α-Nitrogenated Organolithium Compounds from *N*-(Tosylmethyl)amides

Diego A. Alonso, Emma Alonso, Carmen Nájera*, Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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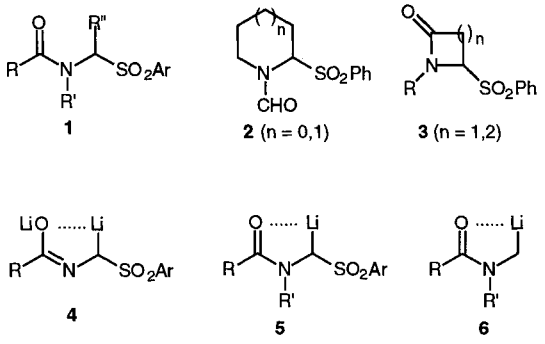
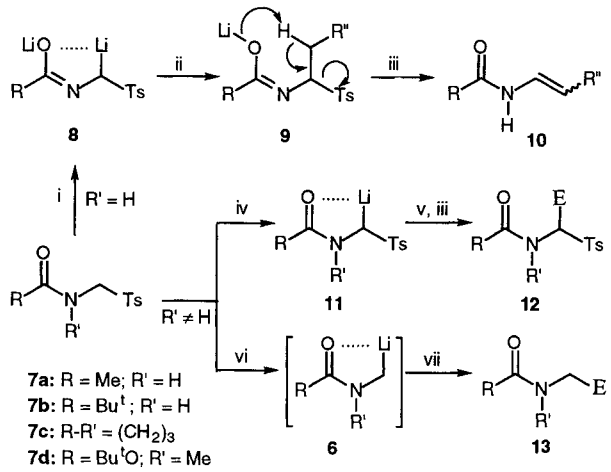
Dedicated to Professor E. J. Corey in recognition of his outstanding contributions to organic chemistry

Abstract: Deprotonation of α-amido sulfones **7** with Bu^{n}Li at -90°C followed by reaction with electrophiles leads, depending on the substitution on the amidic nitrogen to enamides **10** (secondary amides **7a,b**) or functionalised α-amido sulfones **12** (tertiary amides **7c,d**). Naphthalene-catalysed lithiation of tertiary α-amido sulfones **7c,d** in the presence of electrophiles (Barbier conditions) at -78°C affords functionalised amides **13**.

Acyclic (**1**[1]) and cyclic (**2**[2] and **3**[2b,3]) α-amido sulfones are stable crystalline compounds very useful as amidoalkylating agents acting as α-amidoalkyl cationic synthons. The arylsulfonyl group can be easily substituted by oxygen-, sulfur-, nitrogen-, carbon-, and tin-containing nucleophiles.[1-3] This methodology has been used in the synthesis of biologically active compounds such as alkaloids[2b] and β-lactams.[3b] According to the well known ability of the sulfone group to stabilise carbanions,[4] α-amido sulfones should be appropriate precursors for umpoled *d*^{1}-reagents[5] of type **4** or **5**.[6] In addition, amides and carbamates are known to stabilise nitrogen-substituted organolithium compounds by dipole stabilisation as well as internal lithium chelation.[7] On the other hand, sulfones can be also reductively transformed into organolithium compounds[8] by means of an arene-catalysed lithiation methodology.[9] This second feature of the sulfone functionality would allow the use of α-amido sulfones as precursors of α-nitrogen substituted organolithium compounds of the type **6**.[10] We report here on the reactivity of α-amido sulfones as precursors of sulfonyl substituted or unsubstituted α-amido organolithium compounds by means of direct deprotonation or arene-catalysed lithiation, respectively.



α-Amido sulfones **7** are easily prepared by a Mannich-type reaction of amides or carbamates with aqueous formaldehyde and sodium *p*-toluenesulfinate in the presence of formic acid.[12] Direct lithiation of amides **7a** and **7b** with Bu^{n}Li (2 equiv) in the presence of DMPU (2 equiv) was carried out at -90°C for *ca.* 2 min to afford intermediates **8**, which were characterised by deuterolysis giving the corresponding compounds **12** (E = D) in 72 and 70% yield, respectively (>94% deuterium incorporation). Dianions **8** are extremely unstable and could be only alkylated with very reactive alkyl bromides to give, after *in situ* dehydrosulfinylation *N*-acylenamines **10**, probably through an intramolecular elimination process of intermediates **9** (Scheme 1 and Table 1). Compounds **10** were obtained as a mixture of *Z/E* diastereomers, which in the case of allyl, propargyl and benzyl derivatives could be separated chromatographically. For methallyl bromide and *tert*-butyl bromoacetate only the *E*-diastereomers were obtained.



Scheme 1. i, 2 BuLi, 2 DMPU, THF, -90°C; ii, R"CH$_2$Br; iii, NH$_4$Cl; iv, Bu^{n}Li, DMPU, THF, -90°C; v, E+; vi, Li, C$_{10}$H$_8$ cat (4 %), E+, -78°C or THF, -78°C to 20°C (see text); vii, H$_2$O.

