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(*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide: A Vinyl Sulfone as Precursor of a New δ-Acyldienyl Anion Equivalent

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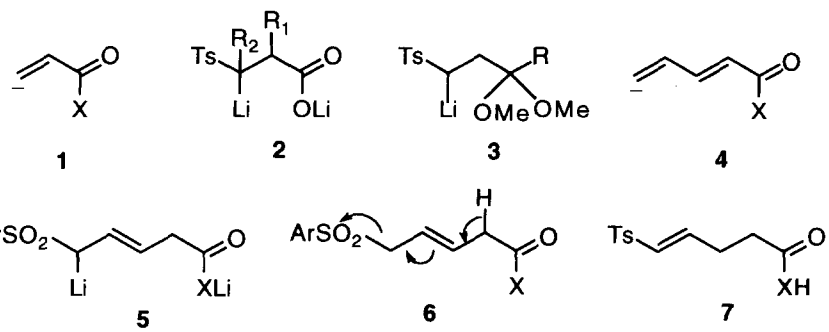
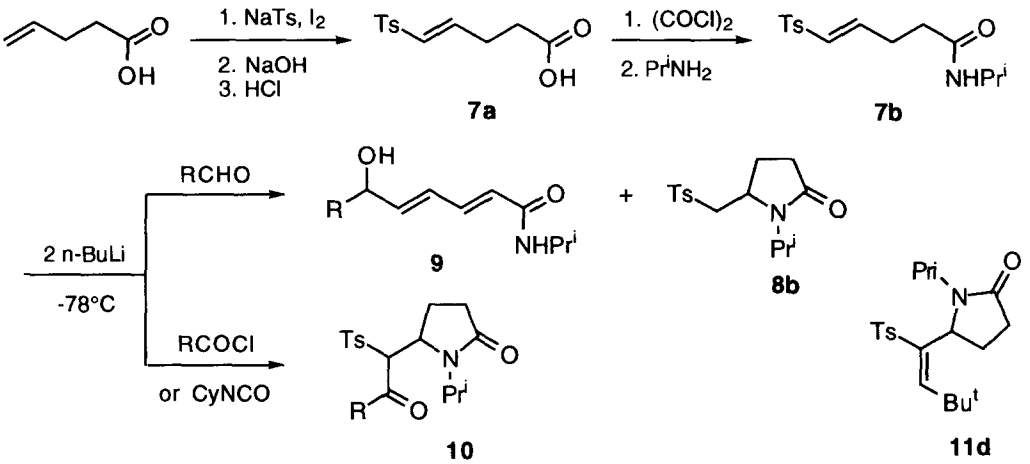
Abstract: (*E*)-*N*-Isopropyl-5-tosyl-4-pentenamide (**7b**), prepared from 4-pentenoic acid by stereoselective iodosulfonylation-dehydroiodination and further amidation with oxalyl chloride and isopropylamine, reacts with two equiv of n-butyllithium at -78°C and then with aldehydes affording stereoselectively (2*E*,4*E*)-6-hydroxy-2,4-hexadienamides **9**. In the case of carboxylic acid chlorides or cyclohexyl isocyanate, dilithiated lactam **8c** undergoes acylation to afford the corresponding lactam derivatives **10**. Copyright © 1996 Elsevier Science Ltd

