Haloacetylated Enol Ethers. 9 [18]. Synthesis of 4-Trifluoromethyl-2-methyl[phenyl]pyrimidines and Tetrahydro Derivatives

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The synthesis of 4-trifluoromethyl-2-methyl[phenyl]pyrimidines and the corresponding tetrahydro derivatives from the cyclo-condensation reaction of β-alkoxyvinyl trifluoromethyl ketones **1a-d** with acetamidine or benzamidine hydrochloride, is reported. For the cyclo-condensation of **1a-d** with acetamidine and benzamidine hydrochloride, two methods were tested: 1 *M* solution of sodium hydroxide (method A) and sodium alkoxide/alcohol (method B). Depending on the structure of the β-alkoxyvinyl trifluoromethyl ketones and the reactions conditions, pyrimidines or tetrahydropyrimidines or a mixture of both compounds were obtained.

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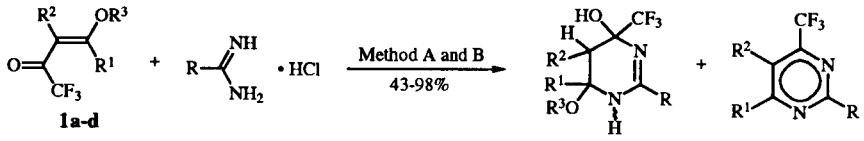
Many pyrimidines or their derivatives have shown remarkable biological activities and they have been widely used in a variety of fields ranging from medicinal to agriculture applications [1-3]. Trifluoromethyl substituted pyrimidines are relatively rare but promising templates for biological activity due to the strong anti-oxidant ability and substantial lipophilicity of the trifluoromethyl group [4]. In a search in the literature we found only two variety of halomethyl substituted five- and six-membered heterocycles, *e.g.* isoxazoles [7,10-13], pyrazoles [14,15], pyrimidinones [16], 2-methylthiopyrimidines [17] and 2-aminopyrimidines [18].

The purpose of this work is to report the results of the cyclo-condensation of β-alkoxyvinyl trifluoromethyl ketones **1a-d** with acetamidine and benzamidine hydrochloride (Scheme 1).

Scheme



Compound	R^1	R^2	R^3
1a	H	H	Et
b	Me	H	Me
c	H	$-(CH_2)_2-$	
d	H	$-(CH_2)_3-$	

R	Compound
Me	2,4
Ph	3,5

methods to obtain trifluoromethyl-2-alkyl[phenyl]-pyrimidines. One of these procedures report the synthesis of 4-fluoro-5-trifluoromethyl-6-methoxy-2-methyl-[phenyl]pyrimidines obtained from the reaction of 1,3,3,3-tetrafluoro-2-trifluoromethylpropenyl methyl ester with acetamidine and benzamidine in the presence of aqueous sodium hydroxide [5]. In a second procedure Ishihara *et al.* [6] prepared a series of 4-alkyl-6-trifluoromethyl-5-fluoropyrimidines from the condensation of 1-alkyl[phenyl]-substituted-2,3,3,4,4,4-hexafluoro-1-diethylphosphate-1-butene with amidine, in good yields.

As a part of our research program we have developed a general one-step procedure for preparing analytical pure β-alkoxyvinyl trihalomethyl ketones from the acylation of several enol ethers [7] or acetals [8,9], in molar quantities. These compounds have been used as precursors for a

The cyclizations did not take place without using a relatively strong base such as sodium hydroxide or alkoxides to liberate the amidines from their hydrochloride salts. Weaker bases such as pyridine and sodium carbonate, gave no positive reactions, nor did cyclization proceed using hydrochloric acid which was successfully utilized in other cyclization of β-alkoxyvinyl trihalomethyl ketones with urea and 2-methyl-2-thiopseudourea sulfate [16,17]. Thus, the cyclo-condensation reactions of β-alkoxyvinyl trifluoromethyl ketones **1**, with acetamidine and benzamidine hydrochloride were carried out using two methods: 1 *M* solution of sodium hydroxide (method A) and sodium alkoxide/alcohol (method B).

The cyclization reactions are shown in Scheme 1 and the most satisfactory results of these reactions are recorded in Tables 1 and 2. Selected physical and spectral data are presented in Tables 3, 4, 5, and 6.

