Regiospecific One-pot Synthesis of New Trifluoromethyl Substituted Heteroaryl Pyrazolyl Ketones

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A convenient and general method for the regiospecific synthesis of three novel series of 1-(2-thenoyl)-, 1-(2-furoyl)- and 1-(isonicotinoyl)-3-alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles, in good yields (53 – 91 %), from the cyclocondensation reactions of 1,1,1-trifluoro-4-alkoxy-4-alkyl(aryl)-but-3-en-2-ones, where alkyl = H and Me; aryl = -C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$ with 2-thiophenecarboxylic hydrazide, furoic hydrazide and isonicotinic acid hydrazide, respectively, is reported. Subsequently dehydration reaction of phenyl substituted 2-pyrazolines with P_2O_5 furnished the corresponding 1*H*-pyrazoles as mixture of regioisomers and in low yields (35 – 36 %).

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Natural products containing pyrazole rings are rare. However, many synthetically produced pyrazoles are biologically active and some are used as pharmaceuticals, herbicides and insecticides [1]. The non-aromatic analogs 2-pyrazolines (4,5-dihydro-1*H*-pyrazoles) have been used as antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agent [2-10]. Some of these compounds showed also anti-inflammatory, anti-diabetic, anesthetic and analgesic properties [11-13].

On the other hand, little is known about the chemistry and the metabolism of thiophen, furan and pyridine, as heterobicyclic ketone derivatives. Particularly, heteroaryl thienyl ketones have been the subject of few publications. Similar compounds as aryl thienyl ketones [14] have antiplatelet effects as a consequence of interfering with cyclooxygenase in the arachadonic acid cascade. For example, 1-hydroxy-2,3-dimethoxyphen-6-yl thienyl ketone is 25 times more active than aspirin [15]. Very interesting is that some pyrazoline isosteres of the ketone moiety of 2,3-dimethoxyphenol thienyl ketone also have *in vitro* antiplatelet activity [16]. During the 1980s, suprofen was approved as an NSAID with potency greater than that of indomethacin. Later, suprofen was removed from the market as a consequence of unexpected toxicity. Tenidap [17] is an exciting new agent with a profile of activity which extends beyond inhibition of the cyclooxygenase (CO) in the arachadonic acid cascade. The structures of suprofen and tenidap present the 2-thenoyl group.

As interesting pyridine substituted heteropolycycles, some 5-aroylamino-3-nicotinoyl(isonicotynoyl)-1,3,4-thiadiazol-2(3*H*)-ones have exhibited anti-inflammatory activity, but devoid of antipyretic properties [18]. Moreover, in a recent work Mamolo *et al*. [19] synthesized a series of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazoles in three-steps in low yields, which involved an aldol condensation, cyclocondensation with hydrazine and N-acylation with isonicotinoyl chloride. These 2-pyrazolines showed interesting antimycobacterial activity *in vitro*.

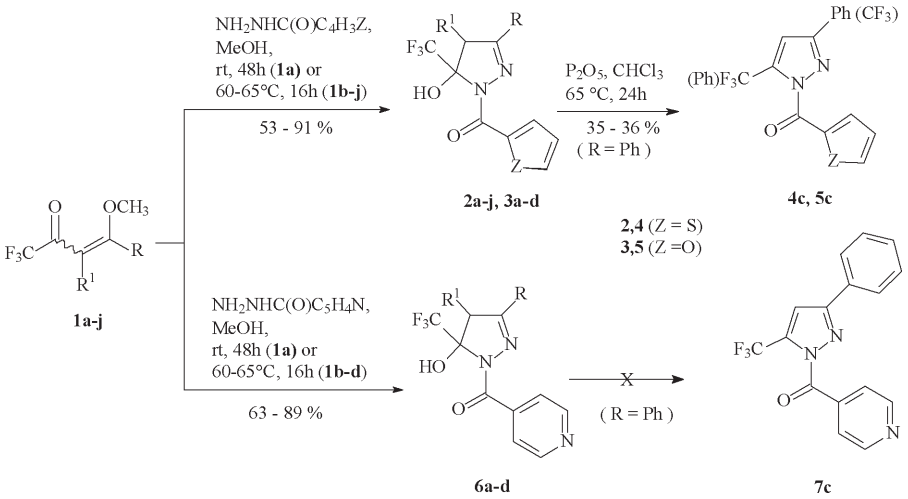
Thus, considering the biological importance of 2-pyrazolines and some ketone derivatives and the fact that the reactions to obtain structurally similar compounds, employing aryl or heteroarylhydrazides and fluorinated β-diketones ($CF_3COCH_2COCF_3$ or CF_3COCH_2COR) are rare in the literature [20-25], we have recently reported a new regiospecific synthetic method to obtain a series of six 3-aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-picolinoylpyrazoles, in a one-step reaction and in good yields from the reaction of β-methoxyvinyl trifluoromethyl ketones with 2-pyridinecarboxamidrazone [26]. However, this work [26] allowed to obtain only picolinoyl derivatives under acid condition. Moreover, the 2-pyridinecarboxamidrazone was previously obtained with some experimental difficulty.

Although the possibility of preparing trihalomethylated pyrazoles and pyrazolines by a regiospecific cyclocondensation reaction of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-(chloro)-3-alken-2-ones with hydrazines has long been explored by our research group [27], a general and systematic methodology that allows the synthesis of new interesting trifluoromethyl substituted heteroaryl pyrazolyl ketones (trifluoromethylated heteroaroylpyrazoles) was not yet developed.

