Haloacetylated Enol Ethers. 7 [7]. Synthesis of 3-Aryl-5-trihalomethylisoxazoles and 3-Aryl-5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles

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β-Aryl-β-methoxyvinyl trihalomethyl ketones **1a-g**, **2a-g** [aryl = *p*-YC_6H_4, where Y= H, Me, OMe, F, Cl, Br, NO_2] are cyclocondensed with hydroxylamine hydrochloride to afford the 3-aryl-5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles **3a-g**, **4a-f** in good yield. The dehydratation of compounds **3a-g** with concentrated sulfuric acid, led the corresponding 3-aryl-5-trichloromethylisoxazoles **5a-g**. An alternative one-pot procedure yields 3-aryl-5-trihalomethylisoxazoles **5,6a-g** directly by cyclocondesation of **1,2a-g** with hydroxylamine hydrochloride in the presence of an excess of concentrated hydrochloric acid.

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Isoxazoles and their derivatives have been recognized as highly useful components in medicinal chemistry [1,2]. Among the available methods for the preparation of substituted isoxazoles, oximation of 1,3-dicarbonyl compounds (mainly β-keto aldehydes and β-diketones) and cyclocondensation of nitrile oxides to unsaturated compounds are by far the most widely utilized [3]. However, with non-symmetrical starting materials, neither of these methods is completely unequivocal with respect to the control of site- and regioselectivities. On the other hand, we have reported a methodology which provides the regiospecific synthesis of halomethylisoxazoles in high yield when β-alkoxyvinyl trihalomethyl ketones were employed as starting materials [4].

In previous works, we described a general procedure to synthesize β-haloacetylated enol ethers, with functionalized acyl groups of the type CX_3CO [4] and CHX_2CO [5]. These compounds are of general interest as precursor for a variety of halo-substituted five- and six-membered heterocyclic compounds, *e.g.* isoxazoles [4-7], dihydroisoxazoles[4-7], pyrazoles [8,9] and pyrimidinones [10,11].

As a part of a series of cyclcocondensation reactions with dinucleophiles containing nitrogen [4-9], the aim of this work is the investigation of the CX_3-group and aryl group effects on the regiochemistry of the reactions of β-aryl-β-methoxyvinyl trihalomethyl ketones **1,2a-g** with hydroxylamine hydrochloride. A systematic study using precursors with X = Cl, F and aryl = *p*-YC_6H_4 [where Y= H, Me, OMe, F, Cl, Br, NO_2] was carried out to examine the scope of these cyclocondensation reactions (Scheme).

The, β-aryl-β-methoxyvinyl[fluoro]chloro methyl ketones **1,2a-g** were synthesized from the reaction of the respective acetophenone dimethyl acetals with trichloroacetyl chloride or trifluoroacetic anhydride [12].

The cyclization of **1,2a-g** with hydroxylamine hydrochloride was carried out in pyridine (**1a-f**) or hydrochloric acid (**1g,2a-f**) in the molar relation 1.0:1.2:1.2 respectively. The mixture was stirred at 70° and refluxed in methanol for 16 hours, to afford the 3-aryl-5-trihalomethyl-4,5-dihydroisoxazoles **3a-g** and **4a-f** in good yields (Scheme, Table 1).

Compounds **3a-g** were dehydrated with 97% sulfuric acid at 35° for 5 hours to afford the corresponding 3-aryl-5-trihalomethylisoxazoles **5a-g** in good yields (Scheme, Table 1). On the other hand, the use of an excess of concentrated hydrochloric acid at 70° for 48 hours allowed the 3-aryl-5-trihalomethylisoxazoles **5,6a-g** from β-aryl-

Table 1

Yields and Melting Points of Compounds **3,5,6a-g** and **4a-f**

Adduct	Method [a]	Product	Mp[b] (°C)	Yield [c]
1a	A	**3a**	156	90
1b	A	**3b**	125	85
1c	A	**3c**	130	90
1d	A	**3d**	125-126	90
1e	A	**3e**	161	89
1f	A	**3f**	172	90
1g	B	**3g**	198	87
2a	B	**4a**	146	75
	D	**6a**	80	67
2b	B	**4b**	61	85
	D	**6b**	79-80	70
2c	B	**4c**	54-55	80
	D	**6c**	74-75	76
2d	B	**4d**	118	87
	D	**6d**	43-44	69
2e	B	**4e**	65-66	85
	D	**6e**	61-62	73
2f	B	**4f**	60	87
	D	**6f**	63-64	68
2g	D	**6g**	113	80
3a	C	**5a**	80-81	93
3b	C	**5b**	76-77	91
3c	C	**5c**	82	85
3d	C	**5d**	73-74	95
3e	C	**5e**	86-87	91
3f	C	**5f**	89	94
3g	C	**5g**	97	92

[a] See Experimental. [b] Melting points determined with a Reichert Thermovar apparatus, and are uncorrected. [c] Yields of isolated compounds.

