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Synthesis of hydroxypyrazoles and 1-methyl-3-isoxazolones via haloform reactions

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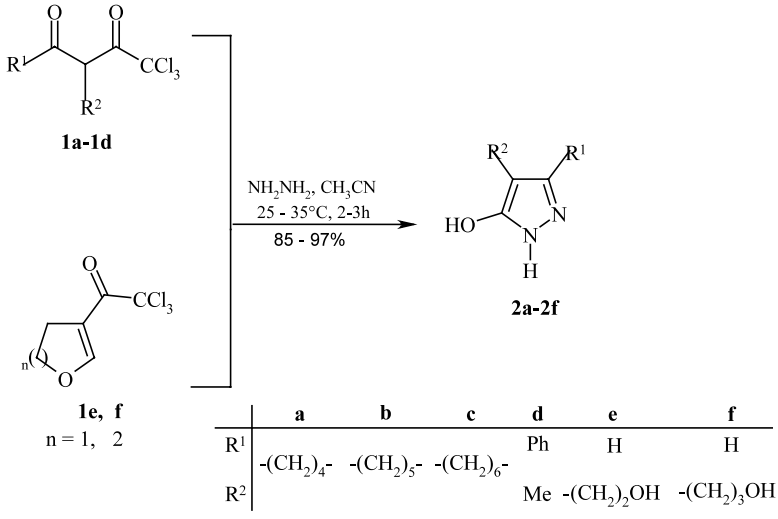
Abstract—The synthesis of a new series of hydroxypyrazoles (**2a–f**) and 2-methyl-3-isoxazolones (**3a–d**) from the cyclocondensation reaction of trichloromethyl-substituted 1,3-dielectrophiles (**1a–f**) with dry hydrazine and *N*-methylhydroxylamine is reported. The regiospecific cyclocondensation took place with the elimination of the trichloromethyl group in a haloform type reaction when acetonitrile under basic medium was used. The structure of compounds **2** and **3** were determined mainly by ^{1}H and ^{13}C NMR spectroscopy. © 2002 Elsevier Science Ltd. All rights reserved.

Pyrazoles and isoxazoles have a long history of applications in pharmaceutical and agrochemical industry.[1] For example, 1*H*-pyrazol-5-ones[2] and isoxazol-5-(3)-ones,[3] have been considered as extremely versatile intermediates in organic synthesis.[4] They have also been applied as biological active compounds[5] (muscimol analogs), pharmaceutical[6] (antipyrine, aminopyrine, isopyrine, nifenazone, piperylone, muzolimine) and agricultural[7] (herbicides and carbamate insecticides) chemistry.

One of the most useful method to obtain pyrazolones and isoxazolones relies on the cyclocondensation of β-ketoesteres or α,β-unsaturated esters with hydrazines or hydroxylamines, respectively.[1–7] For a wide review of the synthesis of pyrazoles and isoxazoles, see Ref. 1. In our systematic study of the reactivity of trihalomethyl-substituted 1,3-dielectrophyle compounds with hydrazines and hydroxylamines a series of pyrazoles and isoxazoles have been synthesized.[8–12] Previous results showed that the cyclocondensation reaction of 1,1,1-



Scheme 1.

Keywords: pyrazoles; isoxazoles; trichloromethyl ketones.

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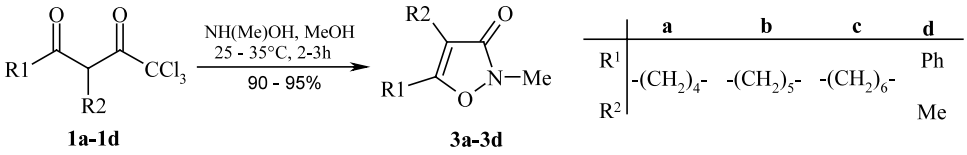

Scheme 2.

trichloro-4-alkoxyalk-3-en-2-ones or 2-trichloroacetyl cyclohexanone with hydroxylamine is regiospecific within a pH between 1 and 13 leading always to the obtaining of 5-trichloromethyl-substituted isoxazoles, independent of the reaction conditions used.[8] However, for the cyclocondensation of the same set of trichloromethyl-substituted 1,3-electrophiles with hydrazine, a direct relationship between the solvent used and the structure of the resulting pyrazole was observed.[9–11] It has been shown that the reactions carried out in polar solvents (DMSO,[10] ethanol,[9] methanol,[10] and water[10]) furnished preferentially 3(5)-carboxylpyrazole derivatives, whereas reactions in less polar solvents (chloroform) 5-trichloromethyl-substituted pyrazoles were obtained.[11]

In addition, it has been reported that the trichloromethyl group in ketones such as 1,1,1-trichloroacetone or 1,1,1-trichloroacetophenone can be substituted by amines furnishing acetamides and benzamides, respectively.[12] It has been reported that the mechanism of this reaction, which undergoes with substitution of the trichloromethyl group, is favored by polar solvents such as water or acetonitrile.[13]

In this work, we wish to report a new aspect of the cyclocondensation of trichloromethyl-substituted 1,3-dielectrophiles **1a**–**f** with dry hydrazine (Scheme 1) and *N*-methylhydroxylamine (Scheme 2) which has been accomplished with the substitution of the trichloromethyl group leading to a series of 3-hydroxypyrazoles **2a**–**f** and 2-methylisoxazol-3-ones **3a**–**d**, respectively.