In view of these observations, we became interested in heterocycles, which may play an important role in the physiological processes of living organisms. Thus, on the course of our research program concerning the application of 4-alkoxy-4-alkyl(aryl)-1,1,1-trihalo-3-alken-2-ones to obtain new trihalomethylated heterocycles, we wish to report the regiospecific synthesis of a new series of 3-alkyl(aryl)-5-trifluoromethyl-5-hydroxy-1-(heteroaroyl)-4,5-dihydro-1*H*-pyrazoles and some aromatic derivatives which have been obtained from the cyclocondensation reaction of 2-thiophenecarboxylic hydrazide, furoic

hydrazide and isonicotinic acid hydrazide with a series of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-alken-2-ones derived from enolethers and phenones (Scheme I).

Scheme I



1-7	a	b	c	d	e	f	g	h	i	j
R	H	Me	Ph	4-MePh	4-MeOPh	4-FPh	4-ClPh	4-BrPh	4-NO_2 Ph	4-MeOPh
R^1	H	H	H	H	H	H	H	H	H	Me

Eighteen trifluoromethylated 2-pyrazolines derived from the reaction of substituted 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones (**1a-j**) with three hydrazides named 3-alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazoles (**2a-j),** -4,5-dihydro-1*H*-1-(2-furoyl)pyrazoles (**3a-d**) and -4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazoles (**6a-d**) were obtained in one-step and regiospecificaly in a very similar and satisfactory yields (55 - 91 %, 53 - 88 % and 63 - 89 %), respectively.

The reactions of **1a-j** with 2-thiophenecarboxylic hydrazide, furoic hydrazide and isonicotinic acid hydrazide were carried out in a molar ratio 1:1 in anhydrous methanol as solvent and all reactions were monitored by TLC. The most satisfactory results were obtained when the reactions were performed under mild conditions at room temperature for 48 hours (**1a**) or at 60 – 65 ºC for 16 hours (**1b-j**). After 48 or 16 hours, the reactions were refrigerated until 10 ºC and the solids were isolated by filtration. In the case of **2a**, **3a** and **6a** the reaction solvent was evaporated almost until the end in order to isolate these compounds by filtration. The crude solid pyrazolines **2a-j**, **3a-d** and **6a-d** were recrystallized from methanol or acetone. It was observed that the reactions of **1a** with 2-thiophenecarboxylic hydrazide, furoic hydrazide and isonicotinic acid hydrazide performed in higher temperatures (≥ 60 – 65 ºC) resulted in polymerizations and under these conditions the products **2a**, **3a** and **6a** could not be isolated.

Subsequently, 5-hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles (**2c, 3c**) were dehydrated only by stirring with a mixture of chloroform and P_2O_5 at 65 ºC for 24 hours by similar procedure described in the literature [29] (Scheme II), reflecting the relative difficulty of this elimination due to presence of the trifluoromethyl group and the acyl substituent at the position 1 of these pyrazolines. After 24 hours, the reactions were filtered, added water to the filtrate and the products isolated by extraction with chloroform. Surprisingly, compounds **4** (**4c** + **4c'**) and **5** (**5c** + **5c'**) were obtained as a mixture of two regioisomers, which have been fully characterized by ^{1}H and ^{13}C NMR and mass spectrometry, in 36% and 35% yields, respectively. The pyrazole isomers **4c**/**4c'** and **5c**/**5c'** were isolated in a 1:1 and 1:2 ratio, respectively, (GC, ^{1}H NMR). Although the flash chromatography would be a recommended method to separate these isomers [31], due to the low yields we decide for the not isolation of these regioisomers. Isomeric pyrazoles can easily be distinguished by their ^{19}F NMR spectra. For example, the 5-CF_3 isomer **4c** resonates at δ = - 58 ppm, in contrast to the more upfield resonance of the 3-CF_3 isomer **4c'** at δ = - 61.4 ppm. We think that the synthesis of 5-trifluoromethylpyrazoles **4c** and **5c** resulted from the expected dehydration reaction of **2c** and **3c**, respectively. Although a

hydrolytic ring opening seems unlikely in the presence of excess of P_2O_5, we think initially that a considerable amount of 2-pyrazolines **2c** and **3c** underwent ring opening reaction with the formation of 1,3-dicarbonyl carbonyl compounds and the respective hydrazides, due to the acid conditions generated by elimination of water at high temperature. Subsequently, a second *in situ* cyclocondensation reaction could occurr to give 3-trifluoromethylpyrazole regioisomers **4c'** and **5c'**. Although it is well documented, that in many cases, the reactions from trifluoromethylated 1,3-dicarbonyl compounds with hydrazines does not present a defined regiochemistry [23,30] and to confirm if a diketone is a likely intermediate, we have performed the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butanedione with 2-thiophenecarboxylic hydrazide under the same elimination conditions. From this attempt no reaction was observed between the above cited reagents. Thus, perhaps protonation of the carbonyl group and a 1,2-shift of this group to the other nitrogen may be considered as an alternative mechanism.

