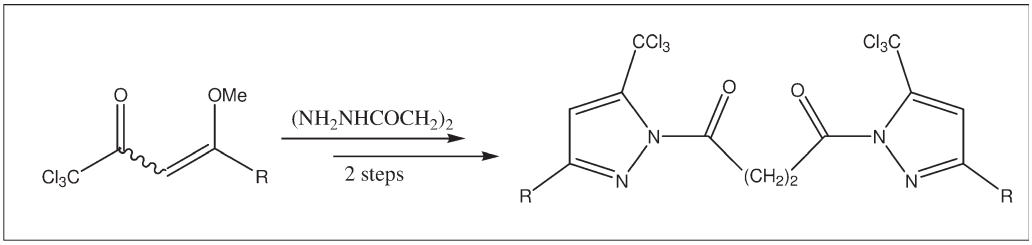
New Succinyl-spaced Pyrazoles: Regioselective Synthesis of 1,4-Bis[5-(trichloromethyl)-1*H*-pyrazol-1-yl]butane-1,4-diones

Helio G. Bonacorso,* Cleber A. Cechinel, Gisele R. Paim, Marcos A. P. Martins, Nilo Zanatta, and Alex F. C. Flores

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, Santa Maria 97.105-900, RS, Brazil
*E-mail: heliogb@base.ufsm.br

Received February 24, 2010
DOI 10.1002/jhet.523
Published online 9 September 2010 in Wiley Online Library (wileyonlinelibrary.com).



The facile and convenient access by a conventional procedure in ethanol as solvent to a new series of succinyl-spaced pyrazoles including 1,4-bis[5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (64–82%) and the respective dehydrated derivatives as 1,4-bis[5-(trichloromethyl)-1*H*-pyrazol-1-yl]butane-1,4-diones in 57–82% yields, from the regioselective cyclocondensation reactions of 4-substituted 4-methoxy-1,1,1-trichloroalk-3-en-2-ones with succinic acid dihydrazide, where the 4-substituents are Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-furyl, and 2-thienyl, is reported.

J. Heterocyclic Chem., **48**, 113 (2011).

INTRODUCTION

Recently, there has been great interest in the synthesis of trifluoromethyl-substituted heteroaromatic compounds due, in part, to the unique biological properties exhibited by fluorine [1]. On the other hand, trichloromethylated heterocycles are relatively rare but promising templates for biological activity. For example, trichloromethyl-substituted benzodiazepines, quinazolines, and pyrimidines have exhibited activity as acetyl cholinesterase and ATPDase inhibitors, anxiolytics, cyclin-dependent kinase (CDKs) inhibitors in cell cycle proteins and ATP and ADP hydrolysis inhibitors in synaptosomes from rat cerebral cortex. Particularly, 3-aryl-5-trichloromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles presented anti-inflammatory and analgesic activity [2].

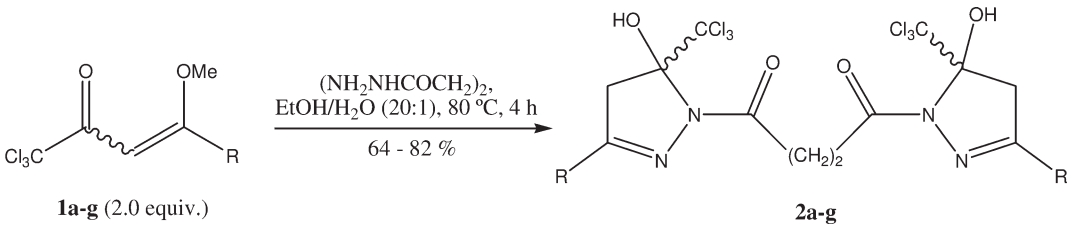
Among several classes of *N*-heterocycles, the 2-pyrazolines have been used as antitumor [3], antibacterial, antifungal, antiviral, antiparasitic, antitubercular, and insecticidal agents [4–11]. Some of these compounds also showed anti-inflammatory, antidiabetic, anesthetic, and analgesic properties [12–14].