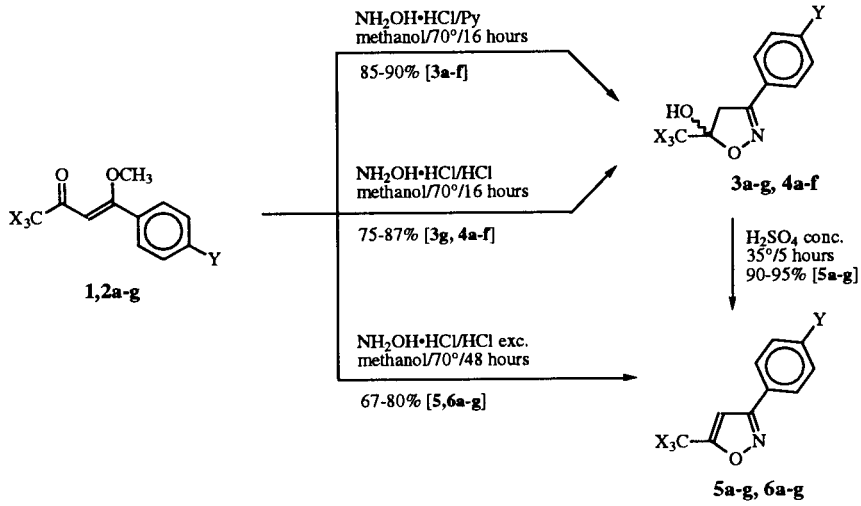
Table 2

Selected Spectral [a]Data of **3,5,6a-g** and **4a-f**

No.	Molecular Formula	Analysis (%) Calcd./Found C	H	N	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J_{C-F} (Hz)
3a	$C_{10}H_8O_2NCl_3$	42.81	2.87	4.99	3.71 (d, 1H, J = 18.6, 4a),	158.0 (C3), 45.2 (C4),
	280.54	42.94	2.85	4.85	4.16 (d, 1H, J = 18.6, H4b)	112.7 (C5), 102.4 (CCl_3)
3b	$C_{11}H_{10}O_2NCl_3$	44.85	3.42	4.76	3.66 (d, 1H, J = 18.5, H4a),	159.9 (C3), 45.3 (C4),
	294.56	45.09	3.41	4.66	4.14 (d, 1H, J = 18.5, H4b)	112.5 (C5), 102.4 (CCl_3)
3c	$C_{11}H_{10}O_3NCl_3$	42.54	3.25	4.51	3.65 (d, 1H, J = 18.4, H4a),	157.4 (C3), 45.3 (C4),
	310.56	42.35	3.29	4.33	4.13 (d, 1H, J = 18.4, H4b)	112.3 (C5), 102.4 (CCl_3)
3d	$C_{10}H_7O_2NFCl_3$	40.23	2.36	4.69	3.70 (d, 1H, J = 18.6, H4a),	157.2 (C3), 45.2 (C4),
	298.53	40.31	2.34	4.55	4.18 (d, 1H, J = 18.6, H4b)	112.8 (C5), 102.3 (CCl_3)
3e	$C_{10}H_7O_2NCl_4$	38.13	2.24	4.45	3.70 (d, 1H, J = 18.6, H4a),	157.3 (C3), 45.1 (C4),
	314.98	38.39	2.29	4.15	4.18 (d, 1H, J = 18.6, H4b)	113.0 (C5), 102.3 (CCl_3)
3f	$C_{10}H_7O_2NCl_3Br$	33.42	1.96	3.90	3.70 (d, 1H, J = 18.5, H4a),	157.2 (C3), 44.8 (C4),
	359.43	33.05	1.92	3.69	4.18 (d, 1H, J = 18.5, H4b)	112.8 (C5), 102.1 (CCl_3)
3g	$C_{10}H_7O_4N_2Cl_3$	36.90	2.17	8.61	3.79 (d, 1H, J = 18.8, H4a),	157.1 (C3), 44.7 (C4),
	325.54	36.98	2.17	8.60	4.27 (d, 1H, J = 18.8, H4b)	113.6 (C5), 102.1 (CCl_3)
4a	$C_{10}H_8O_2NF_3$	51.96	3.49	6.06	3.22 (d, 1H, J = 18.4, H4a),	157.6 (C3), 43.1 (C4), 106.5 (q, C5,
	231.17	51.88	3.59	6.03	3.51 (d, 1H, J = 18.4, H4b)	J = 33.1), 123.7 (q, CF_3, J = 280.1)
4b	$C_{11}H_{10}O_2NF_3$	53.88	4.11	5.71	3.56 (d, 1H, J = 18.9, H4a),	157.6 (C3), 43.7 (C4), 104.6 (q, C5,
	245.20	53.55	3.98	5.54	3.82 (d, 1H, J = 18.9, H4b)	J = 32.6), 123.6 (q, CF_3, J = 285.5)
4c	$C_{11}H_{10}O_3NF_3$	50.58	3.86	5.36	3.81 (d, 1H, J = 18.6, H4a),	157.4 (C3), 43.1 (C4), 104.7 (q, C5,
	261.20	50.52	3.62	5.18	3.69 (d, 1H, J = 18.6, H4b)	J = 33.7), 123.1 (q, CF_3, J = 277.9)
4d	$C_{10}H_7O_2NF_4$	48.21	2.83	5.62	3.58 (d, 1H, J = 18.2, H4a),	156.5 (C3), 42.7 (C4), 106.8 (q, C5,
	249.16	47.98	2.90	5.51	3.97 (d, 1H, J = 18.2, H4b)	J = 32.6), 124.0 (q, CF_3, J = 285.5)
4e	$C_{10}H_7O_2NF_3Cl$	45.22	2.66	5.27	3.58 (d, 1H, J = 18.8, H4a),	156.9 (C3), 43.4 (C4), 105.1 (q,C5,
	265.62	45.31	2.71	5.03	3.99 (d, 1H, J = 18.8, H4b)	J = 33.6), 123.4 (q, CF_3, J = 277.6)
