

TRIFLUOROPYRUVIC ACID HYDRATE IN HETEROCYCLIC SYNTHESIS PART III¹:
A NOVEL SYNTHESIS OF 4-(TRIFLUOROMETHYL)-OXAZOLONES AND OTHER RELATED
COMPOUNDS

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Abstract — Acid-catalyzed reaction of trifluoropyruvic acid hydrate (1) with nitriles is reported. The structure of the resulting compounds is also investigated.

Because of the interesting biological and medicinal activities^{2,3} of organic molecules carrying a trifluoromethyl group, much research has recently been initiated on the synthesis and chemistry of this class of compounds. In previous work from our laboratory we have described the scope and limitations of the synthesis of some trifluoromethylated heterocycles via the reaction of trifluoropyruvic acid hydrate (1) with bifunctional nucleophiles^{4,5}. In connection with our work directed for the development of new simple and efficient procedures for the synthesis of trifluoromethylated heterocycles, we would like to report here on the synthesis of trifluoromethylated oxazolone derivatives by the reaction of (1) with nitriles. The behavior of fluorinated α -hydroxy acids with nitriles has not been investigated before. On the other hand, benzilic acid has been reported⁶⁻⁸ to condense

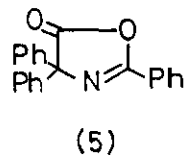
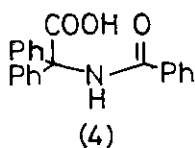
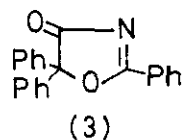
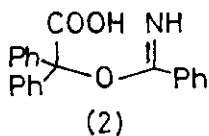
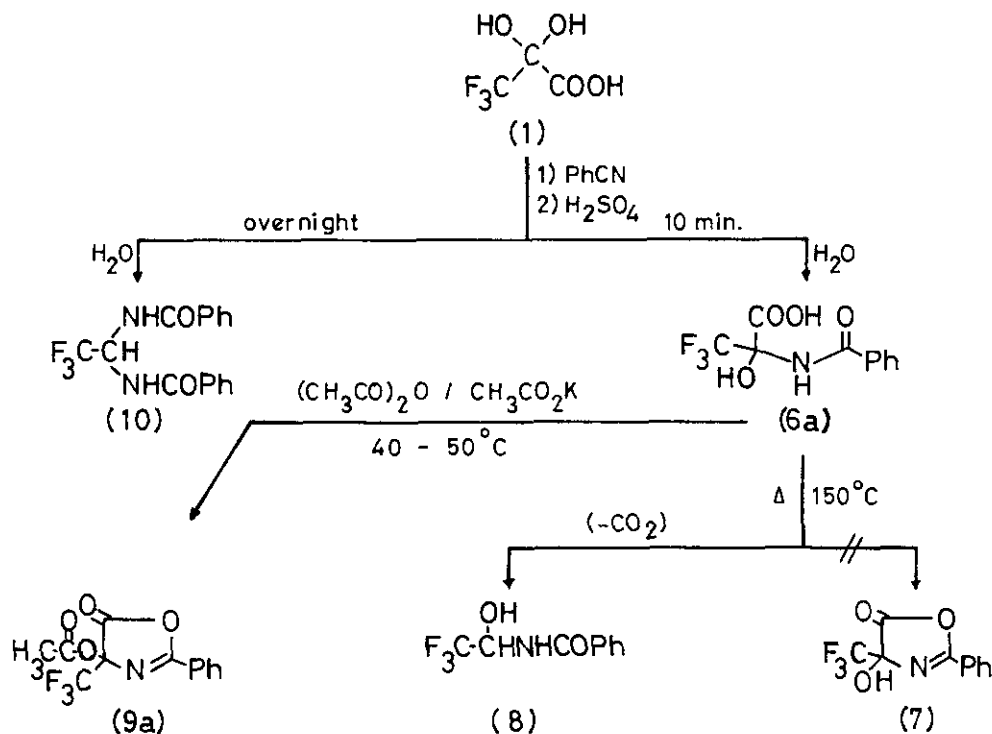


