Haloacetylated Enol Ethers. **13** [19]. Synthesis of *N*-[1-Aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines and 2-Trichloromethyl-4-aryl-3*H*-1,5-benzodiazepines

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The synthesis and isolation of the intermediates *N*-[1-aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines **2a-f** and the corresponding 2-trichloromethyl-4-aryl-3*H*-1,5-benzodiazepines **3c-g** or benzimidazoles **4a-b** derivatives obtained from the intramolecular cyclization of **2a-f** or from direct cyclocondensation reaction of β-alkoxyvinyl trichloromethyl ketones **1a-g** with *o*-phenylenediamine, is reported. Depending of the structure of the β-alkoxyvinyl trichloromethyl ketones or the *N*-[1-aryl(alkyl)-3-oxo-4,4,4-trichloro-buten-1-yl]-*o*-phenylenediamines and the reactions conditions, benzimidazoles or 3*H*-1,5-benzodiazepines were obtained.

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In 1965, Effenberger [1] observed that 1,6-diethoxy-1,5-hexadiene-3,4-dione reacted with several primary and secondary amines (alkyl- and arylamines) in molar ratio 1:2 leading to the 1,6-diamino-1,5-hexadiene-3,4-dione in high yields. In recent years, Gerus and co-workers [2] reported the reaction of the β-alkoxyvinyl trifluoromethyl ketones with ammonia and primary amines to afford β-aminovinyltrifluoromethyl ketones. The reactions of the diamino compounds, ethylenediamine or *o*-phenylenediamine, with two equivalents of the enone gave the respective *N,N*-diaminotrifluoromethyl derivatives. In 1991, protected amino acids were prepared by the reaction of β-ethoxyvinyl trifluoromethyl ketone with L-amino acids in aqueous sodium hydroxide solution and the products were isolated in high yield after acidification of the reaction mixture [3]. We have previously found that the *EE*-conformer of 1,6-diethoxy-1,5-hexadien-3,4-dione reacts with primary amines in molar ration 1:1 to give mainly 1-aminoalkyl-6-ethoxy-1,5-hexadiene-3,4-diones exclusively as *Z,E* isomers. These 1-aminoalkyl-6-ethoxy-1,5-hexadiene-3,4-diones cyclize, under reflux in 1,2-dichlorobenzene, to yield 1-alkyl-1*H*-azepine-4,5-diones by an intramolecular cyclocondensation reaction [4].

On the other hand, it is well known that the intermolecular condensation of *o*-phenylenediamine with β-dicarbonyl compounds, as a one-pot procedure, has been the most widely used method for the synthesis of 3*H*-1,5-benzodiazepines [5,6]. Considering this information, we have investigated the reactions of some β-alkoxyvinyl trichloromethyl ketones with *o*-phenylenediamine, under various conditions. We have found that the synthesis of trichloroacetylated enaminones from β-alkoxyvinyl trichlorometyl ketones, as precursor from trichloromethylated heterocycles has not been reported yet.

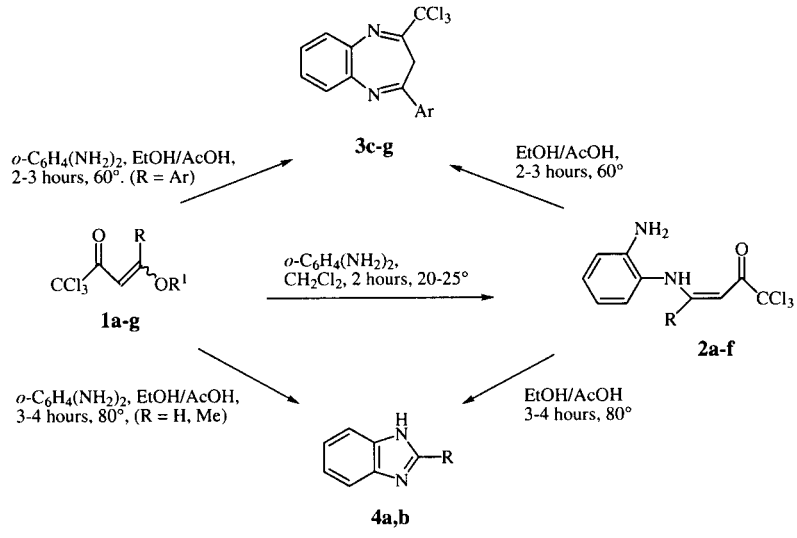
As a part of our research program we have developed a general one-step procedure for preparing analytical, pure β-alkoxyvinyl trihalomethyl ketones from the acylation of several enol ethers [7] or acetophenone dimethyl acetals [8,9], and trichloroacetyl chloride or trifluoroacetic anhydride, in molar quantities. These compounds have been used as precursors of a variety of substituted five- and six-membered heterocyclic halomethyl substituted compounds, *e.g.* isoxazoles [7,10-13], pyrazoles [14,15] and pyrimidines [16-18]. Recently, we have communicated the synthesis of substituted seven-membered 2-trichloromethylated-3*H*-1,5-benzodiazepines from the reaction of β-alkoxyvinyl trichloromethyl ketones with *o*-phenylenediamine [19].