In the course of our ongoing interest in new heterocyclic scaffolds, we have explored the application of 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trichloroalk-3-en-2-ones **1** in the synthesis of novel or uncommon low-molecular weight heterocyclic compounds [15] and have reported not only the synthesis of single-, linked-, or geminated-trihalosubstituted heterocycles but also alkyl- and carbonyl-linked bis-heterocycles [15–20].

Moreover, specifically, bis-pyrazolyl systems containing acyl spacer groups are rare in the literature and new synthetic routes to obtain these compounds and studies of their potential for pharmaceuticals and agrochemicals such as herbicidal agents have been relatively little explored [16–23].

A review of the literature disclosed few publications on the construction of a succinyl spacer bis-(3,5-substituted 1*H*-pyrazoles) system. In 1961, according to a US patent, Wright [16] reported the systematic synthesis and a biological activity study of a series of bis-(4-nitropyrazol-1-yl) spacer compounds, where the linker moiety was an aliphatic hydrocarbon chain [—$(CH_2)_n$—] containing 1–12 carbon atoms, saturated or unsaturated, and substituted by one or more lower alkyl (not more than four carbon atoms) or hydroxyl groups. In the same patent, diacyl group spacers [—CO— $(CH_2)_n$—CO—] with *n* being an integer from 1 to 12 or an ether group of the formula [—$(CH_2)_x$—O—$(CH_2)_y$—], where *x* and *y* were identical or different integers from 1 to 10, or even a divalent cycloalkyl group such as 1,4-cyclohexylene were synthesized and biologically tested. These new bis-pyrazolyl compounds showed useful activity as antiprotozoal agents, especially in the treatment of trichomoniasis (e.g., that caused by *T. vaginalis*). The 1,7 di-(4-nitropyrazol-1-yl)*n*-heptane and their respective

Scheme 1. Synthetic route to 1,4-bis(5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)butane-1,4-diones (**2**).



1a-g (2.0 equiv.) **2a-g**

1,2	a	b	c	d	e	f	g
R	Me	Ph	4-FC_6H_4	4-ClC_6H_4	4-$NO_2C_6H_4$	2-Furyl	2-Thienyl

n-pentane analog were of outstanding activity and low toxicity. Specifically, only 1,1′-succinylbis(3,5-dimethyl-4-nitropyrazole) and the nonsubstituted 1,1′-succinyl bis-(4-nitropyrazole) were prepared using the appropriate 1*H*-pyrazole and succinyl chloride. In 2005, Shi *et al*. [17] reported the synthesis of *N,N*′-butanedioylbis(5-ferrocenyl-3-methyl-1*H*-pyrazole) from the reaction of ferrocenoylacetone and succinic acid dihydrazide. In the same year, Al-Talib *et al*. [18] reported that the reaction of oxalic-, malonic-, and succinic acid dihydrazide with 2,4-pentanedione gave smoothly the corresponding oxalyl-, malonyl-, and succinyl-*N,N*′-bis(3,5-dimethyl-1*H*-pyrazole). It is also important to mention that aroyl and heteroaroyl spacer bis-pyrazoles have been synthesized using 1,3-dicarbonyl compounds or derivatives thereof and, for example, isophthalic acid dihydrazide [19] or 1,3,4-thiadiazole-2,5-dithioglycolic acid dihydrazide [20], respectively.

Until now, no molecules containing an alkanoyl moiety, such as a succinyl bridge, bonding two identical or different trichloromethylated heterocycles have been synthesized.

