A Versatile Synthesis of 3-Phenylsulfonylpyrroles from α-Amino Acids

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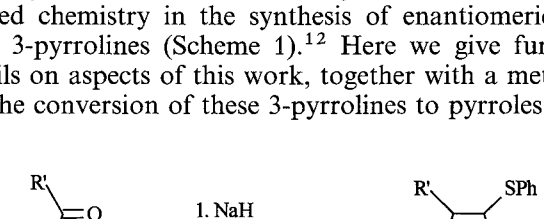
Reaction between α-benzamidoalkyl ketones **4a–e** and the vinyl phosphonium salt **1** produces 3-phenylthio-3-pyrrolines **5a–e** which can be converted into *N*-benzyl-3-phenylsulfonyl pyrroles **7a–e** by *m*-CPBA oxidation, diborane reduction and DDQ aromatisation.

Pyrroles are synthetic targets of interest, not least because they are the building blocks for natural pigments.[1] The traditional Knorr synthesis still represents a very important approach to pyrroles, but other methods continue to be developed.[2–9] We describe here an approach to the pyrrole ring system which allows considerable flexibility in the substitution pattern.

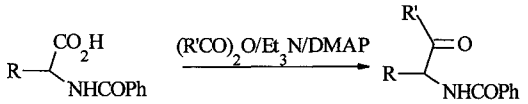
We have previously described the use of the vinyl phosphonium salt **1**[10] in the production of a range of carbocyclic systems,[11] and have recently discussed the use of related chemistry in the synthesis of enantiomerically pure 3-pyrrolines (Scheme 1).[12] Here we give further details on aspects of this work, together with a method for the conversion of these 3-pyrrolines to pyrroles.



Scheme 1

The required *N*-protected α-amino ketones **2** are available either by the method of Rapoport, involving the reaction of *N*-acyl or *N*-sulfonyl α-amino acids with organometallics,[13] or, for the *N*-acyl compounds only, by the rather more economical Dakin–West reaction.[14] These latter workers showed that on heating with acetic anhydride and pyridine a typical α-amino acid is converted into an α-acetamidoalkyl methyl ketone. Further studies indicated that the starting material could be an *N*-acylated α-amino acid and that various anhydrides could be used. A later report described improved milder conditions employing triethylamine–4-dimethylaminopyridine (DMAP) as the base.[15] One major difference between the two approaches to **2** is that the Rapoport method affords enantiomerically pure products, while the Dakin–West reaction leads to racemic product, although this was of no consequence to the work described here.

For this study we have routinely used *N*-benzoyl α-amino acids **3** as starting materials and the DMAP catalysed Dakin–West reaction to generate the ketones **4a–f** (Scheme 2, Table 1). We were unsuccessful in using the Dakin–West reaction on *N*-benzoylserine, although we have not investigated the use of *O*-protected serine derivatives. Reaction of the ketones **4a–f** with the vinyl phosphonium salt **1** in the presence of sodium hydride produced the desired 3-pyrrolines **5a–e** by way of an intramolecular Wittig reaction (Table 2). It was found that better yields were obtained using a mixed solvent system (THF–MeCN, 1:4) than using a single solvent (THF, MeCN or DMF), but the reaction failed with the phenyl ketone **4f**.



Scheme 2

Table 1. Physical and Spectral Data for Ketones **4**

Compound	Yield (%)	mp (°C) (Lit. mp)	IR ν (cm⁻¹)	¹H NMR ($CDCl_3$)[a] δ, J (Hz)
4a	78	68–69 (69[17])	3400, 3280, 3060, 1730, 1630	7.82 (2H, m), 7.55–7.39 (3H, m), 7.15 (1H br s), 4.8 (1H, qn, J = 7), 2.28 (3H, s), 1.48 (3H, d, J = 7)
4b	70	64–66 (64[18])	3380, 2900, 1720, 1630	7.6–7.0 (6H, m), 4.95 (1H, qn, J = 7), 2.4 (2H, q, J = 7), 1.5 (2H, d, J = 7), 1.1 (3H, t, J = 7)
4c	76	110–112 (111[19])	3400, 2900, 1720, 1630	7.75–7.10 (10H, m), 6.88 (1H, d, J = 6.5), 5.07 (1H, q, J = 6.5), 3.25 (2H, m), 2.25 (3H, s)
4d	60	79–81 (80[19])	3200, 2900, 1720, 1630	7.75 (2H, m), 7.51–7.14 (8H, m), 6.92 (1H, d, J = 7), 5.07 (1H, q, J = 6.5), 3.20 (2H, m), 2.50 (2H, q, J = 7.5), 1.06 (3H, t, J = 7.5)
4e	65	95–97 (95[18])	3380, 2900, 1720, 1630	7.85 (2H, m), 7.50 (3H, m), 6.80 (1H, br), 4.95 (1H, dd, J = 7,5), 2.40 (1H, m), 2.30 (3H, s), 1.13 (3H, d, J = 7), 0.88 (3H, d, J = 7)
4f	20	146–147 (146[19])	3200, 2900, 1720, 1640	7.75–7.05 (16H, m), 5.05 (1H, q, J = 6.5), 3.1 (2H, d, J = 6.5)

