Tetrahedron Letters,Vol.29,No.14,pp 1653-1656,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CONVENIENT PROCEDURE FOR THE PREPARATION OF ALKYL AND ARYL SUBSTITUTED N-(AMINOALKYLACYL)SULFONAMIDES

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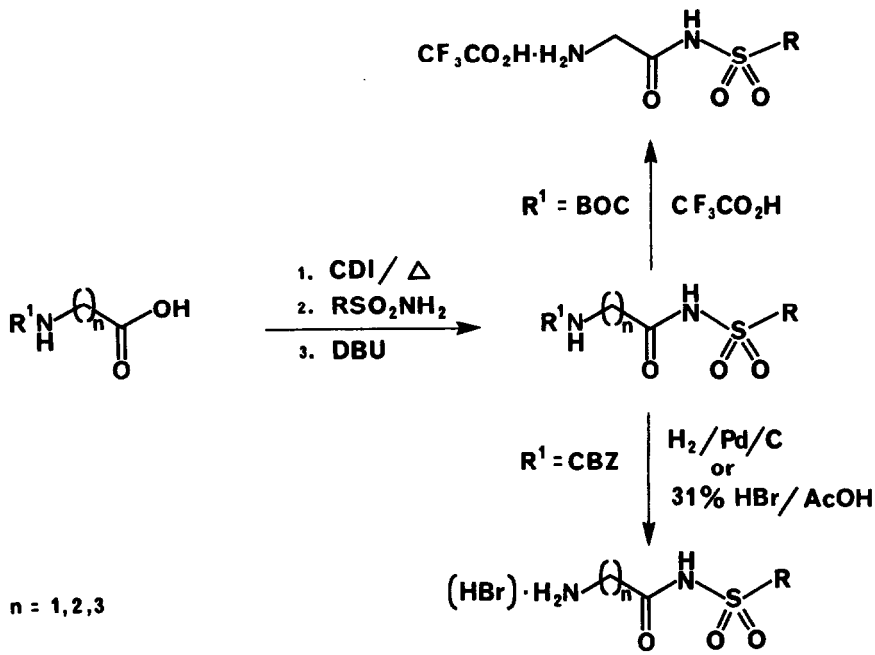
Abstract: A convenient synthesis of N-(aminoalkylacyl)sulfonamides from CBZ potected glycine, β-alanine and GABA is described.

During an investigation into the preparation of new pharmacologically active amino acid analogs we wished to explore the pharmacological properties of compounds which bore both an equiionizable carboxylic acid isostere and lipophilic substituents at this new acidic terminus. It appeared to us that one functionality which provided this combination of features was the N-acylsulfonamide group. Accordingly, we targeted the synthesis of a series of N-(aminoalkylacyl)sulfonamides.

Investigation of the literature for routes by which to prepare these potentially useful compounds revealed a number of alternate procedures[1,2,3,4]. However, from our requirements of generality, ease of synthesis and the need to prepare a range of derivatives in amounts sufficient for pharmacological evaluation, these reported procedures were inadequate to our needs. Consequently, we sought to develop a simple and efficient route by which to prepare these novel structures.

We wish to report here an effective route for the preparation of alkyl and arylsulfonyl substituted amino acid amides. Initially, we investigated the reaction of toluenesulfonamide with carbonyldiimidazole activated t-BOC protected glycine (Scheme). Following prolonged reflux, this procedure gave cleanly but rather slowly the desired N-acylsulfonamide (19) as a crystalline solid (Table). Removal of the t-BOC group was achieved using standard trifluroacetic acid treatment.

Scheme

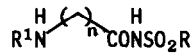


Extending this reaction to methanesulfonamide gave after extended reflux no trace of the desired product. Reasoning that the imidazole already present in the reaction was insufficiently basic to deprotonate the weakly acidic alkyl sulfonamide, we concluded that the addition of a stronger tertiary base to the reaction might deprotonate the methanesulfonamide and hence accelerate the reaction. This was observed to be the case and thus following the addition of an equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the reaction mixture, the desired substituted N-acylmethylsulfonamide was generated. The poor isolated yield (20%), and lack of crystallinity of the product was dramatically improved by changing the amino protecting group to carbobenzyloxy (CBZ) (Scheme), whereupon excellent yields were achieved routinely. An additional benefit of this protecting group change was noted in that crystalline and analytically pure product could be isolated directly from the reaction mixture following addition of the reaction crude to 1N HCl. This work up procedure was found to be completely general. Subsequent deprotection of the CBZ group was achieved either by hydrogenolysis or, where required by functional group incompatibility, by brief treatment with 31% HBr in acetic acid.

The convenience of this synthetic procedure was established through the preparation of a series of alkyl substituted glycine, beta-alanine and GABA analogs (Table).