Table 1. Preparation of *N*-Acylenamines **10**

Starting sulfone	Electrophile R"CH$_2$Br	Product[a] No.	Yield (%)[b]	R_f[c]	*Z/E* ratio[d]
7a	CH$_2$=CHCH$_2$Br	**10aa**	45	0.77[e]/0.71[e]	1/1[f]
7b	CH$_2$=CHCH$_2$Br	**10ba**	59	0.53[g]/0.42[g]	1/1
7b	CH$_2$=CMeCH$_2$Br	**10bb**	33	0.47[g]	-/1
7a	HC≡CCH$_2$Br	**10ac**	33	0.83[e]/0.74[e]	1/3[f]
7b	PhCH$_2$Br	**10bd**	39	0.67[g]/0.50[g]	1/2[f]
7a	Bu^{t}O$_2$CCH$_2$Br[h]	**10ae**	52	0.73[e,i]	-/1
7b	Bu^{t}O$_2$CCH$_2$Br[h]	**10be**	62	0.90[j,k]	-/1

[a] All products **10** were >95% pure (GLC and 300 Mz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS). [b] Based on starting material **7** after column chromatography (neutral alumina, hexane/EtOAc). [c] Silica gel; values for *Z* and *E* diastereomers, respectively. [d] From ^{1}H NMR. [e] EtOAc. f Separated by flash chromatography (silica gel, hexane/EtOAc). g Hexane/diethyl ether: 1/1. [h] DMPU was not added. Mp 84-85°C (hexane/EtOAc). i Diethyl ether. [k] Mp 144-145°C (hexane/EtOAc).

When starting material **7c** and **7d** were treated with Bu^{n}Li in the presence of DMPU at -90°C for 5 min monoanions **11** were obtained and chemically characterised by deuterolysis (Scheme 1 and Table 2). These anions **11** reacted with alkyl halides, carbonyl compounds and carboxylic acid chlorides to give the corresponding sulfones **12**. Acylated compound **12cg** was chemoselectively reduced by means of sodium dithionite[13] (DMF-H$_2$O, 100°C, 1 d) to afford the α-amidophenone **13** [R-R'= (CH$_2$)$_3$; E = PhCO] in 70% yield. Compounds **12ch** and **12dh** derived from ethyl chloroformate are promising precursors of α-amino acids.

Finally, we were able to reductively desulfonate compounds **7c** and **7d** by using lithium and a catalytic amount of naphthalene as the electron carrier. Thus, treatment of an equimolecular mixture of **7c** or **7d** and the corresponding electrophile with an excess of lithium powder and a catalytic amount of naphthalene (4 %) in THF at temperatures ranging between -78 and 20°C (for **7c**) or at -78°C (for

Table 2. Preparation of Functionalised α-Amido Sulfones **12**

Starting sulfone	Electrophile E+	Product[a] No.	Yield (%)[b]	Mp (°C)[c] or R_f[d]
7c	CH_3CO_2D	**12ca**	65	117-118
7d	D_2O	**12da**	82	102-103
7c	CH_2=$CHCH_2Br$	**12cb**	67	115-116
7d	CH_2=$CHCH_2Br$	**12db**	61	0.57
7c	$PhCH_2Br$	**12cc**	64	0.84[e]
7d	$PhCH_2Br$	**12dc**	66	0.53
7c	$Bu^tO_2CCH_2Br$	**12cd**	59	111-112
7c	PhCHO	**12ce**	62[f]	0.79[g]/0.83[h]
7d	$(CH_2)_5CO$	**12df**	63	0.43
7c	PhCOCl	**12cg**	56	0.49[e]
7c	EtO_2CCl	**12ch**	72	0.81[e]
7d	EtO_2CCl	**12dh**	52	0.55

[a] All products **12** were >95% pure (300 Mz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Based on starting material **7** after flash chromatography (silica gel, hexane/EtOAc). [c] Hexane/diethyl ether. [d] Hexane/EtOAc: 2/1. [e] EtOAc. [f] *Erythro/threo*: 1/1. [g] *Erythro*. [h] *Threo*

Table 3. Preparation of Functionalised Amides **13**

Starting sulfone	Electrophile E+	Product[a] No.	Yield (%)[b]	R_f[c]
7d	Bu^tCHO	**13da**	50	0.45
7d	PhCHO	**13db**	45	0.30
7c	Et_2CO	**13cc**	37	0.50[d]
7d	Et_2CO	**13dc**	20	0.43
7d	$(CH_2)_4CO$	**13dd**	30	0.27
7c	$(CH_2)_5CO$	**13ce**	31	0.36[d]
7d	PhCOMe	**13df**	43	0.41
7d	Me_3SiCl	**13dg**	28	0.81

[a] All products **13** were >95% pure (300 Mz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Based on starting material **7** after column chromatography (neutral alumina, hexane/EtOAc). [c] Silica gel, pentane/EtOAc: 4/1. [d] EtOAc

7d) led, after hydrolysis with water, to the corresponding products **13** in moderate yields, the intermediates **6** being probably involved (Scheme 1 and Table 3). The same process as applied to *N*-monosubstituted materials (**7a,b**) failed.

In conclusion, we have proven that *N*-(tosylmethyl)amides or carbamates **7** are adequate precursors for α-nitrogenated organolithium compounds, which by reaction with electrophiles led to polyfunctionalised molecules in one reaction step.

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