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β-Alkoxyvinyl trichloromethyl ketones as *N*-heterocyclic acylating agent. A new access to 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones

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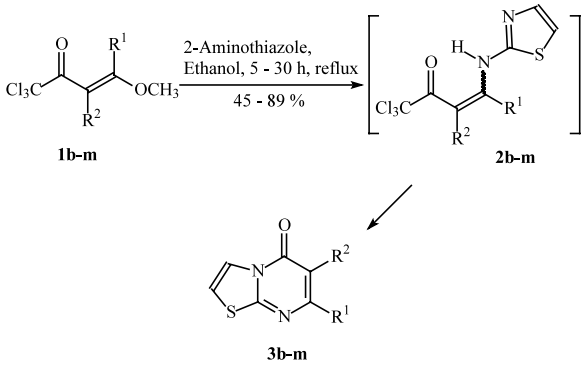
Abstract—Using trichloromethyl substituent as convenient leaving group for the synthesis of interesting bi-heterocyclic compounds, a series of 6-methyl- and 7-alkyl(aryl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones, where alkyl = methyl, *n*-propyl, isopropyl, isobutyl, *n*-hexyl, isopentyl and aryl = phenyl, 4-toluyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl was obtained from a simple and regiospecific reaction of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones with 2-aminothiazole in good yield (45–89%).

Recently, β-alkoxyvinyl trichloromethyl ketones **1** proved to be useful building blocks for the synthesis of five-,[1–5] six-,[6–9] and seven[10,11]-membered trichloromethylated heterocyclic compounds due to one of the better methods to introduce a trichloromethyl group into heterocycles is based on the trichloromethylated building block approach. This approach relies on the trichloroacetylation of enol ethers or acetals to give, in one step and good yields, the above cited ketones **1**. On the other hand, the classical haloform reaction in which the trichloromethyl substituent is a leaving group has long been know[12] and systematic studies involving mechanism of the leaving group ability of the trichloromethyl in many synthetic transformations have been reported.[1,13–19] However, just a few references from the literature report the use of the trichloromethyl substituent as good leaving group in heterocyclic synthesis.[9,20] Furthermore, this synthetic strategy has not been used to obtain bi-heterocycles. Although, the 7-methyl- and 7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones are known,[21] the synthesis of 7-alkyl- and 7-(4-substituted-phenyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones have not received much attention. Specifically, 7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one showed an interesting antiulcer and anti-inflammatory activity after oral administration. Furthermore, this compound has inhibited the Reverse Passive Arthus Reaction (RPAR) in the rat paw and has been considered as a potential candidate for therapeutic applications. [21]



1- 3	a	b	c	d	e	f
R^1	H	H	Me	*n*-Pr	*i*-Pr	*i*-Bu
R^2	H	Me	H	H	H	H

g	h	i	j	k	l	m
i-Pentyl	*n*-Hexyl	Ph	4-MePh	4-OMePh	4-ClPh	4-BrPh
H	H	H	H	H	H	H

Scheme 1.

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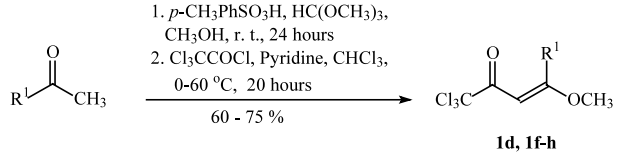
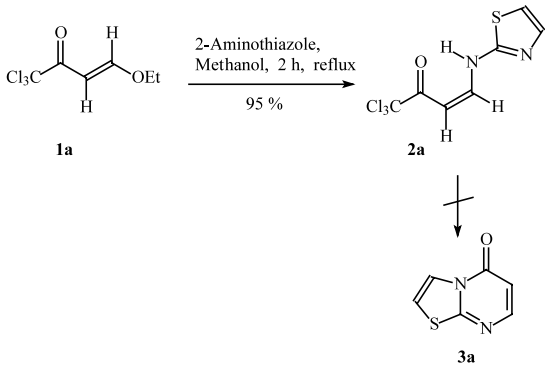
As an extension of our research we wish to report a new route to obtain 6-methyl- and 7-alkyl(aryl)-substituted 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **3** from the reaction of β-alkoxyvinyl trichloromethyl ketones **1** with 2-aminothiazole (Scheme 1). The 4-alkyl(aryl)-1,1,1-trichloro-4-alkoxy-alk-3-en-2-ones are readily available *CCC* synthetic blocks and were prepared from trichloroacetylation of enol ethers (**1a**–**c**)[22] or from enol ethers generated in situ from the respective acetophenone- (**1i**–**m**)[23] or isopropyl methyl ketone–acetals (**1e**)[24] with trichloroacetyl chloride. In order to obtain compounds, bearing an alkyl side chain at the 7-position at the bi-heterocycles **3**, new 4-alkyl-1,1,1-trichloro-4-methoxyalken-2-ones (**1d**, **1f**–**h**)[25,28] were prepared from the reaction of 2-pentanone, 4-methyl-2-pentanone, 5-methyl-2-hexanone and 2-octanone, respectively, with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid (Scheme 2). The acylation reaction using trichloroacetyl chloride in pyridine and chloroform as solvent was carried out in a molar ratio 1:2:2 to obtain **1d**, **1f**–**h**. The most satisfactory reaction time was found to be 20 h in a temperature range from 0 to 60°C. The regiospecificity of the reaction on the methyl carbon of the ketones is achieved under kinetic control, as reported elsewhere.[24] The compounds **1d**, **1f**–**h** show the *E*-configuration. The isomer configurations assigned were based on $^3J_{C5-H3}$ coupling constants and X-ray data of similar compounds.[26,27]