Chart 1

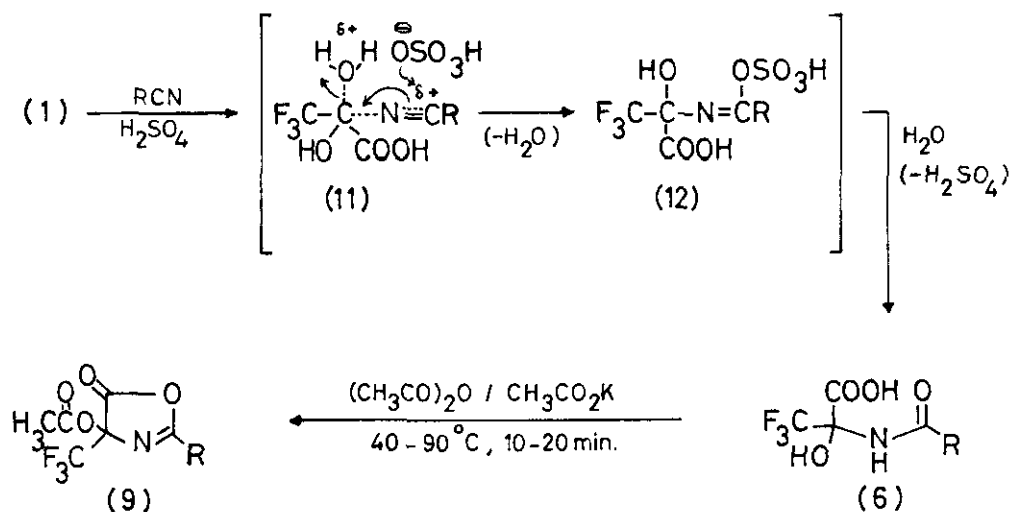
with benzonitrile in the presence of concentrated sulfuric acid forming tri-phenyloxazolidone. Two problems were encountered with this reaction: a) it was mentioned^{6,7} that of the various other nitriles and hydroxy acids, none gave reactions corresponding to those of benzonitrile and benzoic acid, however, Hohenlohe-Oehringen et al.,^{8,9} could extend this reaction to include another nitriles. b) a contradiction was reported^{7,8} concerning the structure of the isolated products. Japp et al.⁶, therefore, formulated their products as structures (2) and (3) (see Chart 1), while Bird⁷ and Hohenlohe-Oehringen⁸ have formulated their products as (4) and (5) depending on the fact that the reaction was that of benzonitrile with the benzoic acid carbonium ion.

From these points of view and considering that trifluoropyruvic acid hydrate as fluorinated α -hydroxy acid, we became interested to see if this procedure might be extended to include another nitriles aiming to generalize this method for the synthesis of trifluoromethylated oxazolones and also to investigate clearly the structure of the isolated products of this reaction. Thus, by the same conditions mentioned^{6,7}, (1) was reacted with benzonitrile to yield α -benzamidotrifluorolactic acid (6_a) (see Scheme 1); however, when the mixture of (1) and benzonitrile was



Scheme 1

heated until it became fluid, after which the whole was poured into concentrated sulfuric acid, stirred overnight at room temperature and then poured into water, a precipitate was formed, collected by filtration, and crystallized from DMF/water to yield white crystals of trifluoroacetylidene dibenzamide (10). Attempted cyclization of compound (6_a) by heating over its melting point afforded only α -benzamidotrifluoroethanol (8); on the other hand, when (6_a) was warmed in acetic anhydride at 40 - 50°C for 20 min. in the presence of freshly fused potassium acetate, it afforded 4-acetoxy-4-trifluoromethyl-2-phenyloxazol-5(4H)-one (9_a) which was purified by column chromatography on silica gel affording a colorless liquid which solidified after a while. Attempts at the hydrolysis of the acetyl group in (9_a) to get compound (7) were unsuccessful. By the same conditions described by Japp and Bird, we could extend this reaction by using another nitriles to get the corresponding acids (6) in good yield (see Scheme 2 and Table 1). However, in some cases we could not isolate the acid in pure form, and in these cases the crude acid was used directly for the cyclization step. The acids (6) were cyclized to the trifluoromethylated oxazolones (9) by the same conditions mentioned above. The structures of the acids (6) and the oxazolones (9) were confirmed by



(6), (9);

a), R = Ph

b), R = Me

c), R = Et

d), R = p-tolyl

e), R = 1-naphthyl

f), R = styryl

Scheme 2

spectral and elemental analyses as shown in Table 2.

The structure of our isolated compounds (6) and (9) was found to be in agreement with that described by Bird⁷ and Hohenlohe-Oehringen⁸ (see Chart 1); thus, compounds (6) revealed in their ir spectra two bands around 1760 and 1660 cm^{-1} attributed to two carbonyl groups, and it also showed a band around 3400 cm^{-1} attributed to -NH group, as well as a broad band extending from 2800 to 3300 cm^{-1} for OH, which proves our structure (6). On the other hand, compounds (9) showed in their ir spectra a high frequency carbonyl band around 1850 cm^{-1} characteristic of the oxazolone -O-(CO)- grouping and a strong band around 1650 cm^{-1} characteristic of the -O-C=N- grouping, as well as showing a band around 1770 cm^{-1} indicates the acetoxy carbonyl group, which also proves our structure (9). The reaction, in our case, is assumed to proceed via the formation of the intermediates (11), (see Scheme 2), which gave the intermediates (12) via elimination of water, then, (12) were hydrolyzed to the acids (6), which in turn were cyclized to the oxazolones (9).

