ORGANIC LETTERS

2001
Vol. 3, No. 23
3671−3673

Syn–Anti Isomerization of Aldols by Enolization

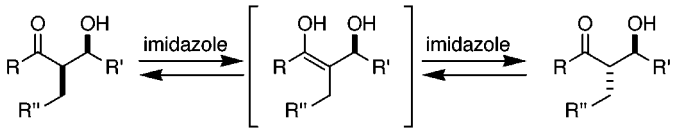
Dale E. Ward,* Marcelo Sales, and Pradip K. Sasmal

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon SK S7N 5C9, Canada

dale.ward@usask.ca

Received August 15, 2001

ABSTRACT



A variety of aldol adducts (i.e., 3-hydroxy ketones) are shown to undergo syn–anti isomerization in the presence of imidazole by an enolization mechanism with negligible retroaldol or elimination products.

The aldol reaction can produce up to two new stereogenic centers, and several stereoisomeric products are generally possible. The reaction is readily reversible, and when mediated by weak bases (e.g., hydroxide, alkoxide, amine), product distribution is generally under thermodynamic control.[1] The advent of modern enolate chemistry and the use of preformed enol(ate) derivatives facilitated rapid development of the "directed" aldol reaction.[2] In this case, product formation is typically under kinetic control although isomerization of metal aldolate intermediates can be facile under certain conditions.[3] The development of methods for stereoselective aldol reactions has been intensively investigated for more that 20 years.[4] Nonetheless, the ability to produce each of the possible aldol stereoisomers selectively, especially from chiral substrates, remains a significant challenge.[4c,5] Isomerization of aldol adducts is an alternative strategy to access aldol stereoisomers. Although there have been several reports of isomerization of cyclic[1,6] and acyclic[3e,7] aldols through a retroaldol mechanism, isomerization of aldols via an enol[8] or enolate[9] is rare. In this paper we report that imidazole effectively catalyzes the syn−anti isomerization of 3-hydroxy ketones by an enolization mechanism with negligible retroaldol or elimination products.

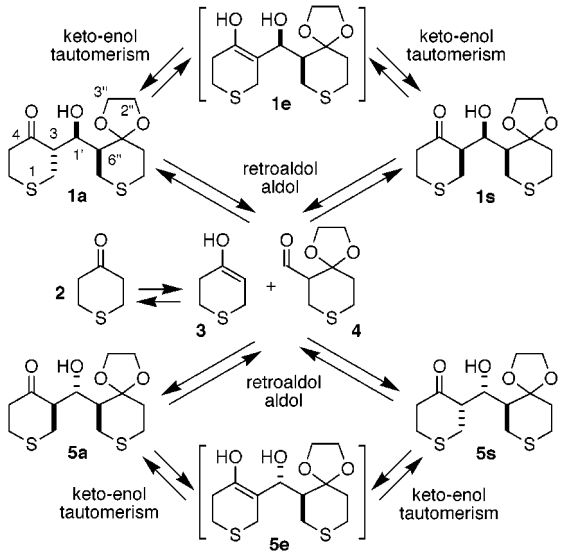
Reaction of **1a**[10] with TBDMS-Cl in the presence of imidazole[11] in CH_2Cl_2 solution failed to give the desired TBDMS ether; however, after 5 days ca. 30% of **1s**[10] was detected and isolated from the reaction mixture. The isomerization of **1a** was readily followed by ^{1}H NMR in $CDCl_3$