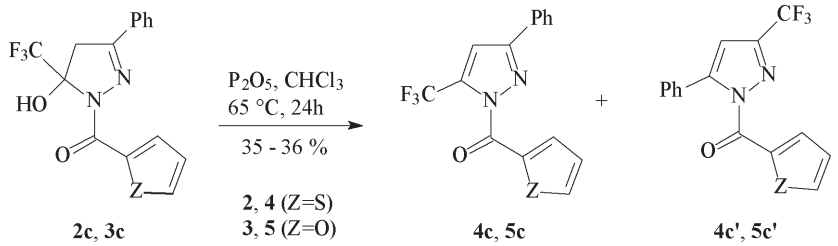
When more strong dehydration conditions were tried, *i. e.*, chloroform/sulfuric acid at reflux, in order to increase the yields for **2c** and **3c** or to dehydrate **6c**, aromatic pyrazoles missing the 2-thenoyl, 2-furoyl and isonicotinoyl groups, were isolated.

The unambiguous ^{1}H- and ^{13}C-NMR chemical shift assignments of 3-alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(heteroaroyl)pyrazoles (**2a-j**, **3a-d**, **4**, **5**, and **6a-d**), were obtained with the help of homo- and heteronuclear COSY, HMQC and HMBC 2D-NMR experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory.

Compounds **2, 3, 6** show the ^{1}H NMR chemical shifts of the diastereotopic methylene protons (H4a and H4b) as a characteristic AB system and as a doublet in the range of δ 3.48 to 4.12 and another doublet in the range of δ 3.09 to 3.84, respectively, with a *geminal* coupling constant in the range of ^2J = 18.8 – 20.0 Hz.

The trifluoromethylated heterocycles **2a-j, 3a-d** and **6a-d** present the typical ^{13}C chemical shifts of pyrazoline

Scheme II



ring carbons in average at δ 151.9 (C3), 44.9 (C4), 91.8 (C5), 123.2 (CF_3). The carbonyl carbon for the trifluoromethylated series **2** and **3** (furoyl and thenoyl derivatives) shows signals in the range of δ 155.4 to 159.0. As expected, for isonicotinoyl derivatives **6** the carbonyl carbon shows signals in the range of δ 164.9 to 165.6.

The 5-hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazole (**6c**) was extremely resistant to dehydration reactions with chloroform/P_2O_5 at reflux for 48 hours or with acetic acid at reflux for 4 hours. We think that the difficulty of dehydration is related to electronic effects of the pyrazoline substituents. In most cases 5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been isolated when the N-1 atom is substituted with a strong electron-withdrawing group that hinders the elimination of water and the subsequent aromatization of the pyrazoline ring [1,30]. In the present case we have a heteroaroyl substituent at N-1 and a trifluoromethyl group with a strong negative inductive effect which also hinders the dehydration reaction. Pyrazolines **2c** and **3c** present 2-thenoyl and 2-furoyl substituents attached to N-1, respectively, where thiophen and furan are π-excessive heteroaromatic compounds. On the other hand, pyrazoline **6c** presents in its structure a combination of effects that prevents from dehydration; an isonicotinoyl substituent with a π-deficient heterocycle (pyridine) and a trifluoromethyl group.

In conclusion, in the present study, we consider the reported one-step and regiospecific cyclocondensation reaction an useful and convenient method to obtain polysubstituted trifluoromethylated pyrazolines, as carbonyl heterobicycles derived from thiophen, furan and pyridine under mild conditions. Unfortunately, dehydration reactions of pyrazolines furnished low yields due to the strong negative inductive effect of the trifluoromethyl group.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. The 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones (**1a-j**) were prepared according to procedure developed previously [28].

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 or Bruker DPX 400 spectrometers (^{1}H at 200.13 MHz or 400.13 MHz and ^{13}C at 50.32 MHz or 100.62 MHz, respectively), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in methyl sulfoxide-d_6 using tetramethylsilane as internal reference. The ^{19}F NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{19}F at 376.30 MHz) in methyl sulfoxide-d_6 using fluorobenzene as external reference and calibrated toward trifluoromethyl chloride. 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 the 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).

General Procedure for the Preparation of 3-Alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)-pyrazoles (**2a-j**).

To a stirred solution of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-buten-2-one **1a-j** (5 mmoles) in 6 ml of methanol, anhydrous 2-thiophenecarboxylic hydrazide (5 mmoles) was added at 20 – 25 °C. The mixture was stirred for 16 hours at 60 – 65 °C (**2b-j**) or for 48 hours at 20 – 25 °C (**2a**). After cooling (< 10 °C), the crystalline solids were collected by filtration, washed with cool methanol and recrystallized from methanol or acetone.

5-Hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)-pyrazole (**2a**).

This compound was obtained as a white solid, yield 64%, mp 128 – 130 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.00 (s, OH); 7.40 (s, H3); 3.51 (d, *J* = 20.0, H4a); 3.17 (d, *J* = 20.0, H4b). (Thenoyl) δ = 8.03 (dd, *J* = 3.6, *J* = 1.4, H3); 7.93 (dd, *J* = 5.0, *J* = 1.4, H5); 7.19 (dd, *J* = 5.0, *J* = 4.0, H4). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 145.8 (C3); 123.2 (q, J_{CF} = 283.6, CF_3); 90.1 (q, ^2J = 33.7, C5); 45.6 (C4). (Thenoyl) δ = 159.0 (C=O); 135.1 (C5); 134.8 (C3); 134.7 (C2); 127.0 (C4).