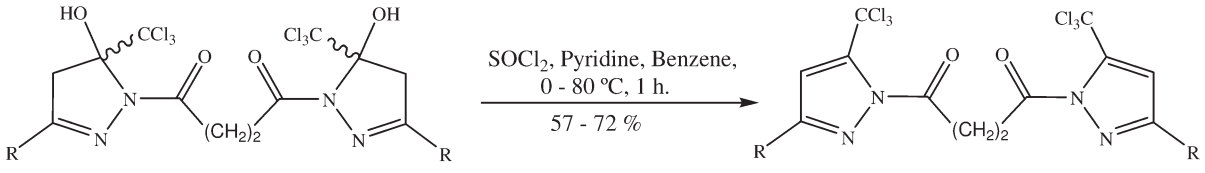
In this context and in an attempt to develop synthetic methods to obtain acyl spacer heterocycles and new trichloromethyl-substituted molecules, we herein report a regioselective methodology for the preparation of a series of 1,4-bis(5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)butane-1,4-diones (**2**) from the cyclocondensation reactions of 4-substituted 4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**1**) with succinic acid dihydrazide in ethanol as solvent under conventional reaction conditions (Scheme 1), and, as an example, the dehydrated bis-pyrazole system, 1,4-bis(5-(trichloromethyl)-1*H*-pyrazol-1-yl)butane-1,4-diones (**3**) from the dehydration reactions of **2** using thionyl chloride and pyridine in benzene media is also presented (Scheme 2).

In this work, we initially carried out the reaction of 4-methoxy-4-(4-fluorophenyl)-1,1,1-trichlorobut-3-en-2-one (**1c**) with succinic acid dihydrazide in 2:1 molar ratio, respectively, in ethanol/water (20:1) as solvent at room temperature.

RESULTS AND DISCUSSION

Since the 1970s, research groups have reported the systematic synthesis of 4-substituted 4-methoxy-1,1,1-trihaloalk-3-en-2-ones (**1**) from the trihaloacetylation reaction of the respective enolethers or acetals with trifluoroacetic anhydride or trichloroacetyl chloride, respectively [1,15]. In this article, 4-methoxy-1,1,1-trichloropent-3-en-2-one (**1a**) was prepared according to ref. [24]; 4-aryl-4-methoxy-1,1,1-trichlorobut-3-en-2-ones (**1b–e**) were synthesized from the reaction of the respective acetophenone dimethyl acetals with trichloroacetyl chloride [25] and 4-heteroaryl-4-methoxy-1,1,1-

Scheme 2. Synthetic route to 1,4-bis(5-(trichloromethyl)-1*H*-pyrazol-1-yl)butane-1,4-diones (**3**).



2b-c, 2e **3b-c**, **3e**

2, 3	b	c	e
R	Ph	4-FC_6H_4	4-$NO_2C_6H_4$

trichlorobut-3-en-2-ones (**1f–g**) were obtained following the procedure from the literature [26].

According to the literature [16], 1,1′-succinylbis(3,5-dimethyl-4-nitropyrazole) and the nonsubstituted 1,1′-succinylbis(4-nitropyrazole) were prepared using the appropriate 1*H*-pyrazole and succinyl chloride in the presence of anhydrous sodium carbonate, when the reactions were carried out in dry acetone as solvent for 20 h at 20°C but no yields were reported.

However, this reaction, monitored by TLC, did not take place and the starting reagents were recovered. Subsequently, when the mixture was heated to reflux, after stirring for 4 h, TLC showed that the reaction proceeded smoothly and gave the product **2c** in 64% yield (Scheme 1).

The most satisfactory results for the synthesis of other compounds **2a–g** were obtained using the above described reaction condition, and these compounds were isolated as stable solids by recrystallization from ethanol/water (20:1 v/v).

Subsequently, after a review of the literature, attempting to obtain aromatic pyrazoles for further biological assays, we chose thionyl chloride/pyridine as the dehydrating agent and report here the conditions required to accomplish the dehydration of two representative examples of compounds **2**, which present a hydroxyl and a trichloromethyl group, a phenyl (for **2b**), a 4-fluorophenyl (for **2c**) or a 4-nitrophenyl (for **2e**), and a succinyl 2-pyrazoline attached directly to the C-5, C-3, and N-1 atom of each pyrazoline ring, respectively (Scheme 2). Due to the relative difficulty to carry out the dehydration reaction, because of the presence of the trichloromethyl substituent and the carbonyl function at positions 5 and 1 of these two bis-succinyl-pyrazolines, **2b**, **2c**, and **2e** were dehydrated to give the respective 3-aryl-substituted 1,4-bis(5-(trichloromethyl)-1*H*-pyrazol-1-yl)butane-1,4-diones **3b**, **3c**, and **3e** in 57–72% yields, only by stirring the mixtures of **3**, thionyl chloride, and pyridine at 80°C for about 1 h in benzene as solvent (Scheme 2), according to procedures similar to those described in the literature [27].

