4-Alkoxy-1,1,1-Trihalo-3-Alken-2-ones as Building Blocks for Trihalomethylated Heterocycles. Synthesis of 4-Trihalomethyl-2-Pyrimidinones.

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4-Trialometil-2-pirimidinonas(**6**,**7**) foram preparadas, em bons rendimentos, a partir de 4-alcoxi-1,1,1-trialo-3-alquen-2-onas(**2**,**3**), e uréia. Os compostos **2**,**3**, provaram ser blocos sintéticos versáteis para a preparação de anéis pirimidínicos substituidos pelos grupos trifluormetil e triclorometil.

4-Trihalomethyl-2-pyrimidinones(**6**,**7**) were prepared by the reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones (**2**,**3**) and urea in good yields. Compounds **2**,**3** proved to be versatile building blocks for the construction of pyrimidine rings having a trifluormethyl and trichloromethyl substituents.

Key-words: *4-alkoxy-1,1,1-trihalo-3-alken-2-ones; 4-trihalomethyl-2-pyrimidinones.*

Introduction

The most typical and widely known method for obtaining pyrimidines is the synthesis involving the so-called [3+3] atom fragment[1,2]. In this case, one of the three atom fragments is usually a 1,3-diketone or a derivative in which the keto groups are replaced by aldehyde, ester, nitrile or imino group, and the other three atom fragments is a dinucleophile of the type N-C-N[3,4].

In this work, we explore the synthetic potential of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones (**2**,**3**) for preparing 4-trihalomethyl-2-pyrimidinones (**6**,**7**), by the cyclocondensation reaction with urea (Scheme). A systematic study using precursors with different structures, was carried out to examine the scope of these cyclo-condensation reactions. The compounds **2** and **3**, are widely used in many applications such as protective groups for amino acids synthesis[5], in hetero-Diels-Alder reactions with various vinylethers[6], and for the synthesis of 3-alkoxypropenoic acids[7,8], 3,3-dialkoxypropanoic esters[9], and 1,1,1-trifluoro-4-amino-3-buten-2-ones[10]. To our knowledge compounds **2** and **3**, have never been used for the synthesis of pyrimidine rings, although the reaction of these compounds with hidroxylamine to give 5-trihalomethyl isoxazolines and isoxazols has been the subject of a recent publication[11].

Preliminary tests of the biological activity of the pyrimidines **6** and **7** showed that some of these compounds have strong antifungal activity and minor changes of the ring substituents give rise to substantial modifications of the biological activity[12].

Results and Discussion

The enolethers **1** used in this synthesis are commercially available or were prepared from the respective aldehyde or ketone.

Compounds **2** and **3** were prepared from the parent enolether by the acylation reaction with trichloroacetyl chloride or trifluoroacetic anhydride in the presence of pyridine. A general procedure for preparing the compounds **2**, **3** by trihaloacetylation of the enolethers (**1**) was reported in a previous work[11], which is a modification of the procedure found in the literature[13-15]. The cyclization was carried out by refluxing **2** or **3** was carried out under reflux for 20 h with an excess of urea in methanol and catalytic amounts of HCl. The compounds **4** and **5** could be obtained only when R^2=Me. The dehydration of **4** and **5** by concentrated sulfuric acid led to the corresponding compounds **6b** and **7b**. For all the other cases, the cyclo-condensation reaction of **2** and **3** with urea produced exclusively the compounds **6** and **7**, respectively. Selected physical and spectral data of **6** and **7** are presented in Table 1.

Further cyclo-condensations of **2** and **3** with other dinucleophiles, such as, thioureas, amidines, guanidine, hydrazine, etc., are under investigation.