Anal. Calcd. for $C_9H_7F_3N_2O_2S$ (264.22): C, 40.91; H, 2.67; N, 10.60%. Found: C, 41.17; H, 2.95; N, 10.70%.

5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2b**).

This compound was obtained as a white solid, yield 65%, mp 83 - 85 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 7.91 (s, OH); 3.50 (d, *J* = 19.0, H4a); 3.13 (d, *J* = 19.0, H4b); 2.09 (s, CH_3). (Thenoyl) δ = 8.03 (dd, *J* = 3.8, *J* = 1.4, H3); 7.90 (dd, *J* = 5.0, *J* = 1.4, H5); 7.18 (dd, *J* = 5.0, *J* = 4.0, H4). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 154.7 (C3); 123.2 (q, J_{CF} = 283.6, CF_3); 91.6 (q, ^2J = 33.6, C5); 47.4 (C4); 15.2 (CH_3). (Thenoyl) δ = 158.6 (C=O); 135.1 (C5); 134.9 (C3); 134.6 (C2); 126.9 (C4).

Anal. Calcd. for $C_{10}H_9F_3N_2O_2S$ (278.25): C, 43.17; H, 3.26; N, 10.07%. Found: C, 43.21; H, 3.51; N, 10.14%.

5-Hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2c**).

This compound was obtained as a white solid, yield 89%, mp 162 - 164 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.23 (s, OH); 3.99 (d, *J* = 19.0, H4a); 3.64 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.11 (dd, *J* = 4.0, *J* = 1.6, H3); 8.00 (dd, *J* = 5.0, *J* = 1.6, H5); 7.24 (dd, *J* = 5.0, *J* = 3.8, H4). (Phenyl) δ = 7.92 – 7.90 (m, 2H, Ph); 7.55 – 7.54 (m, 3H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 152.5 (C3); 123.2 (q, J_{CF} = 283.5, CF_3); 92.2 (q, ^2J = 33.6, C5); 44.0 (C4). (Thenoyl) δ = 158.7 (C=O); 135.5 (C5); 135.4 (C3); 134.3 (C2); 127.0 (C4). (Phenyl) δ = 130.9; 130.0; 128.9; 126.9 (6C, Ph).

Anal. Calcd. for $C_{15}H_{11}F_3N_2O_2S$ (340.32): C, 52.94; H, 3.26; N, 8.23%. Found: C, 52.98; H, 2.93; N, 8.31%.

5-Hydroxy-3-(4-methylphenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2d**).

This compound was obtained as a white solid, yield 89%, mp 140 - 142 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.20 (s, OH); 3.95 (d, *J* = 19.0, H4a); 3.61 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.10 (dd, *J* = 3.6, *J* = 1.2, H3); 7.99 (dd, *J* = 4.8, *J* = 1.2, H5); 7.24 (dd, *J* = 4.8, *J* = 4.0, H4). (Phenyl) δ = 7.79 (d, 2H, Ph); 7.35 (d, 2H, Ph); 2.38 (s, CH_3). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 152.4 (C3); 123.2 (q, J_{CF} = 284.3, CF_3); 92.1 (q, ^2J = 33.7, C5); 44.0 (C4). (Thenoyl) δ = 158.6 (C=O); 135.4 (C5); 135.4 (C3); 134.3 (C2); 127.0 (C4). (Phenyl) δ = 140.9; 129.5; 127.3; 126.9 (6C, Ph); 21.0 (CH_3).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_2S$ (354.35): C, 54.23; H, 3.70; N, 7.91%. Found: C, 53.94; H, 3.65; N, 7.84%.

5-Hydroxy-3-(4-methoxyphenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2e**).

This compound was obtained as a white solid, yield 91%, mp 143 - 144 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.17 (s, OH); 3.95 (d, *J* = 19.0, H4a); 3.61 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.10 (dd, *J* = 3.6, *J* = 1.2, H3); 7.99 (dd, *J* = 5.0, *J* = 1.2, H5); 7.24 (dd, *J* = 5.0, *J* = 4.0, H4). (Phenyl) δ = 7.85 (d, 2H, Ph); 7.09 (d, 2H, Ph); 3.84 (s, OCH_3). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 152.2 (C3); 123.2 (q, J_{CF} = 283.8, CF_3); 92.1 (q, ^2J = 33.7, C5); 44.1 (C4). (Thenoyl) δ = 158.5 (C=O); 135.3 (C5); 135.2 (C3); 134.4 (C2); 126.9 (C4). (Phenyl) δ = 161.4; 128.7; 122.5; 114.4 (6C, Ph); 55.3 (OCH_3).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_3S$ (370.35): C, 51.89; H, 3.54; N, 7.56%. Found: C, 51.61; H, 3.54; N, 7.47%.

3-(4-Fluorophenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2f**).

