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Aldol Condensation of Cycloalkanones with Aromatic Aldehydes Catalysed with $TiCl_3(SO_3CF_3)$†

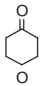
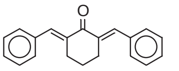
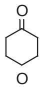
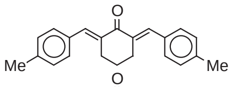
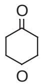
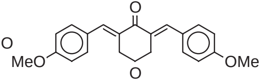
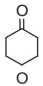
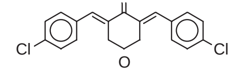
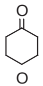
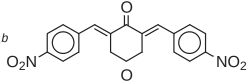
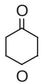
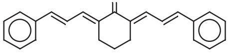
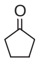
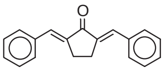
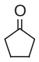
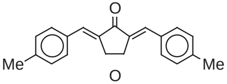
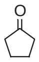
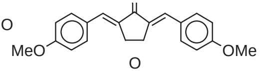
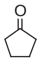
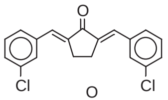
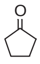
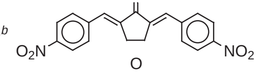
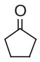
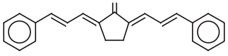
N. Iranpoor,* B. Zeynizadeh, and A. Aghapour

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

Efficient cross-aldol condensation of cyclopentanone, cyclohexanone and 1-indanone with various aromatic aldehydes is catalysed with $TiCl_3(SO_3CF_3)$ at room temperature in excellent yields.

Owing to the importance of the methylene structural unit found in many naturally occurring compounds and antibiotics and the use of α,α'-bis(substituted)benzylidene-cycloalkanones as precursors for synthesis of bioactive pyrimidine derivatives,[1] the condensation of cyclopentanone and cyclohexanone with aromatic aldehydes is of special interest. In addition to the use of strong acidic or basic conditions[2a–d] for aldol-condensation reactions, the use of some metal ions or organometallic compounds as catalyst or reagent has been reported.[3–9] Very recently, we reported the use of anhydrous $RuCl_3$ as catalyst for cross-aldol condensation of aliphatic cycloalkanones and aromatic aldehydes but the reaction was performed in a sealed tube at 120 °C.[10]

Table 1 Cross-condensation of cycloalkanones and aromatic aldehydes catalysed with $TiCl_3(SO_3CF_3)$ at room temperature under solvent-free conditions

Entry	Ketone	Aldehyde	Product	Mol% of catalyst/*t* (h)/ yield(%)[a]	Ref.
1		+ PhCHO		10/0.7/99	9
2		+ $4-MeC_6H_4CHO$		10/0.3/98	13*a*
3		+ $4-MeOC_6H_4CHO$		15/0.8/99	9
4		+ $4ClC_6H_4CHO^b$		10/2/96	14
5		+ $4-N_2OC_6H_4CHO^b$		10/1.5/97	9
6		+ PhCH=CHCHO		10/1/98	9
7		+ PhCHO		15/1.5/96	9
8		+ $4-MeC_6H_4CHO$		15/1/98	13*b*
9		+ $4-MeOC_6H_4CHO$		15/2/97	9
10		+ $3-ClC_6H_4CHO$		15/2.2/99	13*c*
11		+ $4-O_2NC_6H_4CHO^b$		15/2.5/95	9
12		+ PhCH=CHCHO		15/3/94	9

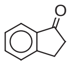
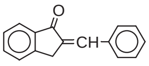
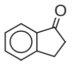
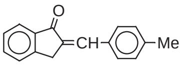
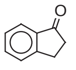
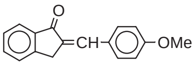
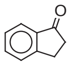
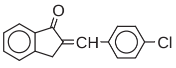
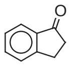
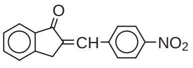
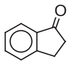
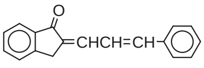
[a]Yield refers to isolated product. [b]The reaction was performed in CH_2Cl_2 (3 ml).

In the course of our studies[11] on catalytic reactions of $TiCl_3(SO_3CF_3)$[12] we observed that this compound can act as a very efficient catalyst for cross-aldol condensation reaction of cycloalkanones with aromatic aldehydes without occurrence of any self-condensation of ketones. Cyclopentanone and cyclohexanone as examples of aliphatic and 1-indanone as an example of aromatic cycloalkanones were condensed with different aromatic aldehydes such as benzaldehyde, 4-chloro-, 4-nitro, 4-methyl- and 4-methoxy-benzaldehyde and cinnamaldehyde in the presence of 0.1–0.2 molar equivalent of $TiCl_3(SO_3CF_3)$ at room temperature under solvent free conditions or in dichloromethane. The yields of the aldol products obtained were found to be excellent. The results obtained for condensation of cyclohexanone and cyclopentanone are shown in Table 1. The condensation reactions of solid aldehydes such as 4-chloro- and 4-nitro-benzaldehyde were performed in CH_2Cl_2 (Table 1, Entries 4, 5, 11; Table 2, Entries 4, 5). Different attempts to do selective monocondensation from only one side of cyclopentanone or cyclohexanone were not successful and mixtures of mono- and di-aldol products were obtained.

