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Unexpected synthesis of (trifluoroethyl)pyrimidines from the heterocyclisation of α-trifluoroacetylpropanenitriles

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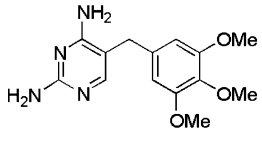
Abstract—Some 4-trifluoromethyl-2-aminopyrimidines analogous to trimethoprim and 5-trifluoroethyl-2,4-diaminopyrimidines analogous to pyrimethamine were prepared from enamino(trifluoromethyl)ketones and α-trifluoroacetylpropanenitriles, respectively. A novel heterocyclisation between a trifluoromethylated β-ketonitrile and guanidine was described.

1. Introduction

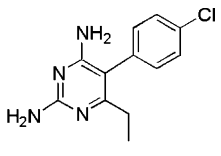
Heterocyclic compounds containing a CF_3 group continue to receive much attention from pharmaceutical communities.[1] Most of the syntheses of such compounds involve heterocyclisation using trifluoromethylated building blocks.[2] Along this route, trifluoromethylated β-enaminoketones are efficient and versatile synthons for the preparation of various nitrogen heterocycles.[3] In the pyrimidine series, we recently reported the preparation of some 4-trifluoromethylpyrimidines and of their derived nucleoside analogues.[4]

The present work was undertaken to apply the methodology to the synthesis of fluorinated aminopyrimidines analogous to trimethoprim (TMP).

Aminopyrimidines trimethoprim (TMP)[5] and pyrimethamine (PYR)[6] have become the reference drugs for prophylaxis and treatment of opportunistic infections due to *Pneumocystis carinii* and *Toxoplasma gondii*.



TMP



PYR

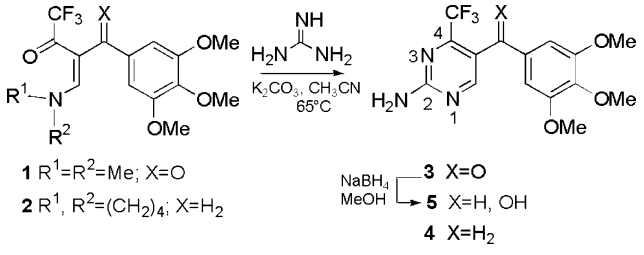
However these drugs are only effective in combination with sulfonamides and frequently induce severe side effects.[5–7] Therefore development of more potent derivatives remains an important goal.

2. Results and discussion

2.1. 2-Aminopyrimidines (Scheme 1)

Enaminoketones **1** and **2** were prepared by procedures described previously,[4] and then were reacted with guanidine hydrochloride to give pyrimidines **3** (65%)[8] and **4** (88%), respectively.

The bisaromatic ketone **3** was easily reduced to alcohol **5** (95%).



Scheme 1.

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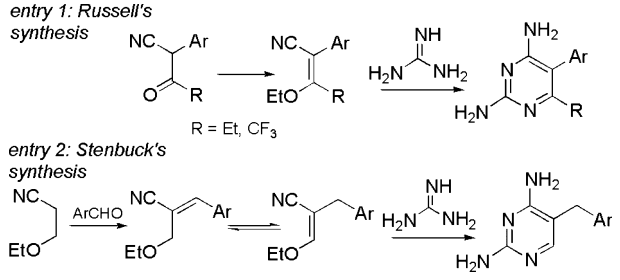
Anti-*Toxoplasma* activities of derivatives **3**, **4** and **5** were assessed in vitro using a tissue culture model combined with an immunoenzymatic assay for quantification of *Toxoplasma* growth; TMP was tested in parallel as a reference drug.[9] Ten concentrations were tested for each compound. Estimated IC_{50} for **3**, **4** and **5** were 28.9, 32.9, 44.2 μg/ml, respectively, versus 4.3 μg/ml for TMP. The inhibitory concentrations were close to those that were found to be cytopathic for tissue culture.

2.2. 2,4-Diaminopyrimidines

Further experiments were conducted in order to prepare compounds closely related to TMP. Therefore we turned to 5-benzyl-6-trifluoromethyl-2,4-diaminopyrimidines, for which, synthesis required other fluorinated intermediates.

