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Direct Conversion of Dipropargylic Sulfones into (*E*)- and (Z)-Hex-3-ene-1,5-diynes by a Modified One-flask Ramberg-Bäcklund Reaction

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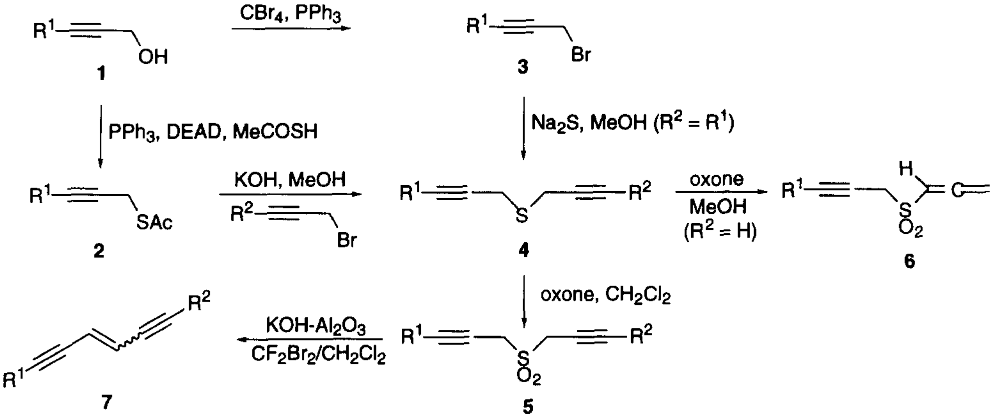
Abstract: (*E*)- and (Z)-enediynes **7** are readily synthesized in good yields from a one-pot modified Ramberg-Bäcklund reaction from dipropargylic sulfones **5**.

Keywords: dipropargylic sulfones, enediynes, Ramberg-Bäcklund reaction

Interest in the construction of the hex-3-ene-1,5-diyne structural unit emerged in the literature[1] long before the discovery of the enediyne antitumor antibiotics calicheamicins, dynemicin A and esperamicins and the related neocarzinostatins,[2] but its recent revival has been fueled by the recognition of the key role of the Bergman cyclization[1f] taking place in the "warhead" portions of these natural products as the origin of their DNA damaging properties.[3] With the exception of a rare instance in which a 3-ene-1,5-diyne substructure was built by manipulation of the carbonyl group in a 2-ene-4-ynal skeleton,[4] there have been mainly two general strategies for the assembly of the enediyne unit. One approach makes use of the Pd(0)-Cu(I)-co-catalyzed coupling of two terminal acetylenes to a stereochemically defined 1,2-dichloroethene[5] or the Pd(0)-mediated cross coupling of two 1-iodoacetylene molecules to a distannylethene,[6] while the other entails the anchoring of a carbon-carbon triple bond to each end of a latent olefinic double bond which is subsequently unraveled by an eliminative process.[1b,d,7] Among the various methodologies adopted in the latter approach, the Ramberg-Bäcklund reaction has been put into good use by Nicolaou for the conversion of cyclic α-chloro-dipropargylic sulfones into the corresponding enediyne arrays.[7a,b] We recently reported a new protocol of the Ramberg-Bäcklund reaction to effect the direct transformation of α- and α'-hydrogen bearing sulfones into alkenes.[8] The successful application of our procedure for the formation of conjugated trienes from diallylic sulfones[9] prompted us to examine similar reactions on the dipropargylic counterparts with the goal to gain direct access to the enediyne unit without resorting to the prior preparation of the α-halosulfone precursors in a separate step. Reported herein are our findings that dipropargylic sulfones are indeed submissive to our Ramberg-Bäcklund reaction conditions to provide an easy entry to readily separable (*E*)- and (Z)-hex-3-ene-1,5-diynes in good yields.