This compound was obtained as a white solid, yield 82%, mp 174 - 176 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.24 (s, OH); 4.00 (d, *J* = 19.0, H4a); 3.65 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.12 (dd, *J* = 3.6, *J* = 1.2, H3); 8.00 (dd, *J* = 5.0, *J* = 1.2, H5); 7.25 (dd, *J* = 5.0, *J* = 4.2, H4). (Phenyl) δ = 7.99 – 7.95 (m, 2H, Ph); 7.42 – 7.38 (m, 2H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 151.5 (C3); 123.2 (q, J_{CF} = 283.8, CF_3); 92.3 (q, ^2J = 33.6, C5); 44.1 (C4). (Thenoyl) δ = 158.6 (C=O); 135.6 (C5); 135.5 (C3); 134.3 (C2); 127.1 (C4). (Phenyl) δ = 163.6 (d, $^1J_{CF}$ = 247.7, 1C, Ph); 129.4 (d, $^3J_{CF}$ = 9.0, 2C, Ph); 126.7 (d, $^4J_{CF}$ = 3.5, 1C, Ph); 116.1 (d, $^2J_{CF}$ = 21.6, 2C, Ph).

Anal. Calcd. for $C_{15}H_{10}F_4N_2O_2S$ (358.31): C, 50.28; H, 2.81; N, 7.82%. Found: C, 50.33; H, 2.78; N, 7.44%.

3-(4-Chlorophenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2g**).

This compound was obtained as a white solid, yield 85%, mp 165 - 167 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.27 (s, OH); 4.01 (d, *J* = 19.0, H4a); 3.65 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.11 (dd, *J* = 3.6, *J* = 1.2, H3); 8.00 (dd, *J* = 5.0,

J = 1.2, H5); 7.25 (dd, *J* = 5.0, *J* = 4.0, H4). (Phenyl) δ = 7.92 (d, 2H, Ph); 7.62 (d, 2H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 151.5 (C3); 123.1 (q, J_{CF} = 283.8, CF_3); 92.3 (q, ^2J = 33.5, C5); 43.9 (C4). (Thenoyl) δ = 158.6 (C=O); 135.6 (C5); 135.5 (C3); 134.2 (C2); 127.0 (C4). (Phenyl) δ = 135.3; 129.0; 128.8; 128.6 (6C, Ph).

Anal. Calcd. for $C_{15}H_{10}ClF_3N_2O_2S$ (374.76): C, 48.07; H, 2.69; N, 7.47%. Found: C, 48.10; H, 2.78; N, 7.50%.

3-(4-Bromophenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2h**).

This compound was obtained as a white solid, yield 89%, mp 164 - 166 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.27 (s, OH); 4.00 (d, *J* = 19.0, H4a); 3.64 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.11 (dd, *J* = 4.0, *J* = 1.6, H3); 8.00 (dd, *J* = 5.0, *J* = 1.6, H5); 7.25 (dd, *J* = 5.0, *J* = 4.0, H4). (Phenyl) δ = 7.84 (d, 2H, Ph); 7.75 (d, 2H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 151.7 (C3); 123.1 (q, J_{CF} = 283.8, CF_3); 92.4 (q, ^2J = 33.5, C5); 43.9 (C4). (Thenoyl) δ = 158.6 (C=O); 135.6 (C5); 135.5 (C3); 134.1 (C2); 127.1 (C4). (Phenyl) δ = 132.0; 129.3; 128.8; 124.4 (6C, Ph).

Anal. Calcd. for $C_{15}H_{10}BrF_3N_2O_2S$ (419.22): C, 42.98; H, 2.40; N, 6.68%. Found: C, 42.94; H, 2.41; N, 6.60%.

5-Hydroxy-3-(4-nitrophenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2i**).

This compound was obtaind as a white solid, yield 55%, mp 203 - 206 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.45 – 8.36 (m, OH); 4.12 (d, *J* = 19.0, H4a); 3.74 (d, *J* = 19.0, H4b). (Thenoyl) δ = 8.18 – 8.14 (m, H3); 8.05 (dd, *J* = 5.0, *J* = 1.2, H5); 7.28 (dd, *J* = 5.0, *J* = 4.2, H4). (Phenyl) δ = 8.45 – 8.36 (m, 2H, Ph); 8.18 – 8.14 (m, 2H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 150.8 (C3); 122.9 (q, J_{CF} = 283.6, CF_3); 92.7 (q, ^2J = 33.7, C5); 43.8 (C4). (Thenoyl) δ = 158.6 (C=O); 135.7 (C5); 135.5 (C3); 133.9 (C2); 127.1 (C4). (Phenyl) δ = 148.3; 136.0; 128.0; 124.0 (6C, Ph).

Anal. Calcd. for $C_{15}H_{10}F_3N_3O_4S$ (385.32): C, 46.76; H, 2.62; N, 10.91%. Found: C, 46.57; H, 2.73; N, 10.80%.

5-hydroxy-3-(4-methoxyphenyl)-4-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazole (**2j**).

This compound was obtained as white solid, yield 71%, mp 142 - 144 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.04 (s, OH); 4.14 (q, *J* = 7.6, H4); 1.25 (d, *J* = 7.6, CH_3). (Thenoyl) δ = 8.10 (dd, *J* = 4.0, *J* = 1.4, H3); 7.99 (dd, *J* = 5.0, *J* = 1.4, H5); 7.24 (dd, *J* = 5.0, *J* = 3.6, H4). (Phenyl) δ = 7.89 (d, 2H, Ph); 7.10 (d, 2H, Ph); 3.84 (s, OCH_3). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 157.4 (C3); 123.7 (q, J_{CF} = 285.8, CF_3); 92.6 (q, ^2J = 32.3, C5); 45.8 (C4); 11.6 (CH_3). (Thenoyl) δ = 158.9 (C=O); 135.4 (C5); 135.3 (C3); 134.3 (C2); 127.0 (C4). (Phenyl) δ = 161.3; 129.3; 121.9; 114.5 (6C, Ph); 55.3 (OCH_3).