The structures of 1,4-bis[5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (**2a–g**) were deduced from NMR experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory [15,28].

Compounds **2** showed ^{1}H-NMR chemical shifts in DMSO-d_6 for the hydroxy protons in the range of δ 7.62 ppm and the four methylene protons (H4) were observed as a typical AB system, as two doublets, in which one of them was on average at δ 3.89 and the other at δ 3.66 ppm, with a geminal coupling constant of 19–20 Hz. Because of the symmetry of compounds **2**, the four ethylene protons (succinyl moiety) appeared as one singlet peak on average at 3.13 ppm. The ^{13}C{^{1}H}-NMR spectra exhibited only one set of peaks, despite the fact that two stereogenic carbons were present in each molecule. The succinyl derivatives **2** also presented the typical ^{13}C-NMR chemical shifts for both pyrazoline rings at δ 153.8 ppm (C3), δ 47.1 ppm (C4), 101.1 ppm (CCl_3), and 98.3 ppm (C5). The two carbonyl and ethylene carbons showed NMR signals in the range of δ 172.9 and 29.3 ppm, respectively. All the signals are consistent with ^{1}H- and ^{13}C-NMR chemical shifts for the pyrazoline and succinyl moieties of this symmetric system.

The dehydrated compounds **3**, being symmetric systems, presented one set of signals in both ^{1}H- and ^{13}C-NMR spectra and, in comparison with **2**, now showed typical chemical shifts for the pyrazole ring for both H-4 on average at 7.92 ppm as singlet peaks.

The ^{13}C{^{1}H}-NMR spectra exhibited chemical shifts, in DMSO-d_6, for both pyrazole ring carbons on average at 154.4 (C3), 92.1 (C4), 103.1 (CCl_3), and 141.9 ppm (C5). Both carbonyl and ethylene carbons showed signals in the range of δ 169.4 and 32.5 ppm, respectively.

In conclusion, 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trichloroalk-3-en-2-ones **1** have been shown to react with succinic acid dihydrazide under conventional and mild conditions to produce, in a one-step reaction, new succinyl spacer bis-(3,5-substituted 2-pyrazolines and 1*H*-pyrazoles), namely, 1,4-bis(5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)butane-1,4-diones **2** (64–82%). The efficient dehydration reaction used for the heterocycles **2** to afford the 1,4-bis(5-(trichloromethyl)-1*H*-pyrazol-1-yl)butane-1,4-diones **3** (57–72%) was also demonstrated.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus. ^{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, and digital resolution ± 0.01 ppm in DMSO-d_6 for **2** and **3** using TMS as internal reference. Infrared spectra were recorded from 4000 to 650 cm^{-1} using a Perkin-Elmer Model Spectrum One FTIR spectrometer with 16 scans and 4 cm^{-1}. This instrument is equipped with a universal ATR sampling accessory supplied with a top plate ZnSe crystal. For ATR data acquisition, 5.0 ± 0.3 mg of solid sample was placed onto the crystal and its spectrum was recorded. Data were handled using Matlab software 6.1 version (The Math Works, Natick, MA). The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

Synthetic procedures. General procedure for the preparation of 1,4-bis[5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (2a–g). A solution of 4-substituted 4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**1a–g**)

(10 mmol), succinic acid dihydrazide (5 mmol), ethanol (20 mL), and distilled water (1 mL) was stirred at 80°C for 4 h. After the reaction time, the solvent was evaporated to half by rotatory evaporator under reduced pressure. After cooling (≤8°C) for 1–2 days, the compounds **2a–g** were obtained pure directly by filtration, washed with cold ethanol, and dried under vacuum apparatus.

