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A NEW FLUORINATION PROCEDURE. FLUORINATION OF 5,7-DIMETHYLPYRAZOLO[1,5-a]PYRIMIDINE

Thomas Novinson, Roland K. Robins, and Darrell E. O'Brien*
ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute
2727 Campus Drive, Irvine, California 92664

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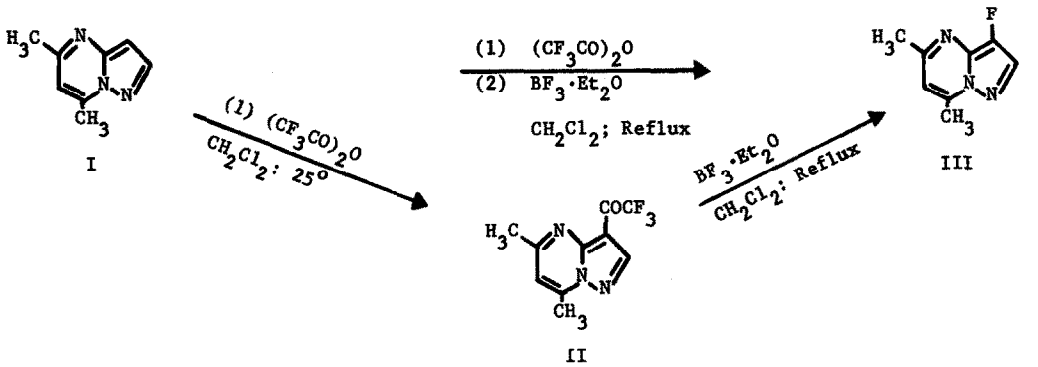
During the course of our investigation of the pyrazolo[1,5-a]pyrimidine ring system,[1] we discovered a novel fluorination reaction which proceeds under mild conditions.

In an attempt to apply the Friedel-Crafts type of acylation to 5,7-dimethylpyrazolo[1,5-a]-pyrimidine I,[2] we treated I with trifluoroacetic anhydride in methylene chloride with boron trifluoride-etherate as the catalyst. The solution was refluxed for 15 hours, followed by neutralization of the reaction mixture with 10% sodium hydroxide solution. Evaporation of the methylene chloride solution afforded 3-fluoro-5,7-dimethylpyrazolo[1,5-a]pyrimidine III as well as the expected 3-trifluoroacetyl derivative II.

3-Fluoro-5,7-dimethylpyrazolo[1,5-a]pyrimidine III was purified by column chromatography on basic alumina utilizing chloroform as the solvent, followed by recrystallization from heptane and had a melting point of 129-30°. Anal. Calcd for $C_8H_8N_3F$: C, 58.2; H, 4.88; N, 25.4; F, 11.5. Found: C, 58.2; H, 4.73; N, 25.5; F, 11.6. The nmr spectrum in $CDCl_3$ exhibited singlets at 2.55 δ (CH_3 at C_5), 2.60 δ (CH_3 at C_7), 6.60 δ (H at C_6), and 8.60 δ (H at C_2) which is essentially identical to the previously described 3-bromo-5,7-dimethylpyrazolo[1,5-a]pyrimidine.[1] The infra-red spectrum (KBr) did not exhibit carbonyl absorption, and the ultra violet spectrum (CH_3OH) exhibited λ_{max} at 232 nm (ε28,400), 280 nm (ε1,815), 292 nm (ε1,650) and 320 nm (ε1,320). The parent peak M^+ in the mass spectrum was 165 (molecular weight of III is 165.17).

In order to study the mechanism of this fluorination reaction, I was treated with trifluoroacetic anhydride in methylene chloride with (and without) boron trifluorodietherate at room temperature. Neutralization of the reaction mixture and evaporation of the methylene chloride solution afforded, in both instances, the expected 3-trifluoroacetyl-5,7-dimethylpyrazolo[1,5-a]pyrimidine II in 50% yields. This product was readily purified by recrystallization from ethanol to afford an analytically pure product that had a melting point of 157-8°. Anal.

Calcd for $C_{10}H_8N_3OF_3$: C, 49.4; H, 3.31; N, 17.3; F, 23.4. Found: C, 49.6; H, 3.26; N, 17.2; F, 23.3. Calcd molecular weight: 243.18. Found: 243. The infra-red spectrum (KBr) exhibited the expected carbonyl absorption (C=O) at 1700 cm^{-1}, and the ultra violet spectrum (CH_3OH) exhibited λ_{max} at 224 nm (ε30,500), 212 nm (ε5,346), and 317 nm (ε10,210) which is quite similar to 3-acetyl-5,7-dimethylpyrazolo[1,5-a]pyrimidine.[1]



I II III

A solution of 5,7-dimethyl-3-trifluoroacetyl pyrazolo[1,5-a]pyrimidine II and boron trifluoride etherate in refluxing methylene chloride affords after 16 hours 3-fluoro-5,7-dimethylpyrazolo[1,5-a]pyrimidine III in 10% yields. Thus, we suggest this fluorination proceeds via the introduction of the trifluoroacetyl group which is then displaced by fluoride ion to yield 5,7-dimethyl-3-fluoropyrazolo[1,5-a]pyrimidine III. To our knowledge this is the first reported example of direct displacement of the trifluoroacetyl group by fluoride ion and indeed the first instance of fluorination with trifluoroacetic anhydride and boron trifluoride etherate. The application of this procedure to the fluorination of other heterocyclic systems in under study.

References

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