Individual propargylic alcohols **1** were chosen as the common starting materials for each reaction sequence in our scheme. These alcohols were either transformed into the corresponding propargylic thiolacetates **2** using the Mitsunobu reaction[10] with thioacetic acid in the presence of triphenylphosphine and diethyl azodicarboxylate, or into the corresponding bromides **3** by reaction with triphenylphosphine and carbon tetrabromide. Coupling of **3** with sodium sulfide in methanol furnished the symmetrical sulfides **4**[11] ($R^1 = R^2$) in good yields. On the other hand, reaction of propargylic bromides **3** with the thiolates generated *in situ* from the thiolacetates **2** afforded the unsymmetrical dipropargylic sulfides **4**[11] ($R^1 \neq R^2$). The displacement of bromide in these reactions took place exclusively on the propargylic carbon with no detectable formation of allenic product arising from an S_N2' process. Oxidation of the dipropargylic sulfides **4** by oxone[12] in dichloromethane gave high yields of the corresponding sulfones **5**.[11] It is noteworthy that if a hydroxylic solvent such as methanol was employed in the oxidation of **4** bearing a terminal acetylenic moiety, rearrangement occurred extensively to give the allenylic propargylic sulfones **6**.



Subjecting the dipropargylic sulfones **5** to our previously described modified Ramberg-Bäcklund reaction protocol (CBr_2F_2, KOH-on-Al_2O_3, *tert*-butanol)[8] invariably led to intractable reaction mixtures, indicating the unsuitability of the use of a protic solvent for these sulfone substrates in our reaction. However, when dichloromethane was used in place of *tert*-butanol, the reaction of each of these sulfones proceeded smoothly at -10°C to give a readily separable mixture (≈ 1:1) of the (*E*)- and (*Z*)-enediynes **7**[11] in combined total yields of 60 - 94% (Table 1). For the enediynes synthesized in this series, the (*E*)-isomers had consistently larger R_f values than those of the corresponding (*Z*)-isomers and each pair were easily separated by flash column chromatography over silica gel. The configurations of the newly formed double bond in the unsymmetrical enediynes was readily diagnosed by the typical coupling constant of 16 Hz and 10Hz for the *trans*- and *cis*-olefinic protons, respectively. For the symmetrical enediyne product where $R^1 = R^2 = Ph$, the issue of stereochemistry was confirmed by comparison of their physical and spectroscopic properties to those reported in

Table 1. Yields (%) of sulfides **4**, sulfones **5** and enediynes **7**.

R^1	R^2	Sulfide 4	Sulfone 5	(*E*)-7	(*Z*)-7
H	n-C_5H_{11}	89	>95	43 (J = 16.1)[a]	37 (J = 10.9)
H	t-Bu	81	>95	33 (J = 16.1)	27 (J = 10.9)
Ph	H	82	>95	49 (J = 16.1)	45 (J = 10.9)
n-C_5H_{11}	Ph	81	87	33 (J = 16.0)	27 (J = 10.0)
t-Bu	Ph	80	87	43 (J = 16.0)	47 (J = 10.7)
n-C_5H_{11}	n-C_5H_{11}	75	90	41[b]	40
Ph	Ph	95	89	40	40

[a]Coupling constants reported in Hz. [b]The fore-running fraction in column chromatography.

the literature.[13,14] We were unable to obtain crystal for the symmetrical enediyne where $R^1 = R^2 = n$-C_5H_{11}, and hence the faster running isomer in chromatographic separation is tentatively assigned to have the (*E*)-geometry.

In summary, we have demonstrated the applicability of our protocol of the Ramberg-Bäcklund reaction in assembling the hex-3-ene-1,5-diyne unit from dipropargylic sulfones without the necessity to prepare the α-halodipropargylic sulfones beforehand. Other applications of our procedure are under investigation in our laboratories.

Experimental procedure for the preparation of enediyne 7:

A solution of the sulfone **5** (2 mmol) in dry dichloromethane (10 ml) was added in one portion to a stirred suspension of alumina-supported KOH (1:1 by weight)[8] (10 g) in dibromodifluoromethane (1 ml) and dichloromethane (10 ml) at -10°C. After 30 min, the mixture was filtered through a short column of silica gel and the filtered cake washed with dichloromethane (20 ml). The filtrate was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with hexane to give the (*E*)- and (*Z*)-enediynes **7** as colorless oils.[15]

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