1,4-Bis[5-(trichloromethyl)-5-hydroxy-3-methyl-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2a). This compound was obtained as a white solid, yield 64%, Mp 170–171°C. ^{1}H-NMR (DMSO-d_6) δ = 7.72 (s, 2H, 2OH), 3.50 (d, J = 19, 2H, 2H-4), 3.32 (d, J = 19, 2H, 2H-4), 2.87 (s, 4H, $2CH_2$), 2.02 (s, 6H, $2CH_3$). ^{13}C-NMR (DMSO-d_6) δ = 173.9 (2C=O), 156.4 (2C-3), 103.4 ($2CCl_3$), 100.9 (2C-5), 49.7 (2C-4), 27.3 ($2CH_2$), 26.2 ($2CH_3$). ATR-IR (ν, cm^{-1}): 3211, 1647, 772. Anal. Calc. for $C_{14}H_{16}Cl_6N_4O_4$ (513.93): C, 32.52; H, 3.12; N, 10.84%. Found C, 32.92; H, 3.48; N, 11.14%.

1,4-Bis[5-(trichloromethyl)-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2b). This compound was obtained as a white solid, yield 73%, Mp 214–216°C. ^{1}H-NMR (DMSO-d_6) δ = 7.92 (s, 2H, 2OH), 7.81–7.83 (m, 4H, 2Ar), 7.48–7.50 (m, 6H, 2Ar), 3.97 (d, J = 18, 2H, 2H-4), 3.78 (d, J = 18, 2H, 2H-4), 3.11 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6) δ = 175.5 (2C=O), 155.1 (2C-3), 131.1, 130.2, 128.8, 126.8 (8C, 2Ar), 103.7 ($2CCl_3$), 102.1 (2C-5), 46.7 (2C-4), 30.1 ($2CH_2$). ATR-IR (ν, cm^{-1}): 3366, 1672, 757. Anal. Calc. for $C_{24}H_{20}Cl_6N_4O_4$ (637.96): C, 44.96; H, 3.14; N, 8.74%. Found C, 44.63; H, 2.89; N, 8.94%.

1,4-Bis[5-(trichloromethyl)-3-(4-fluorophenyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2c). This compound was obtained as a white solid, yield 64%, Mp 188–190°C. ^{1}H-NMR (DMSO-d_6) δ = 7.71–7.78 (m, 4H, 2Ar), 7.27 (s, 2H, 2OH), 7.09–7.17 (m, 4H, 2Ar), 3.92 (d, J = 18, 2H, 2H-4), 3.70 (d, J = 18, 2H, 2H-4), 3.26 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6) δ = 172.3 (2C=O), 163.4 (d, J = 249, 2C-F, 2Ar), 152.6 (2C-3), 128.9, 126.5, 115.7 (6C, 2Ar), 103.3 ($2CCl_3$), 101.7 (2C-5), 46.7 (2C-4), 29.6 ($2CH_2$). ATR-IR (ν, cm^{-1}): 3371, 1645, 772. Anal. Calc. for $C_{24}H_{18}Cl_6F_2N_4O_4$ (673.94): C, 42.57; H, 2.68; N, 8.27%. Found C, 42.98; H, 2.41; N, 7.82%.

1,4-Bis[5-(trichloromethyl)-3-(4-chlorophenyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2d). This compound was obtained as a white solid, yield 82%, Mp 244–246°C. ^{1}H-NMR (DMSO-d_6) δ = 7.43 (s, 2H, 2OH), 7.65–7.70 (m, 4H, 2Ar), 7.39–7.43 (m, 4H, 2Ar), 3.91 (d, J = 18, 2H, 2H-4), 3.62 (d, J = 18, 2H, 2H-4), 3.25 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6) δ = 173.1 (2C=O), 159.7 (2C-3), 132.3, 128.6, 128.5, 126.5 (8C, 2Ar), 86.7 ($2CCl_3$), 78.9 (2C-5), 46.5 (2C-4), 28.6 ($2CH_2$). ATR-IR (ν, cm^{-1}): 3319, 1694, 774. Anal. Calc. for $C_{24}H_{18}Cl_8N_4O_4$ (705.88): C, 40.60; H, 2.56; N, 7.89%. Found C, 40.53; H, 2.83; N, 7.94%.