Table 1

Physical properties of the newly synthesised compounds

R	Cpd. ^{a)}	mp(°C)	Yield ^{b)} %	R	Cpd. ^{a)}	mp(°C)	Yield ^{b)}
Ph	6 _a	139-141	61	Et	6 _c	85-87	97
	9 _a	54 - 55	65		9 _c	liquid	50
	8	122-124	85	p-tolyi	9 _d	70-71	62
	10	258	60				
Me	6 _b	139-140	95.5	1-naphthyl	9 _e	84-85	65
				styryl	9 _f	119-120	65

a) Compounds (6) were purified by crystallization from ethyl acetate/hexane, except that (6_c) was crystallized from petroleum ether. Compounds (9) and (8) were purified by column chromatography on silica gel [eluent: a mixture of equal volumes of ethylacetate and hexane].

Compound (10) was purified by crystallization from DMF/water.

b) Yield after purification.

Table 2

Spectral and elemental analyses of the newly synthesized compounds

R	Cpd.	ir(cm ⁻¹)	¹⁹ Fnmr ^{a)}	¹ Hnmr ^{b)}	elemental analysis		
			δ ppm	δ ppm	calc./ (found)		
			J (Hz)		C%	H%	N%
Ph	6 _a	3440(NH)	2.25	8.66(s, 1H, OH)	45.62	3.04	5.32
		2800-3300(OH)		7.00-8.66(br, 2H, NH&OH)	(45.65)	(3.00)	(5.31)
		1780(CO)					
		1640(CO)		7.50-7.80(m, 2sets, 5H, arom.)			
	9 _a	1865(CO)	2.58	7.43-8.26(m, 2sets, 5H, arom.)	50.17	2.78	4.87
		1770(CO)			(50.21)	(2.70)	(4.98)
		1640(C=N)		2.23(s, 3H, CH ₃)			
	8	3300(NH)	4.00	8.33(br, 1H, NH)	49.31	3.65	6.39
		3100(br, OH)	(5.17)	7.43-8.06(m, 2sets, 5H, arom.)	(49.23)	(3.56)	(6.29)
		1640(CO)		7.00(s, 1H, OH)			
				6.00(m, 1H, CH)			
	10	3300(NH)	-0.5	8.46(d, 2H,	59.62	4.03	8.69
		1665(CO)	(7.05)	J=7.5Hz, 2NH)	(59.89)	(3.84)	(8.51)
Me	6 _b	3350(NH)	2.83	8.00-9.86(br, 3H, 2OH&NH)	29.85	2.98	6.96
		2600-3200(OH)			(29.52)	(2.68)	(6.76)
		1750(CO)		2.00(s, 3H, CH ₃)			
		1645(CO)					

cont. Table 2

Et	6 _a	3390(NH)	2.91	8.66-9.86(br, 2H,	33.48	3.72	6.51
		2800-3300(OH)		OH&NH)	(33.15)	(4.00)	(6.22)
		1755(CO)		8.30(s, 1H, OH)			
		1680(CO)		2.30(q, 2H, CH ₂)			
				1.16(t, 3H, CH ₃)			
	9 _c	1845(CO)	3.08	2.60(q, 2H, CH ₂)	40.16	3.34	5.85
		1780(CO)		2.16(s, 3H, CH ₃)	(40.20)	(3.44)	(5.87)
		1665(C=N)		1.26(t, 3H, CH ₃)			
p-tolyl	9 _d	1840(CO)	3.08	8.00(m, 2H, arom.)	51.82	3.32	4.65
		1775(CO)		7.33(m, 2H, arom.)	(51.60)	(3.43)	(4.54)
		1640(C=N)		2.46(s, 3H, CH ₃)			
				2.20(s, 3H, CH ₃)			
1-naphthyl	9 _e	1840(CO)	2.50	9.16(m, 1H, arom.)	56.97	2.96	4.15
		1760(CO)		7.60-8.43(m, 6H,	(56.78)	(2.83)	(4.13)
		1630(C=N)		arom.)			
				2.26(s, 3H, CH ₃)			
styryl	9 _f	1840(CO)	2.66	7.83(d, 1H, J=16.5	53.67	3.19	4.47
		1780(CO)		Hz, styryl CH)	(53.58)	(3.03)	(4.43)
		1645(C=N)		7.53(m, 5H, arom.)			
				6.66(d, 1H, J=16.5			
				Hz, styryl CH)			
				2.23(s, 3H, CH ₃)			

a) From external CF₃COOH in AcOEt, except compound (10) in DMF.

b) CDCl₃/ DMSO-d₆ (3/1) solvent for all compounds, except (9_c) CDCl₃.

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