β-Acylvinyl anions **1** or their equivalents are interesting carbanionic intermediates with umpolung reactivity, which have been widely used in organic synthesis as d[3] reagents to provide α,β-unsaturated functionality.[1] Previously, we have used lithiated γ-oxosulfones **2**[2] and **3**[3] as useful β-acylvinyl anions equivalents of β-lithiated-α,β-unsaturated-carboxylic acids[2] and -carbonyl compounds,[3] respectively, starting from the corresponding acrylic systems. According to this simple strategy it could be possible to achieve the preparation of vinylogous anion of δ-acyldienyl equivalents **4** by means of intermediates **5**. These type of umpoled d[5] carbanionic reagents have not been already described and should be promising intermediates to transfer α,β,γ,δ-unsaturated functionality[4] present in many natural products.[5] For the preparation of lithiated intermediates **5**, δ-arylsulfonyl substituted β,γ-unsaturated carboxylic acids derivatives **6** coul be good candidates as starting compounds. However, they are very unstable[6] under basic reaction conditions, because they undergo δ-dehydrosulfinylation instead of deprotonation to give the corresponding α-sulfonyl carbanion **5**. The efficient introduction of a tosyl group at the terminal vinyl carbon by a stereoselective iodosulfonylation-dehydroiodination process[7] prompted us to prepare vinyl sulfones of the type **7** as precursors of δ-acyldienyl anion equivalents starting from 4-pentenoic acid. This type of sulfones could be lithiated at the vinylic position[8] and after reaction with electrophiles and subsequent *in situ* isomerization of the double bond to the β,γ-position and final δ-dehydrosulfinylation could afford the corresponding 5-substituted diene systems.

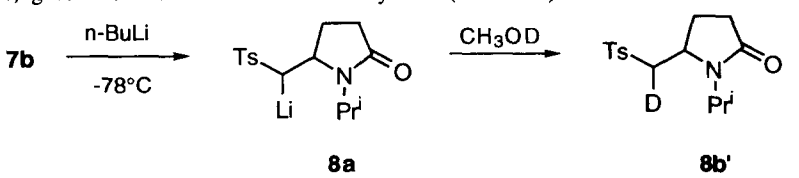


The iodosulfonylation of 4-pentenoic acid (**6**),[9] with sodium *p*-toluenesulfinate and iodine in methanol followed by *in situ* dehydroiodination with 0.5M sodium hydroxide and acidification, gave the expected (*E*)-5-tosyl-4-pentenoic acid (**7a**) in 71% yield. This acid was converted into amide **7b** in 70% yield by treatment with oxalyl chloride and further reaction with isopropylamine. This latter transformation was necessary because the amide moiety should allow the double bond isomerization and the final base-induced dehydrosulfinylation in a more efficient way.[10] When amide **7b** was treated with 2 equiv of n-butyllithium for 30 min at -78°C in THF followed by addition of different aldehydes, the expected 6-hydroxydienamides **9** with 2*E*,4*E*-configuration were stereoselectively obtained (Scheme 1 and Table 1). However, when carboxylic acid chlorides or cyclohexyl isocyanate were used as electrophiles, lactams **10** were isolated as *threo/erythro* diastereomers mixtures (Scheme 1 and Table 1).



Scheme 1.

Together with dienamides **9** some amounts of lactam **8b** was always obtained which, in some cases, could not by separated by chromatography or recrystallization. For this reason was necessary in these cases (Table 1, entries 2-4) to transform compounds **9** into their tetrahydropyranyl derivatives (3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2, rt, 1d),[11] which were separated by column chromatography (silica gel) and hydrolyzed (MeOH and TsOH) to yield pure compounds **9.** Only in the case of pivalaldehyde a 17% of lactam **11d** was also obtained together with compound **9d**. In order to understand the formation of lactam derivatives, the lithiation process was carried out with one equiv of n-butyllithium under the same reaction conditions. After addition of water at -78°C, lactam **8b** was the only obtained product in 90% yield; and after deuterolysis with MeOD, monodeuterated lactam **8b'** in 68% yield[12] (Scheme 2). This result indicates that the deprotonated amide gives very easily intramolecular conjugate addition to the vinyl sulfone[13] to afford the monolithiated lactam **8a**. The reaction with 2 equiv of n-butyllithium afforded dilithiated lactam **8c**, which after treatment with MeOD at -78°C, gave dideuterated lactam **8d** in 50% yield[12] (Scheme 3).