(1) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1−438.
(2) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331.
(3) (a) Dubois, J. E.; Fellmann, P. *C. R. Acad. Sci., Ser. C* **1972**, *274*, 1307−1309. (b) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1081. (d) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330−4337. (e) Swiss, K. A.; Choi, W.-B.; Liotta, D. C.; Abdel-Magid, A. F.; Maryanoff, C. A. *J. Org. Chem.* **1991**, *56*, 5978−5980. (f) Carlier, P. R.; Lo, C. W.-S.; Lo, M. M.-C.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443−2445.
(4) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Heathcock, C. H. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111−212. (c) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23* (4), 99−111. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, 357−389. (e) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947. (f) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374.
(5) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797−800.
(6) (a) Kok, P.; Sinha, N. D.; Sandra, P.; de Clercq, P. J.; Vandewalle, M. E. *Tetrahedron* **1982**, *38*, 2279−2283. (b) Vekgová, H. *Collect. Czech. Chem. Commun.* **1986**, *51*, 930−936. (c) Hui, A.; Fairbanks, A. J.; Nash, R. J.; de Q. Lilley, P. M.; Storer, R.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *47*, 8895−8898. (d) Seto, H.; Fujioka, S.; Kamiya, Y.; Yoshida, S. *Heterocycles* **1998**, *48*, 2245−2251. (e) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.-i.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121−161. (f) Aurrecoechea, J. M.; Fañanás, R.; Arrate, M.; Gorgojo, J. M.; Aurrekoetxea, N. *J. Org. Chem.* **1999**, *64*, 1893−1901.
(7) (a) Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* **1998**, 262−264. (b) Yang, W.; Digits, C. A.; Hatada, M.; Narula, S.; Rozamus, L. W.; Huestis, C. M.; Wong, J.; Dalgarno, D.; Holt, D. A. *Org. Lett.* **1999**, *1*, 2033−2035.
(8) (a) Still, W. C.; Hauck, P.; Kempf, D. *Tetrahedron Lett.* **1987**, *28*, 2817−2820. (b) Yan, T.-H.; Chu, V.-V.; Lin, T.-C.; Tseng, W.-H.; Cheng, T.-W. *Tetrahedron Lett.* **1991**, *32*, 5563−5566.

10.1021/ol016581u CCC: $20.00
Published on Web 10/20/2001

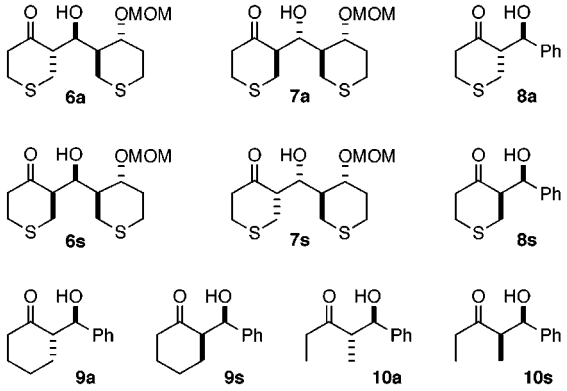
with 10 equiv of imidazole. After ca. 4 days, a 1.5:1 equilibrium mixture of **1s** and **1a**, respectively, resulted. Equilibrium was confirmed by obtaining the same mixture starting from **1s**. These solutions were stable for several weeks with negligible (<5%) retroaldol (as judged by the absence of **4**) or elimination products being detected. Subjecting **5a**[12] or **5s**[12] to the same conditions resulted in a 1.8:1 equilibrium mixture of **5s** and **5a**, respectively. In principle, aldol adducts can isomerize by retroaldol and/or enolization mechanisms (Scheme 1). Whereas all possible

Scheme 1



stereoisomers can result from a retroaldol−aldol pathway, keto−enol tautomerism can interconvert only two stereoisomers. We conclude that the above isomerizations of **1** and **5** proceed via imidazole-catalyzed enolization[13,14] because: (i) **5** was not detected in the isomerization of **1** and vice versa, and (ii) imidazole does not catalyze an aldol reaction between **2** and **4**.

Table 1. Imidazole-Catalyzed Syn−Anti Isomerization of Aldols **1** and **5**−**10**[a]



entry	starting aldol	solvent	aldols at equilibrium[b] (ratio at equilibrium)[c]
1	**1a**	$CDCl_3$	**1s:1a** (1.5:1)
2	**1s**	$CDCl_3$	**1s:1a** (1.5:1)
3	**1a**	CH_2Cl_2	**1s:1a** (1.6:1)
4	**1s**	CH_2Cl_2	**1s:1a** (1.6:1)
5	**1a**	acetone-d_6	**1s:1a** (2.0:1)
6	**1a**	C_6D_6	**1s:1a** (1.4:1)
7	**1a**	CH_3OH	**1s:1a** (1.7:1)
8	**5a**	$CDCl_3$	**5s:5a** (1.8:1)
9	**5s**	$CDCl_3$	**5s:5a** (1.8:1)
10	**5s**	CH_2Cl_2	**5s:5a** (1.9:1)
11	**5s**	acetone-d_6	**5s:5a** (1.6:1)
12	**5s**	C_6D_6	**5s:5a** (1.5:1)
13	**5s**	CH_3OH	**5s:5a** (2.0:1)
14	**5s**	DMF-d_7	**5s:5a** (2.1:1)
15	**6a**	$CDCl_3$	**6a:6s** (1.1:1)
16	**6s**	$CDCl_3$	**6a:6s** (1.1:1)
17	**7s**	$CDCl_3$	**7s:7a** (1.5:1)
18	**8a**	$CDCl_3$	**8a:8s** (1.6:1)
19	**9a**	$CDCl_3$	**9a:9s** (2.0:1)
20	**10s**[d]	C_6D_6[e]	**10a:10s**[f] (1.1:1)[f]

