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Unexpected reaction of 2,2-dihydropolyfluoroalkylaldehydes with ammonia and aldehydes or ketones: a novel synthetic method for 4-fluoroalkyl-1,2-dihydropyrimidine

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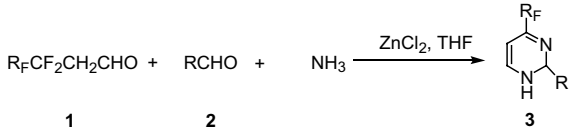
Abstract—4-Fluoroalkyl-1,2-dihydropyrimidines were synthesized in good yields by the tri-component reaction of 2,2-dihydropolyfluoroalkylaldehydes, ammonia and aldehydes, ketones or enol ethers in the presence of zinc chloride under mild conditions.

1. Introduction

It is known that Mannich reaction usually takes place among the tri-component system of aldehydes, ketones and amines. Since its discovery various kinds of substrates and conditions have been studied for more efficient and practical synthetic methods and many of them have widely been used in both research and industry fields.[1] 2,2-Dihydropolyfluoroalkylaldehyde (**1**) is one kind of important fluorine-containing aldehyde and its application in the synthesis of organofluorine compounds has been extensively studied.[2] In the course of our studies on the Mannich reaction of **1** with aldehydes and ammonia, to our surprise, we found that no Mannich-type products only 4-fluoroalkyl-1,2-dihydropyrimidines **(3)** were obtained. 1,2-Dihydropyrimidines are useful intermediates for the synthesis of various biological interest compounds,[3] which were usually obtained by the reaction of diimines with Schiff bases, aldehydes, acetals and ketals.[4] However, fluorinated 1,2-dihydropyrimidine derivatives, which might have potential biological activities by the introduction of fluorine atom or fluorinated group were less reported.[5] Further studies on the reaction showed that the yields of **3** were greatly increased by the addition of zinc chloride (Scheme 1).



R_F = **a**, CF_3; **b**, C_3F_7; **c**, C_3F_6Cl R = **m**, CH_3; **n**, *n*-C_3H_7; **o**, *iso*-C_3H_7

Scheme 1. The reaction of **1** with ammonia and aldehydes.

The reaction took place readily in the presence of zinc chloride under mild conditions. A solution of **1** in THF was first allowed to react with ammonia in the presence of zinc chloride at room temperature for 2 h, then aldehyde was added and the mixture was stirred at 50–60 °C under ammonia atmosphere for a few hours. After simple workup as described in the experimental section, **3** was obtained in good yields. The results are listed in Table 1. The structures of compound **3** were characterized by their NMR, IR and MS spectra, elemental analyses and further confirmed by single crystal X-ray crystallography of compound **3bm** (Fig. 1).[6]

Under similar conditions, ketones and enol ethers could also react with **1** and ammonia to give the corresponding 4-fluoroalkyl-1,2-dihydropyrimidines (Scheme 2). In the case of enol ethers, MeCN was used as solvent instead of

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Table 1. The reaction of **1** with ammonia and aldehydes, ketones or enol ethers

Entry	Reactant (**1**)	Reactant (**2**)	Condition	Product (**3**)	Yield[a] (%)
1	**1a**	CH_3CHO (**2m**)	$ZnCl_2$, THF, 4 h	**3am**	63
2	**1a**	C_3H_7CHO (**2n**)	$ZnCl_2$, THF, 4 h	**3an**	61
3	**1b**	CH_3CHO (**2m**)	$ZnCl_2$, THF, 4 h	**3bm**	74
4	**1b**	C_3H_7CHO (**2n**)	$ZnCl_2$, THF, 4 h	**3bn**	64
5	**1b**	C_3H_7CHO (**2n**)	$BF_3{\cdot}Et_2O$, THF, 4 h	**3bn**	57
6	**1b**	C_3H_7CHO (**2n**)	$FeCl_3$, THF, 4 h	**3bn**	39
7	**1b**	C_3H_7CHO (**2n**)	$AlCl_3$, THF, 4 h	**3bn**	35
8	**1b**	C_3H_7CHO (**2n**)	THF, 4 h	**3bn**	35
9	**1c**	C_3H_7CHO (**2n**)	$ZnCl_2$, THF, 4 h	**3cn**	63
10	**1b**	$CH_3CH(CH_3)CHO$ (**2o**)	$ZnCl_2$, THF, 4 h	**3bo**	65
11	**1b**	CH_3COCH_3 (**2p**)	$ZnCl_2$, THF, 4 h	**3bp**	75
12	**1c**	CH_3COCH_3 (**2p**)	THF, 4 h	**3cp**	40
13	**1c**	CH_3COCH_3 (**2p**)	$ZnCl_2$, THF, 4 h	**3cp**	71
14	**1b**	$CH_3COC_2H_5$ (**2q**)	$ZnCl_2$, THF, 4 h	**3bq**	63
15	**1b**	$CH_3COC_3H_7$ (**2r**)	$ZnCl_2$, THF, 4 h	**3br**	62
16	**1b**	Cyclohexanone (**2s**)	$ZnCl_2$, THF, 4 h	**3bs**	77
17	**1c**	Cyclohexanone (**2s**)	$ZnCl_2$, THF, 4 h	**3cs**	77
18	**1b**	$CH_2{=}CHOC_2H_5$ (**2t**)	$ZnCl_2$, THF, 4 h	**3bt**	42
19	**1b**	$CH_2{=}CHOC_2H_5$ (**2t**)	$ZnCl_2$, MeCN, 8 h	**3bt**	61
20	**1b**	$CH_2{=}C(CH_3)OSi(CH_3)_3$ (**2u**)	$ZnCl_2$, THF, 4 h	**3bu**	36
21	**1b**	$CH_2{=}C(CH_3)OSi(CH_3)_3$ (**2u**)	$ZnCl_2$, MeCN, 8 h	**3bu**	56