The purpose of this work is to report the results of the synthesis of a series of fused seven-membered 2-trichloromethyl-4-aryl-3*H*-1,5-benzodiazepines **3c-g** and the isolation of the intermediates *N*-[1-aryl(aklyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines **2a-f** from the reactions of the 4-alkoxy-4-aryl(alkyl)-1,1,1-trichloro-3-buten-2-ones **1a-f** and *o*-phenylenediamine (Scheme 1).

The reactions of compounds **1a-g** with *o*-phenylenediamine, in dichloromethane at room temperature, led to the *N*-[1-aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines **2a-f**. The enaminone **2g** was not isolated as a pure compound. The same reaction carried out for compounds **1c-g** (R = aryl) in ethanol/acetic acid 4:1 for 2 or 3 hours at 60°, produced only the compounds **3c-g** in 52-79% yields. This reaction was carried out for compounds **1a-b** (R = alkyl) in the same solvent but for 3 or 4 hours at 80°, afforded benzimidazole **4a,b** in 70% and 75% yield, respectively.

Depending on the structure of the precursor, the intramolecular cyclocondensation of compounds **2a-f**, in ethanol/acetic acid 4:1 for 2 or 3 hours at 60° or for 3 or 4 hours at 80°, furnished the 3*H*-1,5-benzodiazepines **3c-f** or the benzimidazole **4a-b** in good yields.

Scheme 1



R^1	Et	Me	Me	Me	Me	Me	Me
R	H	Me	Ph	*p*-MePh	*p*-BrPh	*p*-NO_2Ph	*p*-OMePh
1-4	**a**	**b**	**c**	**d**	**e**	**f**	**g**

Table 1

Selected Physical Data for *N*-[1-Aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines **2a-f**

Compound	Yield (%) [a]	Mp (°) [b]	Molecular Formula	Analysis (%) [c] Calcd./Found C	H	N
2a	90	107-108	$C_{10}H_9N_2OCl_3$	42.96	3.24	10.02
			279.50	42.90	3.24	9.98
2b	92	109-110	$C_{11}H_{11}N_2OCl_3$	45.00	3.78	9.54
			295.50	44.97	3.77	9.45
2c	68	131-133	$C_{16}H_{13}N_2OCl_3$	54.01	3.65	7.88
			355.50	53.96	3.81	7.81
2d	76	138-139	$C_{17}H_{15}N_2OCl_3$	55.12	4.06	7.58
			369.50	55.24	4.23	7.57
2e	94	159-161	$C_{16}H_{12}N_2OBrCl_3$	44.20	2.76	6.44
			434.50	44.21	2.87	6.30
2f	71	169-170	$C_{16}H_{12}N_3O_3Cl_3$	47.94	3.00	10.49
			400.50	47.83	3.12	10.40

[a] Yields of isolated compounds. [b] The melting points are uncorrected. [c] Elemental analysis were performed on a Vario EL Elementar Analysensysteme.

