TRIFLUOROPYRUVIC ACID HYDRATE IN HETEROCYCLIC SYNTHESIS, Part II[1]: SYNTHESIS OF TRIFLUOROMETHYLATED BENZOXAZINE, BENZOTHIAZINE AND BENZOXAZOLE DERIVATIVES

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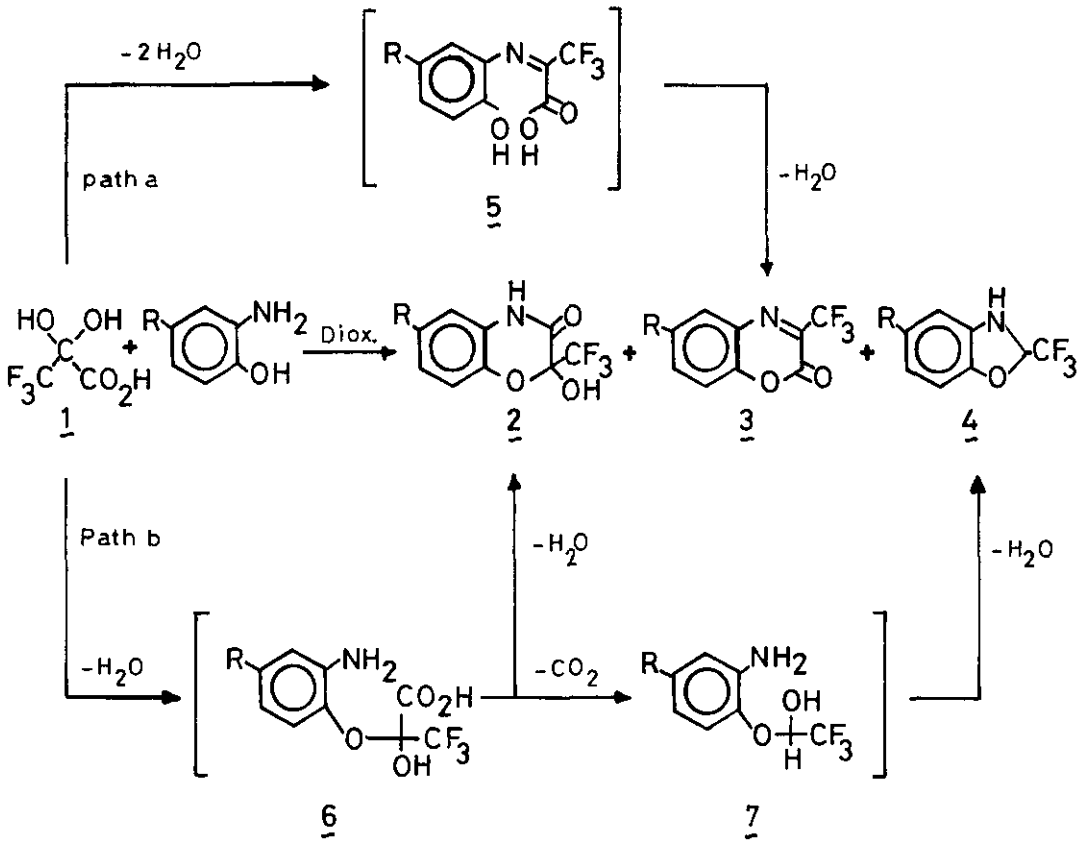
Abstract — Synthesis of 2-hydroxy-2-trifluoromethyl-2H-1,4-benzoxazin-3(4H)-one derivatives, 3-trifluoromethyl-1,4-benzoxazin-2-one derivatives, 2,3-dihydro-2-trifluoromethylbenzoxazole derivatives and 2-hydroxy-2-trifluoromethyl-2H-1,4-benzothiazin-3(4H)-one, by the reaction of trifluoropyruvic acid hydrate with 4-substituted 2-aminophenols and 2-aminothiophenol, respectively, is reported. The effect of the substituent, in the aminophenol ring, on the ratio of the formed isomers of benzoxazine is also investigated.

Recently, fluorine-containing compounds have attracted attention owing to their biological significance[2]. Among various significant factors, the introduction of a trifluoromethyl group into organic molecules is considered as one of the major topics of interest in fluorine chemistry. However, since, it is not easy to introduce a perfluoroalkyl group into heterocyclic rings[3,4], we became interested in the synthesis of trifluoromethyl-containing heterocycles through the reaction of trifluoropyruvic acid hydrate (1) with various bifunctional reagents. Recently, we have been involved in a program aiming to explore the potential scope and limitation of the utility of trifluoropyruvic acid hydrate in heterocyclic synthesis. During this phase of our research, we have developed a facile synthesis of trifluoromethyl-containing hydantoins from the reaction of trifluoropyruvic acid hydrate with urea derivatives[5]. As an extension of this program, we would like to report here on the synthesis of 2-hydroxy-2-trifluoromethyl-2H-1,4-benzoxazin-3(4H)-one derivatives (2), 3-trifluoromethyl-1,4-benzoxazin-2-one derivatives (3), 2,3-dihydro-2-trifluoromethylbenzoxazole derivatives (4) and 2-hydroxy-2-trifluoromethyl-2H-1,4-benzothiazin-3(4H)-one (8), through the reaction of (1) with 4-substituted 2-aminophenols and with 2-aminothiophenol, respectively.