[a] qn = apparent quintet.

Table 2. Physical and Spectral Data for 3-Phenylthio-3-pyrrolines **5**[a]

Compound	Yield (%)	mp (°C)	IR ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)
5a	90	oil	3080, 3000, 1640	7.55–7.16 (10 H, m), 5.10 (1 H, m), 4.34 (1 H, m), 3.98 (1 H, d, J = 14), 1.94 (3 H, s), 1.51 (3 H, d, J = 6.5)
5b	80	oil	2980, 2940, 1640	7.85–7.25 (10 H, m), 5.13 (1 H, m), 4.55 (2 H, m), 3.25 (1 H, m), 2.35 (1 H, m), 1.45 (3 H, d, J = 7), 1.10 (3 H, t, J = 7)
5c	62	116–117	3020, 2930, 1645, 1585	7.45–6.68 (15 H, m), 5.52 (1 H, m), 3.66 (3 H, m), 3.04 (dd, J = 14, 2.5), 2.05 (3 H, s)
5d	60	82–84	3010, 2950, 1640, 1580	7.45–6.68 (15 H, m), 5.36 (1 H, m), 3.70 (3 H, m), 3.02 (dd, J = 2.5), 2.82 (1 H, m), 2.34 (1 H, m), 1.17 (3 H, t, J = 7.5)
5e	55	63–65	3020, 2940, 1640, 1575	7.54–7.12 (10 H, m), 5.19 (1 H, br s), 4.29 (1 H, d, J = 14), 3.95 (1 H, d, J = 14), 2.36 (1 H, m), 1.97 (3 H, s), 1.09 (3 H, d, J = 7), 1.04 (d, J = 7)

[a] No product was isolated from the ketone **4f**.

Table 3. Physical and Spectral Data for 3-Phenylsulfonyl-3-pyrrolines **6**

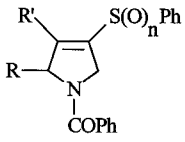
Compound	Yield (%)	mp (°C)	IR ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)
6a	94	129–131	3080, 3000, 1640, 1320	7.88–7.37 (10 H, m), 5.10 (1 H, m), 4.63 (1 H, m), 4.20 (1 H, d, J = 14), 2.19 (3 H, s), 1.49 (3 H, d, J = 6.5)
6b	97	106–108	2980, 2940, 1640, 1420, 1320	7.60–7.05 (10 H, m), 5.13 (1 H, m), 4.35 (2 H, m), 3.05 (1 H, m), 2.25 (1 H, m), 1.40 (3 H, d, J = 7), 1.10 (3 H, t, J = 7)
6c	91	126–128	3020, 2930, 1645, 1585, 1310	7.75–6.95 (15 H, m), 5.38 (1 H, br s), 4.06 (1 H, d, J = 14), 3.52 (2 H, m), 2.97 (1 H, dd, J = 14, 2), 2.31 (3 H, s)
6d	89	103–105	3010, 2950, 1640, 1580, 1320	7.75–6.95 (15 H, m), 5.56 (1 H, br s), 4.08 (1 H, d, J = 14), 3.45 (3 H, m), 2.94 (1 H, dd, J = 14, 2), 2.29 (1 H, m), 1.23 (3 H, t, J = 7.5)
6e	87	115–117	3020, 2940, 1640, 1575, 1310	7.85–7.39 (10 H, m), 5.20 (1 H, br s), 4.54 (1 H, m), 4.25 (1 H, d, J = 14), 2.47 (1 H, m), 1.0 (3 H, d, J = 7), 0.84 (3 H, d, J = 7)

