Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7197-7200, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01637-1

Mild Preparation of Allylic Tartaramide Acetals in DMF

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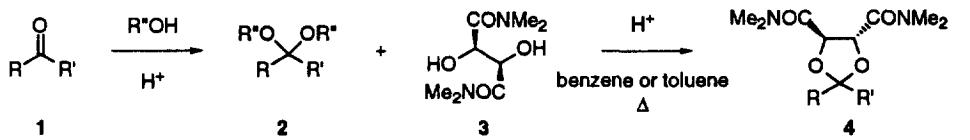
Abstract: The mild preparation of (*E*)-allylic acetals derived from *N,N,N',N'*-tetramethyltartaramide is described. The desired chiral acetals are obtained by transacetalization of the corresponding acyclic acetals with a catalytic amount of pyridinium *p*-toluenesulfonate in DMF at room temperature.

Chiral ketals and acetals have demonstrated a wide range of applicability in directing asymmetric organometallic transformations.[1] The asymmetric induction observed in the reactions of chiral ketals and acetals is derived from the substituents on the dioxolane or dioxane ring, and is therefore a direct function of the nature of these groups. In general, these substituents can be classified into two main subgroups: those that are sterically based (e.g., alkyl or aryl groups), and those that have ligating potential (e.g., ester or amide functionalities). The latter subgroups are most often derivatives of the readily available isomers of tartaric acid. In particular, acetals derived from tartaramides have demonstrated superior levels of stereoselectivity in a variety of synthetic transformations when compared to the corresponding ester derivatives.[2]

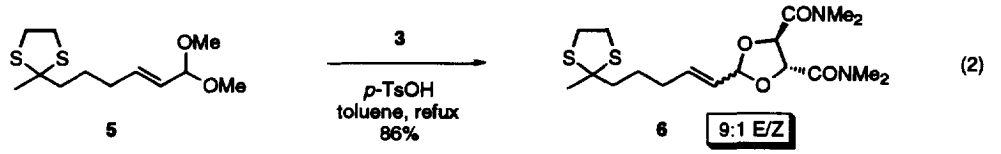
The preparation of tartrate derived ketals and acetals is generally a straightforward procedure. Typically, the diol and a ketone or an aldehyde **1**, in the presence of a catalytic amount of a Brönsted acid, are heated in a high boiling solvent (benzene or toluene) which allows azeotropic removal of water.[3] However, acetalization with *N,N,N',N'*-tetramethyltartaramide **3** does not occur readily with carbonyl substrates, and prior conversion to more reactive acyclic acetals **2** is necessary (eq 1).



1 **2** **3** **4** (1)

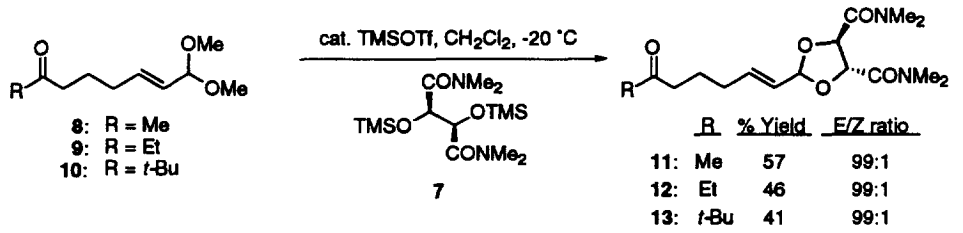
During the course of our studies on the asymmetric cyclization of keto-allylic acetals,[2a] we required a method of preparing E-allylic acetals derived from **3**. When we applied typical transacetalization conditions to the methyl acetal substrate **5**, we obtained the product **6** in good yield (86%), but with poor E/Z stereoselectivity (9:1, respectively, eq 2). We had hoped to resolve this problem by using the method of Noyori, which can be performed at lower temperatures.[4] Indeed, treating several acetals with the bis(trimethylsilyl)ether of *N,N,N',N'*-tetramethyl-L-tartaramide **7** in the presence of trimethylsilyl trifluoromethanesulfonate provided the

desired chiral acetals with excellent E/Z stereoselectivity (Scheme 1). Notably, to induce cyclization the reaction had to be performed at ≥ -20 °C.[5] It appeared that the E/Z ratios observed in these reactions represented equilibrium values, because similar ratios of E/Z-isomers were obtained regardless of the geometry in the starting allylic methyl acetal. Unfortunately, this protocol was hampered by difficulties in the workup, which resulted in low overall yields when working on a small scale.[6]



