

ZrOCl₂ as Efficient Lewis Acid for the Condensation Between Dimedone and Aldehydes

SOMAYYEH PIRI and MOHAMMAD REZA POORHERAVI*

Department of Chemistry, University of Payam Noor, Abhar, I.R. Iran

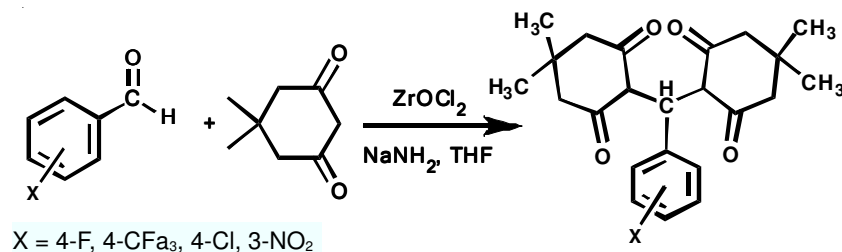
E-mail: mohammad.r.poorheravi@gmail.com

Knoevenagel condensation of benzaldehyde and its derivatives with dimedone was carried out over ZrOCl₂ and NaNH₂. The materials were characterized by ¹H and ¹³C NMR. ZrOCl₂ was found to be a good catalyst for double addition of dimedone to aldehyde. The active methylene group of acetone were chosen to react with benzaldehyde and its derivatives. E-4-Phenylbut-3-en-2-one was found to be the only product of mono Knoevenagel condensation reactions.

Key Words: Heterogeneous catalyst, Knoevenagel condensation, ZrOCl₂, Dimedone.

INTRODUCTION

Knoevenagel condensation is a well-known organic reaction largely employed in order to form C-C bonds for the synthesis of important derivatives in perfume, polymer and pharmaceutical applications¹. Knoevenagel adducts, in fact, are useful intermediates for further transformations, such as Diels-Alder and Michael additions². The reaction is catalyzed by bases, acids or catalysts containing acid-base sites³. Bases such as ammonia, primary amine, secondary amine and their salts⁴ and Lewis acids such as CuCl₂⁵, ZnCl₂⁶ and SmI₃⁷ are some examples that have been employed in Knoevenagel condensation. Alternative procedures employed heterogeneous catalysts, such as zeolites⁸, clays⁹, layered double hydroxides (LDHs)¹⁰, and hydrotalcites¹¹. Various protocols carried out in ionic liquids¹² have also been developed. Herein, we wish to explore a protocol for the synthesis of 2,2'-(phenylmethylene)-bis(5,5-dimethylcyclohexane-1,3-dione) and derivatives using heterogeneous catalyst of ZrOCl₂ and sodium amide under room temperature condition (**Scheme-I**).



Scheme-I

EXPERIMENTAL

NMR spectra were recorded on a Bruker 250 MHz spectrometer using TMS as an internal standard (CDCl₃ solution). All products were characterized by spectra Table-1.