1,4-Bis[5-(trichloromethyl)-5-hydroxy-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2e). This compound was obtained as a white solid, yield 66%, Mp 245–247°C. ^{1}H-NMR (DMSO-d_6) δ = 8.10 (s, 2H, 2OH), 8.28–8.33 (m, 4H, 2Ar), 8.06–8.10 (m, 4H, 2Ar), 4.09 (d, J = 18, 2H, 2H-4), 3.82 (d, J = 18, 2H, 2H-4), 3.14 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6) δ = 171.9 (2C=O), 151.6 (2C-3), 148.2, 135.9, 127.7, 123.9 (8C, 2Ar), 103.1 ($2CCl_3$), 102.2 (2C-5), 46.6 (2C-4), 29.9 ($2CH_2$). ATR-IR (ν, cm^{-1}): 3332, 1699, 779. Anal. Calc. for $C_{24}H_{18}Cl_6N_4O_8$ (727.93): C, 39.42; H, 2.48; N, 11.49%. Found C, 39.54; H, 2.94; N, 11.45%.

1,4-Bis[5-(trichloromethyl)-3-(2-furyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2f). This compound was obtained as a white solid, yield 80%, Mp 223–225°C. ^{1}H-NMR (DMSO-d_6) δ = 7.57–7.58 (m, 2H, 2 Fur), 7.46 (s, 2H, 2OH), 6.85–6.87 (m, 2H, 2Fur), 6.53–6.55 (m, 2H, 2Fur), 3.89 (d, J = 18, 2H, 2H-4), 3.59 (d, J = 18, 2H, 2H-4), 3.22 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6) δ = 172.1 (2C=O), 144.9 (4C, 2Fur), 142.0 (2C-3), 115.0, 112.2 (4C, 2Fur), 103.2 ($2CCl_3$), 101.4 (2C-5), 46.4 (2C-4), 29.8 ($2CH_2$). ATR-IR (ν, cm^{-1}): 3193, 1650, 766. Anal. Calc. for $C_{20}H_{16}Cl_6N_4O_6$ (617.92): C, 38.68; H, 2.60; N, 9.02%. Found C, 38.51; H, 3.01; N, 8.73%.

1,4-Bis[5-(trichloromethyl)-5-hydroxy-3-(2-thienyl)-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (2g). This compound was obtained as a white solid, yield 78%, Mp 208–210°C. ^{1}H-NMR (DMSO-d_6) δ = 7.79–7.81 (m, 2H, 2Thien), 7.48 (s, 2H, 2OH), 7.45–7.50 (m, 4H, 2Thien), 3.97 (d, J = 19,2H, 2H-4), 3.77 (d, J = 19, 2H, 2H-4), 3.11 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6) δ = 171.8 (2C=O), 159.6 (2C-3), 149.4, 127.5, 125.4, 124.5 (8C, 2Th), 104.7 ($2CCl_3$), 101.4 (2C-5), 47.1 (2C-4), 30.2 ($2CH_2$). ATR-IR (ν, cm^{-1}): 3183, 1645, 737. Anal. Calc. for $C_{20}H_{16}Cl_6N_4O_4S_2$ (649.87): C, 36.77; H, 2.47; N, 8.58%. Found C, 36.70; H, 2.88; N, 8.42%.

