JOC*Note*

Olefination of α-Hydroxy or α-Aminoaldehyde Derivatives via Reaction of Their Arylsulfonylhydrazones with Sulfonyl Anions

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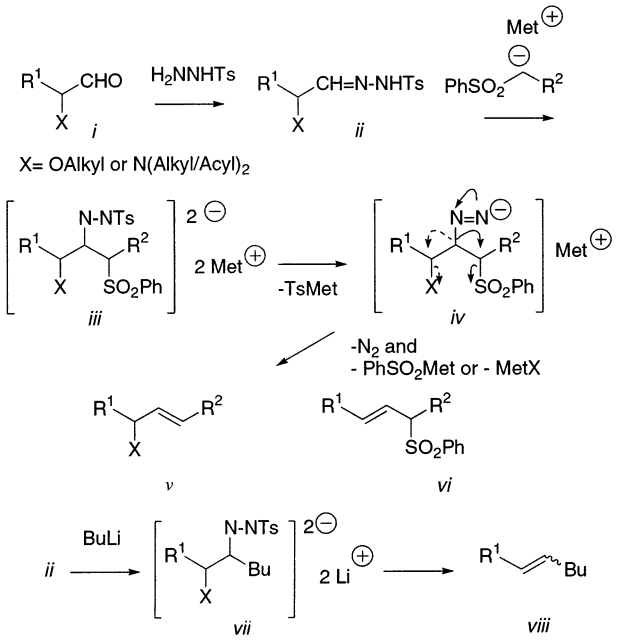
Abstract: Reaction of tosylhydrazones of *O*-substituted α-hydroxy or *N*-substituted α-amino aldehydes (**2**, **7**, **11**, **15**, **17**, and **20**) with selected α-magnesio alkyl phenyl sulfones afforded the respective derivatives of allylic alcohols or allylic amines. 2,3-*O*-Isopropylidene-D-glyceraldehyde (**1**) was transformed into its tosylhydrazone (**2**) and then olefins **4a** with retention of optical purity.

Synthesis of olefins by coupling of aldehydes with alkanes bearing a carbanion-stabilizing group has a pivotal importance in organic chemistry.[1] The classical Marc Julia olefination[2] applying phenyl- (or *tert*-butyl) alkyl sulfones has found numerous applications in target-oriented synthesis.[3] Several modifications of the original three-step procedure have been developed in order to improve its efficiency and stereoselectivity. The reductive elimination step requiring relatively harsh conditions has received a particular attention.[4] Studies on the sulfone-based olefination reactions culminated in the discovery by S. A. Julia and co-workers[5] of a new one-step olefination reaction. The "direct" olefination reaction applies heterocylic sulfones, such as benzothiazoyl, pyridyl, and phenyltetrazoyl sulfone. The latter introduced by Kocienski and co-workers[6] offers high *E*-stereoselectivity. An indispensable feature of heterocyclic sulfones applied in the direct Julia olefination is the presence of a reactive electrophilic C=N bond. Although the Julia−Kocienski olefination reaction proved remarkably successful,[7] it appears that in certain cases application of robust chemically stable phenyl sulfones may still be of advantage.

SCHEME 1



A potentially useful variation of olefination of aldehydes has been reported by Vedejs et al.[8] some time ago. In this method an aldehyde *i*, X = H (Scheme 1) was initially transformed into its tosylhydrazone *ii*, X = H, and then treated with an excess of α-lithio sulfone. Exchange of an active proton for metal and addition of the nucleophile to the tosylhydrazone C=N bond afforded adduct *iii*, X = H. Fragmentation of the intermediate *iii* via *iv* gave olefin *v*, X = H. It is noteworthy that no reducing reagents are involved in the discussed reaction sequence. Some related coupling reactions involving aldehyde tosylhydrazones have also been noted.[9] We have recently found[10] that replacing α-lithium sulfones used in the Vedejs procedure by α-magnesium sulfones makes it possible to evade some side reactions (as the Shapiro fragmentation[11]) and to extend significantly the scope of application of this olefination reaction.