Table 2

Selected ^1H and ^{13}C NMR Spectral Data [a] of Compounds **2a-f**

Compound	^1H NMR, δ (ppm) ^{13}C NMR, δ (ppm)
2a	11.2 (bs, 1H, N-H), 7.5-7.6 (dd, 1H, H1), 6.8-7.5 (m, 4H, aromatic-H), 6.0 (d, 1H, H2), 3.0 (bs, 2H, NH_2). 182.8 (C=O), 151.3 (C1), 137.6-117.7 (6C, aromatic-C), 96.4 (CCl_3), 88.2 (C2).
2b	11.5 (bs, 1H, N-H), 6.6-7.2 (m, 4H, aromatic-H), 5.9 (s, 1H, H2), 3.8 (bs, 2H, NH_2), 2.0 (s, 3H, -CH_3). 180.3 (C=O), 168.7 (C1), 141.7-115.4 (6C, aromatic-C), 96.2 (CCl_3), 87.1 (C2).
2c	11.6 (bs, 1H, N-H), 6.4-6.9 and 7.2 (m, 9H, aromatic-H), 6.0 (s, 1H, H2), 3.6 (bs, 2H, NH_2). 181.8 (C=O), 168.1 (C1), 141.3-116.0 (12C, aromatic-C), 96.9 (CCl_3), 90.3 (C2).
2d	11.7 (bs, 1H, N-H), 6.5-7.0 and 7.1-7.2 (m, 8H, aromatic-H), 6.1 (s, 1H, H2), 3.6 (bs, 2H, NH_2), 2.3 (s, 3H, -CH_3). 181.6 (C=O), 168.2 (C1), 141.4-116.0 (12C, aromatic-C), 97.0 (CCl_3), 90.1 (C2), 19.4 (*p*-CH_3).
2e	11.4 (bs, 1H, N-H), 6.4-6.9 and 7.1-7.5 (m, 8H, aromatic-H), 6.0 (s, 1H, H2), 3.5 (bs, 2H, NH_2). 181.9 (C=O), 166.8 (C1), 141.3-115.9 (12C, aromatic-C), 96.8 (CCl_3), 90.3 (C2).

Table 2 (continued)

Selected ^1H and ^{13}C NMR Spectral Data [a] of Compounds **2a-f**

Compound	^1H NMR, δ (ppm) ^{13}C NMR, δ (ppm)
2f	1.3 (bs, 1H, N-H), 6.4-7.6 and 8.0-8.2 (m, 8H, aromatic-H), 6.0 (s, 1H, H2), 3.8 (bs, 2H, NH_2). 182.2 (C=O), 165.8 (C1), 148.6-116.2 (12C, aromatic-C), 96.6 (CCl_3), 90.8 (C2).

[a] The nmr spectra were recorded on a Bruker DPX-200 (^1H at 200.13 MHz and ^{13}C at 50.32 MHz) in deuteriochloroform/tetramethylsilane.

Table 3

Selected Physical Data for 2-Trichloromethyl-4-aryl-3*H*-1,5-benzodiazepines **3c-g**

Compound	Yield (%) [a]	Mp (°) [b]	Molecular Formula	Analysis (%) [c] Calcd./Found		
				C	H	N
3c	67	110-112	$C_{16}H_{11}N_2Cl_3$	56.88	3.26	8.30
			337.50	56.83	3.34	8.09
3d	79	129-130	$C_{17}H_{13}N_2Cl_3$	58.04	3.70	7.96
			351.50	57.79	3.74	7.82
3e	66	153-154	$C_{16}H_{10}N_2Cl_3Br$	46.10	2.76	6.44
			416.50	45.99	2.58	6.56
3f	55	148-149	$C_{16}H_{10}N_3O_2Cl_3$	50.20	2.61	10.98
			382.50	50.25	2.62	10.65
3g	52	125-127	$C_{17}H_{13}N_2OCl_3$	55.21	3.54	7.62
			367.50	55.00	3.62	7.59

[a] Yields of isolated compounds. [b] The melting points are uncorrected. [c] Elemental analysis were performed on a Vario EL Elementar Analysensysteme.

Table 4

Selected ^1H and ^{13}C nmr Spectral Data [a] for Compounds **3c-g**

Compound	^1H-NMR, δ (ppm) ^{13}C NMR, δ (ppm)
3c	8.0-7.9 and 7.6-7.2 (m, 9H, aromatic-H), 3.6 (s, 2H, $-CH_2-$). 156.3 (C2/C4), 151.7 (C4/C2), 140.0-125.5 (12C, aromatic-C), 96.5 (CCl_3), 32.8 (C3)
3d	7.9-7.8 and 7.6-7.0 (m, 8H, aromatic-H), 3.7 (bs, 2H, $-CH_2-$), 2.3 (s, 3H,.$-CH_3$). 156.9 (C2/C4), 152.4 (C4/C2), 142.0 (CCl_3), 33.4 (C3), 22.0 (*p*-CH_3).
3e	7.9-7.8 and 7.6-7.4 (m, 8H, aromatic-H), 3.6 (bs, 2H, $-CH_2-$). 154.8 (C2/C4), 151.4 (C4/C2), 140.4-125.7 (12C, aromatic-C), 96.3 (CCl_3), 32.4 (C3).
3f	8.3-8.2 and 7.6-7.3 (m, 8H, aromatic-H), 3.7 (bs, 2H, $-CH_2-$). 154.0 (C2/C4), 151.6 (C4/C2), 149.0-124.0 (12C, aromatic-C), 96.3 (CCl_3), 33.0 (C3).
3g	7.9-7.8 and 7.5-6.0 (m, 8H, aromatic-H), 3.6 (bs, 2H, $-CH_2-$), 3.4 (s, 3H, *p*-OCH_3). 162.1 (C2/C4), 150.0 (C4/C2), 141.0-125.9 aromatic-C), 96.7 (CCl_3), 32.7 (C3), 55.2 (*p*-OCH_3).

