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A Novel Access to 4-Fluoropyrimidines from α-Chloro-α'-Trifluoromethylketones

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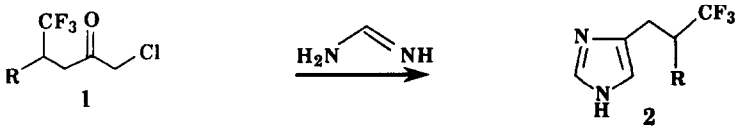
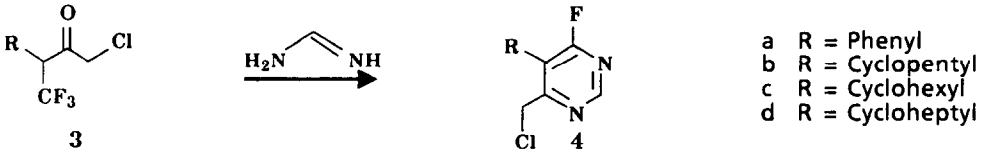
Abstract : *When treated with formamidine acetate and KOH, α-chloro-α'-trifluoromethyl ketones afford, though in moderate yield, 4-fluoropyrimidine derivatives.*

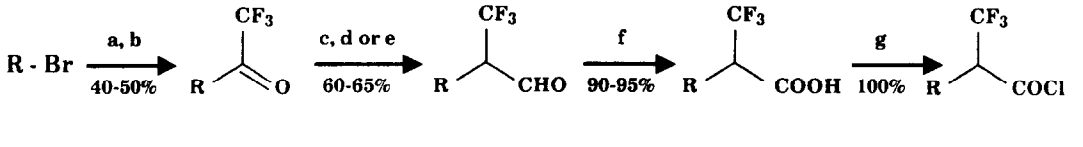
During the course of our investigations in the field of adrenergic antagonists [1], we were confronted with the preparation of 4-substituted imidazoles **2**, routinely obtained by cyclisation of α-chloro-β'-trifluoromethyl ketones **1** with formamidine[2].



We report herein that, when α-chloro-α'-trifluoromethyl ketones **3** are used, a novel cyclisation occurs in which two fluorine atoms of the CF_3 group are displaced to afford 5-substituted 4-fluoro-6-chloromethyl pyrimidines **4** in 23-35% yield [3].



The preparation of ketones **3**, using standard procedures, is described below [4].



Reagents : (a) Mg, Et_2O ; (b) CF_3COONa, THF, 0° ; (c) $Ph_3P^+CH_2OCH_3Cl^-$, LDA, THF, 0° then r.t. ; (d) aq. H_2SO_4, r.t. : (e) $(CH_3)_3S^+I^-$, NaH, DMSO ; (f) $KMnO_4$, aq. H_2SO_4, acetone, 0° ; (g) $SOCl_2$, reflux ; (h) diazomethane, Et_2O, 0° CAUTION, toxic explosive ; (i) gas. HCl, Et_2O, 0°.

The chloroketones **3** (0.03 moles), when treated with an excess of formamidine acetate (0.075 moles) and KOH (0.075 moles) in refluxing chloroform (500 ml), gave after 20-30 hours a red-brown mixture. Acidic washings and purification on silica gel (CH_2Cl_2) afforded pure 5-

substituted 4-fluoro-6-chloromethyl pyrimidines **4** as the major isolated products, the structures of which have been supported by IR, high field ^1H NMR, elemental analysis and mass spectroscopy[5]. No imidazolic compound was detected and the remaining mixture could not be extracted by conventional methods[6].

This new sequence allows a convenient approach to 4-fluoro pyrimidine intermediates, ready for modification at position 6[7]. Further studies seem to be necessary to improve the yields and clarify the mechanism of the reaction[8].

Efforts currently underway in our laboratories include these studies as well as the application of this new method to the synthesis of different pyrimidine pharmaceuticals.

