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Enantioselective Rearrangement of Proline Sulfonamides: An Easy Entry to Enantiomerically Pure α-Aryl Quaternary Prolines

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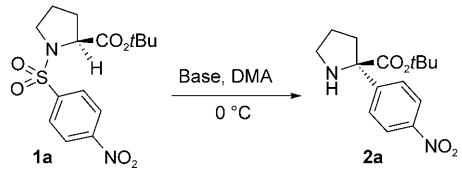
In the past few decades natural and non-natural prolines—and among the latter, α-quaternary derivatives are of great interest—have found wide application in the design of new organocatalysts[1] and chiral auxiliaries[2] for asymmetric synthesis. Furthermore, non-natural proline units have been incorporated in new peptide chains, affording peptidomimetics with different conformational flexibility and correlated drastic changes of their secondary structures.[3] In the best cases, these alterations enhance the resistance of the modified proteins to metabolic and chemical degradation and hence their overall biological activity.

A number of strategies[4]—and, among them, those that adopt the well-known Kawabata's principles of "memory of chirality" (MOC)[5] and of "chiral non-racemic enolate"[6] emerge as the most appealing—have been proposed for the stereoselective synthesis of quaternary α-amino acids. In particular, the synthetic methods for quaternary prolines[7] involve the enantioselective functionalization of L-proline derivatives, for example, through self-reproduction of chirality, diastereoselective alkylation, or transfer of stereochemical information via cyclic ammonium ylides.

Recently, we reported a straightforward protocol for the enantioselective synthesis of quaternary *N*-alkyl-α-4-nitrophenyl-α-amino *tert*-butyl esters, through N-alkylation of the corresponding α-*N*-(4-nitrophenyl)sulfonamido esters, followed by degradative rearrangement, with loss of SO_2.[8] The one-pot overall process is highly stereoselective, *ee*'s up to 98%; in contrast, the reaction conducted with the preformed *N*-alkyl-α-*N*-(4-nitrophenyl)sulfonamido ester gave the corresponding quaternary amino ester with very low *ee*'s, for example, 28% *ee* in the case of *N*-allyl phenylalanine derivative. In the present paper we describe the rearrangement under basic conditions of *N*-(arylsulfonyl)proline *tert*-butyl esters **1**, which showed a different behavior of that found for N-alkylated open-chain sulfonamido esters. Preliminary runs (Table 1), conducted on *N*-(4-nitrobenzenesul-

Table 1. Rearrangement of proline derivative **1a** in the presence of several bases.[a]



Entry	Base	*t* [h]	**2a** [%]	*ee* [%]
1	$NaNH_2$	0.25	90	94
2	$NaNH_2$	1.5	89[b]	96
3	$NaNH_2$	1	68[c]	94
4	NaH	26	79	94
5	NaH/NH_3[d]	1	97	94
6	$LiNH_2$	24	–[e]	–
7	LDA	0.25	–[f]	–
8	LDA	96	40[c]	77
9	*t*BuOK	48	15	92
10	DBU	48	–[e]	–
11	MeONa	48	–[g]	–

[a] Sulfonamide **1a** (1 mmol), base (2.5 mmol), DMA (6 mL), 0°C. [b] At −20°C. [c] In DMF as a solvent. [d] By using NaH and ammonia gas. [e] Starting compund **1a** was recovered unchanged. [f] Starting compound **1a** decomposes. [g] The corresponding *p*-CH_3O sulfonamide **1i** was recovered in 72% yield.

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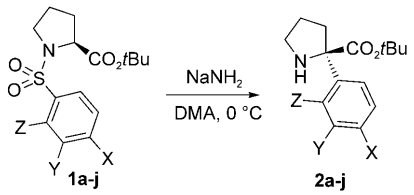
fonyl)-proline *tert*-butyl ester (**1a**), evidenced that the best yields and *ee*'s of the quaternary proline ester **2a** could be reached by using the strong, non-hindered base $NaNH_2$ at 0°C (entry 1), in DMA as the solvent. Longer reaction times were necessary by operating at −20°C (entry 2). The use of DMF instead of DMA as a solvent (entry 3), or NaH as a base (entry 4) resulted in poor yields of **2a**. Starting compound **1a** was quantitatively recovered with $LiNH_2$ (entry 6), while very poor or no results were obtained with the more sterically demanding *t*BuOK, DBU and LDA (entries 7–10). Furthermore, the use of sodium methoxide (entry 11) promoted the $NO_2 \rightarrow$MeO nucleophilic aromatic substitution on the starting sulfonamide and *N*-(4-methoxybenzenesulfonyl)proline *tert*-butyl ester (**1i**) was the sole product. The compound **1i**, in turn, was stable under these reaction conditions and the related quaternary derivative **2i** was not formed, even in traces (see Table 2, entry 13).