[a] The nmr spectra were recorded on a Bruker DPX-200 (^1H at 200.13 MHz and ^{13}C at 50.32 MHz) in deuteriochloroform/tetramethylsilane.

The results of this work suggest that the synthesis of 1,5-3*H*-benzodiazepines **3c-g** or the benzimidazoles **4a-b** does not depend on the first step of the reaction, the synthesis of the β-enaminones **2a-f**. It was observed that the bulky groups at the 4-position of **1a-g** or at **2a-f** favours the formation of the benzodiazepines **3c-g** and that compounds **1a-b or 2a-b** with small groups at this position, are readily converted into benzimidazole **4a-b**.

All reactions are presented in Scheme 1 and the best results of these reactions are shown in Tables 1 and 3. Selected physical and spectral data are presented in Tables 2 and 4.

EXPERIMENTAL

The β-alkoxyvinyl trichloromethyl ketones **1a-b** were prepared according to reference [7] and the β-aryl-β-methoxyvinyl trichloromethyl ketones **2c-f** were synthesized from the reaction of the respective acetophenone dimethyl acetals with trichloroacethyl chloride [8,9]. The ^1H- and ^{13}C-nmr spectra, at

200.13 and 50.32 MHz respectively, were recorded on a Bruker DPX-200 in a 5 mm probe in chloroform-d_1 and tetramethylsilane was used as internal reference. The melting points were taken on a melting point microscope Reichert-Thermovar and are uncorrected. The elemental analysis were performed on an Elementar Analysensysteme Vario EL equipment.

N-[1-Aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines **2a-f**.

General Procedure.

To a stirred solution of *o*-phenylenediamine (20 mmoles) in 80 ml of dry dichloromethane, a solution of the 4-alkoxy-4-aryl(alkyl)-1,1,1-trichloro-3-buten-2-one **1a-f** (20 mmoles) in dry dichloromethane was added for 1 hour at 20-25°. The mixture was stirred for 1 hour at 20-25°. The solvent was evaporated and the solid or crude oily products **2a-b** were recrystallized from methanol or dichloromethane/diethyl ether (3:1) (yields, 68-94%, Table 1). Compound **2g** could not be isolated as a pure compound.

2-Trichloromethyl-4-aryl-3*H*-1,5-benzodiazepines **3c-g** and Benzimidazoles **4a-b** from 4-Alkoxy-4-aryl(alkyl)-1,1,1-trichloro-3-buten-2-ones **1a-g**.

General Procedure.

To a stirred solution *o*-phenylenediamine (6 mmoles) in 4 ml of dry ethanol and 1 ml acetic acid, 4-alkoxy-4-aryl(alkyl)-1,1,1-trichloro-3-buten-2-ones **1a-g** (6 mmoles) were added in small portions at 60°. The mixture was stirred for 2-3 hours at 60° for **1c-g** or for 3-4 hours at 80° for **1a-b**. The solvent was removed and the crude solid products were recrystallized from methanol for **3c-g** or from water for **4a-b** (yields 52-79%, Table 3, **4a** 70%, **4b** 75%).

2-Trichloromethyl-4-aryl-3*H*-1,5-benzodiazepines **3c-g** and Benzimidazoles **4a-b** from *N*-[1-Aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines.

General Procedure.

A solution *N*-[1-aryl(alkyl)-3-oxo-4,4,4-trichloro-1-buten-1-yl]-*o*-phenylenediamines **2a-f** (6 mmoles) in 4 ml of dry ethanol and 1 ml of acetic acid was stirred for 2-3 hours at 60° for **2c-f** or for 3-4 hours at 80° for **2a-b**. The solvent was removed and the crude solid products were recrystallized from methanol **3c-g** or from water for **4a-b** (yields **3c-g** 50-72%, **4a** 73%, **4b** 75%).

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