It was thought of interest to determine whether the tosylhydrazone-mediated olefination may accommodate aldehydes bearing alkoxy or amino groups (*i*, X = OAlkyl or N(Alk/Aryl) in the α-position. It could be reasoned that addition of a metalated sulfone (2 equiv) to *ii* will provide

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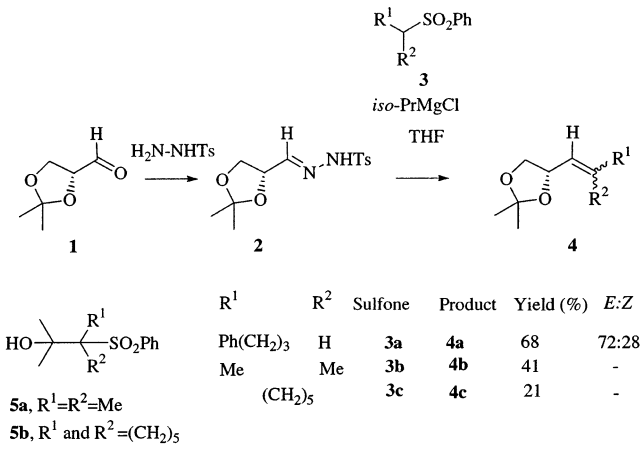
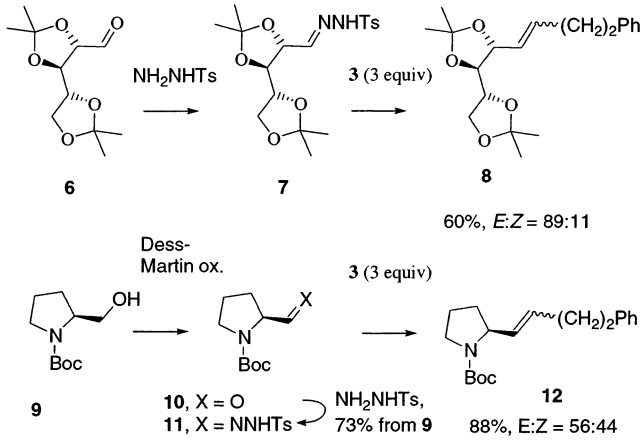
SCHEME 2



R^1	R^2	Sulfone	Product	Yield (%)	*E*:*Z*
$Ph(CH_2)_3$	H	**3a**	**4a**	68	72:28
Me	Me	**3b**	**4b**	41	-
$(CH_2)_5$		**3c**	**4c**	21	-

SCHEME 3



intermediate *iii*, which will fragment to respective derivatives of allylic alcohols or amines, *v*, X = OAlkyl or N(Alk/Aryl). However, elimination of the X-group may occur as well, destroying the stereogenic center (if present) and affording undesired product *vi*. It was recently shown[12,13] that tosylhydazones of some *O*-substituted α-hydroxy and *N*-substituted α-amino aldehydes in reaction with organolithium or Grignard reagents afford olefins *viii*, as illustrated in Scheme 1. In the present work we examine olefination of representative α-hydroxy and α-amino aldehyde derivatives via their tosylhydrazones.

2,3-*O*-Isopropylidene-D-glyceraldehyde (*R*)-**1** (Scheme 2) prepared[14] from di-*O*-isopropylidene-D-mannitol, was treated with tosylhydrazine in diethyl ether.[15] The crude product was purified by chromatography on silica gel using a "dry column" technique[16] to give tosylhydrazone (*S*)-**2** (one isomer, semisolid) in 92% yield from di-*O*-isopropylidene-D-mannitol. In chloroform-*d* solution (*S*)-**2** was unstable; however, in DMSO-d_6 a satisfactory ^{1}H NMR spectrum was obtained, and diagnostic signals in the ^{13}C spectrum were recorded. HPLC analysis (Chiralcel OD-H column) indicated that obtained (*S*)-**2** was virtually enantiomerically pure.

