Note

$ZrCl_4$ as an Efficient Catalyst for Crossed-aldol Condensation of Cyclic Ketones with Aromatic Aldehydes in Refluxing Ethanol

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The aldol condensation reaction of cyclic ketones with aromatic aldehydes in ethanol under reflux conditions using $ZrCl_4$ as a catalyst to afford the corresponding α,α′-bis(substituted benzylidene and cinnamylidene)cycloalkanones in excellent yields has been described. No self-condensation product was produced.

Keywords: Crossed-aldol condensation; $ZrCl_4$; α,β-Unsaturated carbonyl compounds.

INTRODUCTION

The aldol condensation reaction is widely recognized as one of the most important carbon-carbon bond forming reactions in organic synthesis.[1-3] The crossed-aldol condensation is an effective pathway for the synthesis of α,α′-bis(substituted benzylidene)cycloalkanones as precursors for the synthesis of bioactive pyrimidine derivatives.[4] Moreover, this reaction is useful in exploration of the methylene structural unit, which is found in many naturally occurring compounds and antibiotics. Traditionally, the aldol reaction carried out under the influence of strong acids or bases[5] suffers from self condensation of starting material[6] and a reverse reaction.[7] To circumvent these problems, considerable attention has been focused on developing an aldol condensation reaction.

Some metal ions such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) with different ligands have been used for aldol-condensation.[8] Solvent free, microwave irradiation and fluorous solvents have been used for this purpose.[9-11] Recently, the synthesis of α,α′-bis(substituted benzylidene)cycloalkanones has been attracting interest.[12-19] However, some of the methods suffer from one or another disadvantage like long reaction times, low yields, formation of side products and the use of expensive and toxic reagents. Therefore, there is still scope for a newer reagent or catalyst for the condensation of cycloalkanones with aldehydes and ketones.

RESULTS AND DISCUSSION

Recently, more attention has been paid to the application of $ZrCl_4$ chemistry since it is inexpensive, safe, and air and moisture tolerant.[20] In this report, an efficient process of aldol condensation of cyclic ketones like cyclopentanone and cyclohexanone with aromatic aldehydes, containing either electron-releasing or electron-withdrawing groups, catalyzed by $ZrCl_4$ in ethanol under reflux conditions was studied (Scheme I).

Scheme I

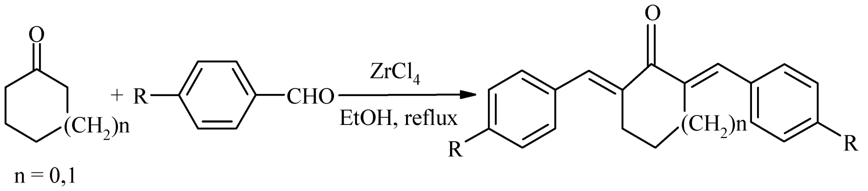

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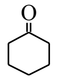
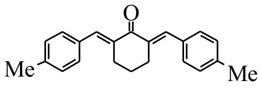
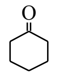
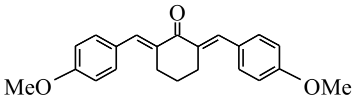
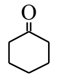
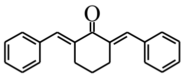
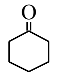
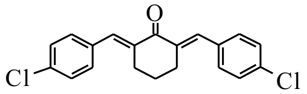
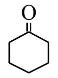
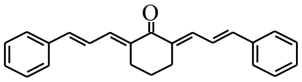
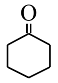
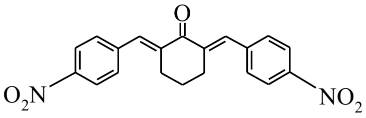
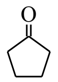
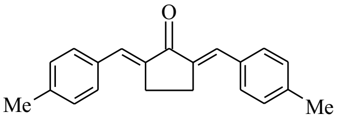
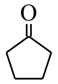
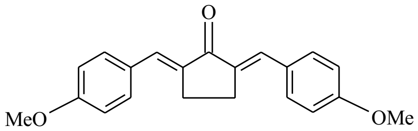
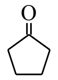
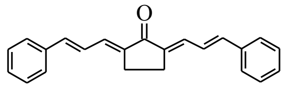
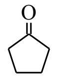
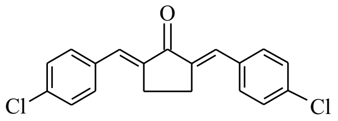
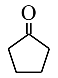
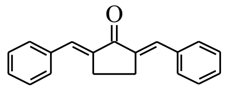
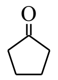
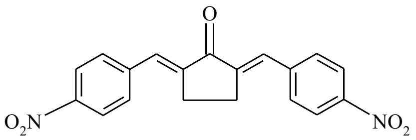
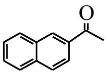
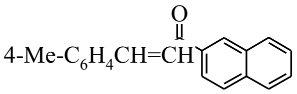
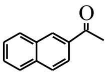
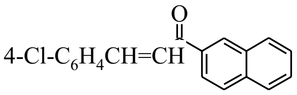
Table 1. Crossed aldol condensation of ketones with aromatic aldehydes in refluxing ethanol using $ZrCl_4$