TABLE-1
NMR DATA FOR PRODUCT 1-10

| Product | NMR data |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 1.103 (6H, S), 1.236 (6H, S), 2.385 (8H, M), 5.543 (1H, S), 7.2 (5H, M), 11.89 (2H, ex. with D); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.38, 29.64, 31.40, 32.72, 46.43, 47.40, 115.57, 125.83, 126.75, 128.20, 138.2, 189.35, 190.13. |
| 2 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 1.01 (6H, S), 1.22 (6H, S), 2.34 (8H, M), 5.48 (1H, S), 7.01 (4H, M), 11.8 (2H, ex. With D); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.38, 29.58, 31.38, 32.20, 46.41, 47.04, (114.82, 115.17, D, ² J = 21 Hz), 115.54, (128.17, 128.3, D, ³ J = 8 Hz), (133.56, 133.61, D, ⁴ J = 3.2 Hz), (159.08, 162.96, D, ¹ J = 245 Hz), 189.38, 190.53. |
| 3 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 1.11 (6H, S), 1.23 (6H, S), 2.35 (8H, M), 5.53 (1H, S), 7.3 (4H, M), 11.7 (2H, ex. with D); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.36, 29.55, 31.42, 32.9, 46.41, 47.01, 115.11, (122.01, 126.5, Q, ¹ J = 283 Hz), (125.11, 125.17, 125.23, 125.29, Q, ³ J = 3.6 Hz), 127.1, (127.89, 128.4, Q, ² J = 32.4 Hz), 142.54, 189.44, 190.74. |
| 4 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 1.1 (6H, S), 1.215 (6H, S), 2.37 (8H, M), 5.469 (1H, S), 7.02 (2H, D, ³ J = 8 Hz), 7.24 (2H, D, ³ J = 8 Hz), 11.87 (2H, ex. With D); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.39, 29.59, 31.40, 32.38, 46.39, 47.01, 115.31, 128.18, 128.2, 131.55, 136.68, 189.42, 190.63. |
| 5 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 1.093 (6H, S), 1.412 (6H, S), 2.38 (8H, M), 5.6 (1H, S), 7.41 (4H, M), 11.9 (2H, ex. With D); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.32, 29.67, 31.41, 31.9, 47, 47.01, 114.79, 120.9, 121.01, 122.2, 128.99, 132.93, 148.38, 189.8, 197. |
| 6 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 2.4 (3H, S), 6.6 (1H, D, ³ J = 16 Hz), 7.48 (6H, M); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.52, 127.15, 128.25, 128.58, 130.52, 134.41, 143.44, 198.43. |
| 7 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 2.31 (3H, S), 6.61 (1H, D, ³ J = 16 Hz), 7.26 (5H, M), ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.59, (115.97, 116.32, D, ² J = 21 Hz), 126.8, (130.06, 130.19, D, ³ J = 8 Hz), 130.61, 142.06, (155, 161.2, D, ¹ J = 389.9 Hz), 198.15. |
| 8 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 2.32 (3H, S), 6.83 (1H, D, ³ J = 16 Hz), 7.49 (1H, D, ³ J = 16 Hz), 7.65 (4H, M); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 29.67, (125.15, 125.21, Q, ⁵ J = 3.59 Hz), (125.88, 125.94, Q, ⁴ J = 3.78 Hz), 128.33, (128.5, 130.59, Q, ¹ J = 132 Hz), (129.07, 129.57, Q, ² J = 31.5 Hz), (137.87, 138.25, Q, ³ J = 24 Hz), 141.27, 197.9. |
| 9 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 2.38 (3H, S), 6.68 (1H, D, ³ J = 16 Hz), 7.5 (5H, M), ¹³ C NMR δ _C (63 MHz; CDCl ₃): 27.66, 127.46, 129.25, 129.37, 132.92, 136.42, 141.82, 198.02. |
| 10 | ¹ H NMR δ _H (250 MHz; CDCl ₃): 2.422 (3H, S), 6.86 (1H, D, ³ J = 16 Hz), 7.5 (5H); ¹³ C NMR δ _C (63 MHz; CDCl ₃): 29.2, 29.68, 122.2, 122.5, 124.7, 129.3, 129.5, 130.0, 133.7, 134.0, 139.9, 140.1, 148.1, 148.2, 206.4. |

Preparation of the product 1-10

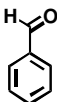
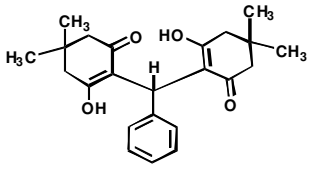
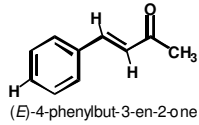
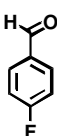
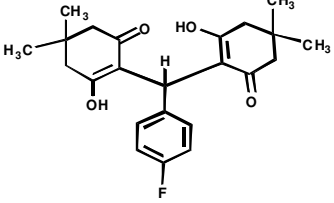
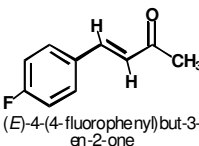
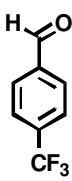
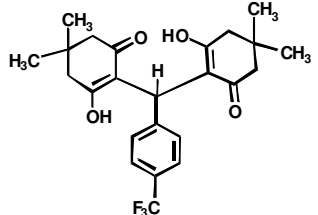
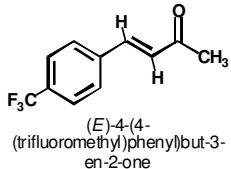
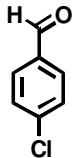
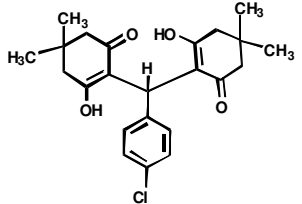
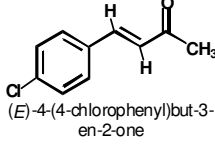
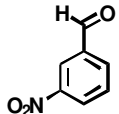
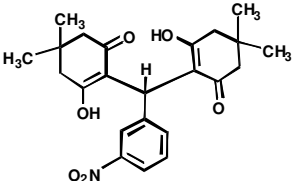
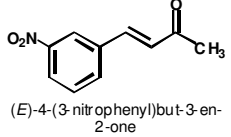
General procedure: A mixture of an appropriate benzaldehyde (1 mmol), dimedone or acetone (1 mmol) and NaNH_2 (2 mmol) in 5 mL THF, were stirred for 1 h. After completion of the reaction which was monitored by TLC, the reaction mixture was poured into water and extracted with diethyl ether (3 mL \times 30 mL). The organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. Column purification (20-30 % EtOAc in petroleum ether) furnished the products.