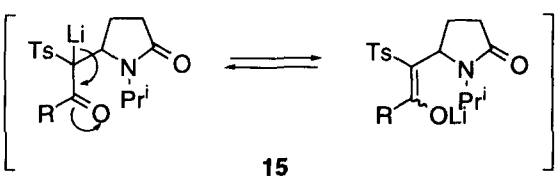
Scheme 2.

Table 1. Synthesis of Compounds **9** and **10**

		product[a]			
entry	electrophile	no.	R	yield (%)[b]	mp (°C)[c] or R_f[d]
1	CH_2O	**9a**	H	42[e]	0.29
2	EtCHO	**9b**	Et	47[e]	0.36
3	PriCHO	**9c**	Pri	33[e]	139-140
4	ButCHO	**9d**	But	32[e,f]	0.56
5	$PhCH_2CHO$	**9e**	$PhCH_2$	48	121-122
6	BnOCOCl	**10a**	OBn	47[g]	0.71[g]
7	PhCOCl	**10b**	Ph	62[h]	0.65[h]
8	CyN=C=O	**10c**	NHCy	58[i]	0.70, 0.56

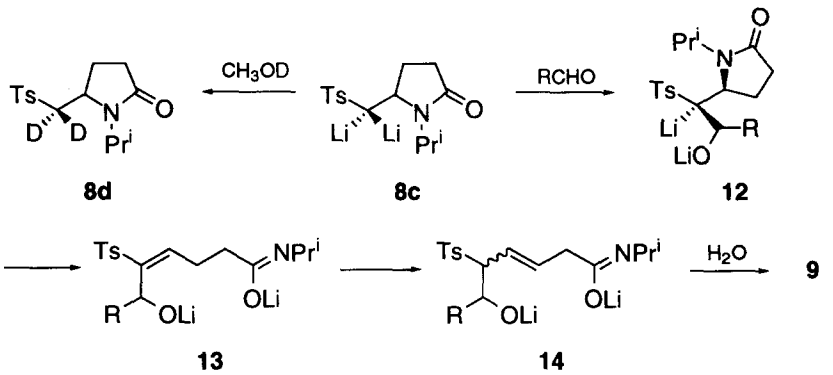
[a] All products were pure (TLC, 300MHz ^1H NMR) and gave satisfactory spectral data (IR, ^1H and ^{13}C NMR, and mass spectra). [b] Isolated yield based on amide **7b**, after column chromatography on silica gel. [c] Hexane/EtOAc. [d] EtOAc. [e] After treatment of crude reaction with dihydropyran (see text), column chromatography and deprotection. [f] A 17% of compound **11d** (Scheme 1) was also obtained. [g] 9/1: *threo/erythro* diastereomers mixture. [h] 3.5/1: *threo/erythro* diastereomers mixture. [i] 3/1: *threo/erythro* diastereomers mixture.

The formation of hydroxydienamides **9** can be explained by a multi-step mechanism: reaction of dilithiated lactam **8c** with the carbonyl compound to give mainly intermediate **12**, which undergoes ß-elimination to lead to the formation of **13**, followed by double bond isomerization to give intermediate **14**, which after final δ-dehydrosulfinylation (probably during the hydrolysis step) furnished compounds **9** (Scheme 3). The formation of compound **11d** in the reaction of dianion **8c** with pivalaldehyde also demonstrates the participation of intermediate **12** and can be explained by β-elimination of the β-oxido instead of the β-amido organolithium compound. In the case of acyl chlorides the β-elimination from intermediate **15** did not take place, because they are stable enolates.



15

In summary, we have found that the dilithiation of (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide, readily accessible from 4-pentenoic acid, and further reaction with aldehydes is an adequate strategy to prepare stereoselectively 6-hydroxy-substituted (2*E*,4*E*)-dienamides acting this sulfone as a δ-acyldienyl anion equivalent precursor. Investigations of useful extensions of this novel synthon are under way.



Scheme 3.

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