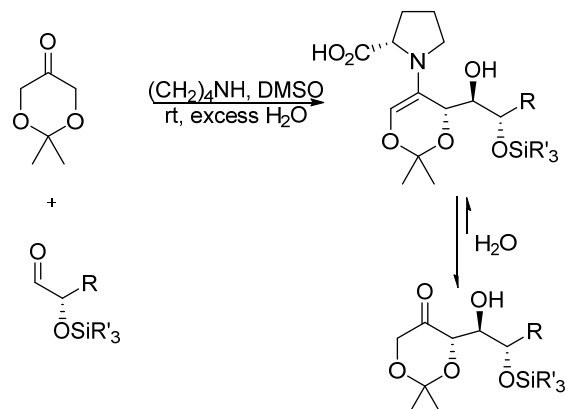
(G) A cross-aldol process was conducted for the reaction between dihydroxyacetone isopropylidene acetal with enantiopure α-silyloxy aldehydes. Reactions proceeded under catalysis of proline and led to high yields of the products. In each case only formation of one stereoisomer was noticed, if excess amounts of water were present in the medium. Progress of the reactions was studied by NMR spectroscopy to study the mechanism of the process. The results suggested that proline acts as a protecting group for the starting ketone and also catalyzes the process [15].
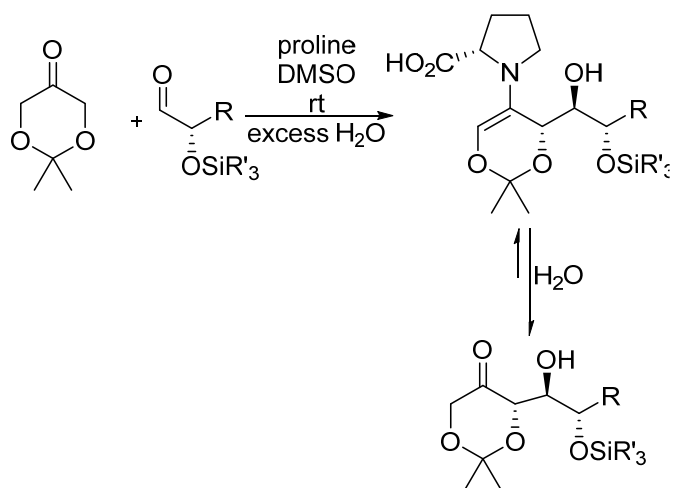
(H) 2,2-Dimethyl-1,3-dioxane-5-one was used in a sequence of reactions for the synthesis of dioxaadamantane core of (±)-tetrodotoxin. The process was conducted with a stereo-controlled 1,3-diol orthoesterification, followed by a water-promoted intramolecular Henry addition, and a [3 + 3] annulation of α-nitro-α,β-enals and 2,2-dimethyl-1,3-dioxan-5-one. The whole result led to a short convenient pathway to the dioxaadamantane core of (±)-tetrodotoxin [16].
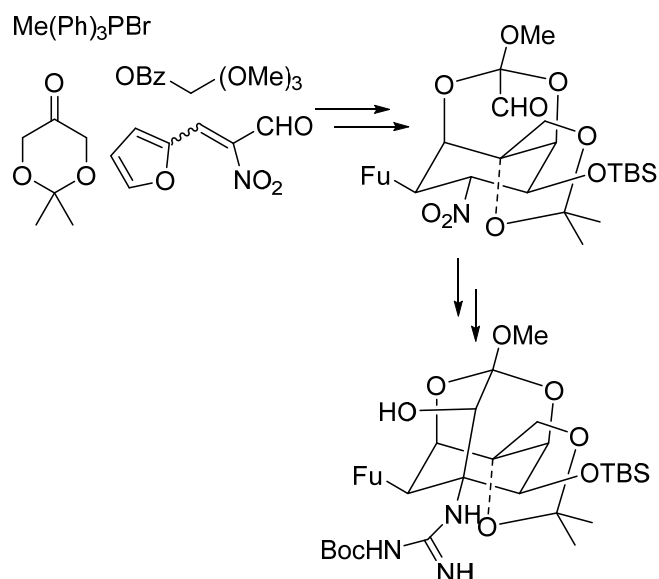
(I) NMR spectroscopy in DMSO-*d*6 was used to study the equilibria between cyclic enamines with 2,2-dimethyl-1,3-dioxane-5-one. Comparison of the exchange results showed a preferable tendency of the carbonyl compounds to convert to the respective enamines. Results also showed that aldehydes are more prone than ketones to give enamines. However, there were some exceptions to this. For example, 1,3-dihydroxyacetone acetals or 3,5-dioxacyclohexanones (2-phenyl-1, 3-dioxan-5-one and 2,2-dimethyl-1,3-dioxan-5-one) had higher tendencies to give enamines than several aldehydes with α-substituents [17].
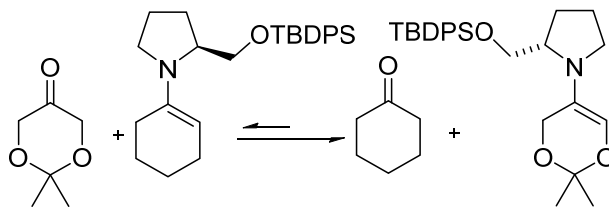
