



Selective aldol condensation or cyclotrimerization reactions catalyzed by FeCl₃



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ABSTRACT

The inexpensive and commercially available FeCl₃ catalyzes the selective homo-aldol condensation of aldehydes into the corresponding α - β unsaturated aldehydes, presumably through an unobserved aldol intermediate. Surprisingly the reaction course can be diverted to produce 1,3,5-trioxanes via aldehyde cyclotrimerization. Selectivity for trioxanes is achieved at lower temperatures and is enhanced by the presence of water, contrary to prior reports. A broad range of aliphatic and aromatic aldehydes are capable of undergoing these transformations; short reaction times, high yields, scalability, and easy purification processes are also described.

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Introduction

Aldol condensation reactions are one of the main synthetic tools for the construction of C–C bonds, both in nature and in synthetic chemistry.¹ The resulting β hydroxy aldehydes are found in many important synthetic targets, including natural products.^{2a} The dehydrated α - β unsaturated aldehyde derivatives are present in important biologically active compounds^{2b} and find important applications in the fields of pharmaceutical, fragrance, plasticizer, detergent, and cosmetic chemistry.³ For example, 2-ethylhexenal is prepared from homo-aldol condensation of butanal. Both 2-ethylhexenal and the product of its hydrogenation (2-ethylhexanol) are valuable commodity chemicals and are used in the synthesis of detergents, plasticizers, coatings, and adhesives. Lastly, the homo-aldol product of pentanal is commercially important and used in the synthesis of plasticizers and detergent alcohols.⁴

However, the generation of homo-aldol condensation products is not a trivial nor straightforward matter as the reactions tend to be non-selective and generally these products are reported as side products from the more useful crossed-aldol reaction.⁵ Thus, a great deal of synthetic effort has been focused in this area. One of the major contributions achieved by the Mukaiyama aldol reaction has been the introduction of the use of enolizable aldehydes.^{6a} This has been the basis for many developments in C–C bond

formation chemistry.^{6b} Nevertheless, the majority of the methods disclosed thus far have reported a reduction in the efficiency of the reaction when enolizable aldehydes are used.⁷

Classically, homo-aldol condensation reactions of aldehydes have been carried out in the presence of aqueous sodium hydroxide⁸ or boric acid in refluxing xylene,⁹ however these conditions are not environmentally friendly since higher concentrations of corrosive residues are produced. In that sense greener alternatives have been described in the literature to catalyze the homo-aldol condensation of aldehydes, for example, the use of pyrrolidine to catalyze the homo-aldol condensation of aliphatic aldehydes; in the presence of benzoic acid or (*p*-dimethylamino)benzoate as cocatalyst.^{10,11} Analogously, diphenylboron perchlorate (Ph₂BClO₄), has been successfully used for self and cross condensation reactions of aliphatic and aromatic aldehydes.¹² Enhanced catalytic activity has been observed employing a heterogeneous catalyst system, 3-*N*-methylaminopropylated mesoporous silica was shown to possess catalytic activity higher than the homogenous amine.¹³ Moreover, the catalyst could be easily recovered by filtration.¹³ Other heterogeneous reactions have been reported using heteropolyacids,¹⁴ chlorinated silica gel,¹⁵ and a solid base catalyst containing aminopropyltrimethoxysilane functionalized chitosan.¹⁶

Further synthetic methodologies for the self condensation of aldehydes have been designed to be used under solvent free conditions; typically microwave irradiation is employed in the presence of catalytic amounts of lysine,¹⁷ and Et₃N–LiClO₄.¹⁸ In general, these synthetic methodologies are applicable to only a small range

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