[a] Imidazole (0.2−0.4 M, ca. 10 equiv) at room temperature. [b] Equilibrium reached in 4−7 days (monitored by ^{1}H NMR). Aldols recovered in >95% yield after aqueous workup. [c] Ratios determined by ^{1}H NMR (relative error estimated at ±10%). [d] A 9:1 mixture of **10s:10a** was used. [e] Reaction at 60 °C for 13 days. [f] Approximately 6% of benzaldehyde was present.

Imidazole-catalyzed isomerizations of **1** and **5** were conducted in several solvents (Table 1). Equilibrium was typically reached in 4−7 days using 10 equiv of imidazole (ca. 0.2−0.4 M) without any indication of retroaldol or elimination products. In all cases the syn aldol diastereomer (**1s** or **5s**) was favored. Less polar solvents (e.g., benzene) led to a relatively greater proportion of the anti aldol diastereomer (**1a** or **5a**) at equilibrium compared to that from more polar solvents (e.g., methanol), although this effect was quite small.

To test the generality of syn−anti isomerization of aldols via enolization **6**,[12] **7**,[12] **8**,[10] **9**,[10] and **10**[3c] were treated with imidazole in $CDCl_3$ solution (Table 1). As with **1** and **5**, the products from isomerizations of **6** and **7** were mutually exclusive and incongruent with a retroaldol pathway. The simple aldols **8** and **9**, derived from reactions of benzalde-

(9) (a) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965−6978. (b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, S. R.; Ong, B. S.; Press, J. B.; RajanBabu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213.

(10) Ward, D. E.; Man, C. C.; Guo, C. *Tetrahedron Lett.* **1997**, *38*, 2201−2202.

(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

(12) See Supporting Information for preparation and determination of relative stereochemical configurations.

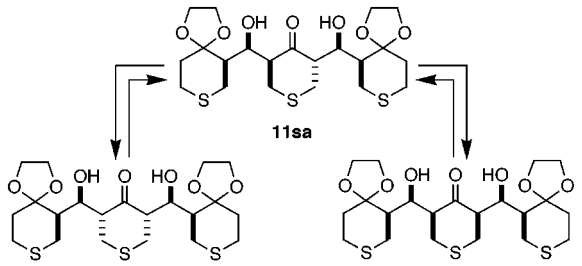
(13) For a review on the mechanism of enolization of ketones, see: Keefe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 7, pp 399−480.

(14) For imidazole catalyzed enolization, see: (a) Mel'nichenko, I. V.; Yasnikov, A. A. *Ukr. Khim. Zh.* **1964**, *30*, 723−728. (b) Breslow, R.; Graff, A. *J. Am. Chem. Soc*. **1993**, *115*, 10988−10989.

hyde with tetrahydrothiopyran-4-one and cyclohexanone, respectively, readily equilibrated in the presence of imidazole to give a slight excess of the anti diastereomer, as expected.[3b,c] Isomerization of the acyclic aldol **10s** was very slow at room temperature; however, heating a benzene[15] solution of **10s** and imidazole at 60 °C for 13 days produced 1.1:1 mixture of **10a** and **10s**, respectively.[16] Despite these much harsher conditions, elimination was negligible and only a small amount of retroaldol occurred (as indicated by the presence of benzaldehyde, 6%).

We also examined the imidazole-catalyzed isomerization of the bisaldols **11**[17] (Table 2). Reactions of **11aa** or **11sa** in

Table 2. Imidazole-Catalyzed Isomerization of Bisaldols **11**[a]



entry	starting bisaldol	solvent	aldols at equilibrium[b] (ratio at equilibrium)[c]
1	**11sa**	$CDCl_3$	**11sa:11ss:11aa** (3.4:1.3:1)
2	**11aa**	$CDCl_3$	**11sa:11ss:11aa** (3.4:1.3:1)
3	**11aa**	CH_2Cl_2	**11sa:11ss:11aa** (4.8:1.4:1)
4	**11aa**	C_6D_6	**11sa:11ss:11aa** (5.4:2.4:1)
5	**11aa**	acetone-d_6	**11sa:11ss:11aa** (9.6:3.8:1)
6	**11aa**	acetone	**11sa** (65%),[d] **11ss** (25%),[d] **11aa** (7%)[d]

