

Tetrahedron Letters 42 (2001) 395-398

TETRAHEDRON LETTERS

From allylic alcohols to aldols via a novel, tandem isomerization-condensation catalyzed by Fe(CO)₅

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Received 6 October 2000; accepted 30 October 2000

Abstract—Allylic alcohols react with aldehydes, in the presence of catalytic amounts of $Fe(CO)_5$ and under irradiation, to give mainly aldol products. A small amount of ketone resulting from the classical isomerization process is also isolated. This new aldol-type reaction is a complete atom economy process occurring under neutral conditions. © 2001 Elsevier Science Ltd. All rights reserved.

The aldol condensation is a fundamental process for the C–C bond formation. Extensive studies on the reaction conditions,¹ the nature of metal and ligands have led in many cases to excellent regio- and stereocontrol in this reaction.² However, it is important to note that most of these procedures use, at some stage, strongly basic or acidic conditions. The extension to middle- and late transition metal enolates appeared more recently. Noteworthy are the seminal studies by Bergman and Heathcock³ and the recent developments in asymmetric synthesis.⁴ Such derivatives are usually⁵ prepared by reaction of standard metal enolates with transition metal halides. More recently, a new approach⁶ based upon the known transition metal mediated isomerization of allylic alcohols to saturated carbonyl derivatives⁷ was developed. Using appropriate Rh and Ni based catalysts, allylic alcoholates have been isomerized to corresponding enolates, followed by aldol reactions.⁶ However, this attractive procedure still occurs under strongly basic conditions.



Scheme 1.

Table 1.

Entry	RCHO	2+3 (yield %)	4 (yield %)	2 syn/2 anti/3/3'
1	PhCHO	74	6	60/29/6.5/4.5
2	HCHO (anh.)	65	18	95/ /5
3	CH ₃ CHO	73	14	66/23/7/3.5
4	PhCH ₂ CHO	73	7	64/24/8/4
5	(iPr) ₂ CHCHO	54	28	62/28/7/3
6	5-Acetoxymethyl-2-furaldehyde	79	12	59/31/7/3

Keywords: aldols; catalysts; transition metals.

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Table 2.

Entry	Alcohol	Aldehyde	8+9 (yield)	10 (yield)	8 syn/8 anti/9/9'
1	7a	R = Ph	46	18	50/38/6/4
2	7a	$R = CH_3$	53	24	62/28/6/4
3	7b	R = Ph	73	5	86//7/7
4	7b	$R = CH_3$	55	7	83//14/3

For iron carbonyl mediated isomerization of allylic alcohols, labeling studies have established a mechanism via π -allyl and enol intermediates.⁸ Trapping of such intermediates (or compounds derived from them) could lead to derivatives equivalent to aldol adducts.⁹ In this communication, we report our preliminary results demonstrating the feasibility of this conceptually appealing strategy. A range of allylic alcohols readily reacted with a variety of aldehydes, in the presence of catalytic amounts (2–5%) of Fe(CO)₅ and under irradiation, to afford the corresponding aldol products in good yield. Additionally, small amounts of ketone resulting from the competitive isomerization reaction were also isolated.

Allylic alcohol 1, efficiently isomerized under iron catalysis,¹⁰ was chosen for the preliminary studies. Irradiating a pentane solution of 1 and benzaldehyde in the presence of 2 mol% of Fe(CO)₅ readily furnished the expected aldols 2 along with a small amount of their regioisomers 3 in 74% yield (2+3). The ketone 4 (6%) resulting from the isomerization of 1 was also isolated (Scheme 1 and Table 1, entry 1).¹¹

The regio- and stereoisomeric ratios were established by 13 C NMR on the crude reaction mixture. 12 A ratio of 60/29/6.5/4.5 was obtained for **2a**, **2b**, **3a**, **3b**. Authentic samples of **2** and **3** were obtained by a classical aldol condensation between 3-octanone and benzaldehyde, 13 however, in very different ratios (29/28/15/28).

Diastereoselective *anti* reduction of **2a** and **2b**,¹⁴ followed by acetonide formation gave **5** and **6** (35% yield, Scheme 2). Comparison of their NMR data with related compounds¹⁵ indicated that **2a** is the *syn* aldol while **2b** is the *anti*.