5 6 (2)

Scheme 1



8: R = Me
9: R = Et
10: R = *t*-Bu

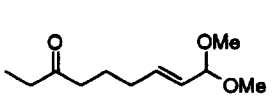
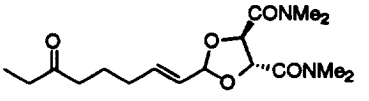
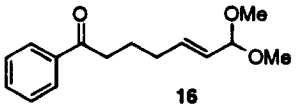
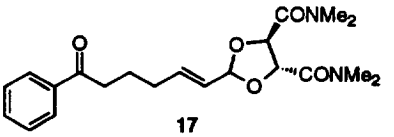
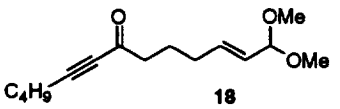
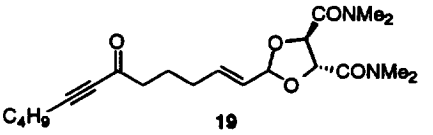
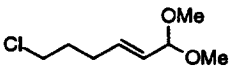
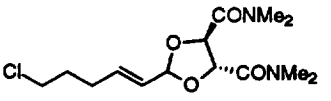
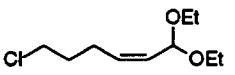
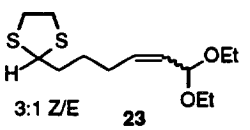
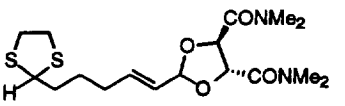
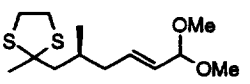
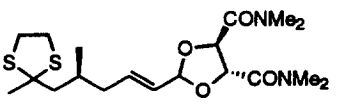
7

	R	% Yield	E/Z ratio
11:	Me	57	99:1
12:	Et	46	99:1
13:	*t*-Bu	41	99:1

The success of the Noyori protocol rests in the high reactivity of the strong Lewis acid, trimethylsilyl trifluoromethanesulfonate, which allows the transacetalization to proceed at relatively low temperatures. We reasoned that higher yields, and good E/Z stereoselectivity, could be achieved if conditions could be found to facilitate the transacetalization with mild Brönsted acids at low temperature. With this in mind, we examined the role of solvents in typical acetalizations. High-boiling solvents, such as benzene and toluene, allow the efficient azeotropic removal of volatile byproducts. However, their non-polar nature implies that these solvents are actually a poor choice from the standpoint of stabilizing polar transition structures.[7] Furthermore, the tartaramide diol **3** is only sparingly soluble in either benzene or toluene. We proposed that a polar solvent, such as DMF, should increase the rate of transacetalization by providing an environment that would stabilize polar transition structures and increase the effective concentration of the diol **3** as well. To test the hypothesis, several substrates were submitted to transacetalization with **3** in DMF in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate.[8] To our satisfaction, the transacetalization proceeded at room temperature (Table 1). Consistently good yields were realized with a wide range of substrates. When compared to the Noyori method, only a slight decrease in stereoselectivity was observed with this protocol. Interestingly, it was unnecessary to remove the alcohol generated in the reaction, even when using as little as 1.4 equivalents of diol **3**. Furthermore, as in the case of the Noyori method, it was unnecessary to protect the ketone functionalities.[9]

In summary, we have developed a mild and convenient method by which allylic tartaramide acetals can be prepared from acyclic acetals in good yields and with high E/Z stereoselectivity. No prior protection of free ketone functionalities is required with this protocol. The success of this method lies in the use of the polar solvent, DMF, which allows the transacetalization to occur at room temperature.

