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Mono and Dilithiation of Benzyl[2-(tosylmethyl)-2-propenyl] amine: New γ-Aminated Allyl Sulfone Anions

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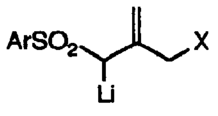
Abstract: **The mono and dilithiation of benzyl-[2-(tosylmethyl)-2-propenyl]amine (4) with n-butyllithium affords the corresponding allylic anions 5a and 5b, respectively. Monoanion 5a reacts regioselectively at the α-position of the sulfone group with deuterium oxide, alkyl halides, propanal, methyl crotonate and ethyl propiolate. Dianion 5b reacts with alkyl halides and ethyl propiolate also at the nitrogen atom to give in the case of dihalides 6, 7, and 8 member nitrogen-containing heterocycles .**

Allylic organolithium compounds **1**[1-5] and **2**[6] derived from γ-functionalized allyl sulfones **3** (X=Cl[1,5,6], Br[2], $SiMe_3$[3], OLi[2b,4]) with isobutene structure are useful intermediates specially in annelation reactions. Monoanion **1**(X=Br)[2a] and dianion **2**[6] have been used as 1,3-dipolar reagents with electrophilic olefins in the construction of methylenecyclopentanes and cyclopentenes, respectively. Morever, dianion **2**[6] has been also used in the synthesis of methylenecyclopropanes and 2,5-dihydrofurans or methylenetetrahydrofurans by reaction with alkyl bromides and carbonyl compounds, respectively. In the case of the alkoxide organolithium compound derivative **1**(X=OLi)[4], methylene δ- and ε-lactones have been prepared. In the present communication we describe the preparation and reactivity of a new organolithium compound **5a** of the type **1** derived from γ-tosyl benzylmethallylamine[7] (**4**) bearing an active hydrogen[8], as well as the corresponding dianion **5b**, and their synthetic applications in the synthesis of nitrogen-containing heterocyclic compounds.



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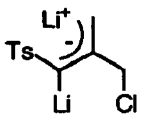

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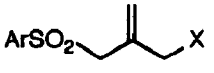

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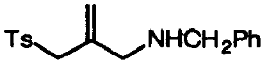

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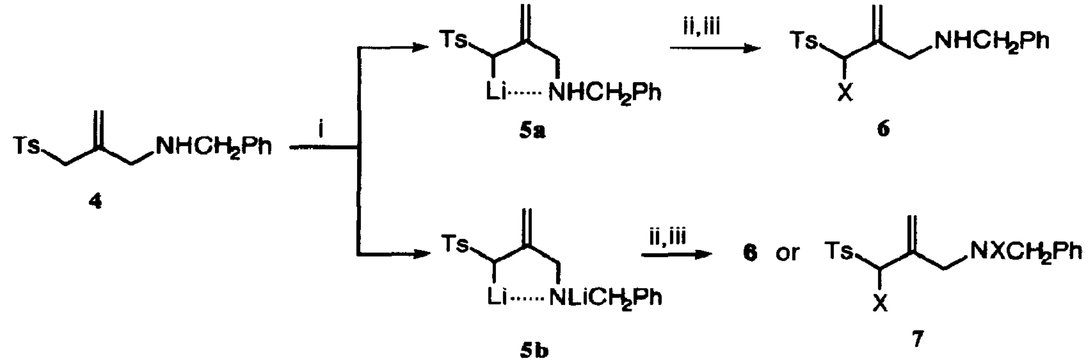
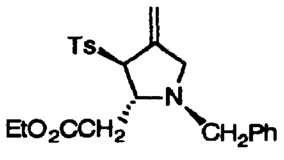
When benzyl-[2-(tosylmethyl)-2-propenyl]amine (**4**)[11] was allowed to react with one equivalent of n-butyllithium in THF at -78°C in the presence of *N,N'*-dimethylpropyleneurea (DMPU, 1 equiv.) as additive for 15 min the monoanion **5a** was regioselectively formed. This monolithium compound reacted with electrophiles such as deuterium oxide, allyl bromide, *tert*-butyl bromoacetate, propanal, and methyl crotonate at the carbon atom to afford compounds **6** (Scheme 1 and Table 1). The dilithiated derivative **5b** was prepared using two equiv. of n-butyllithium and DMPU under the same reaction conditions. This dianion reacted with the same electrophiles at the carbon atom to give compounds **6a,d,e** while with alkyl bromides the alkylation took place at the carbon and nitrogen atoms to provide compounds **7b,c** (Scheme 1 and Table 1). Only some differences have been found between both anions in the diastereomeric ratios obtained in the addition to propanal and methyl crotonate leading to compounds **6d** and **6e**, respectively. Monoanion **5a** was complete stereoselective with methyl crotonate affording the *threo* aminoester **6e**[13], whereas dianion **5b** gave a 1:1 *erythro*/*threo* ratio. However, with propanal **5a** and **5b** lead to 1: 2 and 1: 6 *erythro*/*threo* ratio, respectively (see Table 1).