Table 1

Optimized Yields for the Synthesis of Compounds **2a,c,d** and **4a-d**

Educt	Method [a]	Temperature (°C)/ Time (minutes)	Product	Yield (%) [b]
1a	A	25/60	**2a + 4a**	46/14
1a	A	0/60	**2a**	69
1a	B	0/60	**2a**	77
1b	A	0/60	**4b + 1b' + 1b**	22/25/6
1b	A	25/150	**4b + 1b'**	20/31
1b	B	25/150	**4b**	68
1c	A	25/60	**2c + 4c**	18/24
1c	A	0/60	**2c + 4c**	7/37
1c	B	25/60	**2c**	42
1c	B	0/60	**2c**	45
1d	A	25/60	**2d + 4d**	32/34
1d	A	0/60	**4d**	63
1d	B	25/60	**4d**	43
1d	B	0/60	**4d**	42

[a] Method A: 1 *M* solution of sodium hydroxide. Method B: sodium alkoxide/alcohol (alcohol *e.g.* methanol or ethanol). [b] The yields of the mixture of products were obtained from pmr spectral integration of the crude mixture before purification. The purity of the crude mixture was always above 95%, by nmr. The yields of single products are reported after purification.

Table 2

Optimized Yields for the Synthesis of Compounds **3a,c,d** and **5a-d**

Educt	Method [a]	Temperature (°C)/ Time (minutes)	Product	Yield (%) [b]
1a	A	25/20	**3a + 5a**	39/39
1a	A	0/20	**3a + 5a**	61/37
1a	B	25/30	**3a**	67
1b	A	25/20	**5b**	71
1b	B	25/20	**5b**	72
1c	A	25/20	**3c + 5c**	66/6
1c	B	25/20	**3c + 5c**	44/22
1d	A	25/20	**3d + 5d**	61/17
1d	B	25/20	**3d + 5d**	28/56

[a] Method A: 1 *M* solution of sodium hydroxide. Method B: sodium alkoxide/alcohol (alcohol *e.g.* methanol or ethanol). [b] The yields of the mixture of products were obtained from pmr spectral integration of the crude mixture before purification. The purity of the crude mixture was always above 95%, by nmr. The yields of single products are reported after purification.

Reaction of compound **1a** with acetamidine hydrochloride, by the method A at room temperature, led to a mixture of tetrahydropyrimidine **2a** and pyrimidine **4a** in a ratio of 5:1. The same reaction carried out at 0°, produced only compound **2a** in 69% yield. Pure tetrahydropyrimidine **2a** was obtained in 77% yield by the method B.

The condensation of compound **1b** with acetamidine hydrochloride, by the method A at 0° gave a mixture of pyrimidine **4b**, the 1,1,1-trifluromethyl pentane-2,4-dione **1b'** from the hydrolysis of **1b**, and a trace of the starting material **1b**. This same reaction carried out at 25° with a longer reaction time provided a mixture in a ratio of 1:1.4 of compounds **4b** and β-diketone **1b'**. The starting material **1b** disappeared completely. Therefore, the reaction of compound **1b** with acetamidine hydrochloride in the presence of sodium hydroxide shows a competition between the cyclization and the hydrolysis of the β-alkoxyvinyl ketone to the parent β-diketone with the equilibrium of the reaction favoring slightly the formation of the β-diketone. However, this reaction when carried out by the method B, furnished the expected pyrimidine **4b** as a pure compound in 68% yield. The tetrahydro derivative **2b** was never obtained.

Reaction of compound **1c** with acetamidine hydrochloride, by method A at room temperature, led to a mixture of compounds **2c** and **4c** in a ratio of 1:1.3. The same reaction carried out at 0° gave the same mixture of compounds but in a ratio of 1:5 of **2c** and **4c**. On the other hand, the reaction carried out by method B, only **2c** was obtained.

