Integrated Chemical Process. One-Pot Preparation of Acetylenes by Peterson-Sulfone Elimination

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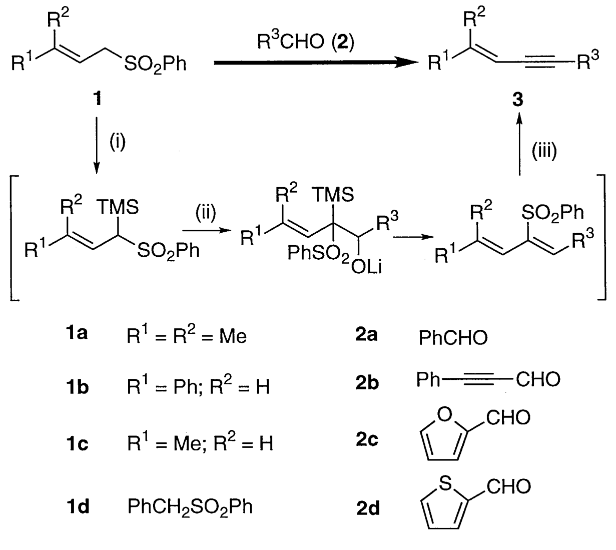
Integration of silylation of α-sulfonyl carbanion, addition of the anion of the resulting α-silyl sulfone to aldehyde, Peterson elimination, and sulfone elimination leads to one-pot synthesis of acetylenes.

Recently, we put forth a new concept for compaction of multi-step chemical processes (ICP: Integrated Chemical Process).[1] In this treatment, the reaction conditions employable in all steps are settled first of all and, then, each step is optimized under these conditions. As a result, all steps are necessarily integrated into a one-pot process. The concept was proved to be effective in a concise synthesis of vitamin A based on double elimination of β-alkoxy sulfone.[2] In addition to this polyene synthesis, we report here one-pot synthesis of acetylenes with recourse to the sulfone elimination chemistry, which, however, has been renewed from the previous double elimination protocol.

According to our mechanistic investigation, the double elimination is initiated by elimination of alkoxide to give vinyl sulfones followed by elimination of sulfonate.[2c] We postulated that Peterson elimination[3] would be incorporated in this process to generate the vinyl sulfone intermediates since this reaction is conducted under basic conditions which are crucial for elimination of sulfone. Combination of Peterson and sulfone eliminations would be of great synthetic significance because trapping of the lithiates of sulfone-aldehyde adducts by a leaving group is no more required.[4] This is indeed the case as depicted in Scheme 1.



(i) BuLi (1.1 equiv.), THF, -78 °C, 30 min, then TMSCl (1.1 equiv.), -78 °C-rt, 1 h. (ii) BuLi (1.2 equiv.), -78 °C, 30 min, and then R'CHO, -78 °C, 1 h and 0 °C, 2 h. (iii) $(TMS)_2NLi$, conditions described in Table 1.

Scheme 1.

Table 1. One-pot preparation of enynes and diynes

entry	1	2	(iii)		3
			$(TMS)_2NLi$ /equiv.	reactn. condition	Yield/%
1	**1a**	**2a**	3	rt/1 h reflux/2 h	77
2		**2b**	10	rt/1 h	88 (65)[a]
3			1.2	rt/1 h reflux/2 h	78
4		**2c**	10	rt/1 h	75
5			3	rt/1 h reflux 2 h	63
6	**1b**	**2a**	10	rt/1 h	85 (58)[b]
7			1.2	rt/3 h	64
8		**2b**	1.2	rt/3 h	79 (50)[b]
9		**2c**	10	rt/1 h	71
10		**2d**	10	rt/1 h	71
11	**1c**	**2a**	10	rt/1 h	63
12		**2b**	10	rt/1 h	66 (36)[b]
13		**2c**	10	rt/1 h	57
14	**1d**	**2b**	1.2	rt/3 h	78
15		**2c**	1.2	rt/3 h	66 (40)[a]

[a] Overall yields by the stepwise acetate process given in parentheses.
[b] Overall yields by the stepwise Peterson-sulfone elimination process given in parentheses.

