Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1589–1593

TETRAHEDRON: *ASYMMETRY*

Racemisation-free synthesis of chiral acylsulfonamides

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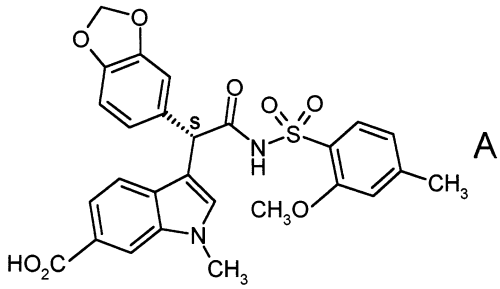
Received 3 May 2001; accepted 5 June 2001

Abstract—The development and application of a synthesis of acylsulfonamide **A** avoiding racemisation of the labile benzylic stereogenic centre is described.

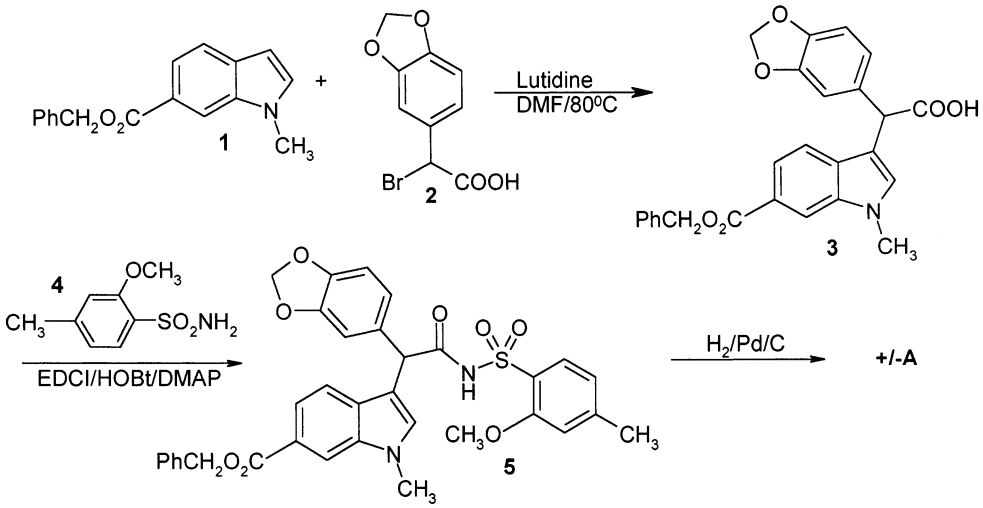
1. Introduction

There are many methods for the synthesis of acylsulfonamides, the most common being reaction of a sulfonamide with a carboxylic acid in the presence of an activating reagent. Frequently the addition of strong bases such as 4-*N*,*N*-dimethylaminopyridine (DMAP) is required.[1–3] The reaction of amides (usually secondary) with sulfonyl chlorides is also used occasionally.[4–6] However, few of these literature methods involve compounds with labile stereogenic centres and many would be incompatible with such molecules. Herein, we describe a strategy for the racemisation-free synthesis of acylsulfonamide **A**, a selective endothelin-A antagonist.[7]



2. Results and discussion

The synthesis of racemic material is outlined in Scheme 1.



Scheme 1.

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0957-4166/01/$ - see front matter
PII: S0957-4166(01)00259-2

The C(3) alkylation of the indole **1** with (±)-α-bromo-3,4-benzodioxole-acetic acid **2** was complete in 3–4 h and proceeded in good yield (61%). The coupling of acid **3**, as its activated 1-hydroxybenzotriazole (HOBt) ester, with **4** required the addition of DMAP due to the poor nucleophilicity of the sulfonamide. This strategy allowed the rapid synthesis of a range of racemic analogues, using 5-, 6- or 7-substituted indoles and a variety of aryl sulfonamides.

