Simple Synthesis of Variously N-Protected α-Aminomethanesulfinate Salts

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The synthesis of α-sulfonopeptides (chain of α-aminosulfonic acid residues linked to each other by a sulfonamide bond) and particularly of the sulfonamide transition state analogs (intercalation of an α-amino sulfonic acid residue in a peptide chain) has remained an elusive goal.[1] We considered this in the context of the overactivation of the sulfonyl group of N-protected α-amino acid intermediate **2** deriving from **1**. *β*-elimination of SO_2Cl was favored over the coupling that would lead to **3**, amines acting merely as bases, not as nucleophiles (Figure 1). To circumvent this, we first took an *intra*molecular approach,[2,3] since stabilization by cyclization of **2** could be faster than *β*-elimination. Though we succeeded in an attempt using an ureyl group in **2** (Y = RNHCO), it was not complete.[4]

An *inter*molecular synthetic route, avoiding sulfonyl activation of **2**, exploits an Umpolung reaction, *i.e.*, electrophilic amination of the corresponding sulf*i*nates **4** with O-sulfonylated (or phosphor(n)ylated) hydroxylamine derivatives **5** (Figure 1). These previously unknown key compounds **4** were obtained only recently, first with Y protecting groups of the sulfonyl type, in a Mannich-like reaction. Coupling (Figure 2, top), in a basic aqueous medium, occurs readily between α-hydroxy sulfinates[5] such as rongalite **6**, and sulfonamides **7** (Y = mesyl, tosyl).[6] Unfortunately the generalization of this reaction with amino derivatives YNH_2 **7** other than sulfonamides is difficult. This is mainly due to the very basic conditions used. Only benzhydryl, ureyl, and probably diphenylphosphinyl protecting groups can be easily introduced.[7] Common protecting groups such as Cbz, Boc, phthaloyl, and benzoyl are not tolerated.

In the course of this latter study,[7] we observed that, with excess ammonia, *sodium*[8] methanesulfinate **(8)** was formed and trapped with phenyl isocyanate.[7] In this paper, we present the generalization of this coupling reaction. It allows the easy introduction of the common protecting groups, which was impossible or very difficult to achieve with the previous method. The results of the study of this coupling reaction **8** → **4** and **10** (Figure 2; bottom) are displayed in Table 1.

Results and Discussion

Since sulfinate **8** can be obtained (just prepared) only in aqueous solution, the reaction is performed under

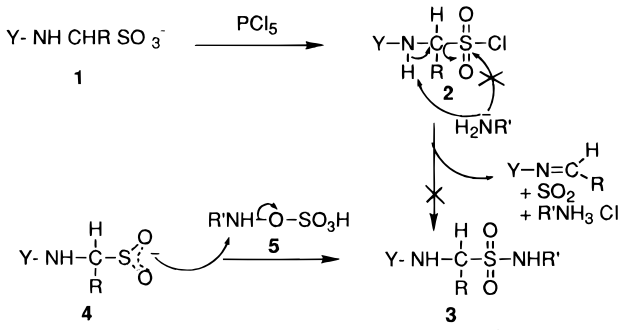

Figure 1.

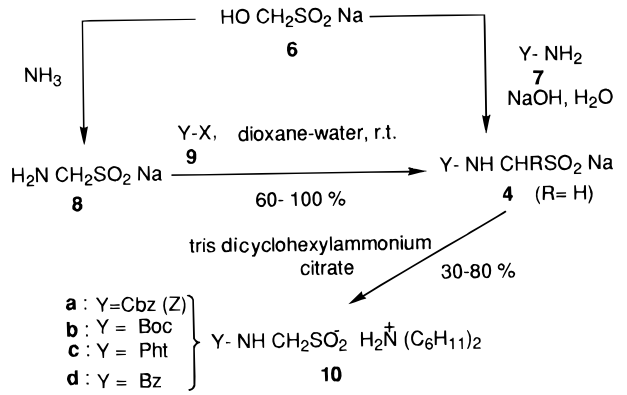

Figure 2.

