Base Assisted Substitution of α-Amidoalkyl Sulfones by Nitromethane Anion. A New Entry to Functionalized α-Amino Acids.
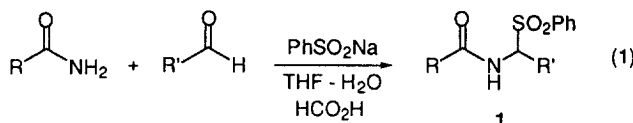
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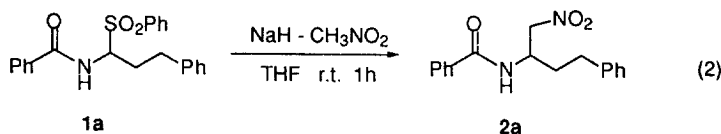Fax +39 737 637345 E-mail: petrini@camserv.unicam.it

Abstract: The nitromethane anion reacts with α-amidoalkyl sulfones in THF affording the corresponding nitro derivatives that upon oxidation with alkaline potassium permanganate give the corresponding N-protected α-amino acids © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Amino acids and derivatives, nitrocompounds, sulfones.

The ability of the phenylsulfonyl group to act as a leaving group in substitution and elimination reactions, is a well recognized feature of this synthetic moiety.[1] Very often, the phenylsulfonyl group must be 'activated' by the vicinal presence of other functional groups in order to be efficiently removed.[2] Cyclic α-phenylsulfonyl ethers can be converted into their 2-substituted derivatives using organomagnesium reagents in the presence of zinc bromide.[3] A three components coupling involving amides, aldehydes and sodium *p*-toluene sulfinate easily affords the corresponding α-amidoalkyl sulfones.[4]

$$R \overset{O}{\underset{}{\|}} NH_2 \ + \ R' \overset{O}{\underset{}{\|}} H \ \xrightarrow[\substack{THF - H_2O \\ HCO_2H}]{PhSO_2Na} \ R \overset{O}{\underset{}{\|}} \underset{H}{N} \overset{SO_2Ph}{\underset{}{\underset{R'}{|}}} \qquad (1)$$

1

These potentially useful substrates have found an occasional utilization in synthesis and recently Pearson *et al.* have used them to generate the corresponding tri-*n*-butylstannyl derivatives and, subsequently, to prepare acyclic nitrogen-substituted organolithium reagents.[5] Substitution of α-amidoalkyl sulfones by stabilized carbanions would be of some interest for the generation of 1,2 and 1,3 difunctionalized synthons.[6] Among synthetically useful 'one carbon atom' nucleophiles, nitromethane undoubtedly occupies a prominent position since once it has been introduced in the framework, the nitro group can be easily turned into a respectable array of functional groups.[7] When α-amidosulfone **1a** is added to the sodium salt of nitromethane in THF a rapid substitution of the phenylsulfonyl group is observed, giving the corresponding nitro derivative **2a** in 88% yield.

$$Ph \overset{O}{\underset{}{\|}} \underset{H}{N} \overset{SO_2Ph}{\underset{}{|}} Ph \ \xrightarrow[\text{THF r.t. 1h}]{NaH - CH_3NO_2} \ Ph \overset{O}{\underset{}{\|}} \underset{H}{N} \overset{NO_2}{\underset{}{|}} Ph \qquad (2)$$

1a   **2a**

In a similar fashion, sulfones **1b-h** obtained from the corresponding aldehydes and benzyl carbamate afford the nitro-substituted products **2b-h** in good yields (Table).[8]

Table. Base assisted substitutions of sulfones **1** into nitroderivatives **2** and their conversion to α-amino acids **3**.

| Entry	Sulfone 1	Nitro 2 Yield [%]	Amino acid 3	Yield [%] (Methyl ester)
a		87		90 (95)
b		78		81 (93)
c		90		88 (97)
d		77		85 (92)
e		80		83 (90)
f		83		78 (92)
g		85		72[a] (91)
h		79		70[a] (88)

[a] The nitro to carboxylic acid conversion has been carried out using sodium nitrite, acetic acid in DMSO (see Ref. 13)

Nitroderivatives **2** are mostly solids and therefore can be easily purified by simple crystallization. From a mechanistic standpoint it is probable that elimination of sulfinic acid, caused by the excess of nucleophile, produces an imine intermediate that is subsequently attacked by the nitronate anion (Scheme 1).
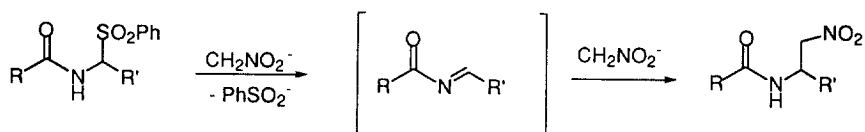
Scheme 1

Indeed, every attempt to obtain the substitution product from oxazolidinone **1i** led only to the recovery of the starting material.
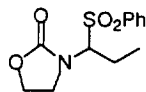
1i