[a] Isolated yields based on **1**.

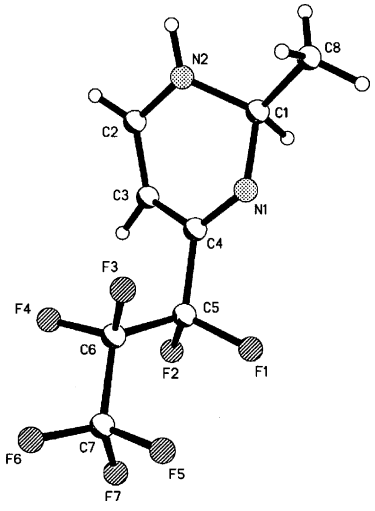
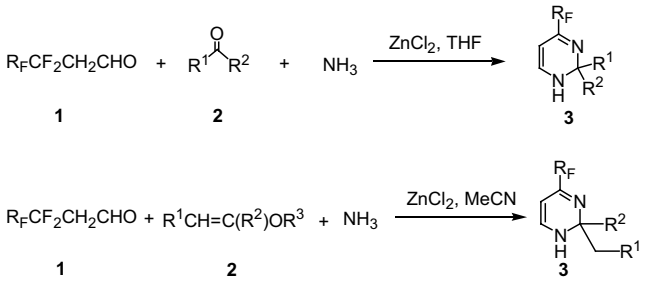


Figure 1. Crystal structure of **3bm** (CCDC 233537).



Scheme 2. The reaction of **1** with ammonia and ketones or enol ethers.

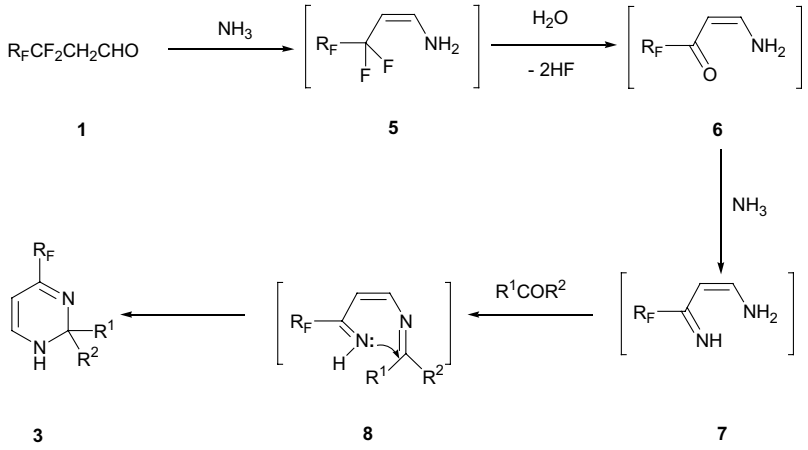
THF and longer reaction time was necessary for better conversion. The reactions could also occur in the absence of zinc chloride but the yields were lower (30–40%). Other Lewis acids such as $BF_3{\cdot}Et_2O$, $FeCl_3$ and anhydrous $AlCl_3$ were tested, but only $BF_3{\cdot}Et_2O$ gave comparable results (Table 1).