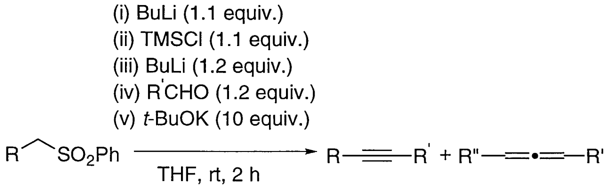
Allylic or benzyl sulfones and aldehydes were coupled to give enynes and diynes in one-pot and the results are summarized in Table 1.

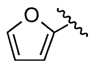
To a THF solution of sulfone **1** was added BuLi and subsequently TMSCl. After 1 h, BuLi and aldehyde were added to this solution. The solution was stirred at -78 °C for 1 h and at 0 °C for 2 h. The sulfone elimination was first attempted by use of *t*-BuOK, which, however, gave unsatisfactory yields. Then, we found that $(TMS)_2NLi$ worked effectively. In general, use of a large excess amount of the base allows the elimination to occur at room temperature while upon decreasing the amount, reaction at refluxing temperature is necessary on some occasions. The yields given in Table 1 are notable as the overall yields of the four-step reactions (silylation, carbon-carbon bond formation, Peterson elimination, and sulfone elimination). Even the lowest overall yield (57%) results from succession of the 87% yield of each step in average and more remarkably, the 88% overall yield is equivalent to 97% x 97% x 97% x 97%, indicative of all steps proceeding almost quantitatively. In Table 1 are given, for comparison, the overall yields both in the conventional stepwise acetate process which involves addition of α-sulfonyl carbanion to aldehyde, isolation of β-acetoxy sulfone, and double elimination with *t*-BuOK (3 equiv.), and in the stepwise Peterson-sulfone elimination method. Apparently, ICP gave rise to much higher yields than the stepwise processes. This implies that material loss during isolation and purification of intermediates in the stepwise processes is suppressed efficiently in ICP.

When alkyl sulfones were subjected to the reaction, a mixture of acetylene and allene was formed (Table 2). This is reasonable due to the presence of a propargylic hydrogen which is labile under basic conditions. The acetylene/allene ratio is thermodynamically controlled and thus dependent on the sulfone and aldehyde components. Notably, β-phenethylsulfone showed a great bias for the allene because of facile conjugation with the phenyl ring.

The typical procedure is as follows. To a THF solution of **1a** (210 mg, 1.0 mmol) was added BuLi (0.69 ml, 1.6 M hexane solution, 1.1 mmol) at -78 °C and the solution was stirred for 30 min. TMSCl (0.14 ml, 1.1 mmol) was added to this solution. The solution was stirred for 1 h and cooled to -78 °C. BuLi (0.75 ml, 1.6 M hexane solution, 1.2 mmol) was added and the solution was stirred for 30 min. To the reaction mixture was added **2b** (0.15 ml, 1.2 mmol). The solution was stirred at -78 °C for 1 h and at 0 °C for 2 h. To this solution was added a THF (1 ml)-hexane (6.3 ml) solution of $(TMS)_2NLi$ (10 mmol) at -78 °C. The solution was stirred at 0 °C for 1 h. The reaction mixture was combined with sat. NH_4Cl solution (15 ml) and extracted with EtOAc (20 ml x 3). The organic layer was washed with brine and dried (Na_2SO_4). The crude product obtained by evaporation was purified by column chromatography on silica gel (hexane) to give 1,1-dimethyl-6-phenyl-1-hexen-3,5-diyne (159 mg, 88% based on **1a**).

Table 2. One-pot preparation of acetylenes and allenes



R	R'	Yield/%	acetylene:allene
n-C_5H_{11}	Ph	74	1.0:1.2
		63[a]	2.1:1.0
$(CH_3)_2CH$-	Ph	68	13.0:1.0
$PhCH_2$-	Ph	46	1.0:34.0

[a] Hexane (3 ml) was added in step (v).

In conclusion, the extremely concise process for acetylenes has been established. ICP gives rise to not only the compaction of the multi-step chemical process but also improvement of the overall yield.

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