Regiospecific Synthesis of Trichloromethyl Substituted 4,5-Dihydro-1*H*-1-tosylpyrazoles

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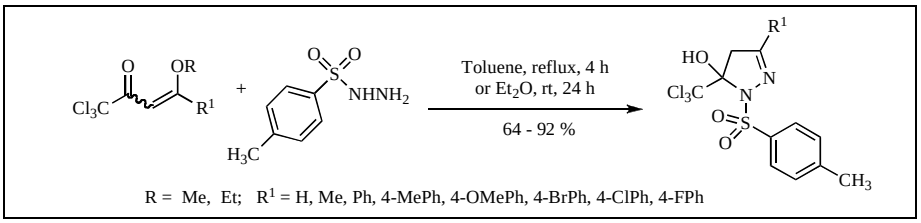

The regiospecific synthesis of a new series of eight 3-alkyl(aryl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazoles is reported. The 1-*p*-tosyl-2-pyrazolines were obtained from the cyclocondensation reaction of 4-alkyl(aryl)-4-alkoxy-1,1,1-trichloroalk-3-en-2-ones, [where alkyl = H, Me and aryl = -C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4,] with *p*-tosylhydrazine in 64 to 92 % yields, employing anhydrous toluene at reflux or diethyl ether at room temperature as the reaction condition.

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In recent years, diaryl and heteroaryl aryl sulfone derivatives have been a new emerging class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and support the idea of developing novel synthetic sulfones as inhibitors of reverse transcriptase (RT) [1-4]. The anti-HIV activity of sulfones was initially discovered at the National Cancer Institute (NCI) in 1993. In the same year, Mc-Mahon *et al.* [1] reported the inhibition of HIV-1 reverse transcriptase by some diaryl sulfones and underscored 2-nitrophenyl phenyl sulfone as a potent inhibitor of RT. Also in 1993, Williams *et al.* [2], in an attempt to optimize the HIV-1 RT inhibitory activity of 2-[(phenylsulfinyl)methyl]-3-(phenylthio)indole with the introduction of a chlorine atom and by oxidizing the sulfur atom to obtain the corresponding sulfone, discovered a high activity of 5-chloro-3-(phenylsulfonyl)indole-2-carboxamide.

The NNRTIs receive great attention because they are HIV-1 selective, low in toxicity, and show favorable pharmacokinetic properties. To date, only three NNRTIs, called nevirapine, delavirdine and efavirenz, are on the market. According to Silvestri *et al.* [3], long therapies lead to the emergence of drug resistant mutant strains. Thus, the development of new anti-AIDS agents active against mutant strains is continuous.

Recently, heteroaryl substituents have been attached to the sulfones and, for example, pyrrolyl aryl sulfones (PASs) have been reported by Silvestri *et al.* [3] and Artico *et al.* [4] as a new class of human immunodeficiency virus type 1 (HIV-1) RT inhibitors acting at the non-nucleoside binding site of this enzyme.

On the other hand, among several classes of N-heterocycles, the 2-pyrazolines have been recognized as antitumor [5], antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents [6-13]. Some of these compounds have also shown anti-inflammatory, anti-diabetic, anesthetic and analgesic properties [14-16]. Particularly, 3-aryl-5-trichloromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles has presented anti-inflammatory and analgesic activity [17].

A review of the literature showed that some heptafluoro-, pentafluoro- and trifluoromethyl pyrazolyl aryl sulfones are known as agrochemical fungicides [18], but the respective 3-aryl-1*H*-pyrazolyl substituted derivatives and the trichloromethylated pyrazolyl aryl sulfone analogues have not been reported as of yet. Moreover, it has been known for a long time that the main methods used to obtain pyrazolyl aryl sulfones include the reactions between 1,3-dicarbonyl compounds and *p*-tosylhydrazine and its derivatives or between pyrazoles and *p*-toluenesulfonyl chloride or between sulfonamides and acetals [19]. However, no publication has been found showing the possibility of a regiospecific and simultaneous introduction of trichloromethyl and substituted aryl groups at the pyrazole ring to obtain pyrazolyl tosyl sulfone derivatives starting from 1,3-dicarbonyl compounds or from β-alkoxyvinyl trichloromethyl ketones and tosylhydrazine.