4f	$C_{10}H_7O_2NF_3Br$	38.74	2.28	4.52	3.61 (d, 1H, J = 18.8, H4a),	157.0 (C3), 43.3 (C4), 105.1 (q, C5,
	310.07	38.57	2.19	4.41	3.98 (d, 1H, J = 18.8, H4b)	J = 33.7), 123.5 (q, CF_3, J = 283.6)
5a	$C_{10}H_6ONCl_3$	45.75	2.30	5.34	7.43 (s, 1H, H4)	163.5 (C3), 103.2 (C4), 169.6 (C5), 85.3
	262.52	45.71	2.48	5.14		(CCl_3)
5b	$C_{11}H_9ONCl_3$	47.60	3.27	5.05	7.39 (s, 1H, H4)	163.5 (C3), 103.1 (C4), 169.5 (C5), 85.4
	277.56	47.58	3.18	5.31		(CCl_3)
5c	$C_{11}H_9O_2NCl_3$	45.01	3.09	4.77	7.35 (s, 1H, H4)	163.2 (C3), 103.1 (C4), 169.4 (C5), 85.5
	293.56	44.87	3.20	4.58		(CCl_3)
5d	$C_{10}H_5ONFCl_3$	42.82	1.80	4.99	7.43 (s, 1H, H4)	161.9 (C3), 102.4 (C4), 168.9 (C5), 84.4
	280.51	43.04	2.03	4.78		(CCl_3)
5e	$C_{10}H_5ONCl_4$	40.45	1.70	4.72	7.49 (s, 1H, H4)	162.7 (C3), 103.3 (C4), 169.9 (C5), 85.3
	296.97	40.56	1.80	4.64		(CCl_3)
5f	$C_{10}H_5ONCl_3Br$	35.18	1.48	4.10	7.47 (s, 1H, H4)	161.9 (C3), 103.2 (C4), 169.8 (C5), 85.2
	341.42	35.46	1.61	4.00		(CCl_3)
5g	$C_{10}H_5O_3N_2Cl_3$	39.06	1.64	9.11	7.56 (s, 1H, H4)	161.9 (C3), 103.5 (C4), 170.2 (C5), 85.0
	307.52	38.91	1.50	8.99		(CCl_3)
6a	$C_{10}H_6ONF_3$	56.35	2.84	6.57	7.66 (q, 1H, J = 0.8, H4)	160.5 (C3), 105.2 (q, C4, J = 2.20), 159.1
	213.16	56.29	2.81	6.46		(q, C5, J = 42.1), 119.2 (q, CF_3, J = 269.5)
6b	$C_{11}H_8ONF_3$	58.16	3.55	6.17	7.60 (q, 1H, J = 0.8, H4)	163.7 (C3), 105.2 (q, C4, J = 2.20), 159.2
	227.19	57.84	3.52	6.02		(q, C5, J = 42.1), 119.2 (q, CF_3, J = 269.4)
6c	$C_{11}H_8O_2NF_3$	54.33	3.32	5.76	7.59 (q, 1H, J = 0.8, H4)	163.5 (C3), 105.1 (q, C4, J = 2.20), 159.0
	243.19	54.11	3.24	5.68		(q, C5, J = 41.9), 119.2 (q, CF_3, J = 269.1)
6d	$C_{10}H_5ONF_4$	51.96	2.18	6.06	7.67 (q, 1H, J = 0.8, H4)	162.9 (C3), 105.2 (q, C4, J = 2.20), 159.6
	231.15	52.07	2.25	5.90		(q, C5, J = 42.1), 119.2 (q, CF_3, J = 269.4)
6e	$C_{10}H_5ONF_3Cl$	48.51	2.04	5.66	7.39 (q, 1H, J = 0.8, H4)	162.9 (C3), 105.5 (q, C4, J = 2.20), 159.5
	247.60	48.59	1.99	5.58		(q, C5, J = 41.8), 119.1 (q, CF_3, J = 269.4)
6f	$C_{10}H_5ONF_3Br$	41.13	1.73	4.80	7.65 (q, 1H, J = 0.8, H4)	162.9 (C3), 105.3 (q, C4, J = 2.20), 159.5
	292.06	41.24	1.72	4.62		(q, C5, J = 42.0), 119.0 (q, CF_3, J = 271.0)
6g	$C_{10}H_5O_3N_2F_3$	46.53	1.95	10.85	7.82 (q, 1H, J = 0.8, H4)	162.3 (C3), 105.8 (q, C4, J = 2.20), 160.0
	258.16	46.58	1.93	10.82		(q, C5, J = 42.3), 118.9 (q, CF_3, J = 269.4)