Tosylhydrazone (*S*)-**2** was used routinely in further reactions immediately after preparation; a sample stored for a few weeks in a refrigerator recemized almost completely. Apparently, racemization occurred markedly faster than decomposition, which may indicate reversible formation of the respective azoene.[17] *rac*-**2** obtained from *rac*-**1** (prepared[18] from 2,3-isopropylideneglycerol) was crystalline and could be stored for several weeks without visible decomposition.

Sulfone **3a** (3 equiv) was treated with *i*PrMgCl in THF (3.1 equiv) at room temperature, and the resulting magnesium derivative was allowed to react with tosylhydrazone (*S*)-**2** (1 equiv). After completion of the reaction (2 h) olefin **4a** was obtained in 68% yield as a mixture of *E* and *Z* isomers in a ratio of 72:28. Samples of each of the isomers were separated and found to be enantiomerically pure (HPLC, Chiralcel OD-H column).

Reaction of the magnesio-derivative of isopropyl phenyl sulfone **3b** with (*S*)-**2** was markedly slower. Olefination product **4b** was obtained in 41% yield along with a side product (10−15% yield) to which the structure of carbinol **5a** was assigned. An analogous reaction using of cyclohexyl phenyl sulfone **3c** afforded the respective olefin **4c** in 21% yield and carbinol **5b** in 26% yield.

Obviously carbinols **5a** and **5b** were generated in reactions of the respective sulfonyl anions with acetone originating from the acetonide protection group in **2**. The stage of cleavage of the acetal function and its mechanism are not quite clear. Most likely, acetone is generated from allylic alcohol derivatives **4b** or **4c** by Lewis acid catalyzed elimination under the reaction conditions. However, fragmentation of the intermediate adducts, *iv* in Scheme 1 (broken-line arrows), cannot be excluded.

3,4:5,6-Di-*O*-isopropylidene-D-sorbitol[19] was oxidized[14] to give 2,3:4,5-di-*O*-isopropylidene-D-arabinose **6** (Scheme 3), and the latter was transformed into tosylhydrazone **7** in the usual way (69% yield). Reaction of **7** with magnesium derivative of sulfone **3a** smoothly afforded olefin **8**, which was isolated in 60% yield, *E*:*Z* = 89:11. High selectivity of this olefination reaction with respect to the *E*-isomer is noteworthy.

Prolinol **9** was oxidized with the Dess−Martin periodinane[20] to give aldehyde **10**, which was transformed into its tosylhydrazone **11** without isolation (73% from prolinol). Reaction of **11** with magnesio sulfone **3a** afforded olefin **12** in 88% yield (*E*:*Z* = 56:44).

Next, we turned our attention to some acyclic acetaldehyde derivatives. Phenoxyacetaldehyde **13** (Scheme 4) was transformed into tosylhydrazone **15**, and the latter was allowed to react with an anion generated from sulfone **3a**. Labile *O*-phenyl allylic alcohol derivative **16** was isolated in 45% yield. *N*-Phenyl-*N*-tosyl-2-aminoethanal **14** in an analogous procedure through tosylhydrazone **17** afforded the respective derivative of allylic

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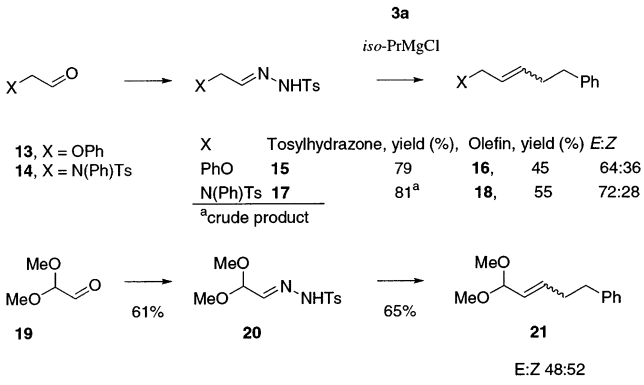
SCHEME 4



amine **18** in 57% yield. Finally, glyoxal 1,1-dimethyl acetal **19** gave tosylhydrazone **20** (61% yield, after chromatography) and then dimethylacetal of α,β-unsaturated aldehyde **21** in 57% yield.