The first approach to enantiomerically pure products relied on the resolution of a homochiral amine salt of the acid **3**, followed by coupling of the sulfonamide under non-racemising conditions. A trial screening programme identified (*R*)- and (*S*)-α-methylbenzylamines as complementary resolving agents for the enantiomers of **3**, with the (*R*)-isomer crystallising the required enantiomer of acid **3**. A single recrystallisation from ethyl acetate gave enantiomerically pure products with e.e.s of >98.5%.[8]

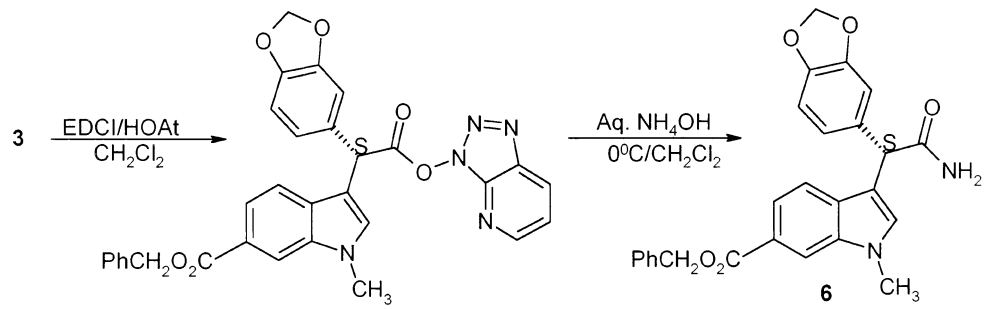
Coupling of the enantiomerically pure acid **3** under the original conditions resulted in complete racemisation due to the basicity of DMAP and the acidity of the doubly benzylic methine proton. Alternative coupling conditions were sought with sulfonamide **4** including (a) catalytic (as opposed to stoichiometric) DMAP (b) reaction of the acid chloride or acid fluoride (using TFFH)[9] of **3** (c) use of PyBrop[9] (d) use of the anion of sulfonamide **4** with the 1-hydroxy-7-azabenzotriazole (HOAt) activated ester of the acid **3**. None of these methods was successful, giving either no reaction or a racemic product.

Further investigation of the original EDCI[9]/HOBt coupling method showed that the HOAt ester of acid **3** could be isolated. Extraction of an ethyl acetate solution of the HOAt ester with 10% aqueous citric acid removed the basic urea by-product and evaporation of the solvent then gave the ester as a foam. HPLC analysis showed that no epimerisation had occurred. The HOAt ester is configurationally stable (possibly due to its sterically hindered environment) and could be treated in dichloromethane solution at 0°C with saturated aqueous ammonia to give the primary amide **6** with no loss of stereochemical integrity[8] (Scheme 2).

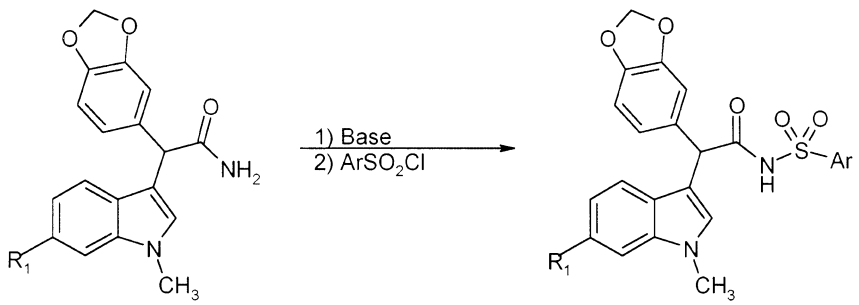
This finding gave rise to the use of the alternative approach to the synthesis of acylsulfonamides, viz. reaction of the primary amide anion of **6** with a sulfonyl chloride.[4–6] This 'reversed' approach had the advantage that the enantiomeric purity established by the original resolution of the acid **3** was preserved by the adjacent and more acidic amide anion. However, the maximum conversion would be only 50% due to the increased acidity of the NH group in the product (Scheme 3).

Deprotonation of the amide was examined with a variety of bases and the results are summarised in Table 1.

Reaction using the non-nucleophilic and bulky phosphazene P-4 base[10] was found to be extremely facile. The base (used as a 1 M solution in cyclohexane) was simply added to a solution of the amide and sulfonyl chloride in THF at −60°C. Further aliquots of base could be added when required, as the halide was not destroyed by it, resulting in much higher conversions. However, the development of intractable coloured impurities halted further developments with this base.



Scheme 2.