Schotten−Baumann conditions; dioxane is used in order to solubilize, at least partially, the acylating reagents **9**. Solvents must be degassed because of the sensitivity to oxidation of some of these sulfinates (particularly the phthaloyl derivative **4c**). Extra base is added when acidic components arising from the X moiety of YX reagents **9**[12−18] are released because is acidic media the ammonium

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(2) Mulliez, M. *Tetrahedron* **1981**, *37*, 2021.
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(6) Mulliez, M.; Naudy, C. *Tetrahedron* **1994**, *50*, 5401.
(7) Leurquin, F.; Mulliez, M. *Phosphorus, Sulfur Silicon* **1994**, *92*, 201.
(8) Previously,[6] we observed that with the *zinc* salt attack is dramatically diverted on the sulfur atom, probably as a result of complexation of nitrogen with the zinc cation. With the sodium salt one cannot exclude such an attack followed by fast transfer to nitrogen.
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(10) Electrophilic amination is advantageously performed directly on the sodium salts **4**, in water, the resulting insoluble sulfonamide derivatives **3** being easily separated by filtration (Mulliez, M. Unpublished results). For example, **4a** leads to the known **3** (R′ = H): Etienne, A.; Le Berre, A.; Lonchambon, G.; Lochey, G.; Cucumel, B. *Bull. Soc. Chim. Soc. Fr.* **1974**, 580. Gilmore, W. F.; Yeih, M. M.; Smith, R. B. *J. Org. Chem.* **1986**, *43*, 4784.
(11) This is the case with HOSu but not with HCl. Therefore, introduction of the protecting group *via* the chloride is restricted to the sodium salt **4**.
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(15) Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. *Rec. Trav. Chim. Pays-Bas* **1960**, *79*, 688.
(16) Richardson, A. G.; Pierce, J. S.; Reid, E. E. *J. Am. Chem. Soc.* **1952**, *74*, 4011. The oxalyl group can repetitively be used successively as a protecting and an activating group: Mulliez, M.; Royer, J. *Tetrahedron* **1984**, *40*, 5143.
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(18) Ramage, R.; Hopton, D.; Parott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans.* **1984**, 1357.
(19) The pH of the reaction mixture must be kept at ∼7−8, the value of the roughly estimated pK_a of the ammonium form of **8**: lower than for glycinate (9.6), as the SO_2^- group is more electron attracting than COO^- and higher than for α-aminomethanesulfonate (5.7: Lacoste, R. G.; Martell, A. E. *J. Am. Chem. Soc.* **1955**, *77*, 5512) as $-SO_2^-$ is less electron attracting than $-SO_3^-$.

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Table 1. Study of the Coupling of α-Aminomethane Sulfinate 8 with Various Acylating Reagent 9 YX. Syntheses of N-Protected α-AminomethaneSulfinates YNH $CH_2SO_2^-$ 4 and 10

acylating reagents[a] Y*X* **(9)**	leading ref	exptl condns	time of completion	isolated compds	yield[b] (%) of Na salt **4**	yield (%) of DCHA salt **10**	recrystallizn solvent	mp (°C)	δCH_2CDCl_3 (CD_3SOCD_3)
Z-*OSu* **(9a)**[12]	12	H_2O−dioxane (1:1) + 0.5 equiv of Na_2CO_3	1 h	**10a**	100	80	H_2O	142−145	3.6 (3.13)
Z-benzotriazolyl **(9a′)**[13]	13	H_2O−dioxane (1:1)	7 days	**10a** + Z-NH_2	50	30	$CHCl_3$-AcOEt	*id.*	*id.*
Boc-*O-Boc* **(9b)**[14]	14	H_2O−dioxane (1:1)	24 h	**10b**	100	40	$ClCH_2CH_2Cl$	102−104[c]	3.56 (3.14)
Pht-*NCOOEt* **(9c)**[15]	15	H_2O−dioxane (1:1)	48 h	**10c**	60	48	EtOH	193−196	4.14
Bz-*imidazolyl* **(9d)**[17]	17	H_2O−dioxane (1:1)	24 h	**10d** + $PhCO_2H$·DCHA **(13)**	60	17	iPrOH	160−165	3.95