A possible mechanism was proposed as shown in Scheme 3. As a proof, the key intermediate **6** has been isolated and identified. The precise role of $ZnCl_2$ in this process has not been elucidated. However, we tentatively propose that the coordination of Zn ion with carbonyl oxygen and NH_3 facilitates the formation of intermediate **7**.

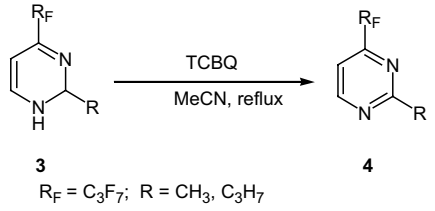
Dehydrogenation of **3bm** and **3bn** with TCBQ (tetrachlorobenzoquinone) in acetonitrile under reflux for 4 h gave the corresponding 4-fluoroalkyl pyrimidines **4bm** and **4bn** in 63% and 75% yields, respectively (Scheme 4).

In conclusion, an unexpected tri-component reaction of 2,2-dihydropolyfluoroalkylaldehydes with ammonia and aldehydes, ketones or enol ethers was described, providing a facile synthetic method for 4-fluoroalkyl-1,2-dihydropyrimidines, which are useful intermediates for the synthesis of various fluorine-containing compounds with biological interest.

A typical procedure for the preparation of **3**: A mixture of **1** (1 mmol) and $ZnCl_2$ (1 mmol) in THF (10 mL) was stirred at room temperature under ammonia atmosphere. After 2 h, **2** (1.5 mmol) in THF (10 mL) were added dropwise. The mixture was stirred at 50–60 °C under ammonia atmosphere for a few hours (monitored by ^{19}F NMR). After cooling, 20 mL water was added and the solution was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water (2×10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (Eluant: ethyl acetate/petroleum ether) to give compound **3**.



Scheme 3. Proposed mechanism of the reaction of **1** with ammonia and aldehydes or ketones.



Scheme 4. Dehydrogenation of **3** with TCBQ.

Selected data for compound **3**: 2-methyl-4-(1,1,2,2,3,3,3-heptafluoropropyl)-1,2-dihydropyrimidine (**3bm**): White solid. mp: 79–81 °C. Anal. Calcd for $C_8H_7F_7N_2$: C, 36.38; H, 2.67; N, 10.61. Found: C, 36.51; H, 2.87; N, 10.38. IR: ν_{max} cm^{-1} 3153, 3018, 2946, 2857, 1613, 1545, 1495, 1354, 1287, 1221, 1186, 1118; ^{19}F NMR (282 MHz, $CDCl_3$, 298 K): δ −80.7 (s, 3F; CF_3), −117.7 (q, AB, 2F, CF_2), −127.1 (s, 2F; CF_2); ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ 6.92 (d, $^3J_{H-H} = 6.6$ Hz, 1H; CH=), 5.39 (d, $^3J_{H-H} = 6.6$ Hz, 1H; CH=), 4.92 (q, $^3J_{H-H} = 6.3$ Hz, 1H; CH), 4.20 (broad, s, 1H; NH), 1.58 (d, $^3J_{H-H} = 6.3$ Hz, 3H; CH_3). MS (EI) *m/z* (% intensity): 265 (2) $[M+1]^+$, 264 (13) $[M]^+$, 263 (5) $[M-1]^+$, 249 (100) $[M-CH_3]^+$, 245 (1.5) $[M-F]^+$, 130 (61) $[M-CH_3-CF_2CF_2]^+$, 169 (3) $[C_3F_7]^+$, 119 (19) $[C_2F_5]^+$, 69 (36) $[CF_3]^+$, 100 (11) $[CF_2CF_2]^+$, 95 (8) $[M-C_3F_7]^+$.

Acknowledgements

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6. Crystal graphic data for **3bm** ($C_8H_7F_7N_2$): M = 264.16, crystal size 0.507×0.424×0.065 mm, $a = 13.286$ (2), $b = 9.0564$ (15), $c = 9.0912$ (15) Å, $\alpha = 90°$, $\beta = 92.301°$ (4), $\gamma = 90°$, $V = 1093.0$ (3) $Å^3$, $\rho_{calcd} = 1.77$ g cm^{-3}, $Z = 4$, monoclinic, space group P2(1)/c, $\lambda = 0.71073$ Å, $T = 293$ (2) K, $F(000) = 528$, $\theta_{max} = 28.27$, $R(int) = 0.09831$, reflections collected 6471, unique 2510, $R1 = 0.0757$ ($I > 2\theta(I)$). $\mu = 0.182$ mm^{-1} (CCDC 233537).