A mixture of compounds **2d** and **4d** in a ratio of 1:1 was obtained when compound **1d** was allowed to react

Table 3

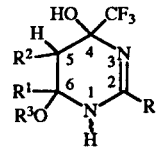
Selected Physical Data for **2a,c**, and **3a,c,d**

Compound [a]	Yield (%) [b]	Mp (°C) [c]	Molecular Formula	Analysis (%) Calcd/Found C	H	N
2a	77	103-105	$C_8H_{13}N_2O_2F_3$	42.48	5.79	12.38
			226.20	42.45	5.73	12.50
2c	45	150-151	$C_8H_{11}N_2O_2F_3$	42.86	4.95	12.50
			224.18	42.84	5.06	12.41
3a	–	–	$C_{13}H_{15}N_2O_2F_3$	54.17	5.24	9.72
			288.27		[d]	
3c	66	141-143	$C_{13}H_{13}N_2O_2F_3$	54.55	4.58	9.79
			286.25	54.47	4.68	9.87
3d	61	158-160	$C_{14}H_{15}N_2O_2F_3$	56.00	5.03	9.33
			300.28	55.89	5.12	9.18

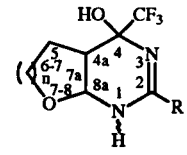
[a] The stereochemistry of the compounds was not determined. [b] Yields of isolated compounds. [c] The melting points were determined on the possible mixture of stereoisomers and are uncorrected. [d] This compound is not stable.

Table 4

^1H and ^{13}C NMR Data [a] for Compounds **2a, c** and **3a, c, d**



2a, 3a



n = 1,2

2c, 3c, d

Compound [b]	^1H-NMR δ, J (Hz)	^{13}C-NMR, δ, J_{CF} (Hz)
2a	6.2-5.0 (bs, 1H, N-H), 4.7-4.5 (m, 1H, H6), 3.7-3.3 (m, 2H, -OCH_2-), 2.1-1.7 and 1.5-1.2 (m, 2H, H5 and H5'), 1.6 (s, 3H, CH_3), 1.1 and 1.0 (2 t, 3H, J = 7.0, CH_3)	156.0, 155.5 (C2), 124.4 (q, $^1J_{CF}$ = 286.0, CF_3), 81.0 (q, $^2J_{CF}$ = 29.5, C4), 79.7, 77.8 (C6), 62.2, 61.9 (C9), 31.2, 30.0 (C5), 21.8, 22.3 (C8), 15.1 (C10)
2c	4.48 (d, 1H, J = 9.6, H7a), 3.9 (t, J = 7.3, H6), 2.2-1.9 (m, 2H, H5), 1.7 (m, 1 H, H4a)	156.2, 155.5 (C2), 125.3, 124.5 (q, $^1J_{CF}$ = 285.3, CF_3), 82.5 (q, $^2J_{CF}$ = 28.9, C4), 81.5, 81.0 (C7a), 66.4, 66.1 (C6), 40.0 (C4a), 25.5, 24.6 (C5), 21.5, 21.2 (CH_3)
3a	7.9-7.4 (m, 5H, Ph), 5.7 (bs, 1H, NH), 4.9-4.7 (m, 1H, H6), 3.8-3.4 (m, 2H, -OCH_2-), 2.2-1.9 and 1.7-1.4 (m, 2H, H5 and H5'), 1.2 and 1.1 (2t, 3H, J = 7.0, CH_3)	153.8 (C2), 126.9, 128.3, 130.2, 132.9 (Ph), 125.6 (q, ^1JC_F = 285.7, CF_3), 79.5 (q, $^2J_{CF}$ = 29.1, C4), 78.8 (C6), 55.6 (C9), 29.7 (C5), 16.9 (CH_3)
3c	8.2 (bs, 1H, N-H), 7.9-7.4 (m, 5H, Ph), 4.8-4.6 (m, 1H, H7a), 4.2-3.8 (m, 2H, H6), 2.1-1.6 (m, 3H, H4a and H5)	152.1 (C2), 132.6, 131.1, 128.3, 127.3 (Ph), 127.3 (q, ^1JC_F = 285.3, CF_3), 93.4 (C7a), 79.1 (q, $^1J_{CF}$ = 285.7, C4), 66.4 (C6), 40.5 (C4a), 21.8 (C5)
3d	8.3 (bs, 1H, N-H), 7.9, 7.5 (m, 5H, Ph), 4.6-4.4 (m, 1H, H8a), 4.0-3.6 (m, 2H, H7), 2.2-1.4 (m, 5H, H4a, H5, H6)	155.7 (C2), 135.1, 130.8, 128.3, 127.4, 126.8 (q, $^1J_{CF}$ = 286.0, CF_3), 82.2 (C8a), 81.5 (q, $2J_{CF}$ = 28.4, C4), 66.2 (C7), 39.5 (C4a), 25.3 (C5), 22.3 (C6)

[a] The nmr spectra were recorded in dimethyl-d_6 sulfoxide/tetramethylsilane. [b] The nmr data were collected on the possible mixture of stereoisomers.