Recently, we have reported an addition/elimination sequence leading to trichloroacetyl and trifluoroacetyl enamine derivatives from the reaction of *o*-phenylenediamine,[29] *o*-aminophenol,[30] 1-naphthylamine[31] and *S*,*S*-dimethylsulfoximide[32] with 4-alkyl(aryl)-1,1,1-trihalo-4-alkoxyalken-2-ones. The acyclic enaminones derived from *o*-phenylenediamine and *o*-aminophenol were submitted to in vitro anti-tumor screens. It was observed that the trichloromethylated compounds exhibit a superior activity if compared to trifluoromethylated analog compounds. The best activity was obtained when the structure was derived from *o*-aminophenol and presented a trichloroacetyl- and a *p*-bromophenyl substituent bound at the carbon-2 and -1, respectively.[30] Thus, the important acyclic precursor *N*-[3-oxo-4,4,4-trichloro-1-buten-1-yl]-2-aminothiazole (**2a**)[25,28] was obtained in 95% using a similar addition/elimination sequence from the reaction of 1,1,1-trichloro-4-ethoxybut-3-en-2-one (**1a**) with 2-aminothiazole in refluxing methanol for 2 h. Unfortunately,



1	d	f	g	h
R^1	*n*-Pr	*i*-Bu	*i*-Pentyl	*n*-Hexyl

Scheme 2.



Scheme 3.

reactions of compound **1a** with 2-aminothiazole in acetonitrile, ethanol, chloroform and *n*-butanol at different temperatures in an attempt to obtain the respective 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3a**), resulted always in the *N*-[3-oxo-4,4,4-trichloro-1-buten-1-yl]-2-aminothiazole (**2a**). When the reactions were carried out at high temperatures (>90°C) complex mixtures of non identified products by ^{1}H and ^{13}C NMR spectroscopy are produced (Scheme 3). In summary, using 4-alkyl-1,1,1-trichloro-4-alkoxy-alk-3-en-2-ones as *N*-heterocyclic acylating agent, this work presented a new, simple and convenient method to obtain 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones (**3b**–**m**)[25,28] from the reaction of (**1b**–**m**) and 2-aminothiazole carried out in dry ethanol under reflux. It was observed that **1b**–**m** did not react with 2-aminothiazole at low temperature (lower than 55°C) and at high temperature (e.g. $\geq$60°C) only the bi-heterocycles **3b**–**m** were obtained. However, this method did not allow one to obtain the compound **3a**, but in this reaction the intermediate **2a** was easily isolated.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. 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 DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in chloroform-d_1 for **1d**, **1f**–**h**, **2a**, **3b**–**m** using TMS as internal reference. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin–Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