General procedure for the synthesis of 1,4-bis[5-(trichloromethyl)-1*H*-pyrazol-1-yl]butane-1,4-diones (3b–c, 3e). A solution of bis-pyrazoline butane-1,4-diones (**2b–c**, **2e**) (2.8 mmol) and pyridine (37.1 mmol, 3 mL) in 50 mL of benzene was cooled to 0°C and thionyl chloride (16.8 mmol, 1.22 mL) diluted in 25 mL of benzene was added dropwise over 10 min. The solution was stirred for an additional 30 min, during which time the temperature was allowed to rise to 20°C. The mixture was then heated under reflux (bath temperature 80°C) for 1 h and then filtered to remove the pyridine hydrochloride at room temperature. The solution was extracted twice with benzene (2 × 50 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure by rotatory evaporator left **3b–c**, **3e** as solid products, which were purified by recrystallization from aqueous ethanol.

1,4-Bis[5-(trichloromethyl)-3-phenyl-1H-pyrazol-1-yl]butane-1,4-dione (3b). This compound was obtained as a white solid, yield 57%, Mp 190–191°C. ^{1}H-NMR (DMSO-d_6): δ 8.04–8.07 (m, 4H, 2Ar), 7.85 (s, 2H, 2H-4), 7.50–7.53 (m, 5H, 2Ar), 3.76 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6): δ 173.3 (2C=O), 154.1 (2C-3), 144.1 (2C-5), 128.8, 128.6, 128.5, 125.3 (8C, 2Ar), 104.9 ($2CCl_3$), 100.3 (2C-4), 28.6 ($2CH_2$). ATR-IR (ν, cm^{-1}): 1760, 761. Anal. Calc. for $C_{24}H_{16}Cl_6N_4O_2$ (601.94): C, 47.64; H, 2.67; N, 9.26%. Found C, 47.96; H, 2.38; N, 9.46%.

1,4-Bis[5-(trichloromethyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl]butane-1,4-dione (3c). This compound was obtained as a white solid, yield 63%, Mp 189–190°C. ^{1}H-NMR (DMSO-d_6): δ 7.87 (s, 2H, 2H-4), 7.34–7.39 (m, 8H, 2Ar), 3.74 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6): δ 162.1 (2C=O), 155.3 (2C-3), 145.0 (2C-5), 127.7, 127.6, 116.4, 116.2 (8C, 2Ar), 101.3 ($2CCl_3$), 89.9 (2C-4), 38.3 ($2CH_2$). ATR-IR (ν, cm^{-1}): 1750, 763. Anal. Calc. for $C_{24}H_{14}Cl_6F_2N_4O_2$ (637.92): C, 44.96; H, 2.20; N, 8.74%. Found C, 44.99; H, 2.04; N, 8.51%.

1,4-Bis[5-(trichloromethyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl]butane-1,4-dione (3e). This compound was obtained as a yellow solid, yield 72%, Mp 131–133°C. ^{1}H-NMR (DMSO-d_6): δ 8.35–8.36 (m, 4H, 2Ar), 8.04 (s, 2H, 2H-4), 7.36 (s, 4H, 2Ar), 3.81 (s, 4H, $2CH_2$). ^{13}C-NMR (DMSO-d_6): δ 169.9

(2C=O), 153.9 (2C-3), 136.6 (C-5), 135.4, 128.3, 127.0, 126.3 (8C, 2Ar), 103.1 ($2CCl_3$), 86.1 (2C-4), 30.8 ($2CH_2$). ATR-IR (ν, cm^{-1}): 1756, 771. Anal. Calc. for $C_{24}H_{14}Cl_6N_6O_6$ (691.91): C, 41.47; H, 2.03; N, 12.09%. Found C, 41.17; H, 2.16; N, 11.83%.

Acknowledgments. The authors are thankful for the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (Proc. Nr. 303296/2008-9). Fellowships from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—CAPES (Cechinel, C. A. and Paim, G. R.) are also acknowledged.

REFERENCES AND NOTES

[1] (a) Welch, J. T. Tetrahedron 1987, 43, 3123; (b) Park, B. K.; Kitterringham, N. R.; O'Neill, P. M. Annu Rev Pharmacol Toxicol 2001, 41, 443; (c) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. Tetrahedron 2007, 63, 7753; (d) Nenajdenko, V. G.; Sanin, A. V.; Balenkova, E. S. Molecules 1997, 2, 186.

