Journal of Fluorine Chemistry 151 (2013) 38–44

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

ANRORC rearrangement in tetrahydro-2*H*-chromenones. Synthesis and structural assignment by NMR, MS, X-ray and DFT calculations of 2-[3(5)-trifluoromethyl-1*H*-pyrazol-4-yl)arylmethyl]cyclohexenones and derivatives

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ARTICLE INFO

Article history:
Received 5 February 2013
Received in revised form 12 March 2013
Accepted 14 March 2013
Available online 25 March 2013

Keywords:
Chromenones
Pyrazoles
ANRORC reactions
Cyclohexenones
DFT calculations

ABSTRACT

This paper describes firstly the synthesis of a new series of 3-hydroxy-2-[(3(5)-(methyl/phenyl)-5(3)-(trifluoromethyl)-1*H*-pyrazol-4-yl)arylmethyl]-cyclohex-2-en-1-ones (2), where aryl = C_6H_5, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$, from an ANRORC ring transformation reaction of 3-acyl-4-aryl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones (1), where acyl = acetyl and benzoyl, in the presence of hydrazine hydrate, at 63–90% yields. In subsequent steps, an oxidative aromatization reaction from 2 was done in an iodine/methanol medium for the preparation of 3(5)-trifluoromethyl-5(3)-methyl-4-[(2,6-dimethoxyphenyl)-(4-methoxyphenylmethyl)]-1*H*-pyrazole (3) at 72% yields. Also, the alkylation reaction using benzyl chloride easily converted a pyrazole like 2 to its *N*-benzyl derivative (4), at 69% yield. Finally, the structural assignment of compounds 2–4 was deduced by mass spectrometry, X-ray crystal diffraction and density functional theory (DFT) calculations, which clearly and unambiguously furnished values very close to those determined from ^{1}H, ^{13}C and ^{19}F NMR data.

1. Introduction

The understanding of the chemical rearrangement of heterocyclic scaffolds into new molecules is an interesting research area because the correct assemblies can provide significant contributions to medicinal chemistry conducting to more complex and poly-substituted structures in good yields and few reaction steps. Additionally, the insertion of fluorine atoms, especially the trifluoromethyl group, imparts a variety of properties to certain medicines, including enhanced binding interactions, metabolic stability, changes in physical properties, and selective reactivities [1].

Chromenes are an important group of heterocyclic compounds. Their structure is present in numerous natural products and they have biological and pharmacological activities, including as a spasmolytic, diuretic, antiviral, antitumoral, and antianaphylactic, among others [2]. Hence, their synthesis holds a special place and considerable efforts are devoted to the development of efficient methods to achieve this.

On the other hand, development in the area of pyrazole synthesis is continuously growing due to their applications in the pharmaceutical and agrochemical industry [3]. In general, conventional approaches for the synthesis of pyrazoles involve the construction of two C–N bonds by the condensation of hydrazines with 1,3-dielectrophilic derivatives [4]. Also, the ANRORC rearrangement that consists of an initial *A*ttack of *N*ucleophiles followed by *R*ing-*O*pening and *R*ing-*C*losure represents a useful tool in the hands of the synthetic heterocyclic chemist for achieving the ring transformation for various pyrazole systems [5–12].

In the context of our research on fluorinated heterocycles, we recently reported the synthesis of chromenones (**1**) [13] and their transformation to 2-fluoro-2*H*-chromenones (**I**) by chemoselective fluorination with DAST [14], and then to chromanes (**II**) as the product of an aromatization reaction with alcohol/iodine [15]; and, also, the resulting product (**III**) from the reduction reactions using $NaBH_4$ (Fig. 1) [16]. Although the degenerated ring transformation S_N(ANRORC) is well established and described in the literature for the reaction of some benzopyran-4-ones (chromanes) [6–10] with

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[1] This paper is dedicated to the more than 100 young students of the Federal University of Santa Maria that lost their lives by the Kiss nightclub fire on January 27, 2013.