A previous paper[6] from our laboratory reported that compounds (3) (R = H, CH_3, Cl) were prepared through the reaction of hexafluoro-1,2-epoxypropane with 4-substituted 2-aminophenols; however, this time we were able to synthesize compounds (3), (2) and (4) in one pot synthesis, and, moreover, we could investigate clearly the effect of the substituent (R), in 2-aminophenol, on the ratio of compounds (2), (3) and (4). Thus, it was found that, when equimolar amounts of (1) (10 mmol) and 2-aminophenol (10 mmol) were heated under reflux in dry dioxane (30 ml), [in the case of 4-nitro-2-aminophenol (50 ml)], until (1) completely disappeared (by ^{19}F-nmr) (see Table 2), a mixture of three products was observed by ^{19}F-nmr; these were assigned as structures (2), (3) and (4) based on spectral data as well as elemental analysis (see Scheme 1 and Table 3), this mixture could be separated by column chromatography on silica gel. (eluent: AcOEt / hexane = 1/10) .



Scheme 1

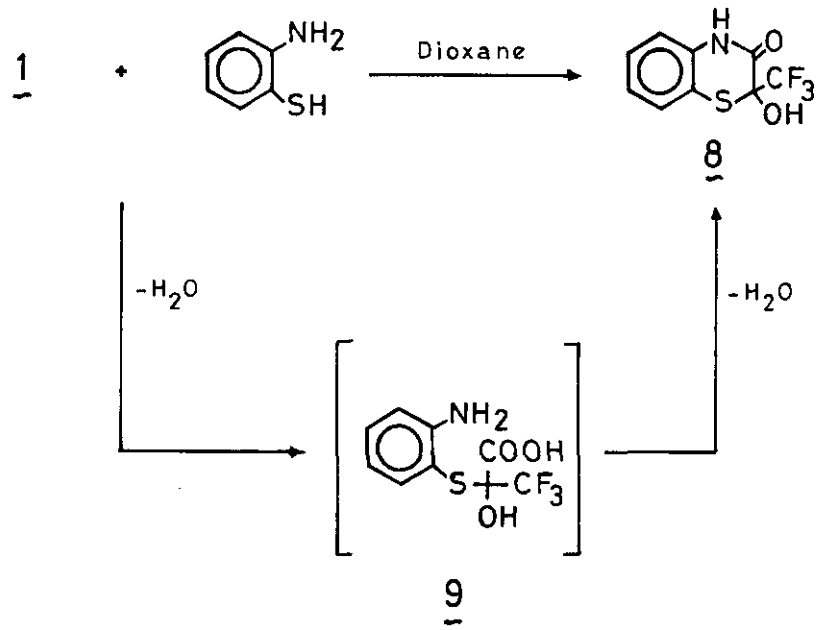
These three sets of compounds could be easily distinguished by ^{19}F-nmr as well as ir spectra; thus, in the ^{19}F-nmr spectra of compounds (2), the CF_3 signal was observed as singlet in a range δ3.5 - 3.6 ppm upfield from external CF_3COOH, and its ir spectra showed a characteristic amide carbonyl absorption at 1680 - 1700 cm^{-1}. However, in the ^{19}F-nmr spectra of compounds (3), the CF_3 signal was observed as singlet in a range δ-6.0 - -7.0 ppm downfield from external CF_3COOH, and its ir spectra showed a characteristic ester carbonyl absorption at 1755 - 1760 cm^{-1}. On the other hand, ^{19}F-nmr spectra of compounds (4) showed a doublet CF_3 signal in a range δ7.33 - 7.66 ppm upfield from external CF_3COOH (J_{CF_3-CH} = 3.76 - 4.70 Hz), and its ir spectra did not show any absorption due to carbonyl group; however, it showed a characteristic -NH absorption, as a sharp peak, at 3325 - 3390 cm^{-1}.

The reaction mechanism leading to the formation of these three compounds could be explained as follows. According to the competition between the amino group and the phenolic group, as nucleophiles in 2-aminophenol, in attacking the α-carbon atom in (1) which is the most active center towards nucleophiles[5,7], the reaction should proceed in two different competitive ways: in path [a] (see Scheme 1) the α-carbon atom in (1) was attacked by the amino group to produce intermediate (5), which undergoes cyclization to give the end product (3); on the other hand, in path [b] the α-carbon atom in (1) was attacked by the phenolic group leading to the formation of intermediate (6), which undergoes either cyclization to give product (2) or decarboxylation to give intermediate (7), which in turn cyclizes to the benzoxazole (4). The competition between path [a] and path [b] is affected by the substituent (R) in 2-aminophenol substrate, as was determined by ^{19}F-nmr spectra of the reaction mixture (see Table 1). Thus, with the increase in the

