Tetrahedron Letters,Vol.28,No.36,pp 4135-4138,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

# TRANSIENT TITANIUM ENOLATE ALDOL CONDENSATIONS

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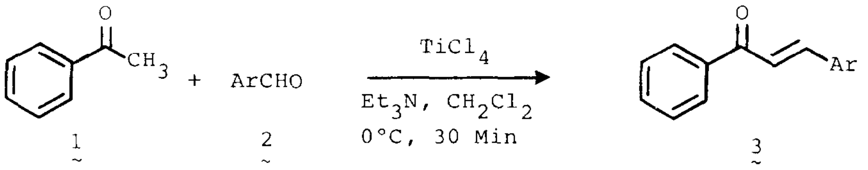
Abstract: A convenient method is described for the generation and subsequent reaction of a proposed titanium enolate with aromatic aldehydes.

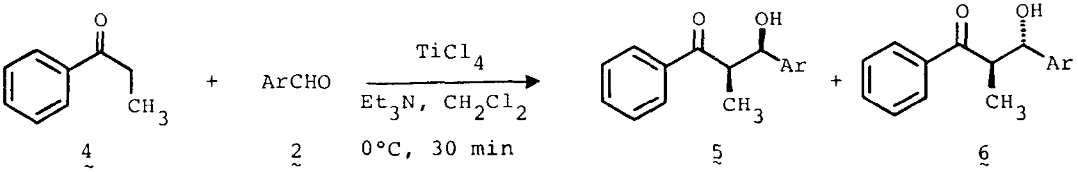
The use of titanium enolates to effect stereoselective aldol condensation reactions has been the subject of recent attention.[1] The titanium enolates provide aldol products with good stereoselectivity as a function of enolate geometry.[1a,b] A minor drawback of this reaction is the need to preform the titanium enolate by either reaction of a silyl enol ether[1c] or the lithium enolate[1d] with a titanium reagent and then further manipulation[2] of these titanium enolates is required prior to condensation with aldehydes. A more convenient method is needed for the generation and use of titanium enolates.[3] Herein we report the results of our study concerning the *in situ* generation of a titanium enolate and concomitant condensation with aromatic aldehydes.

Acetophenone and benzaldehyde were added to a cooled solution of titanium tetrachloride in methylene chloride.[4] Immediately following, one equivalent of triethylamine was added dropwise and the reaction was stirred at 0°C for 30 minutes. After workup, the chalcone derivative, 3, was isolated in 88% yield.



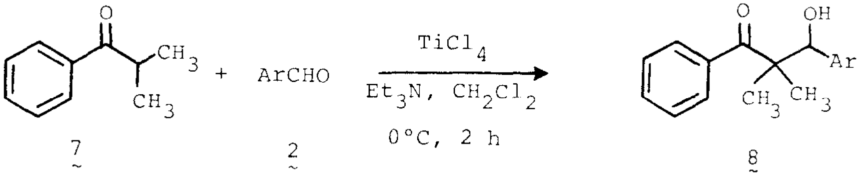
1 2 3

This reaction proved to be general with other aromatic aldehydes,[5] (Table I, entries 1-5). As expected, exclusion of either titanium tetrachloride or triethylamine resulted in no product formation. When propiophenone was reacted with benzaldehyde, under the same conditions, no chalcone derivatives were isolated. The only products isolated were the β-hydroxy ketones 5 and 6 in 91% yield as a 95:5 mixture of syn:anti stereoisomers.

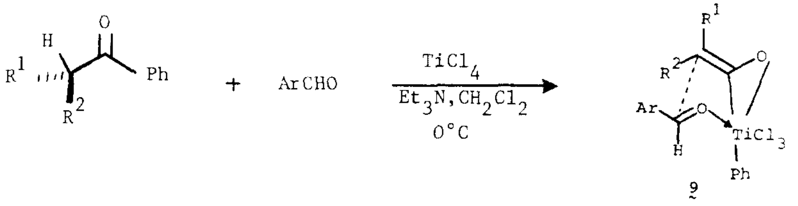


4 2 5 6

This reaction, also, was found to proceed with other aromatic aldehydes[5] providing syn selective products, (Table I, entries 6-10). When isobutyrophenone and benzaldehyde were treated with titanium tetrachloride and then triethylamine, the expected β-hydroxy ketone, 8, was isolated in 98% yield. Reaction of isobutyrophenone with other aromatic aldehydes[5] also provided the requisite β-hydroxy ketones (Table I, entries 11-15). [6]



A possible explanation of the reaction of acetophenone, propiophenone and isobutyrophenone with aromatic aldehydes under the conditions described could be found in the generation of a transitory titanium enolate.



Addition of the aromatic ketone and the aromatic aldehyde to the solution of titanium tetrachloride, followed by treatment with triethylamine, would be expected to yield the transient titanium enolate species 9.[8] Immediately thereafter, the titanium enolate would react with the complexed aldehyde to afford, after workup, the appropriate products. In the case of propiophenone, the geometry of the transient titanium enolate is important in order to understand why there is syn selectivity. Under kinetic conditions it is well known that deprotonation of propiophenone provides a preponderance of the Z-enolate.[9] One could envisage that the conditions described for these aldol condensations provide kinetic control, thereby generating the kinetic enolate which, when reacted with titanium tetrachloride, yields the complex 9 described for propiophenone ($R^1 = CH_3$, $R^2 = H$). Thus, reaction of 9 in the expected orientation[10] would provide for syn selective products.

