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A convenient synthesis of 3-polyfluoroalkyl pyrazoles and 6-polyfluoroalkyl pyrimidines from β-polyfluoroalkyl enaminones

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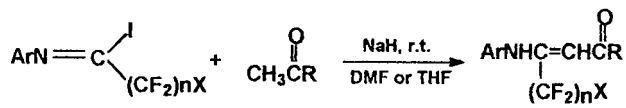
Abstract

3-Polyfluoroalkyl pyrazoles and 6-polyfluoroalkyl pyrimidines can be easily synthesized from the reactions of hydrazine monohydrate or amidine respectively with β-polyfluoroalkyl enaminones which are prepared by the nucleophilic substitution of the anion of a methyl ketone with *N*-aryl polyfluoroalkyl imidoyl iodides. © 1997 Elsevier Science S.A.

Keywords: Polyfluoroalkyl enaminone; Pyrazole; Pyrimidine; Imidoyl iodide

1. Introduction

Fluorinated heterocyclic compounds have attracted much attention because of their unique biological and physiological activities [1]. Among them, fluorinated pyrazoles [2] and pyrimidines [3] have been shown to possess high biological activities as herbicides, fungicides, insecticides, analgesics, antipyretics and anti-inflammatories. Therefore, development of new methodologies for the synthesis of fluorinated pyrazoles and pyrimidines has attracted growing interest. These methods include the synthesis of ring-fluorinated compounds [4] and of pyrazoles [5] or pyrimidines [6] with a perfluoroalkyl group. On the other hand, enaminones are established as synthetic intermediates, particularly in heterocyclic chemistry [7]. Because the most general method for the synthesis of enaminones is the reaction between ammonia or a primary or secondary amine and a 1,3-diketone or 3-keto-ester [8], there are not many reports on their use as β-dicarbonyl equivalents for the synthesis of heterocycles [9,10]. These researches are based on an unusual amine group exchange of tertiary enaminones with hydroxylamine or amidines. However, the amine exchange of aryl enaminones has not been reported so far. In addition, the research on β-polyfluoroalkyl enaminone derivatives (**3**) is also limited in the literature. Herein we describe a convenient synthetic route using β-polyfluoroalkyl enaminones (**3**) for the production of 3-polyfluoroalkyl pyrazoles (**4**) and 6-polyfluoroalkyl pyrimidines (**7**) in good yields under the amine–aniline exchange.



1 **2** **3**

Scheme 1.

The β-polyfluoroalkyl enaminones (**3**) were prepared by nucleophilic substitution of *N*-aryl polyfluoroalkyl imidoyl iodides [11] with the carbanion of an α-methyl ketone (Scheme 1 and Table 1). The reaction was completed during 15 min with sodium hydride as a base in dried DMF or THF at room temperature under nitrogen. The mixture was worked up to give product **3**, which existed as the enaminone rather than the imine structure presumably because of the thermodynamic stability of the β-amino α,β-unsaturated ketone moiety [12]. For entries 8 and 9, the yields were not satisfactory because of the deterioration of compound **1**. A lower temperature only prolonged the reaction time and did not improve the yields.

Treatment of **3** with an excess of hydrazine monohydrate at 60 °C in ethanol proceeded smoothly to afford two products **4** and **5** (Scheme 2 and Table 1). Spectral data of **4** indicated the absence of arylamino-group and there is a single peak of one proton at 6.5–6.9 ppm. It was identified as a 3-polyfluoroalkyl 5-substituted pyrazole by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, MS, IR and elemental analyses. Product **5** was shown to be *p*-toluidine (**5a**) or *p*-anisidine (**5b**).

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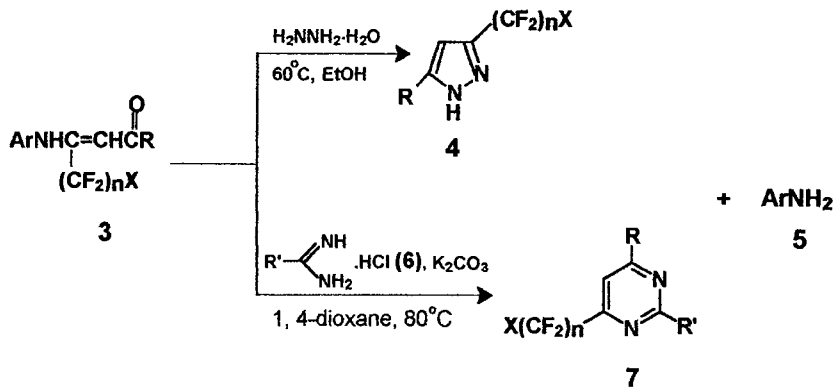
Table 1
Synthesis of β-polyfluoroalkyl enaminones and their conversion into 3-polyfluoroalkyl 5-substituted pyrazoles