(J) An organocatalytic anti-Mannich reaction was developed for dihydroxyacetone and acyclic dihydroxyacetone derivatives which provided a facile route to amino sugars. The reaction was catalyzed with an amino acid and a variety of imines were used. The results complemented previously reported proline-based strategies to prepare amino sugars. In other words, this work presented the first direct catalytic asymmetric Mannich reactions to use unprotected dihydroxyacetone and acyclic protected dihydroxyacetones [18].
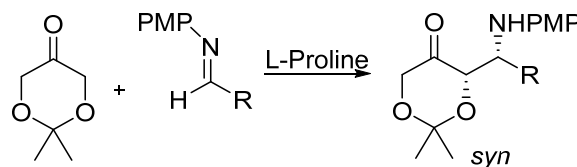
(K) A double crossed-aldol condensation process was reported for the reaction of 1,3-dioxan-5-one with a variety of aromatic aldehydes. The condensation took place in the presence of diethylamine and magnesium bromide diethyl etherate at room temperature. As a result, 4,6-bis(arylmethylidene)dioxan-5-ones were obtained in good yields via a one-pot process. Spectroscopic methods and X-ray crystallography showed that the products have *Z,Z*-configuration for the exocyclic double bonds [19].
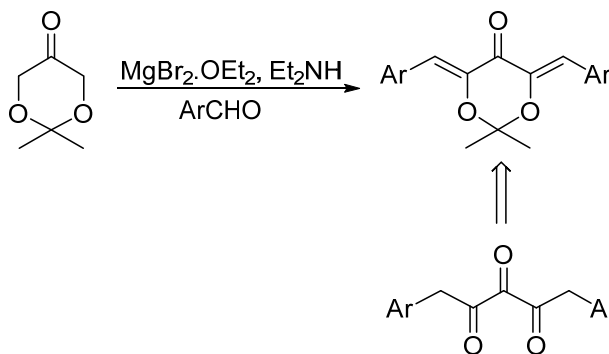
(L) TBS-protected enol of 2,2-dimethyl-1,3-dioxane-5-one underwent a retro-cycloaddition reaction in refluxing toluene to form the respective TBS-protected enal intermediate. The process stereoselectively afforded *Z*-stereoisomer which then cycloadded to 1,3-pentadiene to provide the final trisubstituted chiral cycloheptene with 97:3 tendency for the formation of the exo product [20].
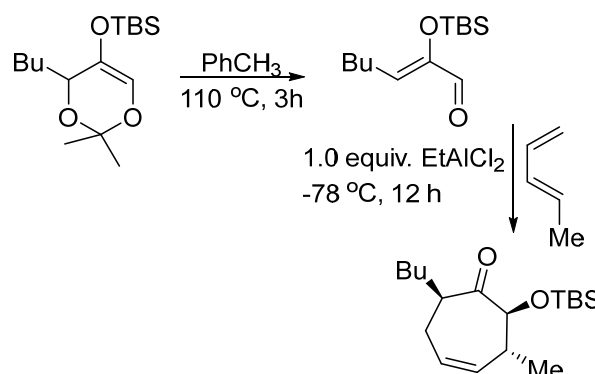
(M) A new group of anti-HIV nucleosides were synthesized via a novel synthetic method leading to isonucleosides. The process took place in six steps by converting 2,2-dimethyl-1,3-dioxan-5-one to a dioxabicyclohexane derivative. First the epoxide group was cleaved with thiophenol and the resulting intermediate was subjected to the Mitsunobu conditions. Use of a nucleobase caused the formation of the desired isonucleoside after the thiophenol group migrated in the course of the reaction. Then the thiophenyl group was removed under radical conditions. Finally, a deprotection step gave racemic mixture of the desired molecule [21].
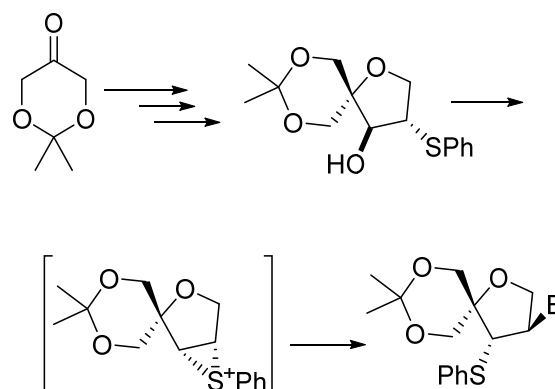
References