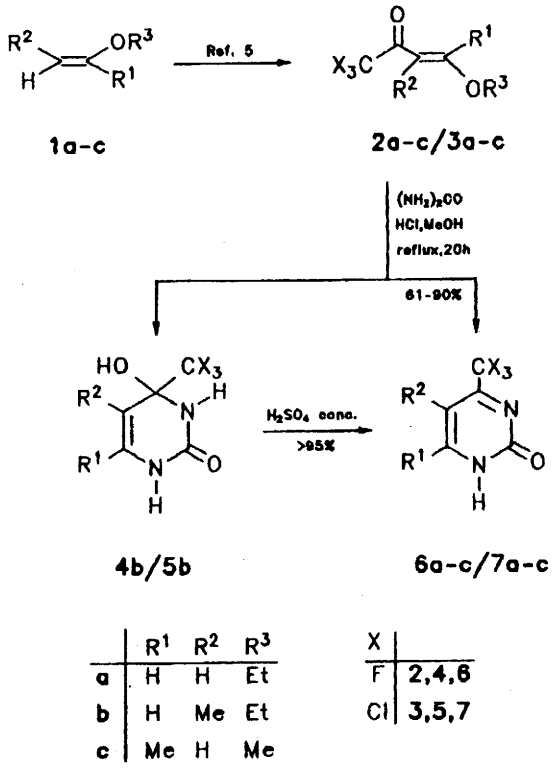
Experimental

General procedure. 4-trifluoro- or 4-trichloromethyl pyrimidin-2-ones (**6**,**7**). Compounds **2** or **3** (5 mmol) and urea (10 mmol), were dissolved in 10 ml of methanol. To the mixture was added 1 ml of concentrated HCl and then refluxed for 20 h. The solvent was partially evaporated and the product was allowed to crystallize by cooling the solution. The solid

Table 1: *Selected physical[a] and spectral[b] data of* **6,7a-c**.

Compound	Yield[c] (%)	m.p.[d] (°C)	^{1}H-NMR δ (ppm),(m) J(Hz)			^{13}C-NMR δ (ppm)				
			H5	H6	Me	C2	C4	C5	C6	CX_3
6a	61	214-216	6.9(d) (6.5)	8.4(dq) (6.5;<1)	-	156.6	161.6	99.5	153.3	119.7
6b	66	158-160	-	8.3(s)	2.2(q) (1.9)	157.2	158.5	111.4	154.5	120.4
6c	71	152	6.8(q) (<1)	-	2.4(d) (<1)	150.8	160.8	99.6	165.1	119.9
7a	90	227-230	7.0(d) (6.5)	8.3(d) (6.5)	-	156.6	171.0	98.8	151.3	95.7
7b	70	196-198	-	8.0(q) (<1)	2.4(d) (<1)	154.2	164.7	107.9	150.7	95.1
7c	66	197-200	6.7(s)	-	2.4(s)	156.3	170.6	98.4	163.0	95.9

[a] *Satisfactory microanalyses (C±0.24, H±0.16, N±0.23) were obtained for all compounds.*
[b] NMR-Spectra were recorded on a BRUKER AC80 (*^{1}H at 80MHz and ^{13}C at 20MHz) in DMSO-D$_6$/TMS.*
[c] *Isolated yield of analytically pure compounds.*
[d] *m.p. were determined on a Reichert Thermovar apparatus and are uncorrected.*



was filtered, washed with cold water, and recrystalised from methanol to give **6** and **7**, respectively.The intermediates **4b** and **5b**, could be isolated and easily dehydrated at room temperature by stirring with conc. H_2SO_4 for 4 h, to give a quantitative yield of **6b** or **7b**.

5b was isolated in 60% yield; mp 200-202°C; ^{1}H-NMR(DMSO-D$_6$) δ 1.8(d,3H), 3.2(s,OH), 5.5(dq,1H), 7.6(s,NH), 9.0(d,NH); ^{13}C-NMR(DMSO-d$_6$) δ 151.9(C2), 95.4(C4), 99.8(C5), 130.3(C6), 106.1(C7), 15.1(C8).

4b was isolated as a mixture of **4b** and **6b** in 1:1 ratio (66% yield), when lower concentration of HCl was used, otherwise **6b** was the only compound detected. Physical data of **4b** obtained from the mixture: ^{1}H-NMR(DMSO-D$_6$) δ 1.8(s, 3H), 3.2(s, OH), 6.5 (dq, 1H), 8.0 (s, NH), 9.0(d,NH); ^{13}C-NMR(DSMO-D$_6$) δ 151.6(C2), 88.1(C4), 97.2(C5), 129.1(C6), 124.4(C7), 12.9(C8).

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