In conclusion, representative aldehydes bearing an alkoxy- or alkylamino group in the α-position in reaction with α-magnesio sulfones afford the respective derivatives of allylic alcohols or allylic amines. 2,3-*O*-Isopropylidene-D-glyceraldehyde afforded tosylhydrazone **2** and the olefination products **4** with virtually complete retention of optical activity.

Experimental Section

***N′*-{(1*E*)-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methylene}-4-methylbenzenesulfonohydrazine (2).** Di-*O*-isopropylidene-D-mannitol (1.0 g, 3.81 mmol) was oxidized with sodium periodate[14] (907 mg) in THF (15 mL) and water (1.7 mL), and the product was isolated with diethyl ether. The thus obtained solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (*R*)-**1** in diethyl ether/THF was dried over anhydrous $MgSO_4$. After removal of the drying agent, tosylhydrazine (1.457 g, 7.82 mmol) was added, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the residue was chromatographed on silica gel (30 g, hexanes/ethyl acetate, gradient elution) to give (*S*)-**2** (2.097 g, 92% from di-*O*-isopropylidene-D-mannitol) as a colorless semisolid mass, $[\alpha]^{23}_D = +18.6$ (*c* 8.3, ethyl acetate). ^{1}H NMR (DMSO-d_6) δ 1.26 (6H, s), 2.39 (3H, s), 3.75 (1H, dd, *J* 8.5, 6.0 Hz), 4.05 (1H, dd *J* 8.6, 6.6 Hz), 4.42 (1H, dt, *J* 6.4, 6.2 Hz), 7.14 (1H, d, *J* 6.4 Hz), 7.41 (2H, apparent d, *J* 8.1 Hz), 7.68 (2H, apparent d, *J* 8.1 Hz), 11.36 (1H, s) ppm. ^{13}C NMR (DMSO-d_6) δ 21.0 (3), 25.2 (3), 26.2 (3), 66.3 (2), 74.5 (2), 109.1 (0), 127.0 (1), 129.5 (1), 135.9 (0), 143.3 (0), 147.8 (1) ppm.

Freshly prepared tosylhydrazone (*S*)-**2** was enantiomerically pure by HPLC (see the following experiment). However, it racemized and slowly decomposed on storing; after several weeks racemization was virtually complete.

***rac*-*N′*-{(1*E*)-[2,2-Dimethyl-1,3-dioxolan-4-yl]methylene}-4-methylbenzenesulfonohydrazine (2).** 2,3-Isopropylideneglycerol (Solketal, Fluka) (1.00 g) was oxidized using the modified[18] Swern method. The aldehyde was purified by chromatography and treated with tosylhydrazine as described above. *rac*-**2** was obtained (776 mg, 34% from Solketal), mp 126−127 °C (*tert*-butyl methyl ether/hexane). HPLC analysis: a Chiralcel OD-H column, hexane/2-propanol, 4:1, 0.5 mL/min, t_R 16.8 and 18.1 min for (*R*)- and (*S*)-enantiomers, respectively.

(4*S*)-2,2-Dimethyl-4-[(1*E*)-4-phenylbut-1-enyl]-1,3-dioxolane (*E*-4a) and (4*S*)-2,2-Dimethyl-4-[(1*Z*)-4-phenylbut-1-enyl]-1,3-dioxolane (*Z*-4a). General Procedure for Reaction of α-Magnesio Sulfones with Tosylhydrazones. To sulfone **3a**[21] (592 mg, 2.27 mmol, 3 equiv), stirred under argon at room temperature, was added *i*PrMgCl (2M in THF, 1.2 mL, 2.4 mmol) (vigorous gas evolution occurred). The mixture was stirred for 1.5 h, and then tosylhydrazone (*S*)-**2** (227 mg, 0.76 mmol) in THF (10 mL) was added portionwise. After consecutive 2 h, the reaction was quenched with concentrated aqueous ammonia (0.3 mL). The solid was filtered off and washed with THF. The combined filtrates were evaporated, and the residue was chromatographed on silica gel (20 g, hexane/ethyl acetate) to give **4a** (120 mg, 68%) as a colorless oil, *Z*:*E* = 21:79, by HPLC (hexanes/ethyl acetate, 9:1), t_R 4.3 min (*Z*-) and 4.6 min (*E*-isomer). Samples of both isomers were isolated using preparative HPLC; enantiomeric purity of each of the isomers was confirmed by analysis on a chiral HPLC column.

