Pergamon

Tetrahedron 54 (1998) 9475–9480

TETRAHEDRON

RuCl$_3$ Catalyses Aldol Condensations of Aldehydes and Ketones

Nasser Iranpoor*, Foad Kazemi

Chemistry Department, College of Sciences, Shiraz University, Shiraz 71454, Iran

Received 15 April 1998; revised 4 June 1998; accepted 11 June 1998

Abstract: Anhydrous RuCl$_3$ catalyses the efficient cross aldol condensations of different ketones with various aromatic aldehydes in sealed tube under solvent free conditions without the occurrence of any self condensations. Regioselective self condensation reaction of some ketones and aldehydes are also described. The catalytic effect of Ru(III) is shown by performing similar reactions under thermal conditions without catalyst.

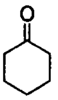
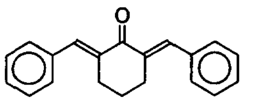
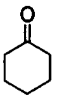
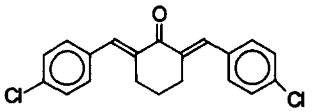
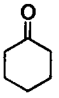
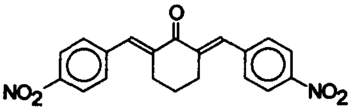
Aldol-condensation reactions are important synthetic reactions and in classical methods, they were performed in the presence of strong acids or bases.[1] In order to do these reactions under neutral conditions, some metal ions are used as catalyst or reagent.[2-6] Due to the importance of methylene structural unit which are found in many naturally occurring compounds and antibiotics and the use of α,α'-bis(substitued) benzylidene cycloalkanones as precursors for synthesis of bioactive pyrimidine derivatives,[7a,b] condensation of cyclopentanone and cyclohexanone with aldehydes and ketones were of special interest. For this purpose, a few catalytic procedure are reported, but these methods usually suffer from some disadvantages. For example, the use of different complexes of metal(II) ions,[3] such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) with different ligands have been used for aldol-condensations.

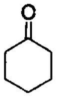
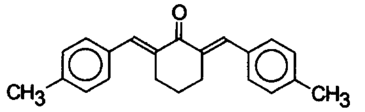
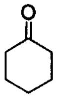
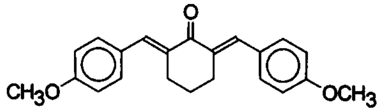
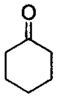
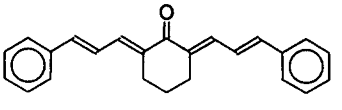
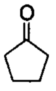
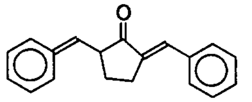
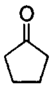
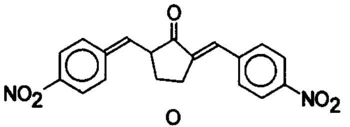
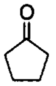
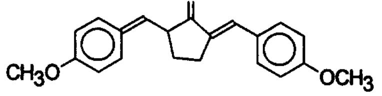
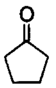
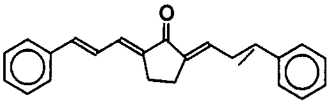
Among these complexes, Co(II)-bipyridyl has been found to be more reactive, but it was mostly used for condensation reactions of aromatic aldehydes and only acetophenone in DMF. The yield of condensation reaction of cycloalkanones such as cyclopentanone with benzaldehyde in the presence of Co-bpy complex is only 38%. Similarly the yield of condensation of cyclohexanone with aromatic aldehydes in the presence of Rh(III) porphyrine is reported to be 30%. The use of Cp_2ZrH_2 in combination with metal salts such as $NiCl_2$ in autoclave (120 °C, 10h) and under inert atmosphere for aldol-condensation of cycloalkanones is also reported.[8] In this reaction, the occurrence of self-condensation as a side reaction is also observed. The use of bis(*p*-ethoxyphenyl)telluroxide (BMPTO) as catalyst has also been reported for cross condensation of cyclohexanone and cyclopentanone with aromatic aldehydes under microwave irradiation.[9] With this method, in most cases, the obtained yields for cross-condensation of cyclohexanone are not very good.