Anal. Calcd. for $C_{17}H_{15}F_3N_2O_3S$ (384.37): C, 53.12; H, 3.93; N, 7.29%. Found: C, 53.12; H, 3.95; N, 7.39%.

General Procedure for the Preparation of 3-Alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-furoyl)pyrazoles (**3a-d**).

To a stirred solution of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-buten-2-one **1a-d** (5 mmoles) in 6 ml of methanol, anhydrous furoic hydrazide (5 mmoles) was added at 20 – 25 °C. The mixture was stirred for 16 hours at 60 – 65 °C (**3b-d**) or for 48 hours at 20 – 25 °C (**3a**). After cooling (< 10 °C), the crystalline solids were collected by filtration, washed with cool methanol and recrystallized from methanol or acetone.

5-Hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-furoyl)pyrazole (**3a**).

This compound was obtained as a white solid, yield 53%, mp 85 – 87 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 7.97 (s, OH); 7.35 (s, H3); 3.48 (d, *J* = 19.0, H4a); 3.14 (d, *J* = 19.0, H4b). (Furoyl) δ = 7.98 (bs, H5); 7.41 (d, *J* = 3.6, H3); 6.67 (dd, *J* = 3.6, *J* = 1.6, H4). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 145.5 (C3); 123.3 (q, J_{CF} = 284.3, CF_3); 90.3 (q, ^2J = 33.7, C5); 45.5 (C4). (Furoyl) δ = 155.9 (C=O); 146.8 (C2); 146.2 (C5); 120.1 (C4); 112.0 (C3).

Anal. Calcd. for $C_9H_7F_3N_2O_3$ (248.16): C, 43.56; H, 2.84; N, 11.29%. Found: C, 43.23; H, 2.84; N, 11.48%.

5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-furoyl)pyrazole (**3b**).

This compound was obtained as a white solid, yield 88%, mp 94 - 96 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 7.93 (s, OH); 3.48 (d, *J* = 19.0, H4a); 3.09 (d, *J* = 19.0, H4b); 2.08 (s, CH_3). (Furoyl) δ = 7.96 (bs, H5); 7.47 (d, *J* = 3.6, H3); 6.67 (dd, *J* = 3.6, *J* = 1.6, H4). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 155.0 (C3); 123.3 (q, J_{CF} = 284.2, CF_3); 91.7 (q, ^2J = 33.6, C5); 47.2 (C4); 15.3 (CH_3). (Furoyl) δ = 155.4 (C=O); 146.5 (C2); 145.6 (C5); 119.9 (C4); 111.8 (C3).

Anal. Calcd. for $C_{10}H_9F_3N_2O_3$ (262.19): C, 45.81; H, 3.46; N, 10.68%. Found: C, 45.79; H, 3.31; N, 10.75%.

5-Hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-furoyl)pyrazole (**3c**).

This compound was obtained as a white solid, yield 80%, mp 153 - 154 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.24 (s, OH); 3.95 (d, *J* = 19.0, H4a); 3.60 (d, *J* = 19.0, H4b). (Furoyl) δ = 8.02 (bs, H5); 7.64 (d, *J* = 3.4, H3); 6.75 (dd, *J* = 3.4, *J* = 1.6, H4). (Phenyl) δ = 7.89 – 7.85 (m, 2H, Ph); 7.54 – 7.51 (m, 3H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 152.8 (C3); 123.2 (q, J_{CF} = 284.5, CF_3); 92.3 (q, ^2J = 33.6, C5); 43.7 (C4). (Furoyl) δ = 155.4 (C=O); 146.8 (C2); 145.5 (C5); 120.2 (C4); 112.1 (C3). (Phenyl) δ = 130.8; 130.0; 128.8; 126.7 (6C, Ph).

Anal. Calcd. for $C_{15}H_{11}F_3N_2O_3$ (324.26): C, 55.56; H, 3.42; N, 8.64%. Found: C, 55.34; H, 3.32; N, 8.61%.

5-Hydroxy-3-(4-Methylphenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-(2-furoyl)pyrazole (**3d**).

This compound was obtained as a white solid, yield 81%, mp 125 - 127 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.20 (s, OH); 3.92 (d, *J* = 19.0, H4a); 3.58 (d, *J* = 19.0, H4b). (Furoyl) δ = 8.02 (bs, H5); 7.64 (d, *J* = 3.8, H3); 6.75 (dd, *J* = 3.8, *J* = 1.6, H4). (Phenyl) δ = 7.76 (d, 2H, Ph); 7.33 (d, 2H, Ph); 2.38 (s, CH_3). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 152.8 (C3); 123.2 (q, J_{CF} = 284.2, CF_3); 92.3 (q, ^2J = 33.6, C5); 43.8 (C4). (Furoyl) δ = 155.4 (C=O); 146.7 (C2); 145.5 (C5); 120.2 (C4); 112.0 (C3). (Phenyl) δ = 140.8; 129.4; 127.0; 126.7 (6C, Ph); 20.9 (CH_3).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_3$ (338.29): C, 56.81; H, 3.87; N, 8.28%. Found: C, 56.67; H, 3.73; N, 8.17%.