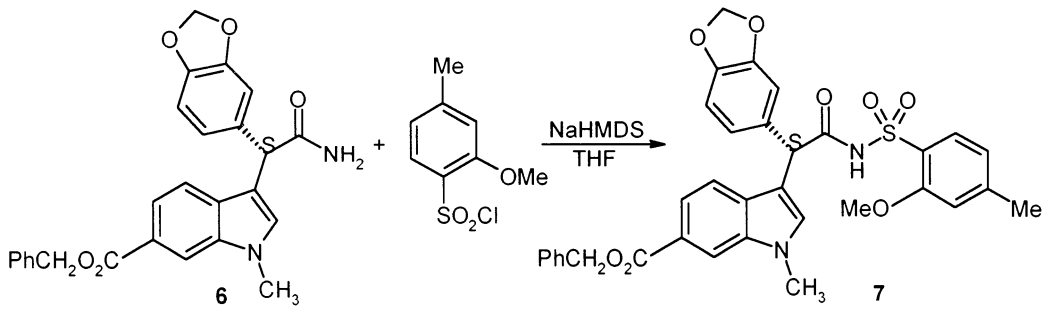
Scheme 3.

Table 1. Deprotonation of amide **6**

Base	Reaction conditions	E.e. maintained	Conversion
NaH	0°C to rt in THF	No	Slow, <20%
sec-BuLi	−60 to −40°C, 1 h in THF	Yes	40%[a]
tert-BuMgCl	0°C to rt in THF	Yes	<20%
P-4 Phosphazene base	−60°C, 1–2 h in THF	Yes	65%
NaHMDS	−60 to −40°C, 2–3 h in THF	Yes	55%

[a] Attack on the ester group by the *sec*-BuLi was seen, giving lower conversions to the desired product.

The use of NaHMDS in THF at −60°C proved to be the reagent of choice for the synthesis of the required acylsulfonamide (Scheme 4), the bulk of the base probably prevents it from attacking either the 6-ester function or the labile methine proton. Stereochemical integrity was preserved in the products and use of extra aliquots of base increased conversion to 55%. The benzyl ester **7** was deprotected by hydrogenolysis (Pd/C). Gram quantities of the desired acylsulfonamide **A** have been prepared using this method.



Scheme 4.

3. Conclusion

A racemisation-free synthesis of acylsulfonamides has been developed and shown to be effective for acyl substrates with labile 'doubly benzylic' stereogenic centres.

4. Experimental

NMR spectra were recorded on Varian Unity Inova spectrometers at 300 or 400 MHz for DMSO-d_6 solutions unless otherwise stated. Chemical shifts are referenced to residual solvent signals. Mass spectra were recorded on a Fisons TRIO 1000 spectrometer using either atmospheric pressure chemical ionisation (APCI) or thermospray (TSP) ionisation modes. Reactions were monitored by TLC on Merck plates (Kieselgel 60 F_{254}) and the plates were visualised under UV light (254 nm) and developed using $KMnO_4$ solution. Column chromatography used Kieselgel 60 (Merck, particle size 0.04–0.063 mm). Organic solutions were evaporated in vacuo at 30–40°C.

4.1. Preparation and resolution of (2*S*)-1,3-benzodioxol-5-yl{6-[(benzyloxy)carbonyl]-1-methyl-1*H*-indol-3-yl}-ethanoic acid 3

Nitrogen gas was bubbled gently through a solution of 1-methyl-6-benzyloxycarbonylindole (9.8 g, 36.9 mmol) and 2-bromo-3,4-benzodioxoleacetic acid (10.5 g, 40 mmol) in DMF (100 mL) at room temperature for 5 min. before immersing the flask in a preheated oil bath at 90°C. Nitrogen was passed through the solution continuously for 4 h. The brown solution was then cooled to room temperature and the solvent evaporated. The oily residue was partitioned between ethyl acetate (300 mL) and aqueous HCl (2 M, 100 mL). The organic layer was separated and washed with further portions of aqueous HCl (2 M, 4×50 mL), saturated aqueous sodium chloride solution (50 mL), dried ($MgSO_4$ plus decolourising charcoal), filtered and evaporated. The residue was chromatographed using a gradient of CH_2Cl_2/CH_3OH from 100/0 to 95/5 in 1% increments of CH_3OH to give **3** as an oil (9.97 g, 22.5 mmol, 61%). The product was dissolved in ethanol (50 mL) and treated with a solution of (*R*)-α-methylbenzylamine (2.72 g, 22.3 mmol) in ethanol (30 mL). The solution was evaporated and the solid residue was recrystallised three times from ethyl acetate (approx. 1000 mL per crystallisation) giving the salt of **3** (2.7 g, 42% of theoretical maximum, 98.8% e.e.); ^{1}H NMR: δ 1.27 (3H, d, $J=6.6$ Hz, C$\underline{H}_3$CH), 3.77 (3H, s, N-CH_3), 4.05 (1H, q, $J=6.6$, 6.84 Hz, $CH_3C\underline{H}$), 4.96 (1H, s, C$\underline{H}$COOH), 5.32 (2H, s, $PhCH_2$), 5.88 (2H, q, $J=5.13$, 0.98 Hz, O-CH_2-O), 6.72 (1H, d, $J=8.06$ Hz, benzodioxole C-5H), 6.8 (1H, dd, $J=1.71$, 8.31 Hz, benzodiox-

