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New Synthesis of Sultams *via* readily generated Iminium Ions

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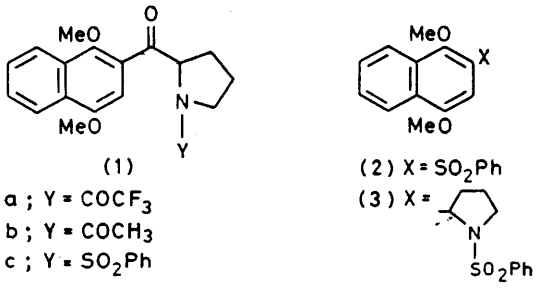
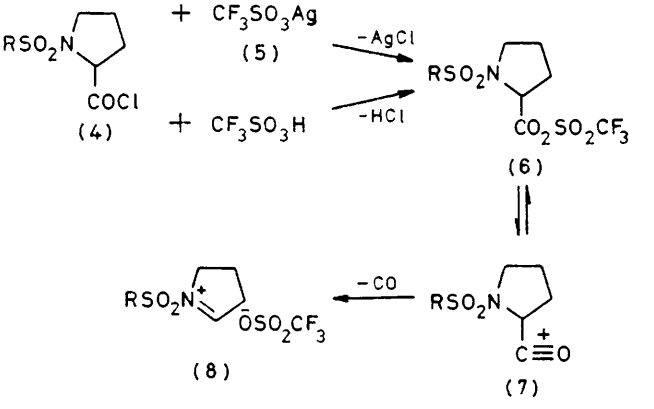
Summary *N*-Arylsulphonylpropyl chlorides (**4**) react instantaneously with silver trifluoromethanesulphonate (**5**) at room temperature to give the iminium salts (**8**), which have provided convenient routes to the sultams 9,10,11,-11a-tetrahydronaphtho[1,8-*de*]pyrrolo[1,2-*b*]thiazine 7,7-dioxide (**9**) and 2,3-dihydro-1*H*-pyrrolo[1,2-*b*][1,2,4]-benzothiadiazine 5,5-dioxide (**11**).

The most successful previous methods for preparing iminium salts were recently reported to include (a) condensation of a carbonyl and a secondary amine, (b) addition to amides, and (c) oxidation of a tertiary amine,[1] and a new method was reported[1] involving heating acid chlorides of α-tertiary amino acids. We now report an alternative method for preparing iminium salts.

Under the conditions under which *N*-acetyl- or *N*-trifluoroacetyl-prolyl chloride acylated 1,4-dimethoxynaphthalene in the presence of silver trifluoromethanesulphonate to give the ketones (**1a**) and (**1b**) in high yields, *N*-phenylsulphonylprolyl chloride gave a sulphone (**2**) and a sulphonamide (**3**) rather than the expected ketone (**1c**); this anomalous reaction was shown to proceed *via* an iminium ion.[2] We have now found that the prolyl chlorides (**4a**—**g**) reacted instantaneously at room temperature with silver trifluoromethanesulphonate (**5**) to give the iminium salts (**8**). Trifluoromethanesulphonic acid but not silver acetate or nitrate led to similar results, suggesting that the reaction proceeds through a mixed anhydride intermediate (Scheme) parallel to that proposed by Effenberger and Epple.[3]



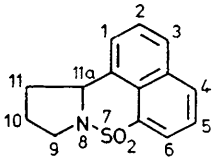


Scheme

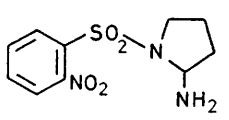
a; R = Ph
b; R = Me
c; R = *p*-MeC_6H_4
d; R = *o*-$O_2NC_6H_4$
e; R = $PhCH_2$
f; R = 2-Cl,5-$O_2NC_6H_3$
g; R = α-naphthyl

We have used the iminium ions (**8g**) and (**8d**) to prepare the *SS*-dioxides (**9**) and (**11**). The chloride (**4g**) was readily converted into the iminium ion (**8g**) which when refluxed in carbon tetrachloride for 18 h gave a brown solid (60% yield), m.p. 130—132 °C, shown to be the expected sultam (**9**);† M^+ *m/e* 259, δ ($CDCl_3$) 2·1 (4H, m, 10- and 11-H_2), 3·2 (2H, m, 9-H_2), 4·4 (1H, t, 11a-H), and 7·3—8·8

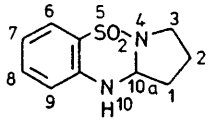
† Satisfactory elemental analyses were obtained.



(9)



(10)



(11)

(6H, ArH). The sultam (**11**) was synthesised as follows: the nitro-compound (**4d**) was converted into the iminium salt (**8d**) and concentrated aqueous ammonia added. After 30 min at room temperature, chromatography on silica gel gave the required amine (**10**) as a thick oil in 40% yield: M^+ *m/e* 271; δ ($CDCl_3$) 2·1 (4H, m, 1-, and 2-H_2), 3·6 (2H, m, 3-H_2), 4·4 (1H, t, 10-H), 6·4 (2H, disappears with D_2O, NH_2), and 7·6—8·2 (4H, Ar-H); ν_{max} (film) 3480, 3380 (NH_2), 1540, 850 (NO_2), 1350, and 1150 cm^{-1} (SO_2N). Reductive cyclisation of (**10**) by heating with iron in acetic acid[4] for 8 h gave (**11**),† m.p. 190—192 °C, M^+ *m/e* 224, the i.r. spectrum of which is similar to those of the drugs hydrothiazide and hydroflumethiazide,[5] both of which have the same dihydro-benzothiadiazine nucleus. Further support for structure (**11**) comes from the n.m.r. spectrum: δ (CD_3SOCD_3) 2·1 (4H, m, 1- and 2-H_2), 3·4 (2H, m, 3-H_2), 4·5 (1H, t, 10a-H), 7·2—8·0 (4H, ArH), and 10·3 (1H, br s, NH).

Hydrothiadiazides are used as diuretic and hypotensive agents. This versatile and simple synthesis, which is expected to be applicable to most α-secondary amino-acids, therefore provides a convenient route to many of these drugs.

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