Thus, considering the importance of 2-pyrazolines, the synthesis of new sulfonyl heterocycle derivatives and the possibility of isolating new trichloromethylated structures with promising biological properties, the aim of this work is to report the results of the cyclocondensation reactions of 4-alkyl(aryl)-4-alkoxy-1,1,1-trihaloalk-3-en-2-ones (**1**) with *p*-tosylhydrazine to obtain a new series of trichloromethylated pyrazolyl-*p*-tolyl-sulfones (**2**).

Recently, β-alkoxyvinyl trihalomethyl ketones **1** have proven to be useful building blocks in the synthesis of five-, six-, and seven-member-trihalomethylated heterocyclic compounds and the trihaloacetylation of enol ethers or acetals has produced, in one-step and with good yields, the ketones **1**. This has been the best method to attach a trihalomethyl group to heterocyclic precursors [20,21].

In particular, the synthetic potential of β-alkoxyvinyl trihalomethyl ketones to obtain a series of novel trihalomethylated 4,5-dihydro-1*H*-pyrazoles (2-pyrazolines) has recently been explored and reported by us [22].

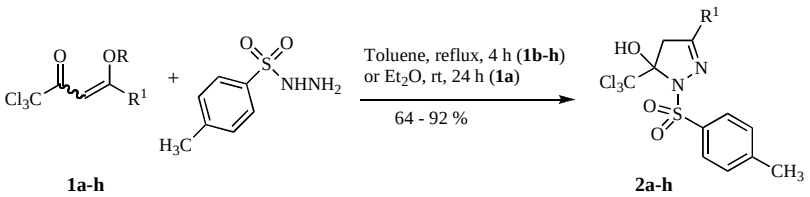
Although many methods have been published about the synthesis of 1*H*-pyrazoles and functionalized derivatives, the attempts to perform the synthesis of a very simple 4,5-dihydro-1*H*-pyrazoles (2-pyrazolines) have not yet been successful [23-26]. With a conventional procedure, pyrazoles have been obtained by direct reactions of β-diketones and derivatives with hydrazines [23]. However, in most cases 5-hydroxy-4,5-dihydro-1*H*-pyrazoles are obtained when the N-1, C-3 or C-5 atoms are substituted by a strong electron-withdrawing group that hinders the elimination of water and the subsequent aromatization of the pyrazoline ring [23]. The electron-withdrawing CF_3 or CCl_3 groups at position 5 would destabilize any carbocation character in an *E*1-like mechanism. In a few cases, some structures of 5-trifluoromethylated- or 5-trichloromethylated-5-hydroxy-1*H*-pyrazolines and intermediates can be isolated [22].

The 4-alkyl(aryl)-4-alkoxy-1,1,1-trichloroalk-3-en-2-ones (**1a-h**) were synthesized from the trichloroacetylation reaction of the respective enolethers (**1a**-**b**) or acetals (**1c-h**) with trichloroacetyl chloride according to previously publications [27].

The reactions of ketones **1b-h** with *p*-tosylhydrazine were carried out in toluene at reflux for 4 hours to achieve the corresponding **2b-h** in 64 - 92 % yield, except for the compound **2a** which was synthesized from ketone **1a** in 72 % yield employing diethyl ether as solvent at room temperature for 24 hours (Scheme 1). All reactions were stirred until the consumption of ketones **1** was confirmed by TLC. After the reaction ended, the compounds were submitted to a low temperature (0-10 ºC), then isolated through simple filtration, washed in cold toluene and recrystallized from ethanol.

The identity of compounds **2** is given by the reactivity of the starting material. Its well documented that the cyclization of **1** with hydrazines bearing electron-withdrawing groups gives exclusively 5-trichloromethyl-2-pyrazolines [21,22]. The fact that 2-pyrazolines instead of pyrazoles are formed is also a clear indication of the position of the *N*-substituent. Yields, selected physical properties, NMR characterization and purity by elemental analyses are listed in the Experimental section.