It is worth noting that 2a and 2b are stable under the reaction conditions (neither reversibility nor epimerization were observed). Furthermore, 4 does not react with benzaldehyde under these conditions.

This reaction could be extended to various aliphatic and heterocyclic aldehydes. In each case, small amounts of regioisomeric aldols and ketones were also obtained (Table 1). This reaction does not require moisture free conditions as exemplified by the result (47% yield) obtained using formaldehyde solution (37% in H₂O). However, lower yields (10–20%) were obtained for sterically hindered aldehydes such as cyclohexane carboxaldehyde and isovaleraldehyde with significant amount of ketone **4**.



Scheme 4.



Scheme 5.

We then investigated the extension to allylic alcohols substituted on the double bond (Scheme 3, Table 2). While we were gratified to note that both 1,2 and 1,1 disubstituted alcohols **7a** and **7b** underwent facile condensation, the former gave slightly lower aldol/ketone ratios (Table 2). The reaction of compound **7b** is particularly interesting as the new C–C bond is formed on the more hindered side, leading to quaternary centers. Such regiocontrol is usually not observed under the classical aldolization reaction conditions.¹

Finally, replacement of pentyl chain by another group was also studied (Scheme 4). The reaction of phenyl substituted derivative **11a** gave a mixture of aldols **12a** (73% yield, *syn/anti*: 58/42) with a small amount (10%) of ketone **13a**.¹⁶ The sterically hindered alcohol **11b** is especially interesting since it gave aldols **12b** not only in good yield (73%) but also with an excellent diastereoselectivity¹⁶ (*syn/anti*: 87/13). Ketone **13b** was also isolated (20%).

A tentative mechanistic proposal can be made for this reaction (Scheme 5). Initial complexation of iron carbonyl to allylic alcohol 14 results in an η^2 complex 15 which undergoes a well-documented⁸ 1,3-hydride migration to afford the enol 18 through the intermediacy of 16 and 17. Then, the key step for this new reaction would be the transformation of the π complex 17 to the σ complexed enol 20, possibly under irradiation.¹⁷ There is ample literature precedence for $\sigma - \pi$ equilibria in various transition metal enolates.¹⁸ Furthermore, a catalytic process starting from silyl enol ethers under UV light irradiation has been demonstrated for the preparation and reaction of rhodium enolates.³ This key intermediate 20 can react with aldehydes to give the

complexed aldol 21 which could afford aldol 22 and regenerate the catalyst. While an open transition state can be speculated for this aldol reaction, a Zimmermann-Traxler cyclic transition state appears more likely since the 16 electron species 20 has a vacant orbital ready for coordination to the carbonyl oxygen atom. The minor amount of regioisomeric products (3, 9), observed when $R = CH_2R'$, could be accounted by a further 1,3-shift of 17 to 23 which would lead to a regioisomeric iron enolate.

In conclusion, we have demonstrated that iron enolates generated catalyticaly from allylic alcohols can be trapped efficiently in an aldol type process. Though the regio- and stereoselectivity can be further improved, this novel catalytic process appears very attractive since it occurs under neutral conditions and complies with total atom economy. We have also studied the extension to other transition metal complexes and this will be reported in due course. Theoretical studies concerning the mechanism is also being actively pursued.

Acknowledgements

We thank P. Guenot (CRMPO Rennes) for performing the mass-spectra experiments and CNRS for a research associate position to R.U.

References

 Comprehensive Organic Synthesis, Additions to C-X π Bonds; Heathcock C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Part 2, 99–319.