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http://dx.doi.org/10.1016/j.jfluchem.2013.03.014

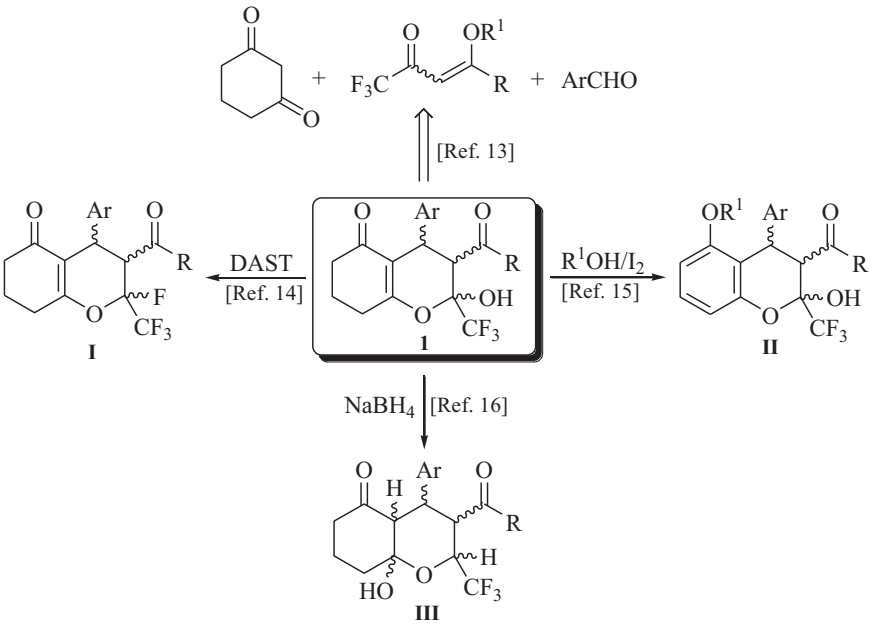


Fig. 1. Synthesis and chemical transformations of tetrahydro-2*H*-chromenones (**1**).

hydrazines to give substituted pyrazole tautomers or mixtures of 1,3- and 1,5-isomers, the specific rearrangement for 3-acyl-4-aryl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones (**1**) has not yet been studied.

With this in mind, we wish now to report the use of the well-known S_N(ANRORC) degenerate ring transformation approach as a valuable method for obtaining a series of 4-functionalized 3(5)-trifluoromethyl-1*H*-pyrazoles (**2**) from the tetrahydro-2*H*-chromenones (**1**), which would be very difficult to obtain by other procedures. A partial aromatization employing methanol/I_2 and an *N*-alkylation reaction using benzyl chloride of 3(5),4-substituted-5(3)-trifluoromethyl-1*H*-pyrazoles is also subsequently presented. Finally, the results of monocrystal X-ray diffraction measurements of one pyrazole from series **2** will be presented. And in order to structurally assign the *N*-benzylpyrazole **4** as either a 1,3- or 1,5-isomer, mass spectrometry analysis and theoretical calculations using the DFT method are employed.

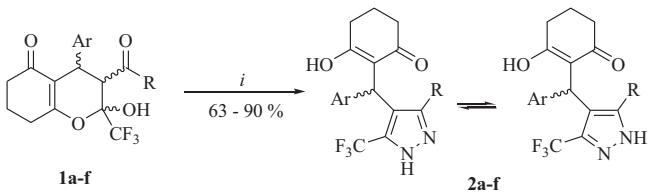
2. Results and discussion

The 2-trifluoromethyl-2*H*-chromenones **1a–f** were readily prepared using a multicomponent reaction (MCR) methodology from 4-methoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalken-3-en-2-ones, aryl aldehydes and 1,3-cyclohexanedione in the presence of a catalytic amount of triethylamine, as described by us previously [13].

The structure of chromenones **1** offers two masked 1,3-dieletrophile building fragments composed of (O1–C2–C3–(C=O)R) and (O1–C8a–C4a–C5=O), which could react with different dinucleophiles and lead to numerous heterocycles – hydrazine in the present case. The synthesis of **2a–f** was done from the reaction of **1a–f** with hydrazine hydrate at a 1:1 molar ratio, using ethanol as the reaction solvent and under reflux for 16 h (Scheme 1). The products were obtained as red solids from recrystallization of a solvent mixture of ethanol:ethyl acetate (1:1 v/v), and as a racemic mixture of enantiomers due to the presence of one asymmetric carbon, which according to the proposed mechanism (Fig. 2) cannot change its configuration. Also, due to the fast NH proton exchange, both enantiomers from the compounds of **2** were identified by NMR as a mixture of tautomers.