Condensation of 1-indanone with aromatic aldehydes was also performed at room temperature in excellent yields. The results obtained are shown in Table 2.

In order to compare the reactivity of $TiCl_3(SO_3CF_3)$ with $TiCl_4$, the reaction of cyclohexanone with 4-chlorobenzaldehyde was studied in the presence of 10

Table 2 Cross-condensation of 1-indanone and aromatic aldehydes with 20 mol% of $TiCl_3(SO_3CF_3)$ at room temperature under solvent-free conditions

Entry	Ketone	Aldehyde	Product	*t* (h)/yield(%)[a]	Ref.
1		+ PhCHO		3.5/96	15
2		+ $4-MeC_6H_4CHO$		2.8/97	16
3		+ $4-MeOC_6H_4CHO$		2.5/96	16
4		+ $4-ClC_6H_4CHO^b$		3/97	17
5		+ $4-O_2NC_6H_4CHO^b$		2.3/97	18
6		+ PhCH=CHCHO		5/96	19

[a]Yield refers to isolated product. [b]The reaction was performed in CH_2Cl_2 (3 ml).

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* To receive any correspondence (*e-mail*: iranpoor@chem.susc.ac.ir).

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 3 Comparison of the condensation reaction of *p*-chlorobenzaldehyde and cyclohexanone in the presence of different catalysts

Entry	Catalyst	Mole% of catalyst	*t*/h	*T*/°C	Yield (%)
1	$TiCl_3(SO_3CF_3)$	10	2	25	96
2	$TiCl_4$	10	4	25	20
3	CF_3SO_3H	10	2	25	25
4	aq. 85% H_2SO_4	10	2	25	45
5	HCl	30	2	25	25
6	$HCl/CF_3SO_3H/SiO_2$	30/10/10	2	25	35
7	$Ba(OH)_2^{2c}$	–	1	reflux	95–98
8	$RuCl_3^{10}$	2	12	120/sealed	94
9	Co(II)/bipyridyl/DMF[4]	10	5	80	52

Concentration of HCl entries 5 and 6 was calculated with the assumption that hydrolysis of $TiCl_3(SO_3CF_3)$ produces three molar equivalents of HCl, one molar equivalent of CF_3SO_3H and one molar equivalent of SiO_2. Except in entries 1, 7 and 8 the yield is referred to GC yield. The reaction was performed under the same reaction conditions as with $TiCl_3(SO_3CF_3)$. The reaction condition was according to the literature.[4]

mole% of $TiCl_4$ under the same reaction conditions as with $TiCl_3(SO_3CF_3)$ (Table 3, Entry 2). The reaction was not complete and only 20% of the product was obtained after 4 h. Addition of 10 mole% of triethylamine did not improve the yield of the reaction. This observation is similar to the results reported for condensation of aromatic aldehydes and aromatic ketones in a non-catalytic reaction with $TiCl_4$.[20] In comparison, the same reaction with $TiCl_3(SO_3CF_3)$ produces the condensation product in 96% yield after 2 h (Table 1, Entry 4). This result ruled out the possibility that the reaction may be catalysed by the water which is produced through the condensation reaction since both $TiCl_4$ and $TiCl_3(SO_3CF_3)$ can hydrolyse in the presence of water.[12] To obtain further evidence, we studied the effects of different acidic catalysts on the condensation reaction of *p*-chlorobenzaldehyde with cyclohexanone. The results of this study are in Table 3. Comparison of the results obtained by our method with some of those reported show the efficiency of this method.

In conclusion, the possibility of performing efficient and catalytic cross-condensations of both aliphatic and aromatic cycloalkanones with aromatic aldehydes at room temperature with excellent yields, easy procedure and simple work-up and ease of handling of $TiCl_3(SO_3CF_3)$ as a solid titanium(IV) compound make this reagent a very suitable catalyst for this type of reactions.

Experimental

All the products are known compounds and were characterized by comparison of their physical data with those of known samples. Infrared spectra were recorded on Perkin-Elmer IR-1I57 G and 781 spectrometers, NMR spectra on a Bruker Avance DPX-250 and mass spectra on a Shimadzu GCMS-QP 1000 EX.

