A Facile Total Synthesis of Isoquinolone Alkaloids

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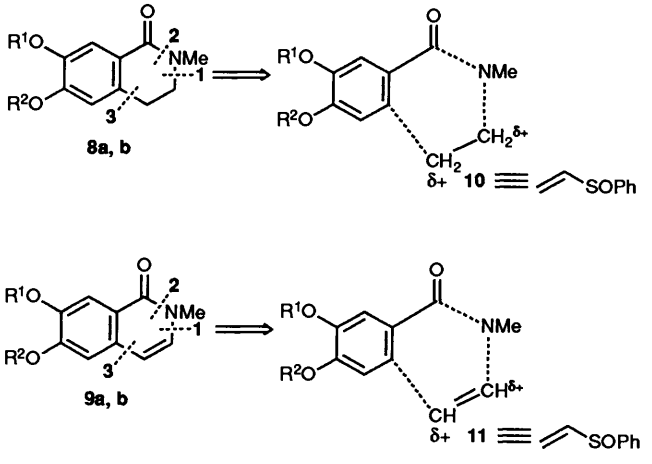
Four isoquinolone alkaloids, *N*-methylcorydaldine **8a**, oxyhydrastinine **8b**, 6,7-dimethoxy-2-methylisocarbostyril **9a** and doryanine **9b**, have been efficiently synthesized from phenyl vinyl sulfoxide *via* the Pummerer type rearrangement as a key step.

Sulfoxide functionality has been used extensively in many areas of organic synthesis;[1] for example, the ability of sulfoxide in activating a conjugated olefin or acetylene as a Michael acceptor[2] and dienophile[3] had been demonstrated. To follow our interest in using unsaturated sulfoxides in organic synthesis,[2d,3c] we now report the use of vinyl sulfoxide as a 1,2-dielectrophilic two-carbon synthon in a highly efficient synthesis of isoquinolone alkaloids.[4]

Isoquinolone alkaloids are a group of naturally occurring alkaloids mainly isolated from *Hernandiaceae* and *Ranunculaceae*. They can be subdivided into two categories: those with a total aromatic nucleus such as 6,7-dimethoxy-2-methylisocarbostyril **9a**,[5] doryanine **9b**,[6] and those which incorporate a C-3, 4-single bond included *N*-methylcorydaldine **8a**[7] and oxyhydrastine **8b**. Our synthesis started from *N*-methyl-2-(phenylsulfinyl)ethylamine **2** which was prepared by Michael addition of methylamine to phenyl vinyl sulfoxide **1** (Scheme 1). Amine **2**



Scheme 1 *Reagents and conditions:* i, DCC, dichloromethane or methanol; ii, acetic anhydride, reflux; iii, TFA, acetic anhydride, toluene, reflux; iv, TCA, benzene, reflux; v, *p*-TSA, toluene, reflux, vi, Raney nickel, ethanol

was then coupled with substituted benzoic acids **3a** and **3b** using dicyclohexylcarbodiimide (DCC)[8] to afford the corresponding amides **4a** and **4b** respectively in good yield. The next step required the activation of the sulfoxide group by Pummerer rearrangement.[9] The aromatic moiety of **4** was available for internal trapping of the presumed sulfenium ion **5** of the Pummerer reaction to furnish the cyclized product. However, direct ring closure of **4** to **7** *via* Pummerer rearrangement resulted in only limited amounts of the expected product (Table 1 entry 1). Therefore a two-step approach was adopted. Firstly, Pummerer rearrangement of **4** in refluxing acetic anhydride yielded acetoxy sulfide **6** in almost quantitative yield. Subsequently, various acidic conditions were explored to effect the ring closure reaction. As shown in Table 1, treatment of **6** with toluene-*p*-sulfonic acid (TSA) in refluxing toluene (entries 3 and 5) not only effected the cyclization, but the cyclized product **7** was further eliminated to yield the completely aromatic series (*i.e.* **9a** and **9b**) of the isoquinolone alkaloids. This represented a facile convergent route for the total synthesis of 6,7-dimethoxy-2-methylisocarbostyril **9a** and doryanine **9b** in a three step reaction sequence starting from **2** in overall isolated yields of 70 and 47% respectively. The spectroscopic data of the products were identical with those reported in the literature.[5,6]

In contrast, the synthesis of C-3, 4-single bond isoquinolones **8a** and **8b** required a more elaborate route. Various attempts to prepare **7** exclusively without contamination of the further eliminated products **9** were not successful. The best conditions for the preparation of **7** from **6** were accomplished in refluxing benzene with trichloroacetic acid (TCA) as catalyst (entries 2 and 4). Apparently, with weaker acid catalyst and lower reaction temperature, the sulfides **7** emerged as the major products.† Desulfurisation of **7** with Raney nickel gave the desired major product **8**. However, the completely aromatic products **9** were also afforded. The crude reduction products could be easily separated on flash column chromatography (silica gel) yielding *N*-methylcorydaldine **8a**[7] and oxyhydrastinine **8b**[10] in 49 and 54% yields respectively.

In conclusion, the heterocyclic ring system of the isoquinolones was efficiently constructed by sequential bond formation (*i.e.* bonds 1 to 3) as illustrated in Scheme 2. From a retrosynthetic consideration, vinyl sulfoxide acted as a vinyl 1,2-dielectrophilic two-carbon synthon **10** for the synthesis of the totally aromatic isoquinolones. For the C-3, 4-single bond series, vinyl sulfoxide could be seen as an alkyl 1,2-dielectrophilic two-carbon synthon **11**. The use of unsaturated sulfoxide as a dielectrophilic two-carbon synthon in the synthesis of other heterocycles is now being actively pursued.

