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PRELIMINARY NOTE

Trifluoropyruvic Acid Hydrate in Heterocyclic Synthesis: a Facile Synthesis of 5-Hydroxy-5-Trifluoromethylhydantoin Derivatives.

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SUMMARY

The reaction of trifluoropyruvic acid hydrate with urea derivatives affords 5-hydroxy-5-trifluoromethylhydantoin derivatives in good yield. The product orientation is consistent with the initial attack on the most active center, in trifluoropyruvic acid hydrate, towards nucleophiles.

Trifluoropyruvic acid hydrate (1) had been synthesized several times before; the most recent method was established by Knunyants et al. in 1966 [1]. However, the chemistry of this reagent, in spite of its versatility, has not been investigated, specially in heterocyclic synthesis. Only one example is reported in the literature, its reaction with semicarbazide hydrochloride [2]. As an extension of this work, we became interested in studying the behaviour of this reagent towards other nucleophiles to synthesize a wide variety of heterocyclic compounds.

We would like to report here on a facile synthesis of 5-hydroxy-5-trifluoromethylhydantoin derivatives via the reaction of (1) with urea derivatives. Various routes for the synthesis of the hydantoin ring have been described. Recently Sonntag [3] and Cadet [4] synthesized 5-hydroxy-5-methylhydantoin via the radiolysis of uracil and thymidine in oxygenated aqueous solutions.

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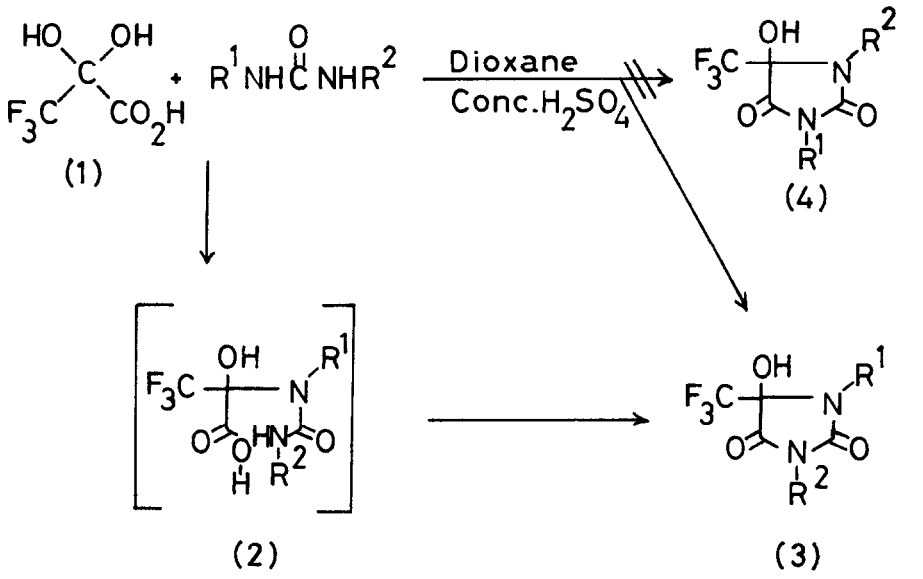
We found we could synthesize the 5-hydroxy-5-trifluoromethylhydantoins (3_{a-g}) in a one-step method via the reaction of (1) with urea derivatives in a boiling dioxane/conc.H_2SO_4 system. For example, to a solution of (1) (0.8 g, 5 mmol) in dioxane (15 ml/conc.H_2SO_4 4 drops) urea (0.3 g, 5mmol) was added, the mixture was refluxed till (1) completely disappeared (by ^{19}F-n.m.r.), the reaction mixture was extracted with AcOEt, which after evaporation, was chromatographed to afford pure (3_a) (0.56 g) as a white solid which was recrystallized from acetone/chloroform mixture to give white crystals. Reactions carried out are summarized in Table 1.



(3);

a; $R^1 = R^2 = H$ b; $R^1 = H$; $R^2 = CH_3$
c; $R^1 = H$; $R^2 = C_2H_5$ d; $R^1 = H$; $R^2 = Ph$
e; $R^1 = H$; $R^2 = CH_2Ph$ f; $R^1 = R^2 = CH_3$
g; $R^1 = R^2 = C_2H_5$

Scheme (1)

TABLE 1

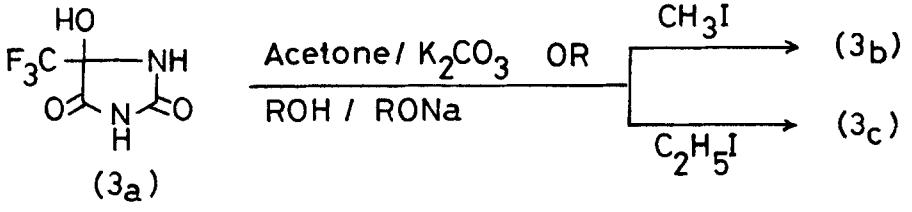
Compd. No.	(3) R^1	R^2		Reaction Cond.[a] reflux (hr.)	Recrystallization Solvent (method of purification)	m.p.(°C)	Y(%)
(a)	H	H	(nc)	7	acetone/chloroform	180-81	61
(b)	H	CH_3	(nc)	6	chloroform	125	69
(c)	H	C_2H_5	(nc)	2	chloroform/n-hexane	110-11	76
(d)	H	Ph	(nc)	3	chloroform	189-90	77
(e)	H	CH_2Ph	(nc)	1.5	chloroform	144-45	88
(f)	CH_3	CH_3	(nc)	8	n-hexane	70-71	71
(g)	C_2H_5	C_2H_5	(nc)	6	(chromatography)	liquid	67

[a] Dioxane was used as solvent in presence of catalytic amounts of conc. H_2SO_4.