ole C-6H), 6.89 (1H, d, $J=1.47$ Hz, benzodioxole C-2H), 7.15–7.58 (13H, complex multiplets, aromatics), 8.0 (1H, s, indole C-7H); APCI-MS m/z: 444.6 (MH^+, 100%). Anal. calcd for $C_{34}H_{32}N_2O_6$ (564.61): C, 72.32; H, 5.71; N, 4.96. Found: C, 71.95; H 5.65; N, 4.92%.

4.2. Preparation of benzyl 3-[(1*S*)-2-amino-1-(1,3-benzodioxol-5-yl)-2-oxoethyl]-1-methyl-1*H*-indole-6-carboxylate 6

The (*R*)-α-methylbenzylamine salt of **3** (2.7 g, 4.8 mmol) was partitioned between ethyl acetate (200 mL) and aqueous HCl (2 M, 100 mL). The organic phase was separated and washed with further portions of aqueous HCl (2 M, 2×50 mL), saturated aqueous sodium chloride solution (50 mL), dried ($MgSO_4$), filtered and evaporated to give the free acid as a foam. To a solution of the acid in CH_2Cl_2 (25 mL) at 0°C was added HOAt (0.85 g, 6.2 mmol) followed by EDCI (1.4 g, 7.3 mmol) in portions over 5 min. After 90 min. the solution was washed with aqueous citric acid solution (10%, 3×10 mL) and saturated aqueous sodium chloride solution (10 mL), dried ($MgSO_4$) and filtered. The filtrate was cooled to 0°C and treated with concentrated aqueous ammonia solution (SG 0.88, 0.7 mL, 14.3 mmol) dropwise over 2 min. After 10 min. the reaction mixture was washed with aqueous citric acid solution (10%, 2×10 mL), saturated aqueous sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (5 mL), dried ($MgSO_4$), filtered and evaporated to give **6** as a solid (1.78 g, 84%, 98.7% e.e.); ^{1}H NMR: δ 3.79 (3H, s, N-CH_3), 5.00 (1H, s, C$\underline{H}$-$CONH_2$), 5.32 (2H, s, PhCH_2O), 5.90 (2H, q, $J=0.98$, 4.89 Hz, O-CH_2-O), 6.76 (1H, d, $J=7.82$ Hz, benzodioxole C-5H), 6.80 (1H, dd, $J=1.23$, 8.07 Hz, benzodioxole C-6H), 6.86 (1H, d, $J=1.47$ Hz, benzodioxole C-2H), 6.94 (1H, br s, amide NH), 7.26–7.62 (9H, complex multiplets, aromatics+amide NH), 8.02 (1H, s, indole C-7H); TSP+MS m/z: 443.0 (MH^+, 100%). Anal calcd for $C_{26}H_{22}N_2O_5$ (442.45): C, 70.57; H, 5.01; N, 6.33. Found: C, 70.11; H, 4.96; N, 6.29%.

4.3. Preparation of benzyl 3-((1*S*)-1-(1,3-benzodioxol-5-yl)-2-{[(2-methoxy-4-methylphenyl)sulfonyl]amino}-2-oxoethyl)-1-methyl-1*H*-indole-6-carboxylate 7