Scheme I



1-2	a	b	c	d	e	f	g	h
R	E	Me	Me	Me	Me	Me	Me	Me
R^1	H	Me	Ph	4-MePh	4-OMePh	4-BrPh	4-ClPh	4-FPh

The unambiguous ^{1}H and ^{13}C NMR chemical shift assignments of 3-alkyl(aryl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazoles (**2a-h**), in DMSO-d_6 or acetonitrile-d_3 as solvent, were done by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory [21,22]. Compounds **2** showed the chemical shifts of the diastereotopic methylene protons (H-4a and H-4b) as a characteristic AB system and as a doublet on average at δ 3.90 and another one at δ 3.48 with a *geminal* coupling constant on average at 19.3 Hz.

The *p*-tosyl group protons are shown in the ^{1}H NMR spectrum as a singlet characteristic for the *p*-methyl substituent in the range of δ = 2.32 – 2.42 and an AB-system of aromatic protons in the low field as a doublet in the range of δ 7.75 – 7.90 and another doublet in the range of δ 7.35 – 7.39 with a coupling constant ($^3J_{HH}$) in a range of 7.9 – 8.2 Hz. Compounds **2** present the typical ^{13}C NMR chemical shifts of pyrazoline ring carbons on average at δ 154.8 (C3), 46.7 (C4), 103.2 (C5) and 103.8 (CCl_3). The C5 and the CCl_3 are distinguished by their different intensities. The CCl_3 group due to its free

rotation and quadrupolar contribution to the relaxation (due to the chlorine atoms) should have longer relaxation time than the C5. Thus, the signal of the CCl_3, in routine ^{13}C NMR spectra, is much shorter than the C5.

In conclusion, one can consider the cyclocondensation reaction reported here a useful, simple, and convenient procedure to obtain regiospecifically new 3-alkyl(aryl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazoles. In addition, this study used β-alkoxyvinyl trichloromethyl ketones **1** in cyclocondensation reactions with *p*-tosyl-hydrazine for the first time.

EXPERIMENTAL

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. ^1H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 (**2b-h**) or acetonitrile-d_3 (**2a**) and using TMS as an internal reference. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (University of São Paulo – USP).

General Procedure for the Preparation of 3-Alkyl(aryl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazoles (**2a-h**). *p*-Tosylhydrazine (3 mmoles) was added to a stirred solution of 4-alkyl(aryl)-4-alkoxy-1,1,1-trichloroalk-3-en-2-ones **1a-h** (3 mmoles) in 2 ml of toluene at 20 – 25 °C. The mixture was stirred for 4 hours at 110 °C, except for **2a**, which was synthesized in diethyl ether at room temperature for 24 hours. After cooling (< 10 °C), the white or yellow crystalline solids were isolated by filtration, washed with cold toluene and recrystallized from ethanol.

5-Hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosyl-pyrazole (**2a**). This compound was obtained as white solid, yield 72 %; Mp. 133-135 °C; ^1H NMR (acetonitrile-d_3): δ = 7.81 (d, 2H, *J* = 8.2, Ts), 7.38 (d, 2H, *J* = 8.2, Ts), 5.74 (s, H-3), 3.52 (d, 1H, *J*= 20.3, H-4a), 3.04 (d, 1H, *J*= 20.0, H-4b), 2.42 (s, 3H, Me-Ts); ^{13}C NMR (acetonitrile-d_3): δ = 145.7 (Ar), 136.1 (C3), 130.2 (Ar), 129.4 (Ar), 118.2 (Ar), 104.4 (CCl_3), 103.2 (C5), 50.8 (C4), 21.5 (Me). *Anal.* Calcd. for $C_{11}H_{11}Cl_3N_2O_3S$ (357.64): C, 36.94; H, 3.10; N, 7.83 %. Found: C, 36.73; H, 3.08; N, 7.74 %.

