Notes

Advantageous Syntheses of Stilbenes via Benzotriazole-Stabilized Anions

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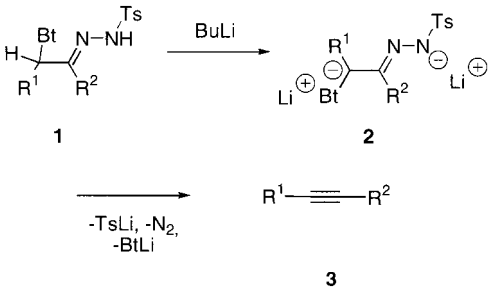
Introduction

Stilbenes are well-known as optical brighteners[1] and synthetic precursors of phenanthrene alkaloids[2] and enantiomerically pure 1,2-diphenylethane-1,2-diamines[3] and diols[4] via asymmetric dihydroxylation. The growing interest in diphenylethylene derivatives is connected with the antileukemic,[5] carcinostatic,[6] and protein-tyrosine kinase inhibitory[7] activities of some synthetic as well as naturally occurring[8] stilbenes, specifically their *trans*-isomers.

Syntheses of stilbenes from aryl aldehydes and stabilized benzyl carbanions have gained increased importance.[9] Frequently, the carbanion is stabilized using octet enlargement, as by P, Si, and S heteroatoms at the α-position of the benzyl intermediate in Wittig,[10] Peterson,[11] and Julia[12] reactions, respectively. In the well-studied Wittig reaction, stilbenes are usually formed in moderate to high yield as a mixture of (*E*)- and (*Z*)-isomers together with triphenylphosphine as a side product.[9] Although the (*E*/*Z*)-ratio can be influenced by varying some of the reaction conditions (solvent, temperature, base, promotor, etc.),[13−15] recent studies[16] indicate that the (*E*/*Z*)-ratio is not affected by changes in concentration, mode of addition, or molar ratio of aldehyde to ylide, and only to a minor extent by the substitution in the aldehyde and aralkylidene−triphenylphosphorane precursors. Peterson olefinations require multistep syntheses of starting arylmethylsilanes, and for stilbenes show low stereoselectivity.[17] Stabilization of the anion by an arylsulfonyl group in Julia olefinations affords high yields of 1,2-diphenyl-2-(phenylsulfonyl)-1-ethanol intermediates, but high stereoselectivity was demonstrated only for aliphatic derivatives.[18,19] Our recently reported[20a,b] addition of benzotriazole-stabilized anions to carbonyl compounds and subsequent in situ low-valent titanium dehydroxybenzotriazolylation of the intermediate diastereoisomeric *N*-(*β*-hydroxyalkyl)benzotriazoles gives predominantly *trans*-alkenes, -dienes, and -trienes.[20b]

Scheme 1



The use of an aldehyde as its enamine derivative can limit possible side reactions, give higher yields, and form selectively *E*-stilbenes.[9] An alternative is the use of arylsulfonylhydrazones,[21] in a process similar to the Shapiro reaction,[22] and we recently[23] demonstrated the utility of α-(1-benzotriazolyl)ketone hydrazones **1** for the preparation of alkynes **3** via dianion **2** (Scheme 1, Bt = 1-benzotriazolyl) by a Shapiro-like reaction.[22,24]

Results and Discussion

We have now found that reactions of benzotriazole derivatives **4** with tosylhydrazones of carbonyl compounds **5** in the presence of strong base provide a smooth entry to *E*-stilbenes (Scheme 2, Table 1). The suggested mechanism of this reaction (Scheme 2) involves the