General Procedure for the Preparation of 3-Phenyl-5-trifluoromethyl-1*H*-1-(heteroaroyl)pyrazoles (**4c, 5c**).

At room temperature **2c** or **3c** (2 mmol) was added into a 25 mL flask containing a mixture of P_2O_5 (2.5 g) and chloroform

(10 ml). After 24 hours under reflux, the residue was removed by filtration. The organic layer (chloroform) was washed with water (3 x 15 ml), dried with anhyd calcium chloride and evaporated. Compounds **4** or **5** were isolated as solids.

3(5)-Phenyl-5(3)-trifluoromethyl-1*H*-1-(2-thenoyl)pyrazole (**4c + 4c'**).

The data listed refers to a mixture of 5-CF_3 and 3-CF_3 isomers (ca. 1:1 ratio). The first GC/MS data refers to a 5-CF_3 isomer. Yellow solid, yield 36%. ^{1}H NMR (DMSO-d_6): (Pyrazole, 5-CF_3) δ = 7.99 (s, H4). (Pyrazole, 3-CF_3) δ = 7.27 (s, H4). (Thenoyl, 5-CF_3) δ = 8.41 (dd, *J* = 4.0, *J* = 1.2, H3); 8.30 – 8.27 (m, H5); 7.36 (dd, *J* = 5.2, *J* = 4.4, H4). (Thenoyl, 3-CF_3) δ = 8.30 – 8.27 (m, H3); 8.23 (dd, *J* = 3.6, *J* = 0.8, H5); 7.36 (dd, *J* = 5.2, *J* = 4.4, H4). (Phenyl, 5-CF_3) δ = 8.10 (d, 2H, Ph); 7.59 – 7.48 (m, 3H, Ph). (Phenyl, 3-CF_3) δ = 7.59 – 7.48 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole, 5-CF_3) δ = 152.8 (C3); 134.3 (q, ^2J = 41.6, C5); 119.2 (q, J_{CF} = 266.6, C F_3); 112.4 (C4). (Pyrazole, 3-CF_3) δ = 148.2 (C5); 143.2 (q, ^2J = 37.8, C3); 120.5 (q, J_{CF} = 267.6, C F_3); 108.7 (C4). (Thenoyl, 5-CF_3) δ = 157.2 (C=O); 139.9 (C5); 139.4 (C3); 130.7 (C2); 127.7 (C4). (Thenoyl, 3-CF_3) δ = 158.9 (C=O); 139.3 (C5); 139.3 (C3); 132.1 (C2); 128.1 (C4). (Phenyl, 5-CF_3) δ = 129.9; 129.6; 128.9; 126.2 (6C, Ph). (Phenyl, 3-CF_3) δ = 129.2; 128.9; 128.7; 128.0 (6C, Ph). ^{19}F NMR (DMSO-d_6) 5-CF_3 (**4c**) δ = -58 ppm; 3-CF_3 (**4c'**) δ = -61.4 ppm. GC-MS (EI, 70 Ev) for $C_{15}H_9F_3N_2OS$ (322.30): *m/z*(%) = 322(M^+,27/16); 133(12/10); 111(100/100); 83(18/13); 51(5/4).

3(5)-Phenyl-5(3)-trifluoromethyl-1*H*-1-(2-furoyl)pyrazoles (**5c + 5c'**).

The data listed refers to a mixture of 5-CF_3 and 3-CF_3 isomers (ca. 1: 2 ratio). The first GC/MS data refers to a 5-CF_3 isomer. Yellow solid, yield 35%. ^{1}H NMR (DMSO-d_6): (Pyrazole, 5-CF_3) δ = 7.95 (s, H4). (Pyrazole, 3-CF_3) δ = 7.26 (s, H4). (Furoyl, 5-CF_3) δ = 8.28 (d, *J* = 0.8, H5); 8.11 (d, *J* = 4.0, H3); 6.91 (dd, *J* = 4.0, *J* = 2.0, H4). (Furoyl, 3-CF_3) δ = 8.26 (d, *J* = 0.8, H5); 8.07 (dd, *J* = 6.4, *J* = 1.6, H3); 6.89 (dd, *J* = 3.6, *J* = 1.6, H4). (Phenyl, 5-CF_3) δ = 7.81 (d, 2H, Ph); 7.57 – 7.47 (m, 3H, Ph). (Phenyl, 3-CF_3) δ = 7.57 – 7.47 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole, 5-CF_3) δ = 153.2 (C3); 134.5 (q, ^2J = 40.9, C5); 119.2 (q, J_{CF} = 266.5, C F_3); 113.3 (C4). (Pyrazole, 3-CF_3) δ = 148.1 (C5); 143.5(q, ^2J = 37.9, C3); 120.5 (q, J_{CF} = 267.2, C F_3); 108.2 (C4). (Furoyl, 5-CF_3) δ = 153.3 (C=O); 150.1 (C2); 143.5 (C5); 125.6 (C4); 113.2 (C3). (Furoyl, 3-CF_3) δ = 154.7 (C=O); 150.5 (C2); 144.0 (C5); 125.8 (C4); 112.0 (C3). (Phenyl, 5-CF_3) δ = 129.8; 129.7; 128.6; 126.2 (6C, Ph). (Phenyl, 3-CF_3) δ = 129.2; 128.8; 128.5; 128.1 (6C, Ph). GC-MS (EI, 70 Ev) for $C_{15}H_9F_3N_2O_2$ (306.24): *m/z*(%) = 306(M^+,8/8); 278(13/13); 133(10/8); 95(100/100); 51(7/6).