Scheme 1. *Reagents and conditions:* i, n-BuLi, DMPU, -78°C; ii, E+; iii, H_2O.

The reaction of organolithium **5a** with ethyl propiolate afforded stereoselectively the *trans*-substituted pyrrolidine derivative **8** resulting from a double Michael addition to give first compound **10**, followed by intramolecular nitrogen attack to the resulting acrylate. However, dianion **5b** gave a 1:1 mixture of pyrrolidine **8** and *(E)*-β-enamino ester **9** resulting from a Michael addition of the lithium amide (Table 1).



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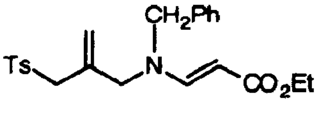

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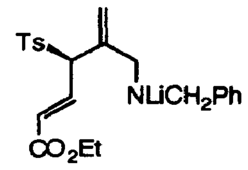

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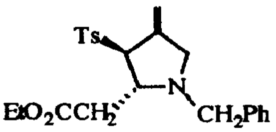
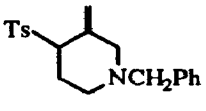
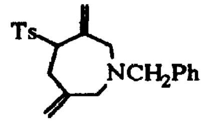
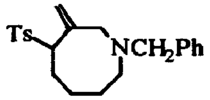
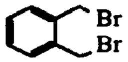
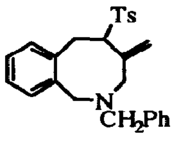
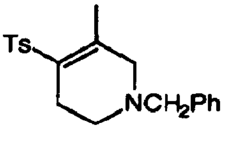
Dianion **5b** was allowed to react with alkyl dihalides in order to study its ability in annelation reactions. The reaction with 1,2-dibromoethane gave mainly the piperidine derivative **7f** together with its isomer **11** and the cyclopropyl derivative **12** in 6:1:2 ratio, respectively. With 3-iodo-(2-iodomethyl)-1-propene the azepine compound **7g** was obtained. When 1,4-dihalides such as 1,4-diiodobutane and α,α'-dibromo-*o*-xylene were used as dielectrophiles azocines **7h** and **7i** were obtained, respectively. Compound **7h** was obtained together with cyclopentane derivative **13** in 1:2 molar ratio (Table 1). Products **12** and **13** were formed due to the formation of an organolithium intermediate of the type **5a'** probably, by intramolecular lithiation of the carbon atom before the cyclization process. This second carbon lithiation has been studied using deuterium oxide as electrophile. Thus when dianion **5b** was allowed to react at -78°C with a ten fold excess of deuterium oxide and the reaction was allowed to warm till 0°C mono and dideuterated compounds **6a** and **6a'** at the carbon