5-Hydroxy-3-methyl-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2b**). This compound was obtained as white solid, yield 70 %; Mp. 153-155 °C; ^1H NMR (DMSO-d_6): δ = 8.32 (br, 1H, OH), 7.75 (d, 2H, *J*= 8.2, Ts), 7.38 (d, 2H, *J*= 8.2, Ts), 3.47 (d, 1H, *J*= 19.5, H-4a), 3.13 (d, 1H, *J*= 19.5,H-4b), 2.39 (s, 3H, Me-Ts), 1.89 (s, 3H, Me). ^{13}C NMR (DMSO-d_6): δ = 159.0 (C3), 144.5 (Ar), 134.8 (Ar), 129.3 (Ar), 128.5 (Ar), 103.5 (CCl_3), 102.1 (C5), 49.8 (C4), 21.5 (Me-Ts), 15.6 (Me). *Anal.* Calcd. for $C_{12}H_{13}Cl_3N_2O_3S$ (371.67): C, 38.78; H, 3.53; N, 7.54 %. Found: C, 38.73; H, 3.37; N, 7.69 %.

5-Hydroxy-3-phenyl-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2c**). This compound was obtained as white solid, yield 81 %, Mp. 147-149 °C; ^1H NMR (DMSO-d_6): δ = 8.58 (br, 1H, OH), 7.84 (d, 2H, *J*= 8.2, Ts), 7.71 (d, 2H, *J*= 7.7, Ph), 7.45(d, 2H, *J*= 7.7, Ph), 7.37 (d, 2H, *J*= 8.2, Ts), 3.98 (d, 1H, *J*= 19.3, H-4a), 3.55 (d, 1H, *J*= 19.3, H-4b), 2.35 (s, 3H, Me-Ts); ^{13}C NMR (DMSO-d_6): δ = 155.2 (C3), 143.6 (Ar), 135.6 (Ar), 130.8 (Ar), 129.6 (Ar), 129.0 v, 128.7 (Ar), 128.4 (Ar), 126.5 (Ar), 103.8 (CCl_3), 103.2 (C5), 46.7 (C4), 20.9 (Me). *Anal.* Calcd. for $C_{17}H_{15}Cl_3N_2O_3S$ (433.74): C, 47.08; H, 3.49; N, 6.46 %. Found: C, 47.05; H, 3.45; N, 6.41 %.

5-Hydroxy-3-(4-tolyl)-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2d**). This compound was obtained as white solid, yield 92 %, Mp. 184-186 °C; ^1H NMR (DMSO-d_6): δ = 8.53 (br, 1H, OH), 7.85 (d, 2H, *J*= 8.2, Ts), 7.6 (d, 2H, *J*= 8.2, Ph), 7.35(d, 2H, *J*= 7.9, Ts), 7.24 (d, 2H, *J*= 7.9, Ph), 3.94 (d, 1H, *J*= 19.0, H-4a), 3.50 (d, 1H, *J*= 19.0, H-4b), 2.32 (s, 3H, Me-Ts), 2.31 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ = 155.2 (C3) 143.6 (Ar), 140.8 (Ar), 135.6 (Ar), 129.3 (Ar), 129.0 (Ar), 128.4 (Ar), 127.0 (Ar), 126.5 (Ar), 103.9 (CCl_3), 103.0 (C5), 46.7 (C4), 20.9 (Me-Ts), 20.8 (Me). *Anal.* Calcd. for $C_{18}H_{17}Cl_3N_2O_3S$ (447.76): C, 48.28; H, 3.83; N, 6.26 %. Found: C, 48.28; H, 3.74; N, 6.34 %.

5-Hydroxy-3-(methoxyphenyl)-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2e**). This compound was obtained as white solid, yield 66 %, Mp. 164-168 °C; ^1H NMR (DMSO-d_6): δ = : 8.48 (br, 1H, OH), 7.82 (d, 2H, *J*= 7.9, Ts), 7.65 (d, 2H, *J*= 8.7, Ph), 7.36(d, 2H, *J*= 7.9, Ts), 6.99 (d, 2H, *J*= 8.7, Ph), 3.93 (d, 1H, *J*= 19.3, H-4a), 2.79 (s, 3H, OMe), 3.47 (d, 1H, *J*= 19.3, H-4b), 2.35 (s, 3H, Me-Ts); ^{13}C NMR (DMSO-d_6): δ = 161.39 (Ar), C, 155.3 (C3), 143.7 (Ar), 135.6 (Ar), 129.1 (Ar), 128.6 (Ar), 128.4 (Ar), 122.2 (Ar), 114.3 (Ar), 104.0 (CCl_3), 103.0 (C5), 55.4 (OMe), 46.8 (C4), 21.0 (Me). *Anal.* Calcd. for $C_{18}H_{17}Cl_3N_2O_4S$ (463.76): C, 48.28; H, 3.69; N, 6.04 %. Found: C, 46.84; H, 3.74; N, 5.96 %.