General Procedure.—In a round bottomed flask was placed a mixture of ketone (5 mmol) and aldehyde (10 mmol). Then 0.5–0.75 mmol of $TiCl_3(SO_3CF_3)$ was added and stirred at room temperature for 0.3–3 h [in the case of solid aldehydes (Tables 1, 2), CH_2Cl_2 (3 ml) was also added]. The completion of the reaction was monitored with GLC or TLC. The mixture was dissolved in 20 mL of acetone–water (40:1) and filtered. The acetone solution was dried with anhydrous sodium sulfate. The solvent was evaporated and the residue chromatographed on a short column of silica gel using $CCl_4-CH_2Cl_2$ (3:2) as eluent. The product was obtained as yellow crystals in 94–99% yield (Tables 1, 2).

Typical Procedure for Cross-aldol Condensation of Cyclohexanone and Benzaldehyde.—To a mixture of cyclohexanone (0.49 g, 5 mmol) and benzaldehyde (1.06 g, 10 mmol), $TiCl_3(SO_3CF_3)$ (0.15 g 0.5 mmol) was added and stirred at room temperature for 42 min until solidification. The completion of the reaction was monitored with GLC or TLC, taking small samples and dissolving in dichloromethane. The mixture was dissolved in 20 mL of acetone–water (40:1) and filtered. After drying the organic solution with anhydrous sodium sulfate, the solvent was evaporated and the residue chromatographed on a short column of silica gel using $CCl_4-CH_2Cl_2$ (3:2) as eluent. The pure 2,6-dibenzylidenecyclohexanone was obtained as yellow crystals in 99% yield (1.35 g), mp 116–117 °C (lit.[9] 117 °C).

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References

1 J. Deli, T. Lorand, D. Szabo and A. Foldesi, *Pharmazie*, 1984, **39**, 539.

2 (*a*) A. T. Nielsen and W. Houlihan, *J. Org. React.*, 1968, **16**, 1; (*b*) R. J. Murray N. H. Cromwell, *J. Org. Chem.*, 1976, **41**, 3540; (*c*) J. V. Sinisterra and A. Garcia-Raso, *Synthesis*, 1984, 502; (*d*) R. L. Reeves, *Chemistry of Carbonyl Group*, ed. S. Patai, Wiley-Interscience, New York, 1966, p. 580.

3 M. Iwata and S. Emoto, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1369.

4 K. Irie and K. I. Watanabe, *Bull. Chem. Soc. Jpn*, 1980, **53**, 1366.

5 R. G. Kelleher, M. A. McKervey and P. J. Vibuljan, *J. Chem. Soc., Chem. Commun.*, 1980, 486.

6 K. I. Watanabe and A. Imazawa, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3208.

7 C. Chuit, R. T. P. Corriu, C. Reye, *Synthesis*, 1983, 294; R. Mahrwald and H. Schick, *Synthesis*, 1990, 593.

8 T. Nakamo, S. Irifune, S. Umano, A. Inada, Y. Ishii and M. Ogawa, *J. Org. Chem.*, 1987, **52**, 2239.

9 M. Zeheng, L. Wang, J. Shao and Q. Zhong, *Synth. Commun.*, 1997, **27**, 351.

10 N. Iranpoor and F. Kazemi, *Tetrahedron*, 1998, **54**, 9475.

11 N. Iranpoor and B. Zeynizadeh, *J. Chem. Res.*, 1998, 466; *Synlett*, 1998, 1079.

12 R. Noftle and G. H. Cady, *Inorg. Chem.*, 1966, **5**, 2182.

13 (*a*) C. E. Garlan and E. Emmet Reid, *J. Am. Chem. Soc.*, 1925, **47**, 2335; (*b*) A. Maccioni and E. Marongiu, *Ann. Chim. (Rome)*, 1958, **48**, 557; *Chem. Abstr.*, 1959, **53**, 5227i; (*c*) N. P. Buu-Hoi and N. D. Xoung, *Bull. Soc. Chim. Fr.*, 1958, 758.

14 A. C. Huitric and W. D. Kulmler, *J. Am. Chem. Soc.*, 1956, **78**, 614.

15 D. N. Kevill, E. D. Weiler and N. H. Cromwell, *J. Org. Chem.*, 1964, **29**, 1276.

16 D. N. Kevill, E. D. Weiler and N. H. Cromwell, *J. Am. Chem. Soc.*, 1966, **88**, 4489.

17 N. P. Buu-Hoi and N. D. Xoung, *J. Chem. Soc.*, 1952, 2225.

18 G. A. Coppens, M. Coppens, D. N. Kevill and N. H. Cromwell, *J. Org. Chem.*, 1963, **28**, 3267.

19 R. Huisgen and W. Rapp, *Chem. Ber.*, 1952, **85**, 826.

20 C. R. Harrison, *Tetrahedron Lett.*, 1987, **28**, 4135.