General Procedure for the Preparation of 3-Alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(isonicotinoyl)-pyrazoles (**6a-d**).

To a stirred solution of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-buten-2-one **1a-d** (5 mmoles) in 6 ml of methanol, anhydrous isonicotinic acid hydrazide (5 mmoles) was added at 20 – 25 °C. The mixture was stirred for 16 hours at 60 – 65 °C (**6b-d**) or for 48 hours at 20 – 25 °C (**6a**). After cooling (< 10 °C), the crystalline solids were collected by filtration, washed with cool methanol and recrystallized from methanol or acetone.

5-Hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-(isonicotinoyl)-pyrazole (**6a**).

This compound was obtained as a white solid, yield 63%, mp 144 – 145 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.26 (s, OH); 7.28 (s, H3); 3.55 (d, *J* = 20.0, H4a); 3.19 (d, *J* = 20.0, H4b). (Isonicotinoyl) δ = 8.71 (d, *J* = 5.0, 2H, Py); 7.52 (d, *J* = 5.0, 2H, Py). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 146.6 (C3); 123.3 (q, J_{CF} = 283.8, CF_3); 90.0 (q, ^2J = 33.5, C5); 45.9 (C4). (Isonicotinoyl) δ = 165.6 (C=O); 149.7 (2C, Py); 142.8 (1C, Py); 122.3 (2C, Py).

Anal. Calcd. for $C_{10}H_8F_3N_3O_2$ (259.19): C, 46.34; H, 3.11; N, 16.21%. Found: C, 46.24; H, 3.15; N, 16.10%.

5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazole (**6b**).

This compound was obtained as a white solid, yield 89%, mp 130 - 133 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.16 (s, OH); 3.54 (d, *J* = 19.0, H4a); 3.14 (d, *J* = 19.0, H4b); 1.95 (s, CH_3). (Isonicotinoyl) δ = 8.69 (d, *J* = 6.0, 2H, Py); 7.51 (d, *J* = 6.0, 2H, Py). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 155.4 (C3); 123.2 (q, J_{CF} = 283.8, CF_3); 91.3 (q, ^2J = 33.7, C5); 47.7 (C4); 15.1 (CH_3). (Isonicotinoyl) δ = 164.9 (C=O); 149.6 (2C, Py); 142.9 (1C, Py); 122.3 (2C, Py).

Anal. Calcd. for $C_{11}H_{10}F_3N_3O_2$ (273.21): C, 48.36; H, 3.69; N, 15.38%. Found: C, 48.10; H, 3.60; N, 15.21%.

5-Hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazole (**6c**).

This compound was obtained as a white solid, yield 80%, mp 200 - 202 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.44 (s, OH); 4.02 (d, *J* = 19.0, H4a); 3.66 (d, *J* = 19.0, H4b). (Isonicotinoyl) δ = 8.76 (d, *J* = 5.0, 2H, Py); 7.70 – 7.63 (m, 2H, Py). (Phenyl) δ = 7.70 – 7.63 (m, 2H, Ph); 7.48 – 7.45 (m, 3H, Ph). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 153.0 (C3); 123.1 (q, J_{CF} = 283.7, CF_3); 92.1 (q, ^2J = 33.7, C5); 44.1 (C4). (Isonicotinoyl) δ = 165.0 (C=O); 149.6 (2C, Py); 142.5 (1C, Py); 122.5 (2C, Py). (Phenyl) δ = 130.8; 129.8; 128.7; 126.6 (6C, Ph).

Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2$ (335.29): C, 57.32; H, 3.61; N, 12.53%. Found: C, 57.33; H, 3.64; N, 12.68%.

5-Hydroxy-3-(4-methylphenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazole (**6d**).

This compound was obtained as a white solid, yield 72%, mp 167 - 169 °C. ^{1}H NMR (DMSO-d_6): (Pyrazole) δ = 8.40 (s, OH); 3.98 (d, *J* = 19.0, H4a); 3.63 (d, *J* = 19.0, H4b). (Isonicotinoyl) δ = 8.76 (d, *J* = 6.0, 2H, Py); 7.64 (d, *J* = 6.0, 2H, Py). (Phenyl) δ = 7.57 (d, 2H, Ph); 7.27 (d, 2H, Ph); 2.34 (s, CH_3). ^{13}C NMR (DMSO-d_6): (Pyrazole) δ = 153.0 (C3); 123.2 (q, J_{CF} = 283.6, CF_3); 92.0 (q, ^2J = 33.6, C5); 44.2 (C4). (Isonicotinoyl) δ = 164.9 (C=O); 149.6 (2C, Py); 142.5 (1C, Py); 122.6 (2C, Py). (Phenyl) δ = 140.8; 129.3; 127.1; 126.6 (6C, Ph); 20.9 (CH_3).

Anal. Calcd. for $C_{17}H_{14}F_3N_3O_2$ (349.31): C, 58.45; H, 4.04; N, 12.03%. Found: C, 58.28; H, 4.08; N, 11.78%.

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