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Notes and References

1. Malen, C. ; de Nanteuil, G. ; Colpaert, F.C. French Patent. Adir, n° 90.14086.
2. Overberger, C.G. ; Shen, C.M. J. Am. Chem. Soc., 1971, 93, 6992-6998.
3. R groups were chosen for structure-activity considerations and were limited to phenyl and several cycloalkyl groups.
4. All compounds gave satisfactory IR and ^1H NMR analyses. Moreover, all new compounds gave satisfactory elemental analyses, and were determined to be pure by tlc or hplc.
5. 4a : R = phenyl ; yield = 23% ; liq. (Eb_{20} 180°C); ^1H NMR ($CDCl_3$, ppm) : 8.95 (s, 1H) ; 7.55 (m, 3H) ; 7.4 (m, 2H) ; 4.5 (s, 2H). ^{19}F NMR ($CDCl_3$, ppm / $CFCl_3$ ext.) : - 59.6(s)
   4b : R = cyclopentyl ; yield = 33% ; mp = 46-48°C ; ^1H NMR (CDCl3, ppm) : 8.7 (d, 1H) ; 4.65 (s, 2H) ; 3.4-3.15 (m, 1H); 2.15-1.65 (m,8H). ^{19}F NMR ($CDCl_3$, ppm / $CFCl_3$ ext.) : - 58.8 (s). Mass spectroscopy : DCI (NH_3) : m/Z : 215 ; Ei (70 eV) : calc : 214,06730 ; found : 214,0669 ; M ± 214 - fragmentations at 179, 172, 137, 112, 68.
   4c : R = cyclohexyl ; yield = 26% ; mp = 62-66°C ; ^1H NMR ($CDCl_3$, ppm) : 8.7 (d, 1H) ; 4.65 (s, 2H) ; 2.85 (m, 1H) ; 2.0-1.2 (m, 10H). ^{19}F NMR ($CDCl_3$, ppm / $CFCl_3$ ext.) : - 58.6 (s).
   4d : R = cycloheptyl ; yield = 35% ; liq. (Eb_1 150°C); ^1H NMR ($CDCl_3$, ppm) : 8.65 (s, 1H) ; 4.65 (s, 2H) ; 3,0 (m, 1H) ; 2.1-1.4 (m, 12H). ^{19}F NMR ($CDCl_3$, ppm / $CFCl_3$ ext.) : - 58.8 (s).
6. When EtONa is used instead of KOH, the third fluorine atom of **4** is displaced as expected to give 4-ethoxy-5-phenyl-6-chloromethyl pyrimidine ; mp = 39-41°C.
   ^1H NMR ($CDCl_3$, ppm) : 8.8 (s, 1H) ; 7.3-7.5 (m, 5H) ; 4.45 (q, 2H) ; 4.35 (s, 2H) ; 1.25 (t, 3H).
7. When treated with 2 eq. of 1-methylpiperazine, compound 4c afforded 4-fluoro-5-cyclohexyl-6-[(4-methylpiperazin-1-yl)methyl]-pyrimidine ; mp = 30-32°C.
   ^1H NMR ($CDCl_3$, ppm) : 8,65 (d, 1H) ; 3.65 (s, 2H) ; 3,0 (m, 1H) ; 2.6-2.3 (m, 8H); 2.25(s, 3H); 2.0-1.2 (M, 10H)
8. This mechanism could involve β-elimination of fluoride, followed by Michael addition of formamidine and cyclisation. Alternatively for cyclisations by nucleophilic displacement of the fluorines of a trifluoromethyl group, see : Strekowski, L.; Wydra, R.L.; Cegla, M.T.; Czarny, A.; Harden, D.B.; Patterson, S.E.; Battiste M.A.; Coxon, J.M. J. Org. Chem., 1990, 55, 4777-4779 ; Ishihara, T.; Okada, Y.; Kuroboshi, M.; Shinozaki, T.; Ando, T. Chem. Letters, 1988, 819-822, and references cited herein.

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