The reaction of the enones **1a**–**f** and hydrazine in acetonitrile (Scheme 1) led to the quantitative isolation of 3-hydroxypyrazoles derivatives **2a**–**f**. The reaction of 4-methoxy-1,1,1-trichloropent-3-en-2-one or the respective dicarbonyl derivative[†] with dry hydrazine under the same reaction conditions used for the substrates **1a**–**f** furnished the 3-methyl-5-carboxy-1*H*-pyrazole[‡] where the trichloromethyl group was hydrolyzed to carboxylic acid instead of undergoing substitution.[10]

The reaction of compounds **1a**–**d** were carried out in equimolar ratios of *N*-methylhydroxylamine hydrochloride and potassium hydroxide in methanol under reflux to furnish 1-methyl-3-isoxazolones **3a**–**d** in good yields (Scheme 2). In this series, for reactions carried out in methanol the products **3a**–**d** were isolated in higher purity and in better yields than the reactions carried out in acetonitrile. The reaction of compounds **1e** and **1f** with *N*-methylhydroxylamine hydrochloride carried out in methanol/potassium carbonate, acetonitrile/potassium hydroxide, and acetonitrile/triethylamine furnished complex mixtures of unidentified compounds.

The synthesis of 2-trichloroacetylcycloalcanones **1a**–**d**, 3-trichloroacetyl-4,5-dihydrofuran (**1e**), and 3-trichloroacetyl-5,6-dihydro-4*H*-pyran (**1f**) has been reported elsewhere.[8,14] Anhydrous hydrazine was obtained from successive distillations of hydrazine monohydrate (Merck art. 804608) over KOH. Acetonitrile p.a. (Fluka 00700) was used as obtained from commercial suppliers. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX400 spectrometer in a 5 mm probe in 10^{-3} M $CDCl_3$ solutions, TMS was used as internal reference.

*Hydroxy-1H-pyrazoles **2a**–**f**. General Procedure*: To a solution of 2-trichloroacetylcycloalcanones (**1a**–**c**), 1,1,1-trichloro-3-methyl-4-phenyl-2,4-butenodione (**1d**), 3-trichloroacetyl-4,5-dihydrofuran (**1e**), or 5-trichloroacetyl-3,4-dihydro-2*H*-pyran (**1f**) (5 mmol) in acetonitrile (5 ml) were added dropwise to a stirred solution of anhydrous hydrazine (0.25 g, 7.5 mmol) in acetonitrile (2 ml). The resulting mixture was stirred for 2 h at 25–30°C and the acetonitrile was removed using a rota-evaporator. The excess hydrazine was removed by washing with water, resulting in a white solid that was dried in a desiccator. The products were identified as hydroxypyrazoles **2a**–**f**. Yields and selected physical and spectroscopic data are reported in Table 1.

*2-Methyl-3-isoxazolones **3a**–**d**. General procedure*: To a solution of 2-trichloroacetylcycloalcanones (**1a**–**c**) or 1,1,1-trichloro-3-methyl-4-phenylbutan-2,4-dione (**1d**) (5 mmol) in methanol (5 ml) was added to a stirred solution of *N*-methylhydroxylamine hydrochloride (0.47 g, 5.5 mmol), potassium hydroxide (0.31 g, 5.5 mmol) in methanol (5 ml). The resulting mixture was stirred for 2 h at 25–30°C. The solution was filtered to remove KCl and the methanol was removed under vacuum. Purification of products was done by column chromatography on silica gel and eluted with 3:1 chloroform/hexane. The products were obtained as oils identified as 1-methyl-3-isoxazolones **3a**–**d**. Yields and selected physical and spectroscopic data are reported in Table 2.

[†] The 4-methoxy-1,1,1-trichloropent-3-en-2-one was synthesized according to procedures in Ref. 8. The respective β-dicarbonyl compound was obtained by hydrolysis in H_2SO_4 50%, 60°C, 4 h.

[‡] $C_5H_6N_2O_2$, mol. wt. 126.12; ^{1}H NMR (400 MHz, DMSO) δ 6.5 (s, 1H), 2.2 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 162.8 (CO_2H), 142.4 (C3), 141.5 (C5), 107.1 (C4), 11.2 (Me). Anal. calcd: C, 47.62; H, 4.8. Found: C, 48.0; H, 4.90%.