Using similar methodology to that given below, but with the exposure to DBU reduced to 10 minutes,[5] the methanesulphonamide derivatives of both CBZ-protected d- and l-alanine were also prepared. Retention of amino acid chiral integrity was demonstrated by optical rotation measurement[6] and by chiral shift NMR,[7] thus further demonstrating the potential of this mild synthetic procedure.

TABLE



Product	R	n	R^1=CBZ Yield[a]	mp, °C	Product	R^1=H Yield	mp,°C (salt, if any)
1	$-CH_3$	1	73	154-5	12	84	191-4 dec[c]
2	$-CH_2CH=CH_3$	1	59	119-20	13	92	134-6 (HBr)[f]
3	$-(CH_2)_4CH_3$	1	75	151-151.5	14	74	189-90[a]
4	$-(CH_2)_7CH_3$	1	76	153-4	15	67	165-6[d]
5	$-(CH_2)_{11}CH_3$	1	75	153-4	16	68	163-4 dec[d]
6	$-CH_2CH_2Ph$	1	64	131-2	17	99	190-1 (HBr)[f]
7	$-(CH_2)_5$-(dimer)	1	57[b]	194-196	18	65	160-3 dec (H_2O)
8	-p-toluene	1	80	155.5-157	19	95	240-2 dec (HBr)[e,f]
9	$-CH_3$	2	84	126.5-127	20	65	187-9[c]
10	$-(CH_2)_7CH_3$	2	77	125-126	21	93	171-3 (HCl)
11	$-(CH_2)_7CH_3$	3	33	121-122	22	72	182-4 (HBr)[e,f]

All compounds gave satisfactory elemental analysis and spectral data. a = Recrystallized from MeOH (analytical solids were often obtained directly in higher yields). b = Recryst. CH_3CN. c = Recryst. H_2O/MeOH. d = Recryst. THF/H_2O; obtained as an analytical solid from hydrogenation. e = MeOH/Et_2O. f = These examples were deprotected by exposure to HBr. All others were deprotected using the alternate hydrogenation procedure.

Measurement of the pKa of these novel amino acid derivatives confirmed the results of earlier studies[2] in that 12 exhibited an identical ionization profile to that of glycine itself.

We are currently exploring the potential utility of this novel carboxylic acid isosteric replacement to other amino acid derivatives.

General Preparative Procedure

All recrystallization conditions, yields and melting points are given in the Table.

Condensation

A solution of the N-carbobenzyloxy amino acid (25 mmol) in dry tetrahydrofuran (THF) (50 ml) is added dropwise to a stirred solution of carbonyldiimidazole (25 mmol) in dry THF (50 ml) under nitrogen. The reaction is stirred (30 min), refluxed (30 min) and allowed to cool to room temperature. The sulfonamide (25 mmol) is added in one portion and the reaction stirred for 10 min before a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (25 mmol) in dry THF (25 ml) is added dropwise. The reaction is stirred overnight then poured into 1N HCl (500 ml). The formed precipitate is washed with water and dried (air or vacuum, room temp).

Deprotection Hydrogen Bromide Procedure - Typical

To N-[[(carbobenzyloxy)amino]acetyl]allylsulfonamide (5.0 g, 16 mmol) in a round bottomed flask (250 ml) was added with stirring a solution of hydrogen bromide in acetic acid (31%, 25 g). After 20 min. the reaction is slowly diluted to 200 ml with diethyl ether and the liquids decanted. The solid is resuspended in ether (200 ml), stirred and the suspension filtered and washed with ether to give as a white solid, 2-amino-N-(allylsulfonyl) acetamide· HBr (13) (3.8 g, 92%).

Hydrogenation - Typical

To a suspension of palladium on carbon (5%, 0.5 g) in water (50 ml) is added a solution of N-[[(carbobenzyloxy)amino]acetyl]pentanesulfonamide (9.5 g, 27.8 mmol) in water (45 ml), ammonium hydroxide (1N, 28 ml) and THF (50 ml). The suspension was hydrogenated (stirring at atmospheric pressure) for three hours, filtered through celite and concentrated to dryness to give 2-amino-N-(pentylsulfonyl)acetamide (14) (5.6 g, 97%).

References

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5. Reaction upon the addition of DBU was apparently immediate. Longer exposure of the reaction mixture to DBU caused increasing racemization to occur. The use of overnight stirring given in the general experimental was for convenience only.
6. L-isomer $[\alpha]_D^{23}$ +11.3°(c = 1.0, DMF), mp 125.5-127°; D-isomer $[\alpha]_D^{23}$ -9.0°(c = 1.0, DMF).
7. Each isomer was determined by NMR chiral shift experiments using $Eu(facam)_3$ to be optically pure within experimental limits (10%).

(Received in USA 11 August 1987)