0040-4020/98/$19.00 © 1998 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(98)00575-4

In the course of our studies on the reaction of epoxides catalyzed with Ru(III),[10] it was observed that self-condensation of acetone as the solvent occurs as a side reaction. On the basis of this observation, we studied the possibility of using Ru(III) as a catalyst for aldol condensation reactions. In this paper, we wish to report that Ru(III) as anhydrous $RuCl_3$ can effectively catalyze both cross and self-condensation reactions of different aldehydes and ketones including cycloalkanones. We studied the cross-condensations of cyclopentanol and cyclohexanol with different aromatic aldehydes such as, benzaldehyde, p-chlorobenzaldehyde, p-nitrobenzaldehyde, p-methyl-benzaldehyde, p-methoxybenzaldehyde and cinnamaldehyde with 0.02 molar equivalents of anhydrous $RuCl_3$ in sealed tube at 120 °C. The reactions were finished within 4-24h and excellent yields (90-97%) of α,α'- bis(substitued) benzylidene and cinnamylidene cyclopentanones and cyclohexanones were obtained. The results are shown in Table 1. Under these conditions, no self-condensation was observed. Different attempts to do selective mono-condensation from only one side of cyclopentanone or cyclohexanone was not successful and a mixture of mono- with some di-aldol products were obtained. The enhanced effect of using sealed tube conditions on the rates and yields of these condensations was shown by performing some reactions in solvent and also in the absence of solvent but not in the sealed tube. When cyclohexanone was reacted with benzaldehyde and 0.2 molar equivalents of Ru(III) under reflux conditions in acetonitrile, no product was obtained after several days. In another experiment, the same reaction was performed with 0.02 molar equivalents of Ru(III) at 120 °C in the absence of solvent and in a flask. After 4 days, only 30% of the aldol product was obtained. In comparison, this reaction with 0.02 molar equivalents of Ru(III) and in sealed tube produces 92% of the condensation product after 10h. The catalytic effects of Ru(III) in these reactions was also shown by performing some of these reactions in sealed tube but in the absence of catalyst. The results of these observations are shown in Table 1

Table 1. Reaction of Various Aromatic Aldehydes with Acyclic Ketones in the Presence of 0.02 Molar Equivalents of Ru(III) in Sealed Tube at 120 °C.

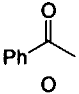
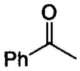
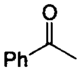
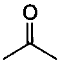
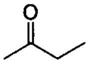
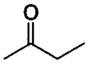
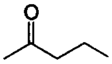
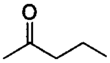
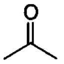
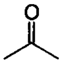
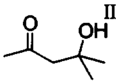
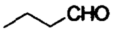
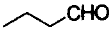
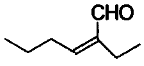
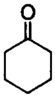
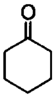
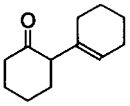
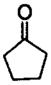
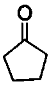
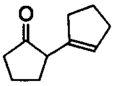
Entry	Starting Material	Time,h/Yield % ^{I}	Product^{II}	mp (°C)
1	 + PhCHO	6 / 95		116-117 (Lit.[9] 117)
2	 + $4\text{-}ClC_6H_4CHO$	12 / 94		147-148 (Lit.[11] 147-148)
3	 + $4\text{-}NO_2C_6H_4CHO$	24 / 96		158.5 (Lit.[9] 159)

4		+ 4-$CH_3C_6H_4CHO$	4 / 93		170 (Lit.[12] 170.1)
5		+ 4-$CH_3OC_6H_4CHO$	12 / 94		204 (Lit.[9]203-204)
6		+ cinnanaldehyde	8 / 95		179 (Lit.[9] 180)
7		+ PhCHO	10 / 92		188.5 (Lit.[9] 188-189)
8		+ 4-$NO_2C_6H_4CHO$	24 / 95		230 (Lit.[9] 230-231)
9		+ 4-$CH_3OC_6H_4CHO$	10 / 94		212 (Lit.[9] 210-211)
10		+ cinnamaldehyde	8 / 97		223 (Lit.[9] 222-224)

[I] The reactions of entries 3 and 10 were performed without catalyst. Reaction time for entry 3 was found to be 120h with 90% yield and the reaction time for entry 10 was found to be 82 h with 89% yield. [II] The products were isolated and identified by their ir, nmr and their mass spectra.