A general method employed for the synthesis of 2,4-diaminopyrimidines consists of condensing enol ethers



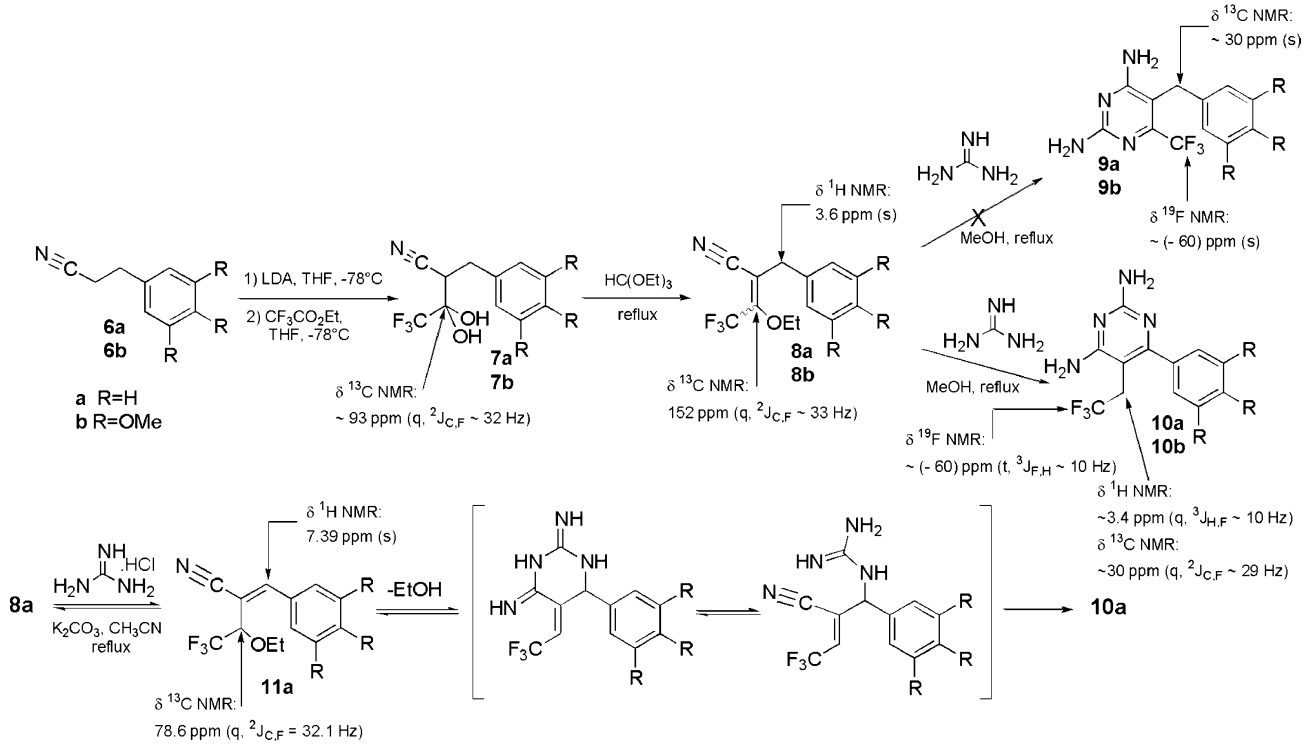
Scheme 2.

of β-ketonitriles with guanidine. In this context, Russell achieved the synthesis of PYR[10] in 1951 and other workers described later the preparation of some trifluoromethyl derivatives[11–13] (Scheme 2, entry 1). Similarly Stenbuck's industrial process for the preparation of TMP[14] involved an α-aryl-β-acrylonitrile which could be in tautomeric equilibrium with its enolic form (entry 2).

So, we envisaged to prepare compounds **9a**,**b** from the enol ethers **8a**,**b**. Claisen condensation of phenylpropionitriles **6a**,**b** (Scheme 3) with ethyl trifluoroacetate using LDA afforded β-ketonitriles[15] in their more stable hydrated forms **7a**,**b** as shown on the ^{13}C NMR spectra ($\delta \sim 93$ ppm instead of 180 ppm) (75 and 63% yields, respectively).

Attempt at catalysed acid condensation of **7a** and guanidine hydrochloride, modeled on the methods sometimes used in nonfluorinated series[16] was unsuccessful (reaction mixture unchanged). As in the above mentioned examples, it was necessary to activate **7a**,**b** as enol ethers. Treatment of **7a** and **7b** by triethyl orthoformate[12] easily gave the compounds **8a** (78%) and **8b** (88%), which were isolated as *Z*,*E* isomeric mixtures, and characterized on the basis of NMR and mass spectra.