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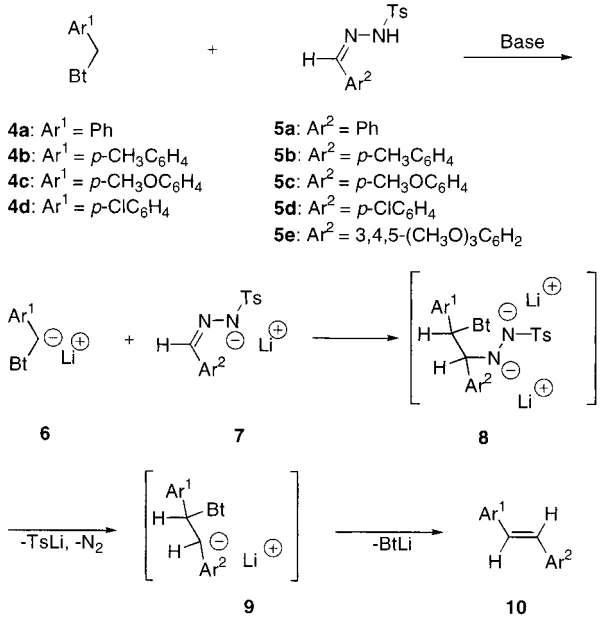
Table 1. Syntheses of *E*-Stilbenes 10 via Benzotriazole-Stabilized Anions

entry	Ar^1	Ar^2	method	base	*E*/*Z* ratio	yield,[a] %
1	Ph	Ph	A	BuLi	92/8	57
2	Ph	*p*-$CH_3C_6H_4$	A	BuLi	90/10	48
3	Ph	*p*-$CH_3OC_6H_4$	A	BuLi	99/1	53
4	*p*-ClC_6H_4	Ph	A	BuLi	98/2	61
5	*p*-$CH_3C_6H_4$	Ph	A	BuLi	–	traces
6	*p*-$CH_3C_6H_4$	Ph	A	LDA	–	traces
7	*p*-$CH_3C_6H_4$	Ph	B	LDA	93/7	65
8	Ph	Ph	B	LDA	99/1	84
9	Ph	*p*-$CH_3C_6H_4$	B	LDA	95/5	79
10	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	B	LDA	100/0	73
11	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	B	LDA	94/6	69
12	Ph	*p*-ClC_6H_4	B	LDA	100/0	81
13	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	B	LDA	100/0	64
14	Ph	3,4,5-$(CH_3O)_3C_6H_2$	B	LDA	99/1	68

[a] Isolated yield of pure *E*-isomer.

Scheme 2

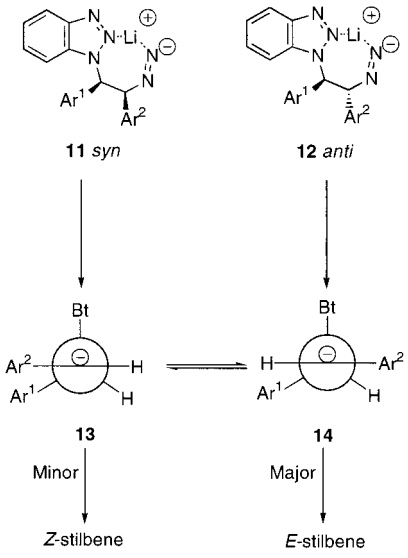


addition[25] of an anion **6** to tosylhydrazone anion **7** with the formation of dianion **8**. Loss of TsLi, nitrogen, and benzotriazole anion leads to the expected olefins **10** via **9**. This pathway is similar to our previous preparation of alkynes,[23] but reflects the lower bond order of the newly formed C–C bonds in the intermediates.

Preparation of Starting Materials. Compounds **4a–d** were synthesized by reactions of benzotriazole with the corresponding benzyl chloride,[26] and **5a–e** as previously reported.[27]

Preparation of Stilbenes. Deprotonation of compounds **4a–d** with *n*-butyllithium (BuLi) or lithium diisopropylamide (LDA) gave dark-green solutions of the corresponding anions, which underwent nucleophilic addition to the tosylhydrazones **5a–e** to form the corresponding stilbenes **10**, with disappearance of the green color. While it is convenient to employ a one-pot procedure (method A: i.e. treatment of a solution of tosylhydrazone and *N*-benzylbenzotriazole in THF with BuLi or LDA), the best results were obtained when anion **6** was