Table 4. Physical and Spectral Data for Pyrroles **8**

Compound	Yield (%)	mp (°C)	IR ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)
8a	65	139–140	3040, 2920, 1620, 1450	7.93 (2 H, m), 7.51 (3 H, m), 7.31 (4 H, m), 7.03 (2 H, m), 5.01 (2 H, s), 2.02 (3 H, s), 1.97 (3 H, s)
8b	56	116–117	3060, 2980, 1630, 1455	7.93 (2 H, m), 7.50 (3 H, m), 7.34 (4 H, m), 7.03 (2 H, m), 5.02 (2 H, s), 2.49 (2 H, q, J = 7.5), 1.99 (3 H, s), 0.85 (3 H, t, J = 7.5)
8c	54	128–129	3020, 2910, 1510, 1305	7.96 (2 H, m), 7.54 (3 H, m), 7.29 (7 H, m), 6.95 (4 H, m), 4.81 (2 H, s), 3.75 (2 H, s), 2.13 (3 H, s)
8d	42	85–86	3060, 2980, 1500, 1305	7.96 (2 H, m), 7.54 (3 H, m), 7.28 (7 H, m), 6.95 (4 H, m), 4.77 (2 H, s), 3.78 (2 H, s), 2.56 (2 H, q, J = 7.5), 0.88 (3 H, t, J = 7.5)
8e	45	120–121	3050, 2980, 1510, 1150	7.95 (2 H, m), 7.53 (3 H, m), 7.35 (4 H, m), 7.01 (2 H, m), 4.90 (2 H, s), 2.82 (1 H, m), 2.05 (3 H, s), 1.12 (6 H, d, J = 7)

Padwa has described[16] an approach to pyrroles in which 1-alkyl-3-phenylsulfonyl-3-pyrrolines were aromatised with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). We therefore chose to oxidise our 3-phenylthio-3-pyrrolines **5a–e** to the corresponding sulfones **6a–e** (Table 3) with *m*-chloroperbenzoic acid (*m*-CPBA) in order to apply the chemistry developed by Padwa. Treatment of the sulfones **6a–e** with DDQ in refluxing benzene gave the corresponding pyrroles **7a–e**, but only in the case of **7a** was the yield of the product acceptable (67%). In all other cases complex mixtures resulted and isolation of the pyrrole was difficult. Suspecting that the problem might lie in the fact that the *N*-acyl-3-pyrrolines **6** could be less easy to oxidise than the corresponding *N*-alkyl compounds, we subjected the *N*-benzoyl-3-pyrrolines **6a–e** to reduction with borane–dimethyl sulfide to afford the corresponding *N*-benzyl derivatives, which, without purification, were subjected to DDQ oxidation to give the desired pyrroles **8a–e** in 45–65% yield over the two steps (Table 4). Other methods of aromatisation of the 3-pyrrolines **6** were also investigated: refluxing with palladium on charcoal, in a range of solvents, gave only

recovered starting material, whereas treatment with *N*-bromosuccinimide (1 equiv) gave a mixture whose ^{1}H NMR and mass spectra suggested the presence of mono-, di- and tribrominated compounds. Consequently base-catalysed dehydrobromination was not attempted.



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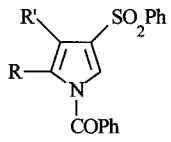
6, n = 2



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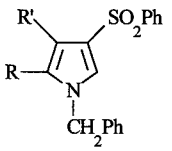

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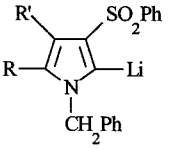

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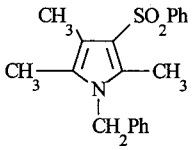

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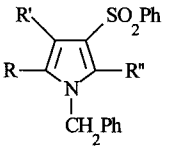

11

(a); R = R' = CH_3
(b); R = CH_3, R' = CH_2CH_3
(c); R = CH_2Ph, R' = CH_3
(d); R = CH_2Ph, R' = CH_2CH_3
(e); R = $CH(CH_3)_2$, R' = CH_3
(f); R = CH_2Ph, R' = Ph

The unsubstituted 5-position in the pyrroles **8** should be open to substitution via the *o*-sulfonyl stabilised lithio derivative **9**. We have demonstrated this with the pyrrole **8a** where metallation with *s*-BuLi followed by quenching with MeI gave the trimethylpyrrole **10** (58%). It is clear from work on closely related compounds that a range of electrophiles can be used in such reactions.[16]

Overall, this novel synthesis allows the production of pyrroles **11** with considerable flexibility in the substituents. The group R is derived from the α-amino acid, R' from the anhydride used in the Dakin–West reaction (or from an organometallic reagent if the Rapoport procedure is used[13]) and R'' from the metallation procedure.