Table 1

No.	R	Relative percentages of the products determined by ^{19}Fnmr (2)	(3)	(4)	Total isolated Yield %
a	H	33	49.5	17.5	61
b	CH_3	28	53	19	62
c	Cl	52	29	19	58
d	NO_2	73	—	27	70

strength of the electron donating property of (R), the reaction proceeded more dominantly in the path [a] direction than in the path [b] direction, leading to formation of compound (3) with a higher ratio. Conversely, with the increase in the strength of the electron attracting property of (R), the reaction proceeded more dominantly in the path [b] direction than in the path [a] direction, leading to formation of compound (2) with a higher ratio. This fact was clarified further when (R) was NO_2, in this case, the reaction proceeded in the path [b] direction exclusively, leading to formation of compounds (2) and (4) only; the formation of compound (3) was not detected by ^{19}F-nmr spectrum of the reaction mixture. In a similar way, 2-aminothiophenol reacted with (1) under the same conditions mentioned above to yield 2-hydroxy-2-trifluoromethyl-2H-1,4-benzothiazin-3(4H)-one (8). The formation of compound (8), apparently, proceeded as shown in Scheme 2; thus, the mercapto group, which is more nucleophilic than the amino group[6], was the first to attack the α-carbon atom in (1) leading to formation of intermediate (9) which undergoes cyclization to give compound (8).



Scheme 2

Table 2

Reaction conditions and physical properties of compounds (2), (3), (4) and (8)

Cpd.	R	Reaction Conditions[a] reflux (h)	Recryst. Solv.	mp(°C) (reported)
2_a	H	3	benzene/pet. ether	144-146
3_a	"	3	pet. ether	78-79 (77-78[6])
4_a	"	3	pet. ether	81-82
2_b	CH_3	1	AcOEt/pet. ether	215-217
3_b	"	1	ethanol/water	121-122 (119-120.5[6])
4_b	"	1	pet. ether	55
2_c	cl	3	benzene	195-197
3_c	"	3	pet. ether	89-90 (88-89[6])
4_c	"	3	——	oil
2_d	NO_2	30	benzene	197-198
4_d	"	30	pet. ether	90-91
8	H	1	water/ethanol	190

a) Dioxane was used as solvent.

Table 3

Spectral data and elemental analysis of the newly synthesized compounds

Cpd.	ir(cm^{-1})	^{19}Fnmr[a] δ ppm J=(Hz)	^{1}Hnmr[b] δ ppm	ms(m/e) M^+	elemental analysis. calc./(found) C%	H%	N%
2_a	3250(NH) 3100(br,OH) 1680(CO)	3.5	11.2(s,1H,NH) 9.0(br,1H,OH) 6.93(m,4H,arom.)	233	46.35 (46.40)	2.57 (2.94)	6.00 (5.99)
2_b	3250(NH) 3050(br,OH) 1680(OH)	3.66	11.0(s,1H,NH) 8.9(br,1H,OH) 7.0(m,3H,arom.) 2.33(s,3H,CH_3)	247	48.58 (48.36)	3.23 (3.10)	5.66 (5.55)
2_c	3250(NH) 3050(br,OH) 1685(CO)	3.50	11.33(s,1H,NH) 9.13(br,1H,OH) 7.0(m,3H,arom.)	267.5	40.37 (40.33)	1.86 (1.71)	5.23 (5.19)
2_d	3300(NH) 3200(br,OH) 1720(CO)	3.58	11.66(s,1H,NH) 9.66(br,1H,OH) 7.63(m,2 sets,3H, arom.)	278	38.84 (38.84)	1.79 (1.59)	10.07 (9.98)
4_a	3390(NH)	7.33 (4.70)	6.86(s,4H,arom.) 5.90(m,1H,CH) 4.23(br,1H,NH)		50.79 (50.57)	3.17 (3.07)	7.40 (7.20)
4_b	3360(NH)	7.58 (4.70)	6.66(m,3H,arom.) 5.86(m,1H,CH) 4.16(br,1H,NH) 2.23(s,3H,CH_3)		53.20 (53.10)	3.94 (4.12)	6.89 (6.74)

cont. table 3

4_c	3390(NH)	7.66	6.80(m,3H,arom.)		42.95	2.23	6.26
		(3.76)	5.93(m,1H,CH)		(42.77)	(2.11)	(6.13)
			4.33(br,1H,NH)				
4_d	3320(NH)	7.50	7.7, 6.9(m,2H,		41.02	2.13	11.96
		(4.70)	1H,arom.)		(41.34)	(2.04)	(12.08)
			6.16(m,1H,CH)				
			4.80(br,1H,NH)				
8	3450(NH)	1.33	10.9(br,1H,NH)	249	43.37	2.40	5.62
	3200(br,OH)		7.50(s,1H,OH)		(43.69)	(2.30)	(5.69)
	1680(CO)		7.06(m,4H,arom.)				

a) From external CF_3COOH in AcOEt as solvent.

b) $CDCl_3$/DMSO-d_6 (3/1) solvent for compounds (2) and (8); $CDCl_3$ for compounds (4).

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