[a] Z = $PhCH_2OCO$; −OSu = *N*-(hydroxysuccinimidyl); Boc = Me_3COCO; Pht = *o*-OCC_6H_4CO−; Bz = PhCO; DCHA = $H_2N(C_6H_{11})_2$. [b] Isolated after concentration to dryness of the extracted ($CHCl_3$) aqueous layer or estimated using ^1H NMR and standards. [c] Adduct with 0.25 $ClCH_2CH_2Cl$.

group is unreactive[19] and sulfinates are unstable.[9] The pH of the reaction mixture must be kept above ∼5 at completion of the reaction, and the products can only be isolated as salts. The sodium salts **4**, being very water soluble, are easily separated from organic byproducts by extraction and are obtained (see **4b**) in a fairly pure state by concentration to dryness.[10] It is wiser, however, to crystallize the compounds as dicyclohexylammonium salts, which, due to the very hydrophobic cation, are less soluble in water than in chloroform, and they can be extracted selectively using this latter solvent, provided that the dicyclohexylammonium salt formed with the X^- group (arising from **9**) is more soluble in water than the salt **10**.[11] In some cases, particularly **10b** and **10d**, the dicyclohexylammonium salts **10** form rather stable adducts with solvents.

The identity of the products **4** and **10** was established by *their conversion into their sulfonamide derivatives* **3**[10] and by conventional means: elemental analysis and IR and NMR (both ^{13}C and ^1H) spectroscopy. Using this latter technique, it is worth mentioning the deshielding effect, as expected, on the αCH_2 of the acyl protecting substituents (compared to δ 3.18 for **8**[7]) and the same specific shielding effect ($\Delta\delta$ ∼0.5 ppm) of DMSO as observed with sulfonates.[3]

Conclusions

The described procedure (Figure 2, bottom) provides chemists with a choice[20] of N-protecting groups for the class of glycine analogs **4** and **10**. Work is in progress that deals with its generalization using Cα-substituted α-aminosulfinates.

Experimental Section

The reactions were performed under argon and with degassed solvents, as described previously.[5,6] Melting points were determined with capillaries and are uncorrected. IR spectra were recorded as Nujol mulls on CaF_2 or NaCl disks. ^1H, ^{13}C (J modulated), and ^{31}P NMR spectra were obtained, respectively, at 80.13, 20.15, and 32.44 MHz. Signals arising from the dicyclohexylammonium cation, with no significant change from one salt to another, are given once (for **10a**).

***N*-(Benzyloxycarbonyl)-α-aminomethanesulfinate, Dicyclohexylammonium Salt (10a). Illustrative Procedure.** To a freshly prepared solution of **8**[7] (6.65 g, 0.5 mmol/g, 13.3 mmol) were added **9a** (recrystallized from 2-propanol) (2.53 g, 10 mmol) and Na_2CO_3 (0.53 g, 5 mmol) with water (20 g) and dioxane (20 g). After 1 h, the resulting solution was concentrated to ∼20 g, diluted with water (∼20 g), and extracted with chloroform (3 × ∼20 g). To the aqueous alkaline phase was added a water (11 g) solution of citric acid (0.67 g, 3.5 mmol) and dicyclohexylamine (1.8 g, 10 mmol). The immediately precipitated oil was extracted with chloroform (3 × ∼20 g) and *the product* **10a** crystallized and isolated (3.3 g, 80% yield): IR ν 3160, 2600−2400, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2−1.7 (m), 2.9 (m), 3.06 (d, J = 7.45 Hz, 2H), 5.07 (s, 2H), 5.74 (br s, 1H), 7.27 (s, 5H), 8.9 (br s, 2H); ^{13}C ($CDCl_3$) δ 24.6, 25.1, 29.1, 52.9, 66.75, 67.4, 127.97, 128.4, 136.6, 153.3. Anal. Calcd for $C_{21}H_{34}N_2O_4S$: C, 61.43; H, 8.35; N, 6.82. Found: C, 61.95; H, 8.51; N, 6.90.