Table 1. Yields and selected physical properties of compounds **2a–f**

No.	Yield (%)[a]	M.p.[b] (°C)	Mol. form. (wt.)	Anal. calcd (found, %)[c]			^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
				C	H	N		
2a	95	235–237	$C_7H_{10}N_2O$ (138.16)	60.85 (60.55)	7.29 (7.33)	20.27 (20.25)	2.41 (-CH_2-); 2.20 (-CH_2); 1.62 (-CH_2-)$_2$	158.6 (C5); 98.8 (C4); 140.1 (C3); 23.2; 22.6; 21.6; 19.2 (-CH_2-)$_4$
2b	95	213–215	$C_8H_{12}N_2O$ (152.19)	63.13 (63.15)	7.95 (7.92)	18.41 (18.37)	2.62 (2H); 2.3 (2H); 1.53 (4H); 1.8 (2H)	159.0 (C5); 99.4 (C4); 139.5 (C3); 28.4; 25.9; 23.8; 21.4; 19.8 (-CH_2-)$_5$
2c	95	191–193	$C_9H_{14}N_2O$ (166.22)	65.03 (65.05)	8.49 (8.49)	16.85 (16.79)	2.6 (-CH_2-); 2.36 (-CH_2-); 1.55 (-CH_2-)$_2$; 1.4 (-CH_2-)$_2$	159.0 (C5); 100.0 (C4); 141.4 (C3); 28.5; 28.34; 25.3; 25.1; 23.8; 19.7 (-CH_2-)$_6$
2d	97	201–205	$C_{10}H_{10}N_2O$ (174.20)	68.95 (68.85)	5.79 (5.75)	16.08 (16.03)	7.55–7.32 (Ph); 2.00 (Me)	160.5 (C5); 96.17 (C4); 139.9 (C3); 131.53; 129.0; 127.7; 126.6 (Ph); 7.9 (Me)
2e	89	Oil	$C_5H_8N_2O_2$ (128.13)	46.87 (46.80)	6.29 (6.29)	21.86 (21.78)	7.18 (H3); 3.5 (-CH_2OH); 2.4 (-CH_2-)	162.6 (C5); 101.7 (C4); 134.9 (C3); 61.5 (CH_2OH); 25.0 (-CH_2-)
2f	85	Oil	$C_6H_{10}N_2O_2$ (142.15)	50.69 (50.70)	7.09 (7.05)	19.71 (19.67)	7.2 (H3); 3.4 (-CH_2OH); 2.1; 1.53 (-CH_2-)	162.5 (C5); 105.7 (C4); 133.5 (C3); 61.3 (CH_2OH); 31.5; 18.1 (-CH_2-)

[a] Yields of isolated compounds.
[b] The melting points are uncorrected.
[c] Elemental analyses were performed on a CHNS–Vario El Elementar Analysensysteme.

Table 2. Yields and selected physical properties for compounds **3a–d**

No.	Yield (%)[a]	Mol. form. (wt.)	Anal. calcd (found, %)[b]			^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
			C	H	N		
3a	90	$C_8H_{11}NO_2$ (153.18)	62.73 (62.76)	7.24 (7.30)	9.14 (9.10)	3.2 (3H) NMe; 2.4 (2H); 2.25 (2H); 1.7–1.85 (CH_2)$_2$-	170.85 (C5); 101.25 (C4); 165.6 (C3); 38.3 (NMe); 21.7, 21.5, 21.18, 18.1 -(CH_2)$_4$-
3b	90	$C_9H_{13}NO_2$ (167.20)	64.65 (64.80)	7.84 (7.90)	8.38 (8.35)	3.2 (3H) NMe; 2.5 (4H); 2.0 (2H); 1.8–1.3 (4H)	171.0 (C5); 101.0 (C4); 165.0 (C3); 36.8 (NMe); 27.8, 26.7, 25.2, 23.5, 23.2
3c	90	$C_{10}H_{15}NO_2$ (181.23)	66.27 (66.25)	8.34 (8.30)	7.73 (7.57)	3.0 (3H) NMe; 2.3 (4H); 1.85 (2H); 1.53 (4H); 1.3 (2H)	171.5 (C5); 100.0 (C4); 164.9 (C3); 38.5 (NMe); 26.8, 26.6, 26.5, 25.0, 23.5, 23.2
3d	95	$C_{11}H_{11}NO_2$ (189.21)	69.83 (69.85)	5.86 (5.80)	7.40 (7.37)	7.45 (5H) Ph; 3.05 (3H) NMe; 1.89 (3H) Me	171.93 (C5); 101.23 (C4); 165.36 (C3); 130.6; 129.0; 128.14; 127.8 (Ph); 40.9 (NMe); 7.41 (Me)

[a] Yields of isolated compounds.
[b] Elemental analyses were performed on a CHNS–Vario El Elementar Analysensysteme.

Acknowledgements

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