According to the ANRORC reaction results in chromenones **1a–f**, we proposed a reasonable mechanism for this reaction, as shown in Fig. 2. The closure ring step of the corresponding ANRORC mechanism for the preparation of pyrazoles **2a–f** can be proposed from the conversion of some 1,3-dicarbonyl compounds into pyrazoles by a [3 + 2] cyclocondensation reaction with the hydrazines and derivatives thereof, as reported previously elsewhere [17]. However, in the present case, the first step reaction (addition of nucleophile) should be preceded by the removal of the hydroxyl group attached to the C-2 of the chromenones **1a–f**. Consequently, the first step of the reaction mechanism would be an initial removal of the most acidic proton of the chromenones **1** by the hydrazine hydrate. Thus, this first action simultaneously promotes the pyran ring opening and the generation of two 1,3-dicarbonyl compounds linked to each other by a methylaryl unit (intermediate **I**). A subsequent nucleophilic attack of the hydrazine on the more reactive carbonyl carbon (due to the presence of the CF_3) yields the intermediate **II**, which furnishes the enamino ketone **III** by dehydration. Finally, an intramolecular cyclocondensation reaction yields a 2-pyrazoline (**IV**), which undergoes a second dehydration to furnish the desired series of 3-hydroxy-2-[(3(5)-(methyl/phenyl)-5(3)-(trifluoromethyl)-1*H*-pyrazol-4-yl)arylmethyl]cyclohex-2-en-1-ones (**2**), that is, the new 2,3,4-substituted pyrazole rings.

As we reported previously [14], chromenones **1** undergo partial aromatization from the reaction with iodine and methanol, which



1,2	a	b	c	d	e	f
Ar	Ph	Ph	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$
R	CH_3	Ph	CH_3	Ph	CH_3	Ph

Scheme 1. Synthesis of 3(5),4-substituted-3(5)-trifluoromethyl-1*H*-pyrazoles. Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, ethanol, reflux, 16 h.

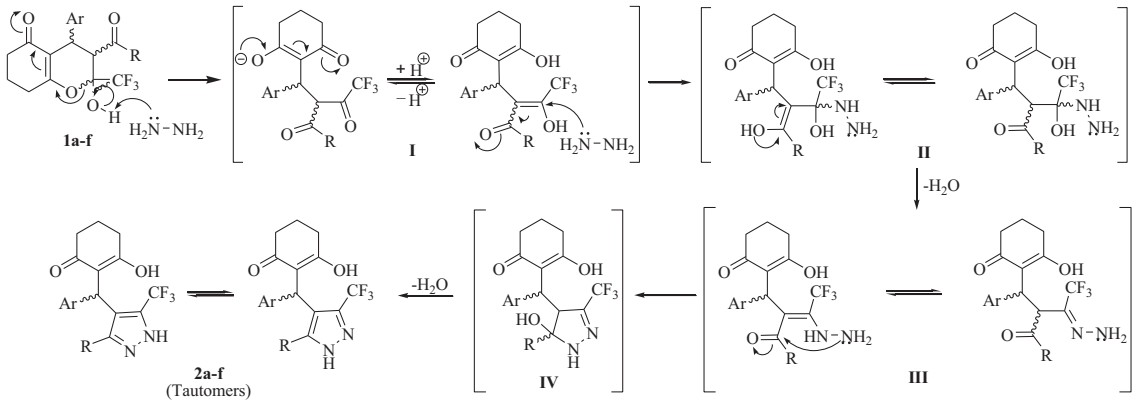


Fig. 2. Proposed mechanism for the ANRORC rearrangement in chromenones (**1**).

also leads to the chromanes (Fig. 1 structure **II**). Thus, we decided to apply the reported methodology, since the pyrazoles of **2** show resemblance to the chromenones of **1**, that is, in the 2-hydroxy-2*H*-chromenones of **1** and in the pyrazoles of **2,** there is a similar cyclic and preserved moiety (–O–C=C–C=O). Consequently, the synthesis of 3(5)-trifluoromethyl-5(3)-methyl-4-[(2,6-dimethoxyphenyl)-(4-methoxyphