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Synthesis of Carbamates of α-Amino Sulfonamides

W. Franklin Gilmore* and Horng-Jau Lin

Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, Mississippi 38677

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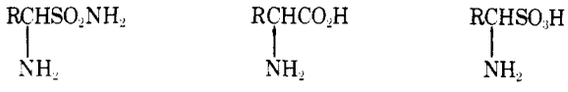
Based on the successful use of the sulfonamido group as a replacement for the carboxyl group in drugs such as the 4-aminobenzenesulfonamides, which are antimetabolites of 4-aminobenzoic acid,[1,2] and acetazolamide, which is a carbonic anhydrase inhibitor,[3] several investigators have suggested[4,5] that the α-amino sulfonamides (1) will be good antimetabol-



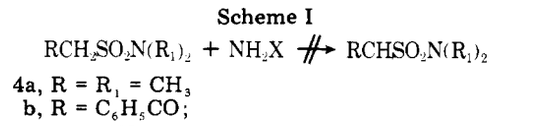
1 2 3

ites of the common amino acids (2). However, all previous attempts to prepare derivatives of the sulfonamides 1 have failed.[4-7] The moderately stable α-amino sulfonic acids (3) are known, but attempts to convert them or their *N*-acyl derivatives to sulfonamides have failed.[8] We now wish to report the first synthesis of carbamates of 1.

Results and Discussion

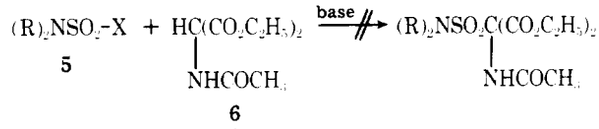
We first tried two general routes to 1 and derivatives of 1. Amination of carbanions of sulfonamides (4) as shown in Scheme I did not give amino sulfonamides. Treatment of **4a** with *n*-butyllithium in THF gave the carbanion which was treated with methyl benzoate to obtain **4b.** However, treatment of the carbanion from **4a** with a series of aminating agents gave only unchanged **4a** after workup. Our opinion is that the anion from **4a** is sufficiently basic to remove a proton from the aminating agents. With less basic carbanions, similar aminations are usually successful. Thus, we tried the amination of the anion of **4b,** which was generated with sodium hydride in DMF or with *n*-butyllithium in ether. The anion of **4b** should be of similar basicity to the anion of diethyl malonate, which can be successfully aminated.[9] Treatment of the anion from **4b** with a series of aminating agents did not furnish the amino sulfonamides. We do not know if the amino sulfonamides formed and decomposed under the basic conditions of these reactions. The amino sulfonamides bear a resem-

Scheme I



4a, R = R_1 = CH_3
b, R = C_6H_5CO; R_1 = CH_3
X = Cl, 2,4-dinitrophenoxy, methoxy, and 2,4,6-trimethylbenzenesulfonyloxy

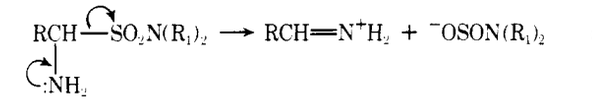
Scheme II



5 6

X = Cl and 4-nitrophenoxy; R = CH_3 and H

blance to cyanohydrins and bisulfite addition products and may decompose as shown in eq. 1.



(1)

Treatment of diethyl acetamidomalonate (**6**) with sulfamoyl chlorides (**5**) in the presence of bases such as sodium hydride, potassium *tert*-butoxide, or triethylamine in solvents such as benzene, ether, dimethoxyethane, acetonitrile, *tert*-butyl alcohol, or DMF did not give the amino sulfonamides. This method, which is shown in Scheme II, gave only unchanged **6.**

As shown in Scheme III, the Curtius rearrangement gave carbamates of amino sulfonamides (**14**).

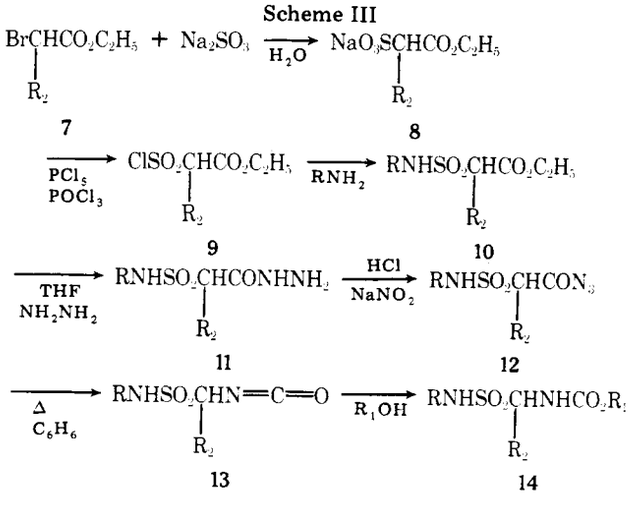
All of the steps in Scheme III proceeded well except the diazotization of **11** and the rearrangement of **12.** The diazotization has only been conducted with hydrochloric acid and sodium nitrite. Other methods of preparing the azides **12** have not been explored. When R = R_2 = H, **11a** was converted to **14a** in 21% yield. When R = *t*-Bu and R_2 = H, **11b** was converted to **14d** in 36% yield. When R_2 was methyl and R was H, the rearrangement of **12** gave only an intractable tar.

In general, the azides **12** and the isocyanates **13** were not isolated; however, **12,** where R and R_2 = H, was isolated. Both infrared and NMR spectra were obtained for the crystalline azide, but the stability of the compound was poor and additional data were not obtained.

Using the method shown in Scheme III, the sulfamoyl carboxylic acid esters (**10**), the sulfamoyl acid hydrazides (**11**), and the carbamates (**14**) shown in Table I were prepared.

A number of methods were tried for converting the carbamates to the free amino sulfonamides. Compound **14a** was heated with 10% hydrochloric acid; however, the only product was a high melting solid which did not have infrared absorption for the SO_2 group. Attempted hydrolysis of **14a** with 30% sodium hydroxide and barium hydroxide did not give an isolable product. Treatment of the isocyanate **13** (R = R_2 = H) with hydrochloric acid gave only ammonium chloride as an isolable product. Catalytic hydrogenation of **14b** and **14e** using palladium on carbon, palladium black, palladium hydroxide on carbon, and Raney nickel in solvents such as ethanol, gla-

Scheme III



7 8 9 10 11 12 13 14

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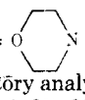
Table I. Properties of Sulfamoyl Esters, Hydrazides, and Carbamates[a]

$RNHSO_2CHCO_2C_2H_5$ (10) | $RNHSO_2CHCONHNH_2$ (11) | $RNHSO_2CHNHCO_2R_1$ (14)

	substituents			properties			
				10			
	R	R_1	R_2	mp, °C	bp, °C	11 mp, °C	14 mp, °C
a	H	ethyl	H	63–64		124–126	135–137
b	H	benzyl	H				146–148
c	H		methyl	71–73		129–131	
d	*t*-Bu	*t*-Bu	H		128–130 (0.25 mm)	120–121	130–132
e	*t*-Bu	benzyl	H				113–114
f	4-ClC_6H_4	ethyl	H	74–76		181–183	148–149
g	*t*-Bu	ethyl	3,4-dibenzyloxybenzyl	80–82		153–154	187–189
h	*t*-Bu	ethyl	3,4-dimethoxybenzyl	89–90		77–78	131–133
i	$-CH(CH_3)CO_2$-*t*-Bu	ethyl	H	oil n^{24}_D 1.4515		oil n^{24}_D 1.4962	74–76
j	$-CH(CH_3)CO_2CH_2C_6H_5$		H	oil n^{25}_D 1.1507			
k	RNH = 	ethyl	H	122–124		134–135	91–93

[a] Satisfactory analytical data (±0.4% for C, H, Cl, N, and S) were reported for all new compounds except **10d**, where all elements were high by 1–2%, **10i**, where C was high by 3.37% and S was low by 1.76%, and **14b**, for which a S analysis was not obtained. [b] **11i**, $[\alpha]^{23}_D$ +6.7° (*c* 2, EtOH); **14i**, $[\alpha]^{23}_D$ +16° (*c* 2, EtOH), derived from D-alanine.

cial acetic acid, or dioxane and water gave only unchanged starting material. When hydrochloric acid was added to the hydrogenation medium, cleavage of the S–N bond occurred. Treatment of **14b** with 45% hydrogen bromide in acetic acid gave ammonium bromide as the only isolable product. Treatment of **14d** with trifluoroacetic acid or 2 N hydrochloric acid in dioxane gave only the *tert*-butylamine salts as isolable products. Thus, we have not been able to convert the carbamates to the amino sulfonamides or salts of the amino sulfonamides.

Experimental Section

All melting points were taken on a Mel-Temp melting point apparatus and are corrected. Infrared spectra were recorded on either a Perkin-Elmer Model 257 or a Beckman IR-23 spectrophotometer. NMR spectra were taken on a Jeolco Model C-60-HL spectrometer using either tetramethylsilane (Me_4Si) or sodium 4,4-dimethyl-4-silapentane-5-sulfonate (DDS) as internal standards. Optical rotations were taken on a Perkin-Elmer Model 141 automatic recording polarimeter. Refractive indices were determined on a Bausch and Lomb apparatus. TLC was carried out on Eastman Chromagram sheets. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Ethyl *tert*-Butylsulfamoylacetate (10d). To a stirred, ice-cooled solution of 3.9 g (53 mmol) of *tert*-butylamine in 40 mL of CH_2Cl_2 was added dropwise 5.1 g (27 mmol) of ethyl chlorosulfonylacetate.[10] The resulting mixture was stirred with cooling for 30 min and then at room temperature for an additional hour. It was washed with 40 mL of H_2O. The dried (Na_2SO_4) CH_2Cl_2 layer was concentrated to give 5.3 g of yellow liquid. Further purification by distillation gave 4.3 g (72%) of **10d:** bp 128–130 °C (0.25 mm); n^{21}_D 1.4575; IR (neat) 3300 (NH), 1730 (CO), 1340 and 1150 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 1.3 (t, 3, CH_3), 1.4 (s, 9, *t*-C_4H_9), 4.03 (s, 2, CH_2, SO_2), 4.23 (q, 2, CH_2), 5.23 (broad signal, 1, NH).

***tert*-Butylsulfamoylacetic Acid Hydrazide (11d).** A mixture of 6.1 g (27 mmol) of **10d** in 20 mL of EtOH and 3.6 g (0.11 mol) of 95% hydrazine was stirred at room temperature overnight. Evaporation of the EtOH and the excess hydrazide gave 6.9 g of solid residue. Recrystallization of this solid from EtOH gave 4.4 g (77%) of **11d:** mp 120–121 °C; IR (KBr) 3365, 3300, and 3120 (NH_2NH and NH_2SO_2), 1675 (CO), 1335 and 1135 (SO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 1.3 (t, 3, CH_3), 3.8 (s, 2, CH_2), 4.65 (broad signal, 4, NH_2NH and NH).

***tert*-Butyl *N*-*tert*-Butylsulfamoylmethylcarbamate (14d).** To a cooled, stirred mixture of 0.98 g (4.7 mmol) of **11d**, 15 mL of H_2O, and 30 mL of Et_2O was added 0.52 mL (6.2 mmol) of 12 N HCl and 0.36 g (5.3 mmol) of $NaNO_2$ in 2 mL of H_2O. Stirring and cooling were continued for 10 min. The Et_2O layer was separated, and the aqueous layer was washed with Et_2O (3 × 20 mL). The combined Et_2O extracts were dried ($CaCl_2$) and added to 30 mL of C_6H_6. The Et_2O was removed by distillation through a 10 cm Vigreux column. When the volume had reached approximately 30 mL, the solution was heated under reflux for 30 min, 10 mL (0.11 mmol) of *t*-BuOH was added, and the mixture was heated under reflux for 1 h. Removal of the solvents gave 0.5 g of a solid. Recrystallization of this solid from C_6H_6 gave 0.45 g (36%) of **14d:** mp 130–132 °C; IR (KBr) 3380 and 3240 (NHCO and $NHSO_2$), 1705 (CO), 1340 and 1140 (SO_2), 845 (O-*t*-C_4H_9) cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 9, O-*t*-C_4H_9), 1.47 (s, 9, N-*t*-C_4H_9), 4.42 (d, 2, CH_2NH), 4.47 and 5.6 (broad signals, 2, NHCO and $NHSO_2$).

Attempted Preparation of *N*-*tert*-Butyl-α-aminomethanesulfonamide. A. From *tert*-Butyl *N*-*tert*-Butylsulfamoylmethylcarbamate (14d). Hydrogen chloride gas was passed through an ice-cooled, stirred solution of 0.35 g (1.3 mmol) of **14d** in 5 mL of EtOH for 1.5 h. The resulting solution was concentrated in vacuo and triturated with 10 mL of anhydrous Et_2O to give 0.15 g of white solid, mp 275 °C; IR (KBr) and NMR (D_2O) spectral data and the melting point of this material indicated that it is *tert*-butylammonium chloride. When the reaction was run with other reagent–solvent systems, such as 2 N HCl in dioxane, 45% HBr in HOAc, and trifluoroacetic acid, only *tert*-butylammonium salts were isolated.

B. With Benzyl *N*-*tert*-Butylsulfamoylmethylcarbamate (14e). To a solution of 0.51 g (1.7 mmol) of **14e** in 20 mL of EtOH was added 0.09 g of 30% Pd/C, and the mixture was placed on a low pressure Paar hydrogenator at 48 psi of H_2 for 18 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo to give unchanged starting material as judged from its NMR spectrum ($CDCl_3$). Similar treatment with 10% $Pd(OH)_2$/C gave the same results.

Treatment of **14e** with 45% HBr in HOAc followed by dilution with anhydrous Et_2O resulted in the isolation of *tert*-butylammonium bromide, which was compared with an authentic sample.

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Registry No.—**9** (R_2 = H), 55896-93-0; **9** (R_2 = methyl), 20449-09-6; **9** (R_2 = 3,4-dibenzyloxybenzyl), 67542-12-5; **9** (R_2 = 3,4-dimethoxybenzyl), 67542-13-6; **10a,** 55897-04-6; **10c,** 55897-05-7; **10d,** 67541-92-8; **10f,** 67541-93-9; **10g,** 67541-94-0; **10h,** 67541-95-1; **10i,** 67541-96-2; **10j,** 67541-97-3; **10k,** 55897-12-6; **11a,** 67541-98-4; **11c,** 67576-97-0; **11d,** 67541-99-5; **11f,** 67542-00-1; **11g,** 67542-01-2; **11h,** 67542-02-3; **11i,** 67542-03-4; **11k,** 67542-04-5; **14a,** 53826-70-3; **14b,** 53826-11-4; **14d,** 67542-05-6; **14e,** 67542-06-7; **14f,** 67542-07-8; **14g,** 67542-08-9; **14h,** 67542-09-0; **14i,** 67542-10-3; **14k,** 67542-11-4; RNH_2 (R = H), 7664-41-7; RNH_2 (R = *t*-Bu), 75-64-9; RNH_2 (R = 4-ClC_6H_4), 106-47-8; D-alanine *tert*-butyl ester, 59624-87-2; D-alanine benzyl ester, 17831-02-6; morpholine, 110-91-8; ethanol, 64-17-5;

benzyl alcohol, 100-51-6; *tert*-butyl alcohol, 75-65-0; *tert*-butylammonium chloride, 10017-37-5.

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Preparation of Iminosulfuranes Utilizing the Dimethyl Sulfoxide–Oxalyl Chloride Reagent[1,2]

S. L. Huang and Daniel Swern*

Fels Research Institute and Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

Received July 10, 1978

In earlier studies,[3,4] we showed that the dimethyl sulfoxide (Me_2SO)–oxalyl chloride (OC) reagent was the most generally useful of a large number of "activated" Me_2SO reagents for the low-temperature (−60 to −10 °C) oxidation of many classes of alcohols to carbonyl compounds in high yields. During those investigations we also examined the reaction of the Me_2SO–OC reagent with selected arylsulfonamides, methanesulfonamide, *p*-toluenesulfonylhydrazide, *p*-nitroaniline, and *p*-nitrobenzamide for the preparation of iminosulfuranes (sulfilimines) at −60, −20, and 0 °C (procedures A, B, and C respectively); the results are reported in this note (Table I).

p-Chlorobenzenesulfonamide was employed as a model; excellent yields (85–94%) of iminosulfuranes were obtained by procedures A, B, and C, although A and C yield products of somewhat higher purity. Since the low temperatures used in procedure A cause solubility problems and require the use of large amounts of solvent to achieve homogeneity, it was abandoned in favor of B and C. On the basis of the melting points of the once-precipitated products and convenience of operation at 0 °C, procedure C was adopted as the preferred procedure. However, it is necessary to use larger quantities of OC as considerable decomposition of the Me_2SO–OC reagent occurs at the relatively high reaction temperature. Operationally, OC is preferably added to the Me_2SO solution of the amino compound to trap as much Me_2SO–OC reagent as possible before it decomposes. With *p*-nitroaniline, aqueous sodium hydroxide is preferred for basification rather than triethylamine (TEA) as product purification seemed easier with the former.

Only one carboximide, *p*-nitrobenzamide, was examined with the Me_2SO–OC reagent (procedure A). The major product (70%) was the nitrile corresponding to the amide; iminosulfurane was the minor product (15%), as determined by LC of the crude reaction mixture. Some unreacted amide was still present. Iminosulfuranes were not isolable from methanesulfonamide and *p*-toluenesulfonylhydrazide upon reaction with the Me_2SO–OC reagent. No further studies were carried out with these amino compounds.

Experimental Section[8]

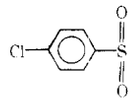
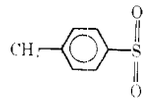
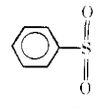
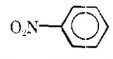
Preparation of Iminosulfuranes (Table I). Procedure C (Preferred Method, 0 °C). To a stirred solution of Me_2SO (5 mL, 71 mmol) and *p*-chlorobenzenesulfonamide (1.92 g, 10 mmol) in CH_2Cl_2 (40 mL) at 0 °C (ice bath) in a 100-mL three-neck flask, OC (1.9 mL, 22 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added in 15 min. After an additional 30 min at 0 °C, TEA (8.5 mL) was added dropwise in ca. 5 min at 0–5 °C. The reaction mixture was allowed to warm to room temperature, diluted with additional CH_2Cl_2 (ca. 120 mL), and washed successively with water (50 mL), sodium chloride solution (50 mL), 2 N NaOH (50 mL), and sodium chloride solution (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was evaporated in a rotary vacuum evaporator at room temperature. The solid residue was dissolved in a minimum quantity of warm CH_2Cl_2 (5–10 mL) and ether (15–20 mL) was added until no further precipitation occurred. After being cooled to 0–5 °C, the precipitate was filtered and dried. IR, NMR, R_f, and melting points were virtually identical with those of an authentic sample.[1,5]

Procedure B (−20 °C). Similar to C except for the higher reaction temperature and the use of a smaller excess of OC (1.3 mL, 15 mmol) and TEA (7.0 mL).

Procedure A (−60 °C). Similar to C except that Me_2SO (1.8 mL, 25.5 mmol) in CH_2Cl_2 (5 mL) was added to OC (0.95 mL, 11 mmol) in CH_2Cl_2 (25 mL) at −60 °C. *p*-Chlorobenzenesulfonamide (1.92 g, 10 mmol) in Me_2SO (8 mL)–CH_2Cl_2 (12 mL) was then added and stirring was continued for an additional 75 min at −60 °C. TEA was added at −60 °C. The remainder of the workup paralleled procedure C.

Miscellaneous. The remaining sulfilimines in Table I were prepared by procedures B and C from Me_2SO, OC, and the appropriate amino compound. With *p*-nitroaniline aqueous NaOH was preferred for basification rather than TEA. The preparative procedures were unsatisfactory with *p*-nitrobenzamide, methanesulfonamide, and *p*-toluenesulfonylhydrazide.

Table I. *S,S*-Dimethylsulfilimines,[a] $(CH_3)_2S^+N^-R$

R	registry no.	procedure[b]	yield, %[c]	mp, °C[c]	lit. mp, °C
	52259-84-4	A	85	116–117	116–117[5]
		B	94	113–115	
		C	90	116–117	
	13150-75-9	B	95	153–155	158–159[6]
		C	89	158–159	
	19871-30-8	B	80	126–127	131[7]
		C	73	128–129	
	27691-52-7	B	73	168–170	172–174[5]

[a] IR and NMR spectra and R_f values (TLC) were identical with those of authentic specimens. [b] Procedure A: −60 °C, 1 h; OC, 11 mmol; arylsulfonamide, 10 mmol. Procedure B: −20 °C, 1 h; OC, 15 mmol; amide or amine, 10 mmol. Procedure C: 0 °C, 0.5 h; OC, 22 mmol; amide, 10 mmol. Excess Me_2SO was used in all cases with CH_2Cl_2 as solvent (see Experimental Section). TEA was used for basification except in the reaction of *p*-nitroaniline in which aqueous NaOH was preferred. [c] After one precipitation–purification step.

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