Table 5

Selected Physical and Mass Spectral Data for **4a-d** and **5a-d**

Compound	Yield (%) [a]	Mp (°C)	Molecular Formula	Analysis(%) Calcd/Found C	H	N	MS (70 eV) M/z
4a	–	oil	$C_6H_5N_2F_3$ 162.11	44.45	3.11 [b]	17.28	
4b	68	oil	$C_7H_7N_2F_3$ 176.14	47.73 47.43	4.01 4.35	15.90 13.62	177 (MH^+, 100), 107 (38), 66 (38)
4c	–	oil	$C_8H_9N_2OF_3$ 206.17	46.61	4.40 [b]	13.59	207 (MH^+, 100), 148 (7), 107 (7).
4d	63	oil	$C_9H_{11}N_2OF_3$ 220.19	49.09 48.77	5.04 5.06	12.72 12.63	220 (M^+, 15), 201 (100), 175 (19), 160 (26), 147 (43), 132 (26), 124(19), 105 (19), 91 (26)
5a	67	96-98	$C_{11}H_7N_2F_3$ 224.19	58.93 58.91	3.15 3.12	12.50 12.57	224 (M^+, 68), 155 (100), 128 (8), 103 (21)
5b	72	60-61	$C_{12}H_9N_2F_3$ 238.21	60.51 60.37	3.81 3.84	11.76 11.68	238 (M^+, 100), 169 (69), 128 (22), 104 (56)
5c	–	–	$C_{13}H_{11}N_2OF_3$ 268.24	58.21	4.13	10.44 [b]	269 (MH^+, 10), 250 (100), 210 (13) 181 (12)
5d	56	–	$C_{14}H_{13}N_2OF_3$ 282.27	59.57 59.48	4.64 4.62	9.92 9.87	283 (MH^+, 100), 259 (63), 223 (17), 197 (17), 159 (9)

[a] Yields of isolated compounds. [b] These compounds could not be purified.

Table 6

^1H and ^{13}C NMR Data [a] for Compounds **4a-d** and **5a-d**

Compound	^1H-NMR, δ, J (Hz)	^{13}C-NMR, δ, J_{C-F} (Hz)
4a	9.1 (d, 1H, J = 5.3, H6), 7.8 (d, 1H, J = 5.3, H5), 2.7 (s, 3H, CH_3)	164.8 (C2), 160.0 (C6), 153.7 (C4, $^2J_{CF}$ = 35.6), 121.5 (CF_3, $^1J_{CF}$ = 285.9), 115.2 (C5), 20.0 (CH_3)
4b	7.3 (s, 1H, H5), 2.7 (s, 3H, CH_3), 2.6 (s, 3H, CH_3)	168.8 (C2), 167.8 (C6), 154.1 (C4, $^2J_{CF}$ = 35.1), 120.0 (CF_3, $^1J_{CF}$ = 288.1), 112.1 (C5), 24.3 (CH_3), 22.9 (CH_3)
4c	8.9 (s, 1H, H6), 3.7 (t, 2H, J = 6.3, CH_2), 2.9 (t, 2H, J = 6.3, CH_2), 2.7 (s, 3H, CH_3)	166.2 (C2), 161.6 (C6), 153.5 (C4, $^2J_{CF}$ = 34.2), 126.5 (C5), 121.6 (CF_3, $^1J_{CF}$ = 287.0), 60.3 (C10), 31.5 (C9), 25.8 (CH_3)
4d	8.7 (s, 1H, H6), 3.7 (t, 2H, J = 6.2, H11), 2.9 (t, 2H, J = 6.2, H9), 2.7 (s, 3H, CH_3), 1.8 (qui, 2H, J = 6.2, H10)	165.6 (C2), 160.7 (C6), 152.1 (C4, $^2J_{CF}$ = 34.0), 129.2 (C5), 121.9 (CF_3, $^1J_{CF}$ = 272.5), 60.5 (C11), 33.0 (C9), 24.7 (CH_3), 24.4 (C10)
5a	9.2 (d, 1H, J = 5.0, H6), 7.8 (d, 1H, J = 5.0, H5), 8.5-8.3, 7.4-7.6 (m, 5H, Ph)	164.0 (C2), 160.9 (C6), 154.5 (C4, $^2J_{CF}$ = 35.9), 121.3 (CF_3, $^1J_{CF}$ = 275.6), 115.5 (C5), 135.6, 131.5, 128.7, 127.8 (Ph)
5b	8.6-8.4, 7.6-7.4 (m, 5H, Ph), 7.3 (s, 1H, H5), 2.6 (s, 3H, CH_3)	170.9 (C2), 163.6 (C6), 153.7 (C4, $^2J_{CF}$ = 35.1), 135.6, 131.4, 128.6, 127.5 (Ph), 121.3 (CF_3, $^1J_{CF}$ = 275.0), 114.9 (C5), 23.9 (CH_3)
5c	9.1 (s, 1H, H6), 8.6-8.4, 7.6-7.4 (m, 5H, Ph), 3.7 (t, 2H, J = 6.2, CH_2), 2.9 (t, 2H, J = 6.2, CH_2)	162.4 (C2), 161.5 (C6) 152.3 (C4, $^2J_{CF}$ = 35.0), 135.2, 131.1, 128.2, 127.1 (Ph), 126.5 (C5), 121.5 (CF_3, $^1J_{CF}$ = 278.4), 59.7 (CH_2), 30.8 (CH_2)
5d	9.1 (s, 1H, H6), 8.6-8.4, 7.6-7.4 (m, 5H Ph), 3.7 (t, 2H, J = 6.2, CH_2), 2.9 (t, 2H, J = 6.2, CH_2), 1.8 (qui, 2H, J = 6.2, CH_2)	161.2 (C2), 160.7 (C6), 151.4 (C4, $^2J_{CF}$ = 34.8), 135.1, 131.7, 127.3, 127.3 (Ph), 128.5 (C5) 121.4 (CF_3, $^1J_{CF}$ = 286.3), 60.2 (CH_2) 32.1 (CH_2), 24.6 (CH_2)