Finally when **8a** was reacted with guanidine as free base,[17] a pyrimidine was obtained, whose structure was **10a** (78%) instead of the TMP analogue **9a**. Similarly **8b** was transformed to **10b** (56%). These compounds were fully characterized.



Scheme 3.

A complementary experience shed light on the mechanism of this unexpected reaction. Treating **8a** with guanidine hydrochloride in the presence of potassium carbonate at reflux did not allow heterocyclisation. Nevertheless, equilibration of the enol ether **10a** to the enenitrile **11a** occurred (ratio 50:50). The tautomer **11a** was isolated and characterized by its spectroscopic data (NMR and MS).

This result suggested that the phenylpyrimidines **10a** and **10b** presumably originate from a 1,4 Michael addition of guanidine on the tautomeric form **11**, followed by EtOH elimination, then cyclisation on the nitrile carbon as shown in Scheme 3.

Unfortunately, compounds **10a** and **10b**, which can be considered as 'inverted' PYR derivatives did not show any significant activity against *Toxoplasma gondii*. This novel type of heterocyclisation is currently under investigation.

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15. General procedure for the preparation of **7a**,**b**. A solution of **6a**,**b** in anhydrous THF was added to a solution of LDA (1.2 equiv. generated in situ) under a nitrogen atmosphere at −78°C. The mixture was stirred for 20 min, and CF_3CO_2Et (1.5 equiv.) was added at −78°C. After stirring for 3 h at −78°C, the reaction mixture was neutralized by aqueous solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The residue was then purified by flash chromatography to give **7a**,**b**.
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17. Typical experimental procedure. Preparation of **10a**,**b**. A solution of guanidine hydrochloride (6 equiv.) in anhydrous methanol (0.3 mL/mmol of guanidine hydrochloride) was added to a stirred solution of sodium methoxide (6 equiv.) prepared in situ in anhydrous methanol (0.3 mL/mmol of sodium methoxide) under an atmosphere of nitrogen at rt. The mixture was stirred for 5 min, filtered, and added to **8a**,**b** (1 equiv.). The reaction mixture was heated to reflux for 4 h, cooled at rt, concentrated in vacuo, and purified by flash chromatography to yield the title compounds. They were fully characterized with relevant spectroscopic data. Selected data: **10a**: EIMS m/z 268 (M^+, 100), 267 (91), 199 (M^+-CF_3, 92); HRMS calcd for $C_{12}H_{11}F_3N_4$: 268.0940. Found: 268.0936. δ_H (DMSO-d_6) 3.40 (q, $^3J_{H,F}=10.5$ Hz, 2H, CH_2), 6.09 (s, 2H, NH_2), 6.56 (s, 2H, NH_2), 7.23–7.49 (m, 5H, Ph-H); δ_C (DMSO-d_6) 29.8 (q, $^2J_{C,F}=29.1$ Hz, $\underline{C}H_2$-CF_3), 92.5 (C-5), 126.9 (q, $^1J_{C,F}=279.1$ Hz, CF_3), 128.3 (CH-ar), 139.9 (C-ar), 162.0 (C-2), 164.3 (C-4), 167.5 (C-6); δ_F (CD_3OD) −62.3 (t, $^3J_{F,H}=10.5$ Hz, 3F, CF_3-CH_2). **10b**: EIMS m/z 358 (M^+, 100), 357 (56), 137 (91); HRMS calcd for $C_{15}H_{17}F_3N_4O_3$: 358.1255. Found: 358.1253. δ_H (DMSO-d_6) 3.44 (q, $^3J_{H,F}=10.9$ Hz, 2H, CH_2), 3.71 (s, 3H, CH_3O), 3.78 (s, 6H, 2×CH_3O), 6.01 (s, 2H, NH_2), 6.51 (br s, 2H, NH_2), 6.59 (s, 2H, 2×H_o); δ_C (DMSO-d_6) 30.0 (q, $^2J_{C,F}=29.0$ Hz, $\underline{C}H_2$-CF_3), 56.1 (2×CH_3O), 60.3 (CH_3O), 92.5 (C-5), 105.7 (2×CH_o), 126.9 (q, $^1J_{C,F}=279.2$ Hz, CF_3), 135.5 (C-ar), 137.2 (C-ar), 152.6 (2×C-ar), 162.0 (C-2), 164.1 (C-4), 167.5 (C-6); δ_F (DMSO-d_6) −58.7 (t, $^3J_{F,H}=10.9$ Hz, 3F, CF_3-CH_2).