In a similar situation a single electron transfer process (SET) has been experienced using a strongly basic nucleophile as tri-*n*-butylstannyllithium.[5] Therefore, reaction of sulfone **1a** with the nitromethane anion has been carried out in the presence of 0.1 equivalents of *p*-dinitrobenzene, a well known inhibitor of electron transfer processes.[9] No change in rate and efficiency of the procedure has been observed in this case thus ruling out any SET mechanism. Nitroamides **2** are structurally similar to those obtained by conjugate addition of nitrogeneous derivatives to nitroalkenes,[10] and represent viable intermediates to N-protected α-amino acids by direct conversion of the primary nitro group into the carboxylic acid group.[11] A reliable method for this conversion makes use of alkaline permanganate solutions as reported in eq. 3.[12]
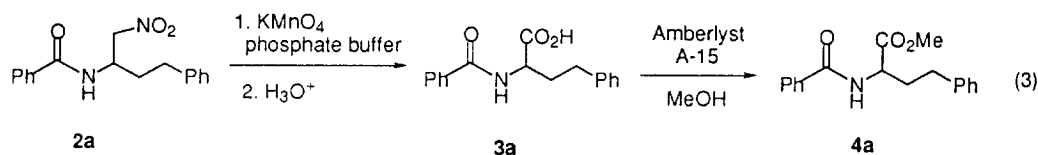
Oxidation of nitroderivatives **2** with potassium permanganate[12b] in phosphate buffer (pH =11) leads, after acidic work up, to the synthesis of the corresponding N-protected α-amino acids in good yield [Table].[13] When a second nitro group is present in the framework (compounds **2e,f**) it is also oxidized to the parent carbonyl derivative and therefore a keto amino acid **3e** and an aminodicarboxylic acid **3f** are readily obtained. Unsaturations are clearly incompatible with the use of permanganate salts and therefore an alternative procedure must be employed with compound **2g**. The sodium nitrite-acetic acid couple in DMSO can be successfully used for this purpose with unsaturated nitro compounds and for substrate **2h** which gives unsatisfactory results with potassium permanganate.[14] The powerful biological activity displayed by α-amino acids represents the reason for a continuous search of new synthetic methods for their preparation .[15] The present procedure constitutes a strategically new device for the assembly of functionalized structures albeit in their racemic form; it is operationally simple and employs cheap starting materials. In this context the emergence of efficient chemoenzymatic syntheses of enantiomerically pure α-amino acids starting from racemic mixtures is of considerable importance since many enantioselective synthetic techniques are far from being practicable for large scale preparations.[16]

References and Notes

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8.   *Typical experimental procedure for preparation of nitrocompounds* **2**: To a stirred suspension of NaH (25 mmol) in dry THF (15 mL), nitromethane (25 mmol) is added dropwise at room temperature. After stirring for 30 min , sulfone **1**[4,5] (5 mmol) dissolved in dry THF (5 mL) is added and the white suspension is stirred   for 1 h at room temperature. The reaction mixture is diluted with chloroform (50 mL) and washed with saturated ammonium chloride. The organic phase is dried over magnesium sulfate and after evaporation of the solvent the crude nitroderivative is purified by crystallization or flash chromatography.

      Selected spectroscopic data for some new compounds prepared: **2f**: M.p. 49°C ; IR (KBr) $v[cm^{-1}]$ = 3420, 1735, 1648, 1550; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.20-1.70 (m, 6H), 1.90-2.15 (m, 2H), 4.06-4.21 (m, 1H), 4.34 (t, J = 6.9 Hz, 2H), 4.51 (d,J = 5.0 Hz, 2H), 5.10 (s, 2H), 5.27 (d,J = 8.0 Hz, 1H), 7.30-7.42 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 25.4, 25.9, 27.2, 31.6, 49.6, 67.4, 75.5, 78.4, 128.3, 128.5, 128.8, 136.15, 155.84; CHN analysis calcd for C$_{15}$H$_{21}$N$_3$O$_6$ (339.14) : C 53.07, H 6.24, N 12.39 ; found: C 53.21, H 6.19, N 12.31. **2h**: M.p. 79°C ; IR (KBr) $v[cm^{-1}]$ = 3425, 1730, 1650, 1550; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.43-1.75 (m, 6H), 3.46(t,J = 5.9 Hz, 2H), 4.11-4.25 (m, 1H), 4.49 (s, 2H), 4.50-4.52 (m, 2H), 5.11 (s, 2H), 5.20 (d,J = 8.0 Hz, 1H), 7.32-7.35 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 22.8, 29.1, 31.4, 49.6, 67.1, 69.7, 73.0, 78.1, 127.6, 127.7, 128.1, 128.3, 128.4, 128.6, 136.0, 138.4, 155.6, CHN analysis calcd for C$_{21}$H$_{26}$N$_2$O$_5$ (386.18) : C 65.25, H 6.79, N 7.25 ; found: C 65.38, H 6.70, N 7.30. **4f**: Oil ; IR (neat) $v[cm^{-1}]$ = 3420, 1735, 1650; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.25-1.42 (m, 2H), 1.53-1.90 (m, 4H), 2.29 (t, J = 7.2 Hz, 2H), 3.65 (s, 3H), 3.73 (s, 3H), 4.31-4.42 (m, 1H), 5.10 (s, 2H), 5.34 (d,J = 8.3 Hz, 1H), 7.31-7.40 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 24.4, 24.7, 32.3, 33.7, 51.5, 52.4, 53.7, 67.0, 128.2, 128.5, 130.1, 133.3, 155.9, 172.9, 173.8; CHN analysis calcd for C$_{17}$H$_{23}$NO$_6$ (337.15) : C 60.51, H 6.88, N 4.15 ; found: C 60.67, H 6.80, N 4.23.**4h**: Oil ; IR (neat) $v[cm^{-1}]$ = 3420, 1735, 1650;^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.35-1.78 (m, 6H), 3.46 (t, ^3J = 6.2 Hz, 2H), 3.74 (s, 3H), 4.31-4.43 (m, 1H), 4.49 (s, 2H), 5.11 (s,2H), 5.31 (d, J = 7.8 Hz, 1H), 7.30-7.42 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 22.2, 29.4, 32.6, 52.5, 54.0, 67.1,70.0, 73.1, 28.8, 128.5, 128.7, 136.4, 138.6, 156.1, 173.1; CHN analysis calcd for C$_{22}$H$_{27}$NO$_5$ (385.19) : C 68.54, H 7.06, N 3.64 ; found: C 68.60, H 6.95, N 3.71.

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