RESULTS AND DISCUSSION

Methylene active compounds carrying two electron withdrawing groups, such as malononitrile, cyanoacetates, malonates and β -ketoesters, are generally used in the known condensations. However, only few examples of β -diketones as starting materials are reported^{13,14}. Very likely, such compounds are less reactive than the other ones since their attitude to form a stable cyclic enol. To test the reactivity of ZrOCl_2 we chose the reaction of dimedone with several aromatic aldehydes in the presence of sodium amide at room temperature.

The best reaction conditions required the use of a 0.001 mol of aromatic aldehyde and a 0.002 mol of NaNH_2 on the 0.001 ZrOCl_2 in THF to obtain over 80 % of conversion in the desired product. In fact the reaction carried out only in the presence of ZrOCl_2 . The first step is Knoevenagel condensation of dimeone with benzaldehyde and its derivatives, then Michael addition or substitution reaction of another dimeone takes place and product **1-5** is formed (Table-2). When zirconium oxy chloride is used, the condensation of dimedone with aromatic aldehydes proceeds rapidly to give 2,2'-(aryl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) in excellent yield in THF. The presence of an electron-withdrawing group on the aromatic aldehyde, increases the reactivity and very good yields in the desired products were obtained. The catalysts condensation of acetone and aromatic aldehydes gave only (E)-(aryl) but-3-en-2-ones **6-10** (Table-2). Only the reaction of 3-nitrobenzaldehyde produced by-product, traces of isomer (Z)-4-(2-nitrophenyl)but-3-en-2-one of the desired product (E)-4-(3-nitrophenyl)but-3-en-2-one, was observed. In conclusion, we have demonstrated interesting application of ZrOCl_2 to act as a Lewis acid in promoting the synthesis of 2,2'-(aryl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) via a Knoevenagel condensation between poorly reactive β -diketones and aromatic aldehydes then Michael addition or substitution reaction of another dimeone. The reaction conditions are very mild, in fact the condensation works at room temperature. Products **1-5** were not produce in the absence of ZrOCl_2 . Notably, reaction of dimeone with aromatic aldehyde led only to the 2,2'-(aryl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) products, any side product was never detected. In addition, the reaction with actone gave generally only the Knoevenagel condensation product, in contrast to other reported examples.

TABLE-2
 SYNTHESIS OF PRODUCT 1-10 USING $ZrOCl_2$ CATALYSTS

| Aldehyde | Dimedone product | Acetone product |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  |  2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 1 |  (<i>E</i>)-4-phenylbut-3-en-2-one 6 |
|  |  2,2'-((4-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 2 |  (<i>E</i>)-4-(4-fluorophenyl)but-3-en-2-one 7 |
|  |  2,2'-((4-(trifluoromethyl)phenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 3 |  (<i>E</i>)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one 8 |
|  |  2,2'-((4-chlorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 4 |  (<i>E</i>)-4-(4-chlorophenyl)but-3-en-2-one 9 |
|  |  2,2'-((3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) 5 |  (<i>E</i>)-4-(3-nitrophenyl)but-3-en-2-one 10 |

REFERENCES

1. L.F. Tietze, U. Beifuss, In *Comprehensive Organic Synthesis*, Pergamon: New York, Vol. 2, pp. 341-394 (1991).
2. L.F. Tietze, *Chem. Rev.*, **96**, 115 (1996).
3. R.L. Reeves and S. Patai, *The Chemistry of Carbonyl Compounds*, Interscience Publishers, New York, p. 567 (1996).
4. G. Jones, *Organic Reactions*, A.C. Cope, 15, John Wiley and Sons, New York, p. 204 (1967).
5. O. Attanasi, P. Fillippone and A. Mei, *Synth. Commun.*, **13**, 1203 (1983).
6. P.S. Rao and R.V. Venkatratnam, *Tetrahedron Lett.*, **32**, 5821 (1991).
7. W. Bao, Y. Zhang and J. Wang, *Synth. Commun.*, **26**, 3025 (1996).
8. S. Saravanamurugan, M. Palanichamy, M. Hartmann and V. Murugesan, *Appl. Catal. A*, **298**, 8 (2006).
9. F. Bigi, L. Chesini, R. Maggi and G. Sartori, *J. Org. Chem.*, **64**, 1033 (1999).
10. M.L. Kantam, A. Ravindra, Ch. Venkat Reddy, B. Sreedhar and B.M. Choudary, *Adv. Synth. Catal.*, **348**, 569 (2006).
11. M.L. Kantam, B.M. Choudary, Ch. Venkat Reddy, K.K. Rao and F. Figueras, *Chem. Commun.*, 1033 (1998).
12. B.C. Ranu and R. Jana, *Eur. J. Org. Chem.*, 3767 (2006).
13. S. Kantevari, R. Bantu and L. Nagarapu, *J. Mol. Catal. A: Chem.*, **269**, 53 (2007).
14. C. Su, Z.-C. Chen and Q.-G. Zheng, *Synthesis*, 555 (2003).

(Received: 19 March 2010; Accepted: 31 July 2010) AJC-8930