Table 1. Transacetalization of Acyclic Allylic Acetals to (*E*)-Allylic Tartaramide Acetals in DMF.[1]

Substrate[2]	Product	% Yield	E/Z ratio
 **14**	 **15**	79	98:2
 **16**	 **17**	89	98:2
 **18**	 **19**	80	98:2
 **20**	 **21**	85	98:2
 **22**	**21**	85	97:3
 3:1 Z/E **23**	 **24**	81	97:3
 **25**	 **26**	79	97:3

[1]All substrates and products gave satisfactory ^{1}H NMR, ^{13}C NMR, and IR data. [2]All substrates were ≥98:2 E/Z, except **22** and **23**, which were ≥98:2 and 3:1 Z/E, respectively.

Acknowledgment: We thank the National Institutes of Health and the National Science Foundation for their generous financial support of this program.

References and Notes

1. For a review, see: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. For more recent work in this field, see: (b) Sammakia, T.; Smith, R.S. *J. Am. Chem. Soc.* **1992**, *114*, 10998, and references cited therein. (c) Aubé, J.; Heppert, J.A.; Milligan, M.L.; Smith, M.J.; Zenk, P. *J. Org. Chem.* **1992**, *57*, 3563. (d) Parrain, J.-L.; Cintrat, J.-C.; Qintard, J.-P. *J. Organomet. Chem.* **1992**, *437*, C19. (e) Longobardo, L.; Mobbili, G.; Tagliavini, T.; Trombini, C.; Umani-Ronchi, A. *Tetrahedron* **1992**, *48*, 1299. (f) Yuan, R.-M.; Yeh, S.-M.; Hsieh, Y.-T.; Luh, T.-Y. *J. Org. Chem.* **1994**, *59*, 8192. (g) For a recent example of the application of chiral acetals to asymmetric cyclopropanations, see: Armstrong, R.W.; Maurer, K.W. *Tetrahedron Lett.* **1995**, *36*, 357.
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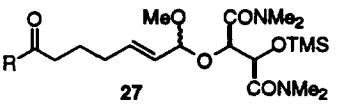
4. (a) Hwu, J.R.; Leu, L-C.; Robl, J.; Anderson, D.A.; Wetzel, J.M. *J. Org. Chem.* **1987**, *52*, 188. (b) Tsunoda, R.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
5. At lower temperatures, only epimeric mixtures of the mixed acetals **27** were formed.



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6. The reagent, bis(O-trimethylsilyl)tartaramide, was inseparable from the products by flash chromatography. To remove the reagent, the crude mixture was treated with aqueous K_2CO_3, which hydrolyzed **7** to the diol **3**. The diol **3** could then be readily washed from the product.
7. It was assumed that the rate-determining step was the formation of a charged transition state (i.e. an oxocarbenium ion) from an uncharged species.
8. Typical Procedure: To a solution of methyl acetal **14** (657 mg, 3.28 mmol) and *N,N,N',N'*-tetramethyl-L-tartaramide (1.31 g, 6.43 mmol) in DMF (15 mL) was added pyridinium *p*-toluenesulfonate (167 mg, 0.66 mmol). The mixture was stirred for 26 h, whereupon saturated $NaHCO_3$ was added to the now homogeneous solution. The mixture was concentrated, and brine was added. The aqueous layer was extracted with EtOAc (3X). The combined organic extracts were washed with brine, back-extracting with EtOAc. After drying ($MgSO_4$) and concentration, the crude was purified by silica gel chromatography (92:8 EtOAc/MeOH), yielding **15** (98:2 E/Z, 883 mg, 79%).
9. Small amounts of products in which both the aldehyde and ketone functionalities were acetalated with the tartaramide diol could have gone undetected by GC due to their high boiling points. This material would have washed out during workup.

(*Received in USA* 30 *July* 1996; *accepted* 19 *August* 1996)