To a solution of **6** (0.5 g, 1.1 mmol) in THF (12 mL) at −60°C (internal temperature) under nitrogen was added NaHMDS (0.207 g, 1.1 mmol, 1.13 mL of 1 M solution in THF) dropwise over 2 min. The pale yellow solution was allowed to warm to −40°C and was treated with a solution of 2-methoxy-4-methylbenzenesulfonyl chloride (0.25 g, 1.1 mmol) in THF (0.5 mL) dropwise over 2 min. After 30 min. the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and allowed to warm to room temperature. The THF was evaporated and the aqueous residue was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with aqueous HCl (1 M, 1×5 mL), saturated aqueous sodium chloride solution (1×5 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (CH_2Cl_2:CH_3OH from 100:0 to 98:2 in 1% increments of CH_3OH) to give **7** as a foam (0.39 g, 0.62 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (3H, s, CH_3-phenyl), 3.44 (3H, s, N-CH_3), 3.74 (3H, s, O-CH_3), 5.04 (1H, s, C$\underline{H}$-$CONHSO_2$), 5.40 (2H, s, PhCH_2O), 5.91 (2H, br d, $J=3.29$ Hz, O-CH_2-O), 6.55 (1H, s, aromatic CH), 6.70 (3H, br s, aromatic CH), 6.86 (1H, d, $J=7.69$ Hz, aromatic CH), 7.06 (1H, s, aromatic CH), 7.19 (1H, d, $J=8.42$ Hz, aromatic CH), 7.3–7.5 (7H, complex multiplets, aromatics), 7.67 (1H, d, $J=8.42$ Hz, aromatic CH), 7.92 (1H, d, $J=8.05$ Hz, aromatic CH), 8.04 (1H, s, indole C-7H), 8.79 (1H, br s, $CONHSO_2$); TSP-MS m/z: 627.5 (MH^+, 100%). Anal. calcd for $C_{34}H_{30}N_2O_8S\cdot0.25CH_2Cl_2$ (647.89): C, 63.49; H, 4.74; N, 4.32. Found: C, 63.64; H, 4.71; N, 4.31%.

4.4. Preparation of 3-((1*S*)-1-(1,3-benzodioxol-5-yl)-2-{[(2-methoxy-4-methylphenyl)sulfonyl]amino}-2-oxoethyl)-1-methyl-1*H*-indole-6-carboxylic acid A

A mixture of **7** (0.93 g, 1.5 mmol) and 5% Pd/C (0.15 g) was hydrogenated at 60 psi and room temperature for 18 h. A further portion of catalyst (0.15 g) was then added and the reaction continued for a further 4 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was recrystallised from CH_2Cl_2/CH_3OH (9:1, ~5 mL) to give **A** as a white solid (0.59 g, 1.1 mmol, 74%, >99% e.e.). ^{1}H NMR: δ 2.31 (3H, s, CH_3-phenyl), 3.58 (3H, s, N-CH_3), 3.74 (3H, s, O-CH_3), 5.19 (1H, s, C$\underline{H}$CONH), 5.93 (2H, d, $J=4.15$ Hz, O-CH_2-O), 6.68 (2H, m, aromatics), 6.78 (1H, d, $J=8.8$ Hz, aromatic), 6.85 (1H, d, $J=8.07$ Hz, aromatic), 6.91 (1H, s, aromatic), 7.12 (1H, s, aromatic), 7.25 (1H, d, $J=8.31$ Hz, aromatic), 7.52 (1H, dd, $J=1.22$, 8.31 Hz, aromatic), 7.63 (1H, d, $J=8.06$ Hz, aromatic), 7.97 (1H, s, indole C-7H), 12.26 (1H, br s, NH), 12.53 (1H, br s, COOH); APCI-MS m/z: 537.7 (MH^+, 100%). Anal calcd for $C_{27}H_{24}N_2O_8S\cdot0.9CH_2Cl_2$ (612.99): C, 54.67; H, 4.24; N, 4.57. Found: C, 54.67; H, 4.18; N, 4.53%.

Acknowledgements

I would like to thank Dr D. J. Rawson for support during this work and his help in the preparation of this paper.

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8. HPLC conditions. For α-methylbenzylamine salts: Chiralpak AD 50×4.6 mm; eluent 60% hexane, 40% *iso*-propyl alcohol (IPA)+0.1% glacial acetic acid. For primary amides: Chiralpak AD 250×4.6 mm; eluent 50% hexane, 50% IPA+0.3% v/v trifluoroacetic acid (TFA)+0.2% v/v diethylamine (DEA). For benzyl ester **7**: Chiralpak AD 250×4.6 mm; eluent 70% hexane, 30% IPA+0.1% v/v TFA. For final compound **A**: Chiralpak AD 250×4.6 mm; eluent 80% hexane, 20% IPA+0.1% v/v TFA. All flow rates are 1.0 mL/min.
9. TFFH = tetramethylfluoroformamidinium hexafluorophosphate. See: Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401. EDCI = 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide HCl. PyBrop = bromo-tris-pyrrolidinophosphonium hexafluorophosphate. See: Coste, J. *Tetrahedron Lett.* **1991**, *32*, 1967.
10. *tert*-Bu-P_4Phosphazenebase = 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino}-2λ^5,4λ^5-catenadi(phosphazene). See: Schwesinger, H.; Schlemper, H. *Angew. Chem.* **1987**, *99*, 1212.