[1] A.R. Massah, R.J. Kalbasi, M. Toghyani, Iran. J. Catal. 2 (2012) 41-49.

[2] R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C.F. Barbas, III, Tetrahedron Lett. 43 (2002) 3817-3820.

[3] D. Basavaiah, G. Veeraraghavaiah, Chem. Soc. Rev. 41 (2012) 68-78.

[4] A. Dhakshinamoorthy, M. Alvaro, H, Garcia, Adv. Synth. Catal. 352 (2010) 711-717.

[5] D. Enders, M. Voith, A. Lenzen, Angew. Chem. Int. Ed. 44 (2005) 1304-1325.

[6] D. Enders, S. Breukers, L.F. Reichenbach, Encyclopedia of Reagents for Organic Synthesis, John Wiley & Sons, 2001.

[7] C. Grondal, D. Enders, Adv. Synth. Catal. 349 (2007) 694-702.

[8] N. Palyam, M. Majewski, J. Org. Chem. 74 (2009) 4390-4392.

[9] M. Yasuda, Y. Saga, T. Tokunaga, S. Itoh, S. Aoki, Tetrahedron 75 (2019) 757-777.

[10] M.J. Poursharifi, M.M. Mojtahedi, M.S. Abaee, M.M. Hashemi, Heterocyclic Commun. 25 (2019) 85-90.

[11] J.M. Trajkovic, Z. Ferjancic, R.N. Saicic, Tetrahedron 73 (2017) 2629-2632.

[12] M.M. Mojtahedi, M. Mehraban, K. Darvishi, M.S. Abaee, Heterocyclic Commun. 23 (2017) 91-95.

[13] M.M. Mojtahedi, K. Darvishi, M.S. Abaee, M.R. Halvagar, Can. J. Chem. 95 (2017) 785-791.

[14] J. Marjanovic Trajkovic, V. Milanovic, Z. Ferjancic, R.N. Saicic, Eur. J. Org. Chem. (2017) 6146-6153.

[15] D. Sánchez, H. Carneros, A. Castro-Alvarez, E. Llàcer, F. Planas, J. Vilarrasa, Tetrahedron Lett. 57 (2016) 5254-5258.

[16] H. Lago-Santomé, R. Meana-Pañeda, R. Alonso, J. Org. Chem. 79 (2014) 4300-4305.

[17] D. Sánchez, D. Bastida, J. Burés, C. Isart, O. Pineda, J. Vilarrasa, Org. Lett. 14 (2012) 536-539.

[18] H. Zhang, S.S.V. Ramasastry, F. Tanaka, C.F. Barbas III, Adv. Synth. Catal 350 (2008) 791-796.

[19] M.S. Abaee, M.M. Mojtahedi, V. Hamidi, A.W. Mesbah, W. Massa, Synthesis 40 (2008) 2122-2126.

[20] R.A. Aungst Jr, R.L. Funk, Org. Lett. 3 (2001) 3553-3555.

[21] Y. Yoshimura, K. Asami, H. Matsui, H. Tanaka, H. Takahata, Org. Lett. 8 (2006) 6015-6018.