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Original and Quick Access to 4-Phenyl-6*H*-pyrrolo[1,2-*a*]thieno [3,2-*f*][1,4]diazepines

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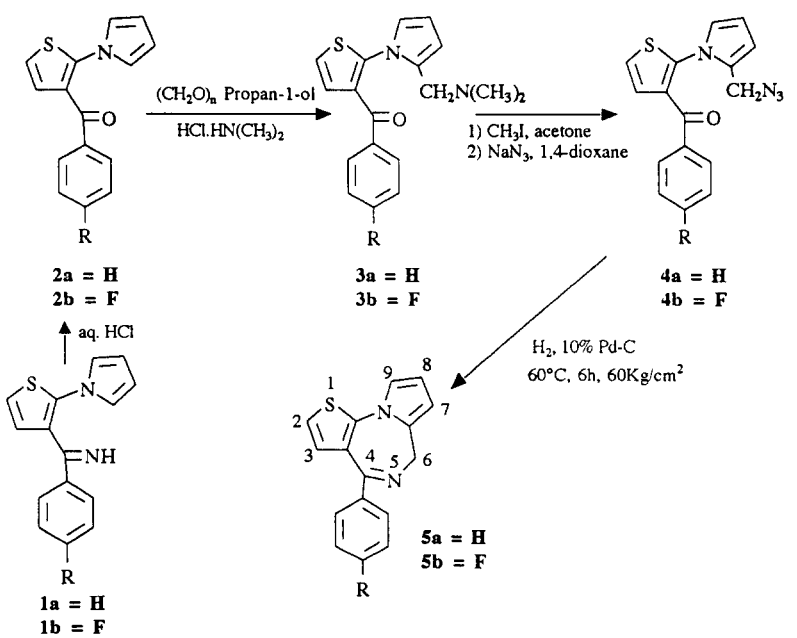
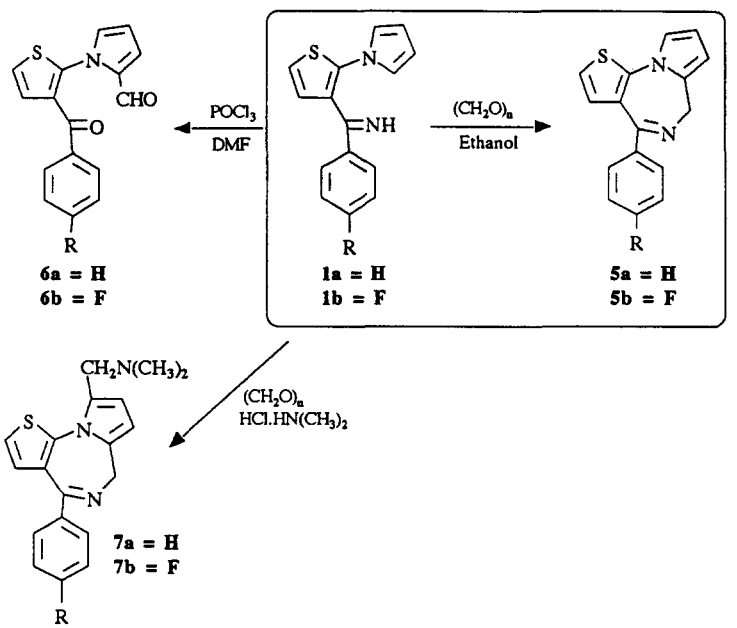
Key Words : phenyl-3-[2-(pyrrol-1-yl)thienyl]methylenimine; paraformaldehyde; pyrrolo[1,2-*a*]thieno [3,2-*f*][1,4]diazepines

Abstract : pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines were obtained in an original one step synthesis by treatment of phenyl-3-[2-(pyrrol-1-yl)thienyl]methylenimines with paraformaldehyde in refluxing ethanol.

In continuation of our work concerning the synthesis of new pyrrolobenzodiazepines,[1-4] we wish to describe here an original one step synthesis of title compounds.
First of all, we synthesized these compounds in 5 steps starting from phenyl-3-[2-(pyrrol-1-yl)thienyl] methylenimines[3] **1a** and **1b** (Scheme 1). These imines were respectively converted into ketones **2a** and **2b** in acidic conditions.[3] Treatment with paraformaldehyde and dimethylamine hydrochloride according to Mannich reaction gave the bases **3a** and **3b**. The quaternary salts were obtained by stirring the Mannich bases with an excess of methyl iodide in acetone at room temperature. The introduction of the azido group was accomplished by displacement of trimethylamine from the quaternary salts using sodium azide to give **4a** and **4b**. Reduction of these azido compounds with hydrogen in presence of 10% palladium-charcoal led directly to diazepines **5a**[5] and **5b** in 10% yield from **1**.



Scheme 1



Scheme 2

To shorter this sequence and to increase the overall yield we studied different routes to introduce directly the missing carbon of **1** to afford the diazepine ring. Starting with imines **1a** and **1b** we first studied the Vilsmeier-Haack reaction which gave aldehydes in the α position of the pyrrole ring but unfortunately led also to the hydrolysis of imines into ketones to give ketoaldehydes **6a** and **6b** (Scheme 2). Then after, all procedures failed to formed the diazepine ring from these compounds. We finally studied Mannich reactions with imines **1a** and **1b**. Treatment with paraformaldehyde and dimethylamine hydrochloride gave surprisingly the diazepines **7a** and **7b** dimethylaminomethylated on the α position of the pyrrole ring, probably as the result of two different reactions : a normal Mannich reaction and an abnormal cyclization. To turn to account this cyclization and to avoid the aminomethylation, we treated the imino compounds **1a** and **1b** with paraformaldehyde alone in refluxing ethanol. In accordance with our hypothesis, diazepines **5a** and **5b** were then isolated in 50% yield. On the other hand, ketones **2a** and **2b** were unreactive towards paraformaldehyde in the same conditions. This difference of reactivity could be explained by the fairly nucleophilic character of ketones **2** which possess an amide vinylog structure compared to the nucleophilic character of imines **1** with an amidine vinylog structure. So, in the case of **1** cyclization followed hydroxymethylation and in the case of **2** retroaldolization led to the starting material.

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5. **5a** : m.p;110°C.(diethyl ether / petroleum ether) ; IR (KBr) 3020, 1590, 1520, 1475, 1325, 1310, 1085, 955 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.55-7.35, m, 6H; 7.19, dd, 1H, H-9; 6.87, d, 1H,H-3; 6.35, t, 1H, H-7; 6.17, dd, 1H, H-8; 4.58, bs, 2H, H-6. ^{13}C NMR (200 MHz, DMSO-d_6) δ 164.04; 144.77; 139.04; 133.55; 129.99; 128.65; 128.06; 124.68; 119.60; 118.84; 111.95; 106.81; 48.00.

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