Boc Derivatives 4b and 10b. The sodium salt **4b** was obtained after concentration of the aqueous alkaline phase to dryness until constant weight. It was proved by ^1H NMR to be dihydrated after addition of a known quantity of sodium acetate as a standard: IR ν 3441, 3333, 3256, 1678 cm^{-1}; ^1H NMR (D_2O) δ 1.45 (s, 9H), 3.57 (s, 2H); ^{13}C NMR (D_2O) δ 30.3, 69.5, 84.3, 160.1, identical to the values given in ref 7.

The dicyclohexylammonium salt, **10b**, soluble in water, was extracted with chloroform. The concentrated extracts were taken up in THF, filtered from some small insoluble material, concentrated to dryness, and crystallized from 1,2-dichloroethane at −30 °C: IR ν 3200, 2700−2400, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.56 (d, J = 6.45 Hz, 2H), 3.71 (s, 1H), 5.33 (br s, 1H).

Phthaloyl Derivative 10c. Commercial (Aldrich) **9c** was satisfactorily recrystallized from acetonitrile. Crystallization under argon of *the product* **10c** from the yellow aqueous phase took several days at 4 °C: IR ν 2700−2400, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (s, 2H), 7.74 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 63.78, 123.1, 132.2, 133.9, 167.4. Anal. Calcd for $C_{21}H_{30}N_2O_4S$: C, 62.04; H, 7.43; N, 6.89. Found: C, 61.91; H, 7.56; N, 6.80.

Benzoyl Derivative 10d. The reaction was performed with a 50% excess of **8** *versus* **9d** (Lancaster), and at completion the pH was still above ∼10. The *hydrolysis salt* **13** first was separated by selective crystallization in MeOH (3.5 g for a 10 mmol residue of coupling), 23% yield: mp 199−200 °C (methanol); IR ν 2700−2400, 1624 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 75.2; H, 9.63; N, 4.61. Found: C, 75.08; H, 9.72; N, 4.55.

Cocrystallization of *the aminolysis product* **10d** with ∼0.5 equiv of protic solvents was observed: with ethanol, mp 138−140 °C; with 2-propanol, mp 138−142 °C. Long drying (∼1 month) at room temperature under reduced pressure (∼10 mm) in the presence of P_2O_5 was necessary in order to remove it: IR ν 3329, 2700−2400, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (d, J = 7 Hz, 2H), 6.66 (br s merged with ^+H_2N DCHA, 1H); ^{13}C NMR ($CDCl_3$) δ 66.2, 127.3, 128.4, 131.5, 134.1, 168.1.

Acknowledgment. We thank Mrs. A. Colomer for recording the IR spectra and Dr. D. Houalla for directing us to ref 1 soon after its publication.

Supporting Information Available: ^1H and ^{13}C NMR spectra for the sulfonates derived from **10b** and **10c** and hydrolysis products (*o*-$EtOCONHC_6H_4CO_2H$·DCHA **(11)**, $PhNHCOCO_2H$·DCHA **(12)**, and $PhCO_2H$·DCHA **(13)** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) This choice should be extended by using reagents **9** with proper leaving groups. These can lead both to rate enhancement and to more selective aminolysis, avoiding the two side reactions observed: ammonolysis, as with **9′a**, resulting of the decomposition of **8**, and hydrolysis as observed partially with **9d** and completely with ethyl oxanilate[16] **9e** and diphenylphosphinyl chloride[18] **9f**.