[a] The nmr spectra were recorded in deuteriochloroform/tetramethylsilane.

with acetamidine hydrochloride by method A at room temperature, but at 0° as well as by method B, compound **4d** was the only product isolated.

The yields of cyclization of compounds **1a-d** with benzamidine hydrochloride are shown in Table 2. The cyclization of **1a** in a 1 *M* solution of sodium hydroxide showed temperature dependence in the ratio of tetrahydro pyrimidine **3a** to pyrimidine **5a**. The reaction carried out at room temperature provided a mixture of **3a** and **5a** in equal amounts. At lower temperatures, as expected, tetrahydropyrimidine **3a** was obtained as the major product. The tetrahydropyrimidine **3a** was identified by ^1H nmr but it was too unstable to be isolated as a pure compound. The same reaction carried out by method B furnished only the thermodynamically more stable pyrimidine **5a**.

Cyclization of **1b** by both methods A and B gave only pyrimidine **5b** in good yields. Reaction of **1c** with benzamidine hydrochloride by method A resulted in a mixture of tetrahydropyrimidine **3c** as the major compound and only a trace of pyrimidine **5c** was observed. The same reaction carried out by method B gave a mixture of compounds wherein **3c** was still the major compound. Compound **3c** was obtained as a single compound by recrystallization from chloroform, whereas **5c** was not recovered from the mother solvent. A similar trend was observed for the reaction of **1d** with benzamidine hydrochloride, however, **5d** was recovered as a pure compound.

EXPERIMENTAL

The β-alkoxyvinyl trifluoromethyl ketones **1a-d** were prepared according to reference [7]. The ^1H- and ^{13}C-nmr spectra were recorded at 80.13 and 20.15 MHz respectively on a Bruker AC-80 in a 5 mm probe in Chloroform-d_1 or dimethyl-d_6 sulfoxide. Tetramethylsilane was used as the internal reference. The mass spectra were recorded on an Ion Trapp Detector Finnigan Mat 80A connected to a GC Varian 3400 equipped with a fused silica capillary column SE-30, 50 m, 0.32 mm ID. The progress of the reactions was monitored with an HPLC LKB Broma equipped with a pump LKB 2241, rheodyne injector, UV detector LKB 2151, and a two channel plotter LKB 2210. The hplc runs were performed on a C-18 analytical column (250 x 4.6 mm, 5μ) and methanol/water (70:30) as the mobile phase. The purity of the compounds were analyzed on a GC Carlo Erba Mega Series 5300, equipped with a fused silica capillary column SE-30, 50 m, 0.32 mm ID, split-splitless injector, FID detector, and Spectra Physics integrator SP 4270. The melting points were taken on a Reichert-Thermovar melting point microscope and are uncorrected. The elemental analyses were performed on Elementar Analysensysteme Vario EL equipment.