3-(4-Bromophenyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2f**). This compound was obtained as white solid, yield 86 %, Mp. 199-201 °C; ^1H NMR (DMSO-d_6): δ = 8.59 (br, 1H, OH), 7.82 (d, 2H, *J*= 8.2, Ts), 7.66 (s, 4H, Ph), 7.37 (d, 2H, *J*= 8.2, Ts), 3.99 (d, 1H, *J*= 19.5, H-4a), 3.53 (d, 1H, *J*= 19.5, H-4b), 2.36 (s, 3H, Me-Ts); ^{13}C NMR (DMSO-d_6): δ = 154.5 (C3), 143.9 (Ar), 135.5 (Ar), 132.1 (Ar), 131.9 (Ar), 129.2 (Ar), 128.9 (Ar), 128.6 (Ar), 128.6 (Ar), 128.5 (Ar), 124.5 (Ar), 103.8 (CCl_3), 103.5 (C5), 46.6 (C4), 21.0 (Me). *Anal.* Calcd. for $C_{17}H_{14}BrCl_3N_2O_3S$ (512.63): C, 39.83; H, 2.75; N, 5.46 %. Found: C, 40.05; H, 2.74; N, 5.48 %.

3-(4-Chlorophenyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2g**). This compound was obtained as white solid, yield 64 %, Mp. 198-200 °C; ^1H NMR (DMSO-d_6): δ = 8.60 (br, 1H, OH), 7.83 (d, 2H, *J*= 8.1, Ts), 7.73 (d, 2H, *J*= 8.4, Ph-Cl), 7.50 (d, 2H, *J*= 8.4, Ph-Cl), 7.36 (d, 2H, *J*= 8.1, Ts) 3.98 (d, 1H, *J*= 19.5, H-4a), 3.55 (d, 1H, *J*= 19.5, H-4b), 2.34 (s, 3H, Me-Ts); ^{13}C NMR (DMSO-d_6): δ = 154.3 (C3), 143.7 (Ar), 135.5 (Ar), 132.7 (Ar), 129.1 (Ar), 128.8 (Ar), 128.5 (Ar), 128.4 (Ar), 124.3 (Ar), 103.7 (CCl_3), 103.4 (C5), 46.5 (C4), 20.9 (Me). *Anal.* Calcd for $C_{17}H_{14}Cl_4N_2O_3S$ (468.18): C, 43.61; H, 3.01; N, 5.98%. Found: C, 43.82; H, 2.90; N, 6.19 %.

3-(4-Fluorophenyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-tosylpyrazole (**2h**). This compound was obtained as white solid, yield 73%, Mp. 155-157 °C; ^1H NMR (DMSO-d_6): δ = 8.61 (br, 1H, OH), 7.90 (d, 2H, *J*= 8.2, Ts), 7.82 (d, 2H, *J*=5.4, Ph-F), 7.80 (d, 2H, *J*=5.4, Ph-F), 7.39 (d, 2H, *J*= 8.2, Ts), 7.29 (m, 2H, Ph-F), 4.03 (d, 1H, *J*= 19.4, H-4a), 3.61(d, 1H, *J*= 19.4, H-4b), 2.35 (s, 3H, Me-Ts); ^{13}C NMR (DMSO-d_6): δ =164.7 (Ar),162.2 (Ar),154.4 (C3), 143.7 (Ar), 135.6 (Ar), 129.1 (Ar), 129.0 (Ar), 128.5 (Ar), 126.3 (Ar), 126.3 (Ar), 116.0 (Ar), 115.7 (Ar), 103.8 (CCl_3), 103.3 (C5), 46.8 (C4), 20.9 (Me). *Anal.* Calcd for $C_{17}H_{14}Cl_3FN_2O_3S$ (451.73): C, 45.20; H, 3.12; N: 6.20 %. Found: C, 45.09; H, 3.13; N, 6.13 %.

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