[a] The nmr-spectra were recorded on a Bruker AC 80 (^{1}H at 80 MHz and ^{13}C at 20 MHz) in acetone-d_6/TMS. Elemental analysis were performed on a Vario EL Foss apparatus.

Scheme



β-methoxyvinyl trihalomethyl ketones **1,2a-g** to be obtained directly in a one-pot procedure with similar overall yield (Scheme, Table 1).

The results show that the presence of CX_3 group is a determining factor on the regiochemistry of the reaction. It was not observed any effect of the aryl substituent (Y) or the procedure used on the regiochemistry of the reaction.

Many compounds thus synthesized could be isolated from the reaction mixture in sufficiently high purity already. However, when necessary the compounds were filtered through column with 5 g silica (25 mm diameter, silica gel 60, 0.0040-0.063 mm). Recrystallizations were performed from methanol.

The isolated compounds were identified by ^{1}H- and ^{13}C nmr and confirmed by elemental analysis (Yields and physical constants are accumulated in Tables 1 and 2).

EXPERIMENTAL

Synthesis of 3-Aryl-5-trihalomethyl-4,5-dihydroisoxazoles **3a-g, 4a-f.**

General Procedure.

A solution of β-aryl-β-methoxyvinyltrihalomethylketones **1a-g, 2a-f** (16.8 mmoles) in pyridine (**1a-f**, 20.2 mmoles) or concentrated hydrochloric acid (**1g, 2a-f**, 20.2 mmoles) was prepared in a 100 ml flask. To this solution was added hydroxylamine hydrochloride (20.2 mmoles) in methanol (30 ml). The mixture was stirred for 16 hours at 70°. The solvent was evaporated in a rotavapor and the residue was extracted with dichloromethane (50 ml). The organic layer was washed with 0.5*N* hydrochloric acid solution (**1a-f**) or 10% sodium carbonate solution (**1g, 2a-f**) (3 x 100 ml), distilled water (1 x 100 ml) and dried with anhydrous sodium sulfate. Then the solvent was removed and the product (**3a-g, 4a-f**) was dried under vacuum. When necessary, the product was recrystallized from methanol (yields, 75-90%, Tables 1 and 2).

One-Pot Synthesis of 3-Aryl-5-trihalomethylisoxazoles **5,6a-g.**

General Procedure.

In a 50 ml flask a mixture of β-Aryl-β-methoxyvinyl trihalomethyl ketones **1,2a-g**, (10 mmoles) and hydroxylamine hydrochloride (11 mmoles in 5 ml of methanol) and concentrated hydrochloric acid (50 mmoles) was stirred at 70° for 48 hours. The mixture was poured slowly on 50 ml of 10% sodium carbonate solution and then extracted with dichloromethane (2 x 50 ml). The combined organic fractions were washed with deionized water, dried with anhydrous sodium sulfate and the solvent removed in a rotavapor. When necessary the product was recrystallized from methanol (yields, 67-80 %, Tables 1 and 2).

Synthesis of 3-Aryl-5-trichloromethylisoxazoles **5a-g.**

General Procedure.

In a 25 ml flask a mixture of 3-aryl-5-trichloromethyl-4,5-dihydroisoxazoles **3a-g**, (5 mmoles) in 5 ml of dichloromethane and concentrated sulfuric acid (5 mmoles) was stirred at 35° for 5 hours. The mixture was poured slowly on 50 ml of ice water and the solution was extracted with dichloromethane (3 x 30 ml). The combined organic fractions were washed with deionized water, dried with anhydrous sodium sulfate and the solvent removed in a rotavapor. When necessary the product was recrystallized from methanol (yields, 90-95%, Tables 1 and 2).

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