The configuration of the hydantoin ring formed is suggested to be (3) not (4), as is shown in scheme 1. Depending on the fact that the NH_2 group attacks the α-C atom in (1) as reported in the literature [2] and also from our results now under investigation, the pathway for the formation of the hydantoins (3) can be suggested as the free NH_2 group in a urea derivative attacking preferentially the α-C atom in (1) leading to the formation of the intermediates (2) which cyclize to the hydantoins (3) as is shown in scheme 1.

Also it was found from ^{1}H-n.m.r. of compound (3_a) that the peak at δ10.7 ppm, which corresponds to the most acidic proton in (3_a) had disappeared in the ^{1}H-n.m.r. spectra of compounds (3_{b-g}) (see Table 2). It is well known that the proton attached to the nitrogen atom at position 3 in the hydantoin ring is the most acidic one, owing to the keto-enol equilibrium involving the two neighboring carbonyl groups. Therefore, the disappearance of this proton in the compounds (3_{b-g}) (^{1}H-n.m.r.) means that it must be the one that is replaced by alkyl or aryl groups which gives more evidence for our suggested structure (3).

Moreover, we found that the alkylation of (3_a) with CH_3I or C_2H_5I in boiling acetone/K_2CO_3, for few hours gave the corresponding alkylhydantoin derivatives (3_b) and (3_c) respectively in 60% conversion. However, when the alkylation was carried out in CH_3OH/CH_3ONa and in C_2H_5OH/C_2H_5ONa with stirring at room temperature, the corresponding (3_b) and (3_c) were formed in 100% conversion as determined by ^{19}F-n.m.r. These results may also give more evidence for our suggested structure (3), as it is well known that the nitrogen atom at position 3 in the hydantoin ring is more readily alkylated than is the other nitrogen atom [5].



Scheme (2)

TABLE 2

Compd. (3)	IR(cm^{-1})	^{19}F NMR[a] δ ppm	^{1}H NMR[b] δ ppm	MS(m/e) M^+	Elemental Analysis calc. (found) C(%)	H(%)	N(%)
a (nc)	3100-3300(br,OH,NH) 1800,1750(C=O)	+4.33(s,CF_3)	8.00(br,1H,NH) 8.33(s,1H,OH) 10.7(br,1H,NH)	184	26.08 (26.54)	1.63 (1.67)	15.21 (15.78)
b (nc)	3150-3300(br,OH,NH) 1800,1710(C=O)	+4.33(s,CF_3)	3.00(s,3H,CH_3) 8.00(s,1H,OH) 8.90(br,1H,NH)	198	30.30 (30.13)	2.52 (2.41)	14.14 (14.47)
c (nc)	3350(NH),3200(br,OH) 1800,1710(C=O)	+4.16(s,CF_3)	1.80(t,3H,CH_3) 3.53(q,2H,CH_2) 8.06(s,1H,OH) 9.06(s,1H,NH)	212	33.96 (33.42)	3.30 (3.22)	13.20 (13.38)
d (nc)	3200-3500(br,OH,NH) 1800,1730(C=O)	+4.15(s,CF_3)	7.46(m,5H,Ar-H) 8.20(s,1H,OH) 9.20(s,1H,NH)	260	46.15 (46.13)	2.69 (2.39)	10.76 (10.88)
e (nc)	3150-3300(br,OH,NH) 1800,1720(C=O)	+4.50(s,CF_3)	7.33-7.60(2s,5H,Ar-H) 4.66(s,2H,CH_2) 8.2(br,1H,OH) 9.2(br,1H,NH)		48.17 (48.43)	3.28 (3.19)	10.21 (10.02)
f (nc)	3300(br,OH) 1800,1710(C=O)	+2.16(s,CF_3)	2.93(s,3H,CH_3) 3.03(s,3H,CH_3) 8.20(s,1H,OH)	212	33.96 (33.73)	3.30 (3.29)	13.20 (13.08)
g (nc)	3350(br,OH) 1800,1720(C=O)	+2.91(s,CF_3)	1.16(2t,6H,2CH_3) 3.50(2q,4H,2CH_2) 6.00(br,1H,OH)		36.84 (36.55)	4.82 (4.47)	12.28 (12.06)

[a] From ext. CF_3COOH in CH_3CO_2Et.

[b] The mixture of $CDCl_3$/DMSO-d_6 (3:1) was used as solvent.

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