Table 2. Reactivity of different proline sulfonamido esters **1a–j**.[a]



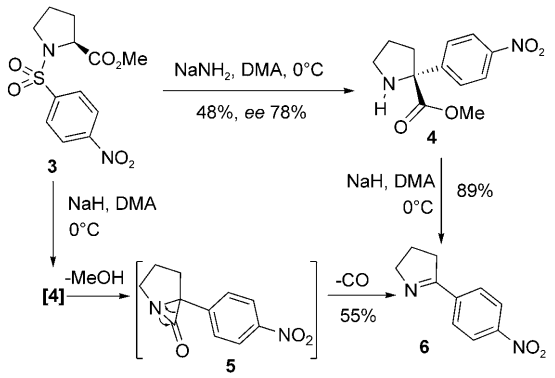
Entry	Sulfonamide	X	Y	Z	*t* [h]	Product	Yield [%]	*ee* [%]
1	**1a**	NO_2	H	H	0.25	**2a**	90	94
2	**1b**	NO_2	CF_3	H	0.33	**2b**	64	94
3	**1b**	NO_2	CF_3	H	48	**2b**	–[b,c]	–
4	**1c**	NO_2	H	OMe	0.5	**2c**	50	91
5	**1c**	NO_2	H	OMe	24	**2c**	64[b]	93
6	**1d**	CN	H	H	0.33	**2d**	61	96
7	**1d**	CN	H	H	48	**2d**	44[b]	96
8	**1e**	H	H	NO_2	0.33	**2e**	54	94
9	**1e**	H	H	NO_2	48	**2e**	–[b,c]	–
10	**1f**	H	NO_2	H	48	**2f**	–[c]	–
11	**1g**	NO_2	H	NO_2	0.5	**2g**	–[d]	–
12	**1h**	Me	H	H	24	**2h**	–[c]	–
13	**1i**	MeO	H	H	24	**2i**	–[c]	–
14	**1j**	$CON(CH_2)_4$	H	H	24	**2j**	–[c,e]	–

[a] Sulfonamide **1** (1 mmol), $NaNH_2$ (2.5 mmol), DMA (6 mL), 0°C. [b] Reaction by using NaH (2 mmol). [c] Starting sulfonamide was recovered unchanged. [d] The substrate rapidly decomposed. [e] Pyrrolidine amide.

The elevated reaction rates, together with the high yields and *ee*'s, highlight the paramount efficiency of $NaNH_2$: in fact, the reaction was 10^2 times faster than with NaH, even if the formation of the anion took about 5 min with both bases. By using sodium amide, the ammonia produced in the process, in all probability, solvates the sodium ion associated to the carbanion derived from **1a**, forming a loose ion-pair that is much more reactive than the unsolvated tight ion-pair generated by deprotonation with sodium hydride. A run conducted by generating the anion with NaH and then saturating the reaction mixture with anhydrous ammonia gas confirmed this hypothesis: the target product **2a** was isolated in very good yield and *ee* (entry 5).

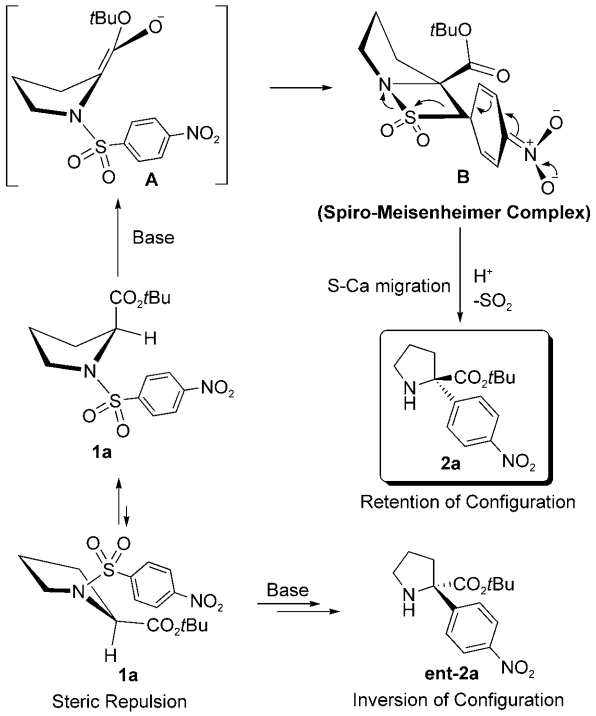
With the aim of extending the rearrangement to the synthesis of different quaternary α-aryl proline derivatives **2**, the best reaction conditions found for **1a** were then applied to a series of substituted arylsulfonamido proline esters **1b–j** (Table 2).