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25. Yields, physical data and reaction time of new compounds **1–3**: **Compd** [mp (°C) or bp (°C/Torr), yield (%), reaction time (h)]: **1d** [(102/5.5), 75, 20]; **1f** [(108/3.0), 65, 20]; **1g** [(132/6.4), 60, 20]; **1h** [(147/5.7), 73, 20]; **2a** [(155–157), 95, 4]; **3b** [(120–122), 46, 16]; **3c** [(128–130), 45, 16]; **3d** [(76–78), 89, 12]; **3e** [(121–123), 47, 30]; **3f** [(115–116), 51, 30]; **3g** [(105–107), 59, 30]; **3h** [(93–94), 74, 10]; **3i** [(172–174), 80, 5]; **3j** [(200–202), 64, 5]; **3k** [(180–182), 69, 5]; **3l** [(213–215), 83, 5]; **3m** [(220–222), 81, 5].
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28. Compounds **1–3** were fully characterized by spectroscopic methods and gave satisfactory analytical and spectral data. **1d**: $C_8H_{11}Cl_3O_2$, mw 245.53, ^{1}H NMR ($CDCl_3$): δ 5.97 (s, H3), 3.81 (s, OCH_3), 2.77 (t, CH_2), 1.58 (sext, CH_2), 0.98 (t, CH_3); ^{13}C NMR ($CDCl_3$): δ 183.8 (C4), 179.8 (C2), 97.9 (CCl_3), 89.7 (C3), 56.2 (OCH_3), 35.2 (CH_2), 20.5 (CH_2), 13.8 (CH_3). **1f**: $C_9H_{13}Cl_3O_2$, mw 259.56, ^{1}H NMR ($CDCl_3$): δ 6.00 (s, H3), 3.80 (s, OCH_3), 2.70 (d, CH_2), 2.03 (m, CH), 0.96 (d, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 183.2 (C4), 179.9 (C2), 98.0 (CCl_3), 90.3 (C3), 56.1 (OCH_3), 41.7 (CH_2), 27.4 (CH), 22.3 ($2CH_3$). **1g**: $C_{10}H_{17}Cl_3O_2$, mw 273.58, ^{1}H NMR ($CDCl_3$): δ 5.96 (s, H3), 3.79 (s, OCH_3), 2.78 (t, CH_2), 1.64 (sept, CH), 1.45 (q, CH_2), 0.94 (d, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 184.4 (C4), 179.9 (C2), 98.0 (CCl_3), 89.6 (C3), 56.2 (OCH_3), 35.7 (CH_2), 31.6 (CH_2), 28.2 (CH), 22.3 ($2CH_3$). **1h**: $C_{11}H_{17}Cl_3O_2$, mw 287.61, ^{1}H NMR ($CDCl_3$): δ 5.96 (s, H3), 3.80 (s, OCH_3), 2.78 (t, CH_2), 1.55 (m, CH_2), 1.32 (m, $3CH_2$), 0.88 (t, CH_3); ^{13}C NMR ($CDCl_3$): δ 183.9 (C4), 179.8 (C2), 97.9 (CCl_3), 89.5 (C3), 56.1 (OCH_3), 33.4 (CH_2), 31.3 (CH_2), 29.0 (CH_2), 26.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3). **2a**: $C_8H_9Cl_3N_2OS$ (*Z*-isomer), mw. 287.59, ^{1}H NMR ($CDCl_3$): δ 11.45 (bs, NH), 8.00 (dd, J=12.0, J=8.2, H1′), 7.41 (d, J=3.4, H4), 6.94 (d, J=3.4, H5), 7.23 (d, J=8.2, H2′); ^{13}C NMR ($CDCl_3$): δ 183.5 (C=O), 161.2 (C2), 147.1 (C1′), 140.2 (C4), 113.1 (C5), 95.9 (CCl_3), 91.1 (C2′). **3g**: $C_{11}H_{14}N_2OS$, mw 222.30, mp 105–107°C, ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, J=5.0, H3), 7.01 (d, 1H, J=5.0, H2), 6.17 (s, 1H, H6), 2.60 (t, 2H, CH_2), 1.60 (m, 3H, CH_2 and CH), 0.95 (d, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 168.4 (C7), 162.3 (C8a), 158.6 (C5), 121.6 (C3), 110.8 (C2), 103.1 (C6), 37.3 (CH_2), 35.6 (CH_2), 27.5 (CH); 22.2 ($2CH_3$). Anal. calcd C, 59.43; H, 6.35; N, 12.60. Found: C, 59.34; H, 6.34; N, 12.64. **3m**: $C_{12}H_7BrN_2OS$, mw 307.16, mp 220–222°C, ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 1H, J=5.0, H3), 7.87 (d, 2H, J=8.7, Ph), 7.60 (d, 2H, J=8.7, Ph), 7.04

(d, 1H, $J=5.0$, H2), 6.71 (s, 1H, H6); ^{13}C NMR ($CDCl_3$): δ 162.8 (C8a), 160.1 (C5), 158.9 (C7), 135.2, 131.9, 128.7, 125.3 (Ph), 121.8 (C3), 111.5 (C2), 100.6 (C6). Anal. calcd C, 46.92; H, 2.30; N, 9.12. Found: C, 46.94; H, 2.44; N, 9.03.

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