THF was distilled from potassium metal and MeCN was distilled from 4 Å molecular sieves. Flash chromatography was carried out with Merck 7734 silica gel and solvents were distilled prior to use. Petrol refers to 40–60 °C petroleum spirit. IR spectra were recorded as KBr discs or liquid films on a Pye-Unicam SP3-100 spectrophotometer and ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AC250 instrument. Chemical shift values are relative to tetramethylsilane.

Compounds **5a–e**, **6a–e**, **7a**, **8a–e** and **9** gave C,H,N analysis ± 0.4%.

α-Benzamido Ketones 4; General Procedure:
The appropriate *N*-benzoyl-α-amino acid (20 mmol) and anhydride (42 mmol) were stirred with Et_3N (4 mL, 29 mmol) and DMAP (0.1 g, 0.82 mmol) at 60 °C for 30 min, or until carbon dioxide evolution had ceased. Glacial AcOH (30 mL) was added and stirring was continued for 30 min. The mixture was concentrated under reduced pressure, shaken with excess 2 M aq NaOH and extracted several times with Et_2O. The combined ether layers were washed with 2 M aq HCl and water, dried ($MgSO_4$) and evaporated to give the product.

3-Phenylthio-3-pyrrolines 5; General Procedure:
To a stirred mixture of the α-benzamido ketone **4** (10 mmol) and 1-(phenylthio)vinyltriphenylphosphonium iodide **(1)** (12 mmol) in dry MeCN–THF (4:1) (100 mL), under N_2 at 0 °C, was added sodium hydride (60% dispersion, 11 mmol) in small portions. Once the effervescence had ceased, the reaction mixture was warmed to r.t. and stirred for 2 h. The mixture was poured into water (100 mL) and extracted several times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (EtOAc–petrol, 3:7).

3-Phenylsulfonyl-3-pyrrolines 6; General Procedure:
To a stirred solution of the 3-phenylthiopyrroline **5** (1 mmol) in dry THF (10 mL) at −78 °C was added *m*-CPBA (2.5 mmol). The mixture was allowed to warm to r.t. stirred for a further 6 h, poured into water (50 mL), and extracted several times with EtOAc. The combined organic layers were washed with sat. aq $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated to give the crude product. Analytical samples were obtained by recrystallisation from EtOH.

3-Phenylsulfonylpyrroles 8; General Procedure:
To a stirred solution of the 3-phenylsulfonyl-3-pyrroline **6** (10 mmol) in dry THF (50 mL), under N_2 at 0 °C, was added borane–dimethyl sulfide complex (2 mL, 10 M, 20 mmol). The mixture was stirred at r.t. for 6 h, poured into water (100 mL) and extracted several times with EtOAc. The combined organic layers were washed with sat. aq $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. The residue was taken up in benzene (50 mL), and stirred vigorously while DDQ (2.5 g, 11 mmol) was added in one portion. After stirring at r.t. for 3 h the mixture was poured into sat. aq $NaHCO_3$. The layers were separated and the aqueous layer was extracted several times with EtOAc. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc–petrol, 1:4).

***N*-Benzoyl-2,3-dimethyl-4-phenylsulfonylpyrrole (7a):**
Prepared from the 3-phenylsulfonyl-3-pyrroline **6a** and DDQ (1.2 equiv) in benzene as described above (67%), mp 46–48 °C.
IR: ν = 3010, 2980, 1640 cm^{-1}.
^{1}H NMR: δ = 7.75–7.20 (11 H, m), 2.45 (3 H, s), 2.10 (3 H, s).

***N*-Benzyl-2,3,5-trimethyl-4-phenylsulfonylpyrrole (9):**
To a stirred solution of *N*-benzyl-2,3-dimethyl-4-phenylsulfonylpyrrole **(8a)** (100 mg, 0.3 mmol) in dry THF (5 mL), under N_2 at −78 °C, was added *s*-BuLi (0.28 mL, 1.3 M, 0.36 mmol). The mixture was stirred at −78 °C for 1 h and then quenched with MeI (1 mL). The reaction mixture was poured into 2 M aq NaOH (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (EtOAc–petrol, 1:4) to give the product as a white solid (60 mg, 58%), mp 130–131 °C.
^{1}H NMR: δ = 7.90–6.55 (10 H, m), 4.85 (2 H, s), 2.45 (3 H, s), 2.10 (3 H, s), 1.95 (3 H, s).

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