- For recent reviews on enantioselective aldol additions, see: (a) Bach, T. Angew. Chem., Int. Ed. Engl. 1994, 33, 417–419. (b) Sawamura, M.; Ito, Y. In Catalytic Asymmetric Synthesis; Ojima, I., Ed.; VCH: New York, 1993; 367–388. (c) Machajewski, T. D.; Wong, C. H. Angew. Chem., Int. Ed. Engl. 2000, 38, 1352–1374. (d) Johnson, J. S.; Evans, D. A. Acc. Chem. Res. 2000, 33, 325–335. (e) Denmark, S. E.; Stavenger, R. A. Acc. Chem. Res. 2000, 33, 432–440 and references cited therein.
- 3. Slough, G. A.; Bergman, R. G.; Heathcock, C. H. J. Am. Chem. Soc. 1989, 111, 938–949 and references cited therein.
- (a) Sodeoka, M.; Ohrai, K.; Shibazaki, M.; J. Org. Chem. 1995, 60, 2648–2649. (b) Sodeoka, M. Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibazaki, M. Synlett 1997, 463–466. (c) Fujimura, O. J. Am. Chem. Soc. 1998, 120, 10032–10039.
- For other possibilities, including catalytic reductive aldol reactions see: Taylor, S. J.; Morken, J. P. J. Am. Chem. Soc. 1999, 121, 12202–12203 and references cited therein.
- Gazzard, L. J.; Motherwell, W. B.; Sandham, D. A. J. Chem. Soc., Perkin Trans. 1 1999, 979–993 and references cited therein.
- (a) Trost, B. M.; Kulawiec, J. J. Am. Chem. Soc. 1993, 115, 2027–2036. (b) Backvall, J. E.; Andreasson, U. Tetrahedron Lett. 1993, 34, 5459–5462. (c) Marko, I. E.; Gautier, A.; Tsukazaki, M.; Llobet, A.; Plantalech–Mir, E.; Urch, C. J.; Brown, S. M. Angew. Chem., Int. Ed. Engl. 1999, 38, 1960–1962. (d) Slugovc, C.; Ruba, E.; Schmid, R.; Kirchner, K. Organometallics 1999, 18, 4230–4233.
- (a) Hendrix, W. T.; Cowherd, F. G.; von Rosenberg, J. L. Chem. Commun. 1968, 97–99. (b) Cowherd, F. G.; von Rosenberg, J. L. J. Am. Chem. Soc. 1969, 91, 2157–2158.
- In the case of some Rh complexes, it was possible to characterize and to trap simple enols by three electrophiles in *ene*-type reactions, see: Bergens, S. H.; Bosnich, B. J. Am. Chem. Soc. 1991, 113, 958–967.
- (a) Damico, R.; Logan, T. J. J. Org. Chem. 1967, 32, 2356–2358. (b) Iranpoor, N.; Mottaghinejad, E. J. Organomet. Chem. 1992, 423, 399–404.

- 11. Representative experimental procedure: To a pentane solution (10 ml) of octen-3-ol 1 (500 mg, 3.9 mmol) in 25 ml pyrex flask was added freshly distillated benzaldehyde (800 μ l, 7.8 mmol). Argon was bubbled (10 min) through the mixture followed by addition of Fe(CO)₅ (10 μ l, 0.076 mmol). The reaction mixture was irradiated with a Philips HPK125 W lamp until disappearance of allylic alcohol (1 h). The reaction mixture was filtered through silica gel (1 cm) and purified by column chromatography (petroleum ether: ether 7/1 v/v) to give ketone 4 (32 mg, 6%) and then a mixture of aldol products 2 and 3 (672 mg, 74%). All diastereoisomeric mixtures of aldol products gave spectra (IR, ¹H and ¹³C NMR) consistent with their assigned structure and satisfactory high resolution mass measurement and/or combustion analysis.
- Spectra were recorded with two different relaxation delays (2 s and 16 s) and same ratios were obtained. Whenever possible, these were also confirmed using ¹H NMR.
- Ketone and LDA were reacted (10 min) at low temperature (-80 or -100°C) then the aldehyde was added. At -45°C, the reaction was quenched and the mixture of diastereoisomeric aldols was purified by column chromatography. Similar reactions were done for the other aldols.
- Evans, D. A.; Chapman, K. T.; Carreira, E. M. J. Am. Chem. Soc. 1988, 110, 3560–3578.
- (a) Enders, D.; Osborne, S. J. Chem. Soc., Chem. Commun. 1993, 425–426. (b) Shirai, F.; Gu, J.-H.; Nakai, T. Chem. Lett. 1984, 1931–1934. (c) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. J. Chem. Soc., Perkin. Trans. 1 1995, 317–338.
- 16. It should be noticed that at longer reaction time retroaldol reaction was observed along with a decrease in the yield of aldol products and diastereoselectivity.
- 17. It is important to note that the irradiation must be maintained during the reaction, otherwise the process stops immediately.
- See for instance: Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. Organometallics 1991, 10, 3326–3344.