Scheme 3



formed separately and then added by cannula to a solution of preformed *N*-lithio tosylhydrazone **7** (method B). This procedure, and the use of LDA instead of BuLi, minimizes side reactions of tosylhydrazone[25] and improves yields of the stilbenes (Table 1). In all cases only the *E*-stilbene was isolated after recrystallization or chromatography. According to GCMS analysis of the crude reaction mixture, the *E*/*Z*-ratio was greater then 10:1. Similar alkene formation via the reaction of tosylhydrazone anions with α-lithio sulfides, sulfones, thioacetals, hemithioacetals, and nitriles[21] shows *E*:*Z* ratios in the range of 2:1 to 1:2, although the *E*-isomer was formed predominantly from *β*-methylstyrene. The high stereoselectivity of our novel olefination probably is connected to the formation of intermediates **11** and **12** in which the lithium is chelated by the neighboring nitrogen of the benzotriazole substituent (Scheme 3). This greater stabilization of the intermediate by a benzotriazolyl group, as compared to a phenylthio or alkylsulfinyl group and the strain in syn intermediate **11** being larger than in **12** makes the formation of the anti isomer more favorable. Further loss of nitrogen leads to the predominant formation of the less-strained anion **14**, which yields *E*-stilbene as the major product.

Conclusion

Convenient and stereospecific stilbene syntheses starting from tosylhydrazones of benzaldehydes with substituted *N*-benzylbenzotriazoles are described. This one-step method, which includes a Shapiro-type transformation, offers good stereoselectivity with predominant formation of *E*-isomers and compares favorably with the Wittig, Peterson, and Julia reactions. It provides an alternative to the recently described[20a,b] McMurry type dehydroxybenzotriazolylation route to olefins.

Experimental Section

Melting points were determined on a hot stage apparatus without correction. ^1H and ^{13}C NMR spectra were obtained on a 300 MHz spectrometer (300 and 75 MHz respectively) in chloroform-*d*.

THF and DME were distilled under nitrogen immediately prior to use from a purple solution containing benzophenone/sodium. Column chromatography was carried out on MCB silica

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gel (230−400 mesh). Other chemicals were used as obtained from commercial sources. Reactions were routinely carried out under nitrogen atmosphere with magnetic stirring.

General Synthetic Procedure. Method A. Compounds **4a**−**d** (2 mmol) and **5a**−**e** (2 mmol) were dissolved in THF (30 mL) in a reaction flask under nitrogen and cooled to −78 °C. BuLi (2.85 mL, 1.4 M, 4 mmol) or LDA (2.7 mL, 1.5 M, 4 mmol) was added in one portion. The dark-colored solution was stirred for 12 h while the temperature was raised to 20 °C. The mixture was quenched with water. Hexanes (50 mL) were added, and the organic phase was separated, washed with 10% Na_2CO_3 (2 × 50 mL) and water (50 mL), and then dried (Mg_2SO_4 anhydrous). Concentration under reduced pressure followed by silica gel column chromatography with hexanes/ethyl acetate (4:1) as the eluent gave stilbenes **10**.

Method B. Compounds **5a**−**d** (2 mmol) were dissolved in THF (30 mL) in a reaction flask under nitrogen and cooled to −78 °C. BuLi (2.85 mL, 1.4 M, 4 mmol) or LDA (2.7 mL, 1.5 M, 4 mmol) was added in one portion (solution 1). Separately, a solution of **4a**−**e** (2 mmol) in 20 mL of THF at −78 °C under nitrogen was treated with BuLi (2.85 mL, 1.4 M, 4 mmol) or LDA (2.7 mL, 1.5 M, 4 mmol) (solution 2). Solution 2 was added dropwise to solution 1 by cannula, and the mixture was stirred for another 12 h while the temperature was allowed to rise to 20 °C. A workup and isolation procedure similar to that in method A gave stilbenes **10**.

Supporting Information Available: ^1H and ^{13}C spectral data of stilbenes **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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