Entry	Ar, *n*, X, **1**	R, **2**	Solvent	**3**, yield (%)[a]	**4**, yield (%)[a]
1	*p*-$CH_3C_6H_4$, 2, Cl, **1a**	Ph **2a**	THF	**3aa** 67	**4a** 93
2	*p*-$CH_3OC_6H_4$, 2, Cl, **1b**	Ph **2a**	THF	**3ba** 77	**4a** 95
3	*p*-$CH_3OC_6H_4$, 4, Cl, **1c**	Ph **2a**	THF	**3ca** 68	**4b** 86
4	*p*-$CH_3OC_6H_4$, 1, F, **1d**	Ph **2a**	THF	**3da** 72	**4c** 90
5	*p*-$CH_3OC_6H_4$, 2, Cl, **1b**	2-furan **2b**	THF	**3bb** 56	**4d** 79
6	*p*-$CH_3OC_6H_4$, 4, Cl, **1c**	2-furan **2b**	THF	**3cb** 64	**4e** 50
7	*p*-$CH_3OC_6H_4$, 1, F, **1d**	2-furan **2b**	THF	**3db** 73	**4f** 72
8	*p*-$CH_3OC_6H_4$, 2, Cl, **1b**	t-Bu **2c**	DMF	**3bc** 42	**4g** 71
9	*p*-$CH_3OC_6H_4$, 2, Cl, 1b	CH_3 **2d**	DMF	**3bd** 11	**4h** 72

[a]Isolated yields.



Scheme 2.

Table 2
Synthesis of 6-polyfluoroalkyl pyrimidines from β-polyfluoroalkyl enaminones

Entry	Enaminone **3**	Amidine **6**	Reaction time (h)	**7**, yield (%)[a]
1	**3ba**	R′ ≡ Ph **6a**	12	**7a** 90
2	**3ca**	R′ ≡ Ph **6a**	12	**7b** 93
3	**3da**	R′ ≡ Ph **6a**	12	**7c** 96
4	**3ba**	R′ ≡ CH_3 **6b**	20	**7d** 96
5	**3ca**	R′ ≡ CH_3 **6b**	20	**7e** 94
6	**3da**	R′ ≡ CH_3 **6b**	20	**7f** 70
7	**3bb**	R′ ≡ Ph **6a**	12	**7g** 98
8	**3cb**	R′ ≡ Ph **6a**	12	**7h** 98
9	**3db**	R′ ≡ Ph **6a**	12	**7i** 80
10	**3bb**	R′ ≡ CH_3 **6b**	20	**7j** 70
11	**3cb**	R′ ≡ CH_3 **6b**	20	**7k** 84
12	**3db**	R′ ≡ CH_3 **6b**	20	**7l** 71

All reactions were carried out at 80 °C.
[a]Isolated yields.

Furthermore, treatment of **3** with 1.5 equivalent of benzamidine hydrochloride (**6a**) in the presence of 4.0 equivalents of potassium carbonate in 1,4-dioxane resulted in the formation of a 2-phenyl 4-substituted 6-polyfluoroalkyl pyrimidine in 80%–90% overall yields after 12 h (Scheme 2). For acetamidine hydrochloride (**6b**), the reaction time was longer and the yield was comparatively lower than for benzamidine (Table 2). Dioxane was a good solvent whereas ethanol or THF did not give satisfactory results. Thus, the β-polyfluoroalkyl enaminones served as β-dicarbonyl equivalents, the bifunctional *N*-nucleophile attacked the β-polyfluoroalkyl enaminones on the carbonyl carbon followed by ring closure with the cleavage of one molecule of aryl amine. The reaction was mild and clean and the yield was satisfactory. It provides a new usage of β-polyfluoroalkyl enaminones in the synthesis of polyfluoroalkyl pyrazoles or pyrimidines.

2. Typical experimental procedure

Preparation of **3ca**. A flask fitted with a nitrogen inlet was charged with acetophenone (528 mg, 4.4 mmol), sodium hydride (176 mg, 60% dispersion in mineral oil, 4.4 mmol) and 8 ml anhydrous THF. The mixture was stirred at room temperature for 20 min. Then *N*-(*p*-methoxyphenyl) ω-chloro-octafluorobutyl imidoyl iodide [11] (1.98 g, 4.0 mmol) in 2 ml dry THF was added with a syringe during 2 min and the resulting mixture was stirred for 15 min. After work-up in the usual way the crude product was purified by flash column chromatography on silica gel (petroleum ether (b.p. 60–90 °C):ethyl acetate 20:1) to give **3ca** as yellow crystals (1.33 g, 68%), m.p. 100–102 °C. ^{1}H NMR (90 MHz, $CDCl_3$) 12.73 (br.s. 1H, NH), 8.05–6.85 (m, 9H, Ar–H), 6.40 (s, 1H, C=CH), 3.90 (s, 3H, CH_3O) ppm; ^{19}F NMR (56.4 Hz, $CDCl_3$, $CFCl_3$ as the external standard) 67.1 (m,

2F, CF_2Cl), 107.4 (m, 2F, $=CCF^2$), 119.1 (m, 4F, CF_2CF_2) ppm; IR (ν, cm^{-1}) 2974, 2847, 1618, 1593, 1507, 1206, 1100–1140; MS 489 ($M^+ + 2$, 10.46), 487 (M^+, 30.27), 252 (M^+-Cl$(CF_2)_4$, 100.00); analysis calculated for $C_{20}H_{14}ClF_8NO_2$ C 49.25, H 2.89, N 2.87, F 31.16; found C 49.28, H 2.80, N 2.73, F 31.18.

Preparation of **4d**. Hydrazine monohydrate (30 mg, 0.62 mmol) was added to a solution of **3bb** (100 mg, 0.26 mmol) in ethanol (3 ml) and the mixture was heated to 60 °C for 2 h with stirring. The cold mixture was then extracted with diethyl ether (20 ml×3) and the organic layer was washed with brine followed by drying over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (petroleum ether (b.p. 60–90 °C):ethyl acetate 3:1) to give **4d** as colorless crystals (55 mg, 93%) and **5b**. **4d** had m.p. 88–90 °C; ^{1}H NMR (90 MHz, $CDCl_3$) 7.55 (s, 1H), 6.73–6.49 (m, 3H, H-furan) ppm; ^{19}F NMR (56.4 Hz, $CDCl_3$, $CFCl_3$ as the external standard) 70.2 (s, 2F, CF_2Cl), 108.8 (s, 2F, CF_2) ppm; ^{13}C NMR (75.4 MHz, CDCl3) 141.95(t, $J=29$ Hz, C^3), 101.91 (s, C^4) ppm; IR (ν, cm^{-1}) 3131, 2905, 1631, 1504, 1413, 1263, 1134; MS 270 ($M^+ + 2$, 31.10), 268 (M^+, 86.10), 183 (M^+-CF_2Cl, 100.00); analysis calculated for $C_9H_5ClF_4N_2O$ C 40.25, H 1.88, N 10.43, F 28.29; found C 40.20, H 1.83, N 10.40, F 28.20.

Preparation of **7a**. Benzamidine hydrochloride (**6a**) (61 mg, 0.39 mmol) and K_2CO_3 (144 mg, 1.04 mmol) were added to a stirred solution of **3ba** (100 mg, 0.26 mmol) in dioxane (3 ml). The mixture was stirred for 12 h at a temperature of 80 °C. Then the cold mixture was washed with saturated aqueous NH_4Cl solution and extracted with diethyl ether (20 ml×3). The organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether (b.p. 60–90 °C):ethyl acetate 100:1) to give **7a** as colorless crystals (100 mg, 90%) and **5b**. **7a** had m.p. 122–123 °C; ^{1}H NMR (90 MHz, $CDCl_3$) 8.68 (m, 2H, Ph-H), 8.38 (m, 2H, Ph-H), 7.95 (s, 1H, heterocyclic-H), 7.58 (m, 6H, Ph-H); ^{19}F NMR (56.4 Hz, $CDCl_3$, $CFCl_3$ as external standard) 68.2 (s, 2F, CF_2Cl), 113.8 (s, 2F, CF_2-ring) ppm; IR (ν, cm^{-1}) 1587, 1572, 1548, 1382, 1367, 1164, 1151, 1087; MS 366(M^+, 100.00); analysis calculated for $C_{18}H_{11}ClF_4N_2$ C 58.95, H 3.02, N 7.64, F 20.72; found C 59.06, H 3.06, N 7.52, F 20.25.

In conclusion, a convenient synthetic method has been developed for the preparation of pyrazoles or pyrimidines with a variety of substitution patterns from β-polyfluoroalkyl enaminones and hydrazine monohydrate or amidines respectively. This work broadened the utility of β-polyfluoroalkyl enaminones in organic synthesis and provided a convenient synthesis for fluoroalkyl heterocycles.

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