[2] Souza, F. R.; Fighera, M. R.; Lima, T. T. F.; Bastiani, J.; Barcellos, I. B.; Almeida, C. E.; Oliveira, M. R.; Bonacorso, H. G.; Flores, A. E.; Mello, C. F. Pharmacol Biochem Behav 2001, 68, 525.

[3] Taylor, E. C.; Patel, H.; Kumar, H. Tetrahedron 1992, 48, 8089.

[4] Roelfvan, S. G.; Arnold, C.; Wellnga, K. J Agric Food Chem 1979, 84, 406.

[5] Kedar, R. M.; Vidhale, N. N.; Chincholkar, M. M. Orient J Chem 1997, 13, 143.

[6] Singh, A.; Rathod, S.; Berad, B. N.; Patil, S. D.; Dosh, A. G. Orient J Chem 2000, 16, 315.

[7] Katri, H. Z.; Vunii, S. A. J Ind Chem Soc 1981, 58, 1968.

[8] Das, N. B.; Mittra, A. S. Ind J Chem B 1978, 16, 638.

[9] Azarifar, D.; Shaebanzadeh, M. Molecules 2002, 7, 885.

[10] Holla, B. S.; Akaberali, P. M.; Shivanada, M. K. Farmaco 2000, 55, 256.

[11] Palaska, E.; Aytemir, M.; Tayfun, I.; Erol, K.; Dilek, E. Eur J Med Chem Chim Ther 2001, 36, 539.

[12] Regaila, H. A.; El-Bayonk, A. K.; Hammad, M. Egypt J Chem 1979, 20, 197.

[13] Krishna, R.; Pande, B. R.; Bharthwal, S. P.; Parmar, S. S. Eur J Med Chem 1980, 15, 567.

[14] Husain, M. I.; Shukla, S. Ind J Chem B 1986, 25, 983.

[15] Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. Curr Org Chem 2004, 1, 391; and references therein.

[16] Wright, D. E. May & Baker Ltd, US Patent 2,979,512, 1961.

[17] Shi, Y.-C.; Sui, C.-X.; Cheng, H.-J. Acta Cryst E 2005, 61, m1563.

[18] Al-Talib, M.; Tashtoush, H.; Al-Ghoul, A.; Ziemer, B.; Koert, U. J Heterocycl Chem 2005, 42, 287.

[19] Moore, J. A.; Mehta, P. G. Macromolecules 1995, 28, 444.

[20] Rutavichyus, A.; Valyulene, S.; Kuodis, Z. Chem Heterocycl Compd 1997, 33, 118.

[21] Denisova, A. B.; Sosnovskikh, V. Y.; Dehaen, W.; Toppet, S.; Meervelt, L. V.; Bakulev, V. A. J Fluorine Chem 2002, 115, 183.

[22] Hanamoto, T.; Hakoshima, Y.; Egashira, M. Tetrahedron Lett 2004, 45, 7573.

[23] Angerman, A.; Franke, H.; Geisler, J.; Johann, G.; Rees, R.; Schering AG, US Patent 4,008,200, 1991.

[24] Martins, M. A. P.; Colla, A.; Clar, G.; Fischer, P.; Krimmer, S. Synthesis 1991, 483.

[25] Martins, M. A. P.; Siqueira, G. M.; Flores, A. F. C.; Clar, G.; Zanatta, N. Quim Nova 1994, 17, 24.

[26] Flores, A. F. C.; Brondani, S.; Rosa, A.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 8701.

[27] Padwa, A. J Org Chem 1965, 30, 1274.

[28] Bonacorso, H. G.; Oliveira, M. R.; Wentz, A. P.; Wastowski, A. D.; Oliveira, A. B.; Hoerner, M.; Zanatta, N.; Martins, M. A. P. Tetrahedron 1999, 55, 345.