The presence on the aromatic ring of an electron-withdrawing group (EWG), which must be able to stabilize an intermediate Meisenheimer complex, is essential for the reaction progress. For that reason, compounds **1a–e**, bearing *ortho*- and *para*-nitro or *para*-cyano groups, gave good results, whereas compounds containing in the arylsulfonyl moiety *meta*-nitro (entry 10) or electron-donating groups, such as methyl or methoxy (entries 12 and 13), were unreactive. The presence of substituents in the *ortho*- or *meta*-position on the aromatic ring (entries 2, 4 and 8), increasing the steric hindrance, was detrimental to the overall process, decreasing the reaction yields. The *N*-(2,4-dinitrobenzenesulfonyl)proline *tert*-butyl ester **1g**, in contrast, reacted rapidly, but gave only a series of byproducts (entry 11). The pyrrolidine carboxamide **1j** (entry 14) was unreactive, due to the low ability of the carbonyl EWG. Finally, rearrangement of methyl ester **3** (Scheme 1) using sodium amide gave the expected proline **4**, even if with low yield, whereas with sodium hydride 2-(4-nitrophenyl)-1-pyrroline (**6**) was only formed, possibly through formation of an unstable bicycle aziridinone **5**, and elimination of carbon oxide from this intermediate. This hypothesis was corroborated by direct conversion of the isolated methyl ester **4** into pyrroline **6** (Scheme 1).



Scheme 1. Rearrangement of sulfonamido methyl ester **3**.

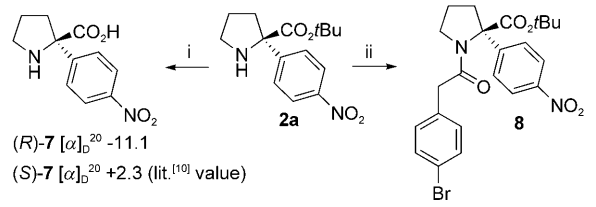
Similarly to open-chain derivatives, the formation of a spiro-Meisenheimer complex (Scheme 2) is supposed to be the key step of the degradative rearrangement. Deprotonation of the less crowded conformer of the substrate **1a**, in which the arylsulfonyl group is far from the *tert*-butyl ester, gives the non-racemic enolate **A**.[9] This intermediate, through a *Re*-face attack, evolves into a chiral spiro-Meisenheimer complex **B** that, in turn, undergoes the stereoselective S–C_α migration of the aryl group, with an overall con-



Scheme 2. Mechanism of the Rearrangement.

figuration retention. Compounds **1b**–**e**—due to the rigidity of the proline ring and the presence of aryl groups that generate similar or increased steric hindrance—are expected to rearrange through the same stereochemical pathway. The high *ee* values found for the products **2a**–**e** prove the elevated difference of stability of the two possible conformers of the starting sulfonamide **1** (Scheme 2), thus supporting our hypothesis.

To confirm the rearrangement stereochemistry, **2a** was transformed into the carboxylic acid hydrochloride (*R*)-**7** (Scheme 3, path i). The comparison of its optical rotatory value with that of the literature enantiomer (*S*)-**7**[10] (the only quaternary proline derivative of this type known) was not decisive for determining the geometry of compound (*R*)-**7**.[11] Compound **2a** was then converted into the corresponding acyl derivative **8** (path ii) that, after crystallization, was subjected to X-ray analysis (Figure 1). The absolute configuration was determined by anomalous dispersion scattering and the refined Flack parameter[12] for the actual configuration was 0.012(14) (see details in deposited crystallo-



Scheme 3. Preparation of compound (*R*)-**7** and **8**. Reagents and conditions: i) TFA, $CHCl_3$, 70 °C. ii) (4-Bromophenyl)acetyl chloride, pyridine, 5 °C.

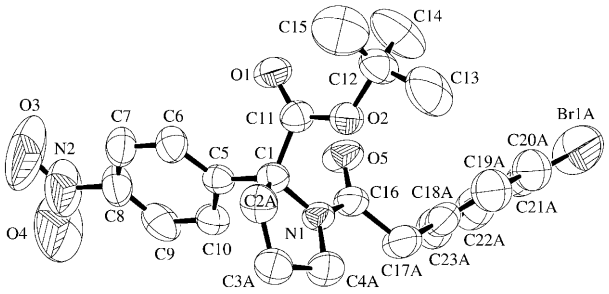


Figure 1. ORTEPIII projection of derivative **8** with the crystallographic numbering scheme. Ellipsoids at 50% probability level. Only one of the groups (atoms with the suffix A) used to model the disorder is plotted. For clarity H atoms were omitted.

graphic data).[13] Several derivatives of compounds **2b**–**e** were prepared, but none of these compounds could be obtained in a crystalline form suitable for X-ray crystal structure determination. However, the comparison of both chiral HPLC retention times (the major enantiomer eluted second) and sign of optical rotations (minus, in all cases) of **2a**–**e**,[14] even if empirical correlations, indicate that compounds **1b**–**e** presumably rearrange following the same stereochemical course observed for **1a**.