6-Ethoxy-4-hydroxy-4-trifluoromethyl-3,4,5,6-tetrahydromethylpyrimidine (**2a**). General Procedure.

Method A.

To a solution of 0.71 g (7.5 mmoles) of acetamidine hydrochloride in 7.5 ml (7.5 mmoles) of 1 *M* solution of sodium hydroxide kept under 0°, was added 0.84 g (5.0 mmoles) of **1a** which was also cooled at 0°. The mixture was stirred vigorously at 0° for 60 minutes. An oil was obtained which was extracted with chloroform, dried over anhydrous sodium carbonate and the solvent was removed in a rotavapor. A white solid was obtained which was recrystallized from chloroform yielding 0.78 g (69%) of **2a**. Compound **2c** was recrystallized from chloroform. Compound **2b** was never observed and compound **2d** could not be isolated as a pure compound.

4-Trifluoromethyl-2,6-dimethylpyrimidine (**4b**). General Procedure.

Method B.

To a solution of sodium methoxide, prepared from sodium (0.18 g, 7.5 mmoles) and methanol 10 ml, was added (0.71 g, 7.5 mmoles) of acetamidine hydrochloride. The resulting salt was removed by filtration and to the filtrate was added 0.84 g (5 mmoles) of **1b** with vigorous stirring. The mixture was kept under vigorous stirring at room temperature for 150 minutes. The methanol was removed with rotavapor and the resulting oil was added to distilled water and extracted with chloroform (3 x 20 ml). The organic layer was dried over anhydrous magnesium sulfate and the solvent was vacuum evaporated resulting in an oil which was further purified by column chromatography on silica gel 60 (230-400 mesh ASTM). Elution with dichloromethane gave 0.6 g (68%) of **4b**. Compounds **4a** and **4c**, were not isolated as pure compounds, however these compounds were pure enough for nmr and ms spectral data. Compound **4d** was purified by column chromatography as was compound **4b**.

4-Hydroxy-2-phenyl-4-trifluoromethyl-1,4,4a,5b,7a-hexahydrofuro[2,3-*d*]pyrimidine (**3c**). General Procedure.

Method A.

To a solution of (1.17 g, 7.5 mmoles) of benzamidine hydrochloride in (7.5 ml, 7.5 mmoles) of a 1 *M* solution of sodium hydroxide was added (0.84 g, 5.0 mmoles) of **1c**. The mixture was stirred for 20 minutes at room temperature. A precipitate was observed as soon as the vinyl ketone **1c** was added to the benzamidine solution. The solid was filtered, washed with water and dried in a desiccator. A mixture of **3c** and **5c** was obtained in a ratio of 12:1 (64%:6%). Compound **3c** was isolated from **5c** by extraction with chloroform followed by recrystallization from methanol. Compound **5c** was not recovered from the recrystallization solvent. Compound **3a**, when recrystallized from chloroform, converted itself to the compound **5a**. Compound **3d** was isolated from **5d** and purified by the same procedure used for **3c**. Compound **3b** was never obtained.

4-Trifluoromethyl-2-phenylpyrimidine (**5a**). General Procedure.

Method B.

To a solution of sodium ethoxide, prepared from (0.18 g, 7.5 mmoles) of sodium and 10 ml of dry ethanol was added (1.17 g, 7.5 mmoles) of benzamidine hydrochloride. The sodium chloride, which precipitate in ethanol, was filtered and the filtrate was collected in a round bottom flask (0.84 g, 5.0 mmoles) of **1a** was added to the filtrate and the mixture was stirred for 30 minutes, at room temperature. The ethanol was evaporated in a rotavapor and the resulting solid was washed with water and dried in desiccator. The white solid was compound **3a** which when recrystallized from chloroform, **5a** was the only product recovered. Compound **5b** was recrystallized from chloroform, the compound **5c** was not recovered as a pure compound and **5d** was isolated from **3d** by extraction with chloroform and recrystallized twice from chloroform.

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