Table 1. Reaction of Intermediates **5** with Electrophiles

		Product			
Intermediate	electrophile	no.	X or structure	yield (%)[a]	mp (°C)[b] or R_f[c]
5a	D_2O	**6a**	D	77[d]	45-46
5b		**6a**		70[e]	
5a	$CH_2{=}CHCH_2Br$	**6b**	$CH_2CH{=}CH_2$	75	0.44
5b		**7b**		71	0.70[f]
5a	*t*-BuO_2CCH_2Br	**6c**	$Bu^tO_2CCH_2$	60	0.77
5b		**7c**		50	0. 36[g]
5a	EtCHO	**6d**	EtCHOH	72[h]	0.39[i,j], 0.48[i,k]
5b		**6d**		56[l]	
5a	(*E*)-$MeCH{=}CHCO_2Me$	**6e**	$MeCHCH_2CO_2Me$	61[k]	0.64
5b		**6e**		60[m]	
5a	$HC{\equiv}CCO_2Et$	**8**		56	0. 78[i]
5b		**8**		25[n]	
5b	$Br(CH_2)_2Br$	**7f**		30[o]	144-145
5b		**7g**		43	112-113
5b	$I(CH_2)_4I$	**7h**		21[p]	123-124
5b		**7i**		32	198-199

[a] Isolated yield after flash chromatography (silica gel) based on starting amine **4**; all compounds were fully characterized by their spectroscopic data (IR, ^{1}H and ^{13}C NMR, and mass spectra). [b] From hexane/ether. [c] For oils, in hexane/ether: 3/7. [d] 67% of deuterium (300 MHz ^{1}H-NMR). [e] 98% of deuterium (300 MHz ^{1}H-NMR). [f] Hexane/ether: 1/1. [g] Hexane/ether: 2/1. [h] *Erythro/threo*: 1/2 (^{1}H NMR). [i] Ether. [j] *Erythro* . [k] *Threo*. [l] *Erythro/threo*: 1/6 (^{1}H NMR). [m] *Erythro/threo*: 1/1 (^{1}H NMR). [n] 29% of compound **9** (R_f 0.50, ether) was also obtained. [o] 10% of compound **11** (R_f 0.83, ether) and a 5% of compound **12** (R_f 0.66, ether) were also obtained. [p] 43% of compound **13** (R_f 0.59, ether) was also obtained.



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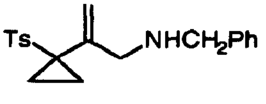

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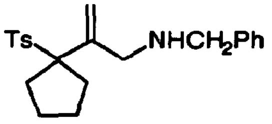

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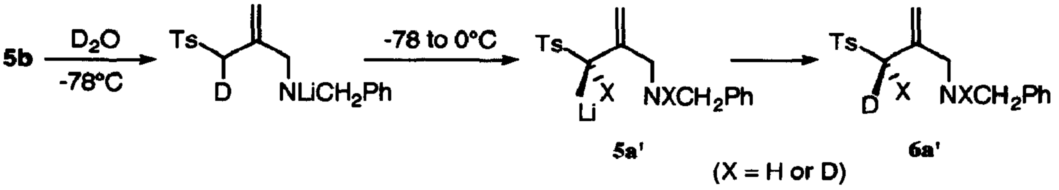
atom (*ca.* 1:1 mixture; 90% yield and 98% of deuterium deduced from ^{1}H and ^{13}C NMR) were obtained (Scheme 2). The existence of monoanions **5a** and **5a'** is a consequence of the pK$_a$ values[14] for hydrogens in α-position to the sulfone and attached to nitrogen.



Scheme 2

Work is in progress in order to study more synthetic aplication of these anions, specially in the preparation of medium size nitrogen-containing heterocycles[15].

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15. We are grateful to DGICYT of the Spanish Ministerio de Educación y Ciencia (MEC, Project no. PB91-0751) for financial support. D. A. A. thanks MEC for a predoctoral fellowship.

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