In summary, a series of EWG bearing *N*-(arylsulfonyl)-proline *tert*-butyl esters **1** have been stereoselectively transformed under mild reaction conditions, with good yields and excellent *ee*'s, into the quaternary α-aryl-α-proline derivatives **2**. These new hindered quaternary prolines are not easily accessible through other synthetic protocols. The enantioselectivity is promoted by the rigidity of the proline ring and the geometric distribution of the functional groups around the enolate anion, which allows the stabilization of a favored conformer.

Experimental Section

Synthesis of (*R*)-*tert*-butyl 2-(4-nitrophenyl)pyrrolidine-2-carboxylate (2a): General procedure for the rearrangement of *N*-(arylsulfonyl)proline esters 1: In a flame-dried, round bottomed flask cooled at 0 °C, containing a mixture of 95% sodium amide (103 mg, 2.5 mmol) and anhydrous *N*,*N*-dimethylacetamide (DMA, 1.5 mL), a solution of sulfonamido ester **1a** (356 mg, 1 mmol) in DMA (4.5 mL) was rapidly added by syringe, under nitrogen atmosphere. The heterogeneous mixture was stirred until the reaction was complete (15 min, TLC analysis: AcOEt/hexane - 1:4), then was quenched with saturated NH_4Cl solution (2 mL). After extraction with AcOEt (3×5 mL), the organic phase was washed with water (3×2 mL) and brine (3 mL), dried over $MgSO_4$, and evaporated under reduced pressure; the crude was purified by flash column chromatography (FCC: AcOEt/hexane 1:4) on silica gel. Product **2a** (263 mg, 90%) was isolated as a clear wax; $[\alpha]_D^{20} = -36.6$ ($c = 0.8$ in $CHCl_3$), *ee* 94% (CHIRALCEL OJ-H, hexane/*i*PrOH (95:5), flow rate 1 mL min^{-1}, P 26 bar, $t_1 = 10.321$, $t_2 = 12.062$); ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta =$ 8.39–8.35 (m, 2H), 7.82–7.79 (m, 2H), 3.62–3.44 (m, 2H), 3.04–2.95 (m, 1H), 2.61–2.50 (m, 1H), 2.39–2.23 (m, 1H), 2.17–2.04 (m, 1H), 1.43 ppm (s, 9H). ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 168.1$ (CO), 148.3, 141.6 (2 C_{Ar}), 127.6, 123.7 (4 C_{Ar}H), 85.2, 74.2 (2 C), 44.7 (CH_2N), 33.3, 21.8 (2 CH_2), 26.2 ppm (3 CH_3 *t*Bu); IR (Nujol): $\tilde{\nu} = 3276$, 1720, 1519, 1461, 960, 863 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{20}N_2O_4$: C 61.63, H 6.90, N 9.58; found: C 61.66, H 6.87, N 9.63.

Synthesis of pyrroline 6 by reaction of methyl ester 4 with NaH: A solution of sulfonamido ester **4** (50 mg, 0.2 mmol) in anhydrous DMA (0.9 mL) was added to a suspension of 60% sodium hydride (20 mg, 0.5 mmol) in anhydrous DMA (0.3 mL) at 0°C, under nitrogen atmosphere. The resulting solution was stirred at 0°C until the reaction was complete (30 min, TLC), then was quenched and purified as given in the general procedure for the rearrangement of esters **1**. Pyrroline **6** (34 mg, 89%). FCC: AcOEt/hexane (1:4); yellow solid, m.p. 85–86°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.28$–8.23 (m, 2H), 8.02–7.97 (m, 2H), 4.16–4.10 (m, 2H), 3.01–2.94 (m, 2H), 2.15–2.05 ppm (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.7$ (C=N), 148.9, 140.2 ($2C_{Ar}$), 128.5, 123.7 ($4C_{Ar}H$), 62.0, 35.1, 22.7 ppm ($3CH_2$); IR (Nujol): $\tilde{\nu} = 1617$, 1595, 1513, 1334, 856, 726 cm^{-1}; MS (ESI): m/z (%) calcd for $C_{10}H_{10}N_2O_2$ $[M+H]^+$: 191.1 (100), 192.1 (11.0), found 191.2 (100), 192.2 (11); elemental analysis calcd (%) for $C_{10}H_{10}N_2O_2$: C 63.15, H 5.30, N 14.73; found: C 63.12, H 5.35, N 14.70.

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Keywords: enantioselectivity · prolines · rearrangement · sulfonamides

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[13] CCDC-765702 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] See the Supporting information for $[\alpha]_D$'s and HPLC chromatograms.

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