Entry	Ketone	Aldehyde	Time (h)	Yield (%)	Product	Mp (°C)	
						Reported	Found
1		4-MeC_6H_4CHO	4	95		170[9]	167-168
2		4-$MeOC_6H_4CHO$	4	96		203-204[8]	201-203
3		C_6H_5CHO	5	95		117[8]	115-117
4		4-ClC_6H_4CHO	5	93		147-148[9]	147-148
5		C_6H_5CH=$CHCHO$	2.5	98		180[8]	182-183
6		4-$NO_2C_6H_4CHO$	5.5	90		159[8]	158-160
7		4-MeC_6H_4CHO	2	96		220[13]	220-221
8		4-$MeOC_6H_4CHO$	5	92		210-211[8]	212-214
9		C_6H_5CHO	6	90		188-191[8]	188-190
10		4-ClC_6H_4CHO	5	92		225[13]	223-225
11		C_6H_5CH=$CHCHO$	2	96		222-224[8]	225-227
12		4-$NO_2C_6H_4CHO$	6	90		230[8]	229-231
13		4-MeC_6H_4CHO	7	87	 4-Me-C_6H_4CH=CH	142-143[13]	142-145
14		4-ClC_6H_4CHO	7	85	 4-Cl-C_6H_4CH=CH	163-165[13]	162-164

The results are summarized in Table 1. The reactions were completed within 2-6 h and excellent yields of the products were obtained (entries 1-12). The control experiment indicates that no product of the crossed-aldol condensation could be obtained in the absence of the catalyst. It was found that a catalyst loading of only 0.2 mmol was required to perform the reaction. Under these conditions, no self-condensation of the starting materials was observed. Attempt for monocondensation from one side of the cycloalkanones, in the presence of lower amounts of the aldehydes, was not successful.

The reactions of acyclic ketones such as 2-acetylnaphthalene with aromatic aldehydes were also examined and the products were obtained in excellent yields (Table 1, entries 13 and 14).

When the reactions were examined in different organic solvents such as acetonitrile, dichloromethane, chloroform, water and n-heptane, we found that ethanol was the best solvent due to high yield and shorter reaction times.

In conclusion, the present method is an efficient and selective procedure for the synthesis of α,α'-bis(substituted benzylidene and cinnamylidene)cycloalkanones from cyclic ketones with aromatic aldehydes in refluxing ethanol. A simple procedure and the use of ethanol as a solvent are expected to contribute to the development of more benign crossed-aldol reactions. In addition, using an inexpensive catalyst is another advantage.

EXPERIMENTAL SECTION

General

All yields refer to isolated products. Products were characterized by comparison of their spectroscopic data (^{1}H NMR, IR) and physical properties with those reported in the literature.[8,9,13]

General procedure for crossed-aldol condensation

In a 25 mL round bottomed flask, ketone (1 mmol), aromatic aldehyde (2 mmol) and $ZrCl_4$ (0.4 mmol, 0.092 g) were added, and the solution was stirred magnetically under reflux conditions for an appropriate period of time (Table 1). On completion of the reaction, as indicated by TLC, the mixture was cooled to room temperature. Then 20 mL of water was added to the reaction mixture, and the precipitate thereby formed was filtered. The product was washed with ethanol and recrystallized from ethanol to give the pure products in 85-98% yields.

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REFERENCES

1. Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 2, parts 1.4-1.7.
2. Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
3. Smith, M. B.; March, J. *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure*; John Wiley & Sons: New York, 2001; pp 1218-1224.
4. Deli, J. *Pharmazie* **1984**, *39*, 539.
5. Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1.
6. Nakano, T.; Irifune, S.; Umano, S.; Inada, A.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1987**, *52*, 2239.
7. Hathaway, B. A. *J. Chem. Educ.* **1987**, *64*, 367.
8. Irie, K.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1366.
9. Iranpoor, N.; Kazemi, F. *Tetrahedron* **1998**, *54*, 9475.
10. Zheng, M.; Wang, L.; Shao, J.; Zhong, Q. *Synth. Commun.* **1997**, *27*, 351.
11. Yi, W.-B.; Cai, C. *J. Fluorine Chem*. **2005**, *126*, 1553.
12. Huang, D. F.; Wang, J. X.; Hu, Y. L.; Zhang, Y. M.; Tang, J. *Synth. Commun.* **2002**, *32*, 971.
13. Salehi, P.; Khodaei, M. M.; Zolfigol, M. A.; Keyvan, A. *Monatsh. Chem.* **2002**, *133*, 1291.
14. Wang, S. X.; Li, J. T.; Geng, L. J. *J. Chem. Res. (S)* **2003**, 370.
15. Deng, G. S.; Ren, T. G. *Synth. Commun.* **2003**, *33*, 2995.
16. Salehi, P.; Khodaei, M. M.; Zolfigol, M. A.; Boddaghi Fard, M. A. *J. Braz. Chem. Soc*. **2004**, *15*, 773.
17. Zhang, F. L.; Su, N.; Gong, Y. F. *Synlett* **2006**, 1703.
18. Concellon, J. M.; Concellon, C. *J. Org. Chem*. **2006**, *71*,

4428.

19. Arnold, A.; Market, M.; Mahrwald, R. *Synthesis* **2006**, 1099.
20. Kumar, V.; Kaur, S.; Kumar, S. *Tetrahedron Lett*. **2006**, *47*, 7001.