[a] Imidazole (0.4−1.0 M) at room temperature. [b] Equilibrium reached in 6−10 days (monitored by ^{1}H NMR). Aldols recovered in >95% yield after aqueous workup. [c] Ratios determined by ^{1}H NMR (relative error estimated at ±10%). [d] Isolated yield.

all cases led to a mixture of the same three aldols, clearly indicating isomerization by an enolization mechanism.[18] Interestingly, although the ratio of the C_S symmetrical aldols (**11ss**, **11aa**) at equilibrium was solvent-dependent (1.3−3.8:1), the unsymmetrical bisaldol **11sa** consistently comprised 60−65% of the mixture. As with previous examples, the isomerizations proceeded without giving significant amounts of elimination or retroaldol products.[19]

(15) Chloroform solutions were not stable to prolonged heating.

(16) Holt et al. (ref 7b) obtained a 5:4 mixture of **10a** and **10s** by isomerization of **10** in the presence of Ti(O*i*-Pr)$_4$ (retroaldol mechanism).

(17) Ward, D. E.; Guo, C.; Sasmal, P. K.; Man, C. C.; Sales, M. *Org. Lett.* **2000**, *2*, 1325−1328.

(18) There are 20 diastereomers possible for **11**. In principle, all diastereomers could be produced from **11aa** or **11sa** via a retroaldol−aldol mechanism, whereas enolization can only interconvert the three diastereomers shown.

Table 3. Rate of Isomerization of **5s** in $CDCl_3$ at Room Temperature[a]

entry	base	[base] (M)	[**5**][b] (M)	$t_{1/2}$ (h)[c]
1	pyridine	0.22	0.016	[d]
2	Et_3N	0.40	0.016	110
3	DMAP	0.22	0.016	14
4	imidazole	0.10	0.016	49
5		0.20	0.016	19
6		0.20	0.030	21
7		0.40	0.030	8.9
8		0.40	0.060	8.4
9		0.40	0.120	8.9
10		0.80	0.030	3.4
11	Ti(O*i*Pr)$_4$	0.036	0.018	[e]

[a] Monitored by ^{1}H NMR by integration of HC-1′ for **5s** and **5a**. At equilibrium, a 1.8:1 ratio of **5s:5a** was obtained. [b] Initial concentration of **5s**. [c] The half-life for equilibration: $t_{1/2} = \ln(2)/k_{obs}$ where k_{obs} is determined from the slope of the line obtained by plotting $\ln([\mathbf{5s}]_{equilibrium} - [\mathbf{5s}]_t)$ vs t (≥8 data points over 2 half-lives; $R^2 > 0.99$). Relative error estimated at ±10%. [d] No isomerization after 200 h. [e] Reaction in CH_2Cl_2 at 0 °C gave elimination only (cf. ref 7).

We briefly examined the effect of other bases and reaction conditions on the rate of equilibration of **5s** in $CDCl_3$ (Table 3). Catalysis by DMAP was at least as effective as imidazole although Et_3N was considerably less efficacious, and pyridine did not catalyze isomerization of **5s**. As expected, the rate of equilibration was dependent on the molar concentration of imidazole (compare entries 7, 8, and 9) but not on the stoichiometry (compare entries 4, 6, and 8). The data obtained suggest a reaction order in imidazole of 1.3[20] implying a complex mechanism.[13]

In summary, we have demonstrated that imidazole is an effective catalyst for syn−anti isomerization of aldols via an enolization mechanism. Isomerizations are high yielding and occur with little or none of the usual byproducts arising from competing elimination or retroaldol reactions. The process can provide access to diastereomers unavailable by other methods, and although stereoselectivity under these conditions is typically modest, useful amounts of material can be obtained by recycling if necessary.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available: Preparation, spectroscopic data, and determination of relative configurations of **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016581U

(19) In some experiments, a small amount (1−3%) of aldehyde **4** was detected after prolonged reaction.

(20) The slope of the line obtained by plotting $\ln(k_{obs})$ vs ln([imidazole]) for entries 4, 6, 7, and 10. Regression analysis on these four data points yields a slope of 1.28 ± 0.13 (95% confidence interval).