TABLE I. TRANSIENT TITANIUM ENOLATE ALDOL PRODUCTS

| Entry | Ketone | ArCHO | Temp/Time | Product[a] | Yield | Ratio[b] 5:6 |
|---|---|---|---|---|---|---|
| 1 | 1 | H | 0°C/30 min | 3 | 88% | |
| 2 | 1 | p-$CH_3$ | 0°C/30 min | 3 | 96% | |
| 3 | 1 | p-$CH_3O$ | 0°C/30 min | 3 | 86% | |
| 4 | 1 | o-$CH_3O$ | 0°C/30 min | 3 | 82% | |
| 5 | 1 | p-$NO_2$ | 0°C/30 min | 3 | 64% | |
| 6 | 4 | H | 0°C/30 min | 5 & 6 | 91% | 95:5 |
| 7 | 4 | p-$CH_3$ | 0°C/30 min | 5 & 6 | 94% | 96:4 |
| 8 | 4 | p-$CH_3O$ | 0°C/30 min | 5 & 6 | 95% | 89:11 |
| 9 | 4 | o-$CH_3O$ | 0°C/30 min | 5 & 6 | 96% | 87:13 |
| 10 | 4 | p-$NO_2$ | 0°C/30 min | 5 & 6 | 98% | 87:13 |
| 11 | 7 | H | 0°C/2h | 8 | 98% | |
| 12 | 7 | p-$CH_3$ | 0°C/2h | 8 | 96% | |
| 13 | 7 | p-$CH_3O$ | 0°C/2h | 8 | 92% | |
| 14 | 7 | o-$CH_3O$ | 0°C/2h | 8 | 89% | |
| 15 | 7 | p-$NO_2$ | 0°C/2h | 8 | 70% | |

a. All products exhibited physical and spectral properties consistent with literature reports.[6,7]

b. Ratio of 5:6 determined from 200 MHz $^1H$ NMR of the crude reaction mixture.

In conclusion, the reaction described allows for fascile generation and use of a proposed titanium enolate. The products isolated are very clean and where appropriate, syn selectivity is observed.

## References and Notes

1. (a) Nerz-Stormes, M.; Thornton, E.R. Tetrahedron Lett. 1986, **27**, 897.(b) Siegel, C.; Thornton, E.R. Tetrahedron Lett. 1986, **27**, 457.(c) Nakamura, E.; Shimada, J-I; Horiguchi, Y.; Kuwajima, I. Tetrahedron Lett. 1983, **24**, 3341.(d) Reetz, M.T.; Peter, R. Tetrahedron Lett. 1981, **22**, 4691.(e) Reetz, M.T. Angew. Chem., Int. Ed. Engl. 1984, 23, 556. (f) Reetz, M.T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. Angew Chem., Int. Ed. Engl. 1983, **22**, 989; Angew. Chem. Suppl. 1983, 1511.

2. Titanium enolate is prepared in one solvent and then changed to another solvent for reaction.

3. Founding papers, although no mention of titanium enolate is expressed. Lehnert, W. Tetrahedron Lett. 1970, 4723. Lehnert, W. Tetrahedron 1972, 28, 663. Tetrahedron, 29, 635.

4. Typical procedure: To a cooled (0°C) solution of 11.0 mmol $TiCl_4$ dissolved in 35 mL dry $CH_2Cl_2$ was added 10.0 mmol of acetophenone and 10.0 mmol benzaldehyde dissolved in 10 mL $CH_2Cl_2$. After 5 minutes 11.5 mmol triethylamine dissolved in 5 mL $CH_2Cl_2$ was added. The reaction was stirred at 0°C for 30 minutes, poured into ice water and extracted with ether. The organic phase was washed with water and brine, dried over anhy.$MgSO_4$, filtered and concentrated in vacuo to afford, after chromatography, a pure sample of 3 in 88% yield.

5. Attempted reaction with alkyl aldehydes, under the conditions described in ref. 4, afforded a multitude of uncharacterizable products.

6. Products attainable previously by the reaction of Sn with α-bromo ketones to form the Sn enolate and then condensation with aldehydes. Harada, T.; Mukiayama, T. Chem Lett. 1982, 467.

7. Heathcock, C.H.; Davidsen, S.K.; Hug, K.T.; Flippin, L.A. J. Org. Chem. 1986, 51, 3027 and references therein.

8. This Titanium complex would be expected to be the complex from which reaction would occur. Complexation of the titanium with two molecules of ketone could most certainly occur however, self condensation would be slow at best and by virtue of the fact that no self condensation products are observed lends credence to the postulated intermediate 9 . Although this complex suffices to explain our results, it should be noted that its existence has not been proven.

9. Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J. J. Org. Chem. 1980, 45, 1066.

10. Predicted by classical chair transition state theory: Evans, D.A.; Nelson, J.V.; Taber, T.R. Topics in Stereochemistry, 1982, 13, 1. Heathcock, C.H. "Asymmetric Synthesis" Vol. 2, Morrison, J.D. Ed., Academic Press; New York, 1983; Chapter 2.

(Received in USA 24 February 1987)