In order to ascertain the scope and limitations this catalyzed condensation, the method was further applied to the condensation of aliphatic and aromatic ketones with aromatic aldehydes. We first studied the condenasation of acetophenone with different aromatic aldehydes with 0.02 molar equivalents of Ru(III) in sealed tube at 120 °C. Although reaction times are longer than the reactions of cycloalkanols, but the condensation products were obtained in excellent yield (Table 2, Entries 1-3). Similar reactions in the presence of Cu(II) or Cu(II) with coexistance of Zn(II) have been reported to failed to give any product after 139h. The same condensations catalyzed with Co-bpy have been performed in the presence of aromatic aldehyes(1.875 mmol) and excess of benzophenone(5 ml) in DMF(5 ml) at 80 °C in moderate to high yields. It was known that the base-catalyzed reactions of 2-butanone with benzaldehyde gave preferentially the condensation product at C_1 of ketone, while, the acid catalyzed reaction occurred preferentially at C_3. The obtained results from condensation of 2-butanone and 2-pentanone with different aromatic aldehydes showed excellent regioselectivity with the occurrence of condensation from C_3. The results of condensation reactions of acyclic ketones are shown in Table 2.

Table 2. Table 1. Reaction of Aromatic Aldehydes with Acyclic Ketones in the Presence of 0.02 Molar Equivalents of Ru(III) in Sealed Tube at 120 °C.

Entry	Ketone	Aldehyde	Time,h / Yield%	Product	mp or bp (°C)
1		PhCHO	72 / 90	PhCH=CHCOPh	55-57 (Lit [5], 55-58)
2		$4\text{-}CH_3C_6H_4CHO$	72 / 92	$4\text{-}CH_3C_6H_4CH{=}CHCOPh$	98.5-99 (Lit [5], 97-98)
3		$4\text{-}CH_3OC_6H_4CHO$	72 / 94	$4\text{-}CH_3OC_6H_4CH{=}CHCOPh$	75-76 (Lit [5], 75-77)
4		PhCHO	24 / 85	$PhCH{=}CHCOCH_3$	41-41.5 (Lit [2], 41-42)
5		PhCHO	16 / 90	$PhCH{=}C(CH_3)COCH_3$	38-39 (Lit [13], 37-38)
6		$4\text{-}CH_3OC_6H_4CHO$	16 / 93	$4\text{-}CH_3OC_6H_4CH{=}C(CH_3)COCH_3$	150-152/7 torr) (Lit [13], 173-174/12 torr)
7		PhCHO	16 / 91	$PhCH{=}C(C_2H_5)COCH_3$	130-135/12 torr (Lit.[14], 144-145/22 torr)
8		$4\text{-}CH_3OC_6H_4CHO$	16 / 95	$4\text{-}CH_3OC_6H_4CH{=}CH(Et)COCH_3$	155-158/7 torr (Lit.[14],178-170/12 torr
9			24 / 90	[II] 	NMR: 3.2 (IH, s), 2.5(2H, s), 2.1 (3H, s),1.2 (6H, s); IR; OH: 3450, C=O:1705 cm^{-1}. [15]
10			4 / 95		164-165/10 torr (Lit[16], 155-160/9 torr
11	 (III)		48 / 82		141-144/13 torr (Lit[6], 142/13 torr)
12	 (III)		48 / 80		120-124/12 torr (Lit [8], IR: 2930, 2850, 1445,1120 cm^{-1}.

[I] Isolated yields. [II] Reaction occurs under reflux condition in the flask.
[III] 5-8% of α-β-unsaturated ketones were also obtained from self-condensation of cyclopentanone and cyclohexanone.

Self-condensations of ketones and aldehydes were also studied with this catalyst. Self-condensation of acetone occurred under reflux conditions in flask and therefore, under these conditions no dehydration was observed (Table 2, Entry 9). Other acyclic and cyclic ketones and aldehydes were self-condensed in sealed tube and high yields of the dehydrated products were obtained (Table 2, Entries 10-12). In conclusion, the possibility of performing cross-and self-condensations in excellent yields, easy work-up and excellent regioselectivity make this method a useful addition to the present methodologies.