Data for 4a (*Z*): $[\alpha]_D$ −13.2 (*c* 0.8, hexane). ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, s), 1.39 (3H, s) 2.3−2.5 (2H, m), 2.5−2.9 (2H, m), 3.35 (1H, t, *J* 8.1 Hz), 3.76 (1H, dd *J* 7.1, 6.1 Hz), 4.70 (1H, dd *J* 15.5, 8.0 Hz), 5.33−5.48 (1H, m), 5.57−5.75 (1H, m), 7.1−7.4 (5H, m) ppm; on irradiation at δ 2.41 multiplet at δ 5.33−5.48 collapsed to a doublet of doublets, *J* 10.6, 8,56 Hz, and that at δ 5.57−5.76 to a doublet, *J* 10.8 Hz. ^{13}C NMR ($CDCl_3$) δ 26.0 (3), 26.8 (3), 29.7 (2), 35.7 (2), 69.2 (2), 71.9 (1), 109.0 (0), 126.0 (1), 128.0 (1), 128.3 (1), 128.5 (1), 133.5 (1), 141.2 (0) ppm.

Data for 4a (*E*): $[\alpha]_D$ + 24.4 (*c* 3.8, hexane). ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, br s), 1.42 (3H, s,), 2.30−2.45 (2H, m), 2.60−2.80 (2H, m), 3.53 (1H, t, *J* 8.0 Hz), 4.04 (1H, dd, *J* 6.1, 2.0 Hz), 4.35−4.55 (1H, m), 5.46 (1H, ddt, *J* 15.3, 7.8, 1.4 Hz), 5.83 (1H dt *J* 15.3, 6.6 Hz), 7.1−7.4 (5H, m) ppm; on irradiation at δ 2.37 multiplet at δ 5.46 collapsed to a doublet of doublets, *J* 15.2, 7.9 Hz, and that at δ 5.83 to a doublet, *J* 15.2 Hz. ^{13}C NMR ($CDCl_3$) δ 26.0 (3), 26.7 (3), 34.1 (2), 35.3 (2), 69.4 (2), 77.2 (1), 109.0 (0), 125.8 (1), 127.9 (1), 128.28 (1), 128.34 (1), 134.7 (1), 141.5 (0) ppm. **4a**(*E*) HRMS (EI): calcd for $C_{15}H_{20}O_2$, 232.14633, found 232.14694.

***rac*-2,2-Dimethyl-4-[(1*E*)-4-phenylbut-1-enyl]-1,3-dioxolane (*E*-4a) and *rac*-2,2-dimethyl-4-[(1*Z*)-4-phenylbut-1-enyl]-1,3-dioxolane (*Z*-4a)** were prepared in an analogous way from ***rac*-1**. Pure compounds *rac*-*Z*-**4a** and *rac*-*E*-**4a** were separated by preparative HPLC and analyzed on chiral analytical HPLC columns. Resolution of *rac*-(*Z*)-**4a** was achieved on a Chiralcel OD-H column (hexane/2-propanol, 9:1): t_R 10.1 min (*S*-enantiomer) and 11.4 min (*R*)-enantiomer. *rac*-(*E*)-**4a** was separated on a Chiralcel OJ column (hexane-2-propanol, 9:1): t_R 14.1 min (*S*)-enantiomer and 16.4 min (*R*)-enantiomer.

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Supporting Information Available: General experimental conditions; full experimental procedures for compounds **4b**, **4c**, **5a**, **5b**, **7**, (*E*)-**8**, (*Z*)-**8**, **11**, (*E*)-**12**, (*Z*)-**12**, **15**, (*E*)-**16**, (*Z*)-**16**, **17**, (*E*)-**18**, (*Z*)-**18**, **20**, (*E*)-**21**, and (*Z*)-**21**; and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0499118

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