Experimental

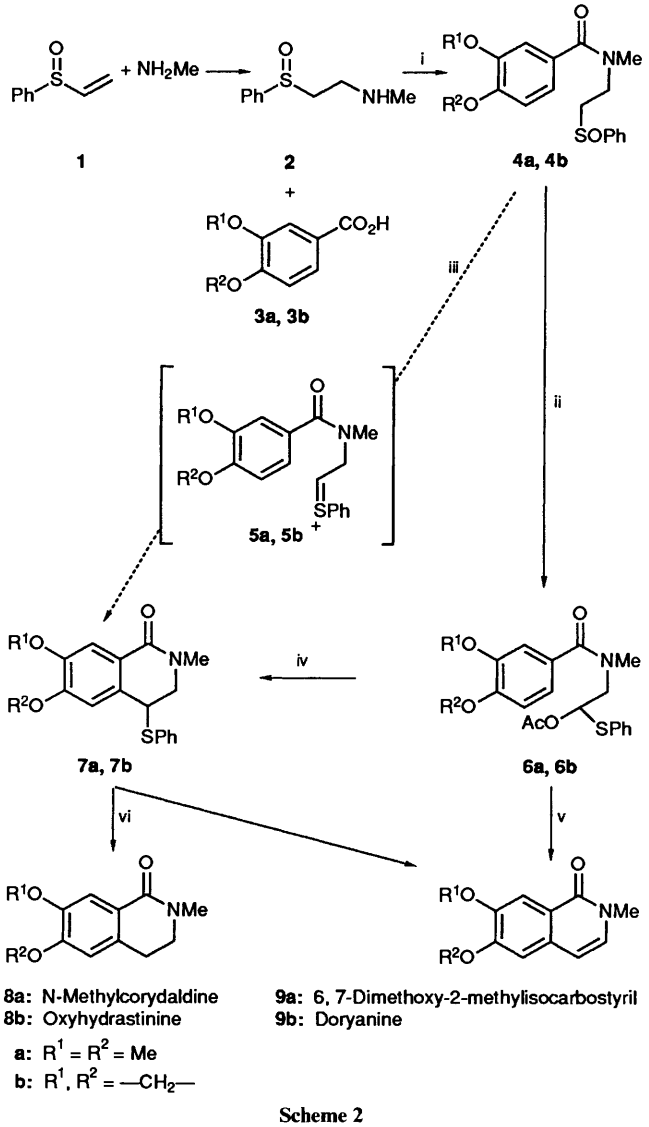
Formation of **6** *by the Pummerer Rearrangement.*—A mixture of sulfoxide **4a** (233 mg, 0.67 mmol) and acetic anhydride (8 cm^3) was refluxed under a nitrogen atmosphere for 6.5 h. After cooling, the acetic anhydride was removed under reduced pressure. Chromatography of the organic residue on a flash column (silica gel: 50% ethyl acetate in light petroleum) afforded the Pummerer product **6a** as a colourless liquid (220 mg, 84%); ν_{max}(neat)/cm^{-1} 1632 and 1744; δ_H(60 MHz; $CDCl_3$) 2.07 (3 H, s), 3.03 (3 H, s), 3.70 (2 H, m), 3.87–3.90 (total 6 H, br s), 6.33 (1 H, t, *J* 7.0), 6.87 (3 H, m) and 7.27 (5 H, m); *m/z* 389.1293 (Calc. for $C_{20}H_{23}NO_5S$: *M*, 389.1297).

Typical Procedure for the Cyclization **6** *to* **9**.—A mixture of

† *Selected spectral data.* For **7a** ν_{max}(neat)/cm^{-1} 1644; δ_H(60 MHz; $CDCl_3$) 3.08 (3 H, s), 3.73–4.01 (total 2 H, m), 3.73–3.87 (total 6 H, br s), 4.30 (1 H, t, *J* 3.5), 6.45 (1 H, s), 7.22 (5 H, m) and 7.47 (1 H, s); *m/z* 329.1078 (Calc. for $C_{18}H_{19}NO_3S$: *M*, 329.1086).

Table 1 Attempted ring closure in the synthesis of isoquinolones

Compound	Entry	Reactant (conc.)	Solvent	Conditions	Duration (t/min)	Product(s) [Yield (%)]
4a	1	TFA, AC_2O (0.01, 0.1 ml/ml)	toluene	reflux	25	**7a** (10%)
6a	2	TCA (0.243 g/ml)	benzene	reflux	42	**7a**/**9a** (48/14%)
	3	TSA (0.320 g/ml)	toluene	reflux	40	**9a** (93%)
6b	4	TCA (0.180 g/ml)	benzene	reflux	51	**7b**/**9b** (41/24%)
	5	TSA (0.192 g/ml)	toluene	reflux	28	**9b** (75%)



Scheme 2

the Pummerer product **6a** (144 mg, 0.37 mmol) and toluene-*p*-sulfonic acid monohydrate (1.28 g, 6.74 mmol) in toluene (4 cm^3) was refluxed for 40 min. After cooling to room temperature, the reaction mixture was basified with saturated aqueous sodium carbonate. The resulting solution was extracted with dichloromethane (3 × 30 cm^3) and the combined organic extracts were dried, filtered and evaporated under reduced pressure. Chromatography of the organic residue on a flash column (silica gel; 60% ethyl acetate in light petroleum) gave 6,7-dimethoxy-2-methylisocarbostyril **9a** as a colourless solid (75.4 mg, 93%). The melting point and spectroscopic properties agreed with those reported in the literature.[5]

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