Experimental: Products were characterized by comparison of their physical data M.P, IR, NMR and mass spectra with those prepared accordance with the literature procedures. Infrared spectra were recorded on a Perkin Elmer IR-157 G and a Perkin Elmer 781 spectrometer. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX.

General procedure for cross-aldol condenation of cycloalkanones with aldehydes catalyzed with $RuCl_3$ in sealed tube: Cycloalkanone (5 mmol), aldehyde (10.1 mmol) and anhydrous $RuCl_3$ (0.1 mmol) were placed in a glass tube and sealed. The sealed tube was placed in an oil bath and heated at 120 °C for 4-24 h. After cooling to room temperature, the sealed tube was opened. The reaction mixture was purified by either of the following procedures: (a) The reaction mixture was powdered and poured into cold ethanol (25 ml) and stirred for 5 min. and filtered. The crystalline product was further washed subsequently with water, 10% aqueous sodium bicarbonate, water, cold ethanol and dried. (b) The reaction mixture was added to 10% aqueous sodium bicarbonate (10 ml). The product was extracted with $CHCl_3$ (3x20ml). The organic solution was washed with water, dried with anhydrous sodium sulfate and evaporated. Recrystalization of the product with ethanol or chromatography on a short column of silica-gel afforded the crystalline products (92-96%).

Cross-aldol condensation reactions of cyclopentanone with benzaldehy as typical procedure: A glass tube containing cyclopentanone (0.421 g, 5 mmol) and benzaldehyde (1.072 g, 10.1 mmol) and anhydrous $RuCl_3$ (0.021 g, 0,1 mmol) were placed in a glass tube and sealed. The sealed tube was placed in an oil bath and heated at 120 °C for 10 h. After cooling to room temperature, the sealed tube was opened. The reaction mixture was powdered and poured into cold ethanol (25 ml) and filtered. The crystalline product was further washed subsequently with water, 10% aqueous sodium bicarbonate, water and cold ethanol and dried (1.23 g, 95%, m.p. 188-188.5 °C, Lit.[9] 188-189 °C). The obtained bright yellow crystals are very pure but further purification can be done by recrystalization in ethanol. The obtained yield after recrystalization was found to be 1.197 g, 92% (m.p. 189 °C).

Acknowledgment: We are thankful to Shiraz University Research Council for partial support of this work. The assistance of Mr. N. Maleki for running the NMR spectra and Dr.A. A. Jarahpoor for running mass spectra is also acknowledged.

References:

1. (a) Nielsen, A. T.; Houlihan, W. *J. Org. React.* **1968**, *16*, 1. (b) Reeves, R. L. *Chemistry of Carbonyl Group*, S. Patai (ed.), Wiley Intersciences, New York, 1966, 580-593.
2. Iwata, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1369.
3. Irie, K.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1366.
4. Kelleher, G.; Mc Kerrey, M. A.; Vibuljan, P. *J. Chem. Soc. Chem. Commun.* **1980**, 486.
5. Watanabe, K.; Imazawa, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3208.
6. Chuit, C.; Corriu, P. J. P.; Reye, C. *Synthesis* **1983**, 294.
7. Deli, J.; Lorand, T.; Szabo, D.; Foldesi, A. *Pharmazi* **1984**, *39*, 539.
8. Nakamo, T.;. Irifune, S.; Umano, S.; Inada, A.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1987**, *52*, 2239.
9. Zeheng, M.; Wang, L.; Shao, J.; Zhong, Q. *Synthetic Commun.* **1997**, *27*, 351.
10. Iranpoor, N.; Kazemi, F. *Tetrahedron* **1997**, 53, 11377.
11. Huitric, A. C.; Kulmler, W. D.; *J. Am. Chem. Soc.* **1956**, *78*, 614.
12. Garlan, C. E.; Emmet Reid, E.; *J. Am. Chem. Soc.* **1925**, *47*, 2335.
13. Woodruft, E. H.; Conger, T. W. *J. Am. Chem. Soc.* **1938**, 60, 465.
14. Bogert, M. T.; Davidsen, D. *J. Am. Chem. Soc.* **1932**, *54*, 334.
15. Conant, J. B.; Tuttle, N. *Org. Synthesis, Coll. Vol. 1*, 1941, 199.
16. Roch, R. A.; Ralph, P. A. U.S. pat. 2, 982, 784; C. A. **1961**, *55*, 20962.