Ring Monofluorinated Hydroxypyrazoles

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(Received January 16, 1981)

Synopsis. 3-Alkyl(or aryl)-4-fluoro-5-hydroxypyrazoles and their 1-methyl derivatives were prepared by the reaction of methyl α-fluoro-β-alkyl(or aryl)-β-keto esters with hydrazine hydrate or methylhydrazine in ethanol. The reaction of arylhydrazines with α-fluoro-β-keto esters gave only hydrazones which could not be cyclized to pyrazoles.

There has been the growing interest in utilization of some kind of monofluoro organic compounds because of their biological activities[1] and several practical methods for monofluorination of organic molecules have been developed in these days.[2] From this point of view, we have revealed that α-fluoro-β-keto esters (**1**), potent intermediates for monofluoroheterocycles, can be prepared easily from trifluoroethene or from hexafluoropropene.[3] As the first example of preparation of monofluoroheterocycles from α-fluoro-β-keto esters, we now wish to report the preparation of 3-alkyl(or aryl)-4-fluoro-5-hydroxypyrazoles by the reaction with hydrazine or with methylhydrazine. There has been no reports on pyrazole compounds carrying a fluorine atom directly attached to the ring.

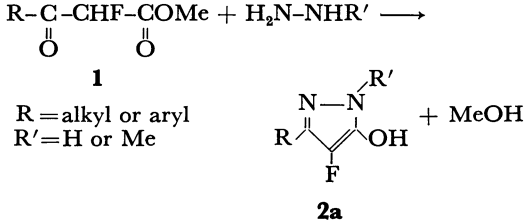
β-Diketones are generally known to cyclize easily into pyrazoles by treating them with hydrazines.[4] The reactions between α-fluoro-β-keto esters with hydrazine or methylhydrazine proceeded smoothly in refluxing ethanol, and 3-alkyl(or aryl)-4-fluoro-5-hydroxypyrazoles (**2a**) were obtained as expected in good yields (Table 1).

TABLE 1. PREPARATION OF 3-ALKYL(OR ARYL)-4-FLUORO-5-HYDROXYPYRAZOLES **2a**[a]

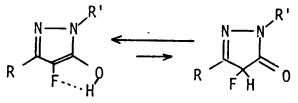
R	R′	Yield %	Mp °C	^{19}F NMR[b] CF
Me	H	52	104—106	112
Pr	H	53	126—128	110
Ph	H	61	184—186	110
4-MeC_6H_4	H	98	205—206	110
4-ClC_6H_4	H	94	230—233	109
Me	Me	56	101—103	112.5
Pr	Me	58	123—125	111
Ph	Me	65	130—132	110
4-MeC_6H_4	Me	80	200—202	110
4-ClC_6H_4	Me	79	229—230	109
4-$Me_2NC_6H_4$	Me	58	250—252	110.5
3-MeC_6H_4	Me	52	220—221	110
4-FC_6H_4	Me	85	234—235	112

a) New compound: The structures were confirmed on the basis of their IR and NMR spectral data and the microanalysis was satisfactory agreement with the calculated value. b) Chemical shifts are given in δ ppm from ext. CF_3CO_2H in DMSO-d_6.

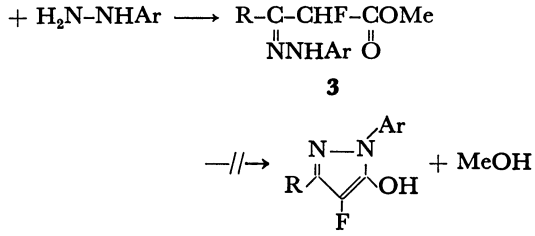
The structures of the fluoropyrazoles obtained was confirmed from their ^{19}F and ^{1}H NMR and mass



spectra. The ^{19}F NMR spectra in DMSO-d_6 solution revealed only one singlet signal at about 110 ppm upfield from external CF_3CO_2H, while in the ^{1}H NMR spectra one broad signal due to the OH proton appeared at ≈δ 10 as well as the other signals due to alkyl or aryl protons. In addition, no absorption band due to a carbonyl group was observed in the spectra of these pyrazole compounds. These results suggest that these compounds prefer the hydroxypyrazole type structure to the pyrazolone type one. This may be ascribed to the hydrogen bonding formation between the oxygen atom and the fluorine atom, which stabilizes the enol form **2a** rather than the keto form **2b**.



Arylhydrazines and tosylhydrazine, on the other hand, reacted with **1** to give only hydrazones **3** and none of cyclized compounds were obtained. This is in contrast to the case with non-fluorinated β-keto esters, which give readily pyrazolone compounds with arylhydrazines.



Experimental

Typical procedures are described below.

4-Fluoro-5-hydroxy-1-methyl-3-phenylpyrazole (2a) (R=Ph, R′=Me). A mixture of methyl α-fluorobenzoylacetate (1.96 g, 10 mmol), methylhydrazine (0.46 g, 10 mmol), and ethanol (5 ml) was refluxed for 3 h. On cooling the reaction mixture was filtered and the solid material was recrystallized from ethanol, affording a fluoropyrazole compound in 65% yield, mp 130—132 °C. ^{1}H NMR (DMSO-d_6) δ: 3.60 (CH_3), 7.50 (ArH), 9.87 (OH); ^{19}F NMR (DMSO-d_6) δ: 110 ppm from ext. CF_3CO_2H. Found: C, 62.86; H, 4.85; N, 14.61%. Calcd for $C_{10}H_9N_2OF$: C, 62.50; H, 4.72; N, 14.57%. M^+, 192.

2,4-Dinitrophenylhydrazone of Methyl α-Fluorobenzoylacetate. A mixture of methyl α-fluorobenzoylacetate (0.4 g, 2 mmol), 2,4-dinitrophenylhydrazine (0.42 g, 2 mmol), and concd sulfuric acid (2 ml) in ethanol (10 ml) was stirred for 24 h at room temperature. The solid material was collected by filtration and recrystallized from ethanol to give the hydrazone in 80% yield, mp 196—198 °C. IR (KBr): 3300 (NH), 1760 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.90 (CO_2CH_3), 6.77 (CHF, $J_{H-F}=45$ Hz), 7.52—9.07 (ArH), 11.87 (NH); ^{19}F NMR (DMSO-d_6) δ: 112 ppm from ext. CF_3CO_2H. Found: C, 49.29; H, 3.53; N, 15.25%. Calcd for $C_{15}H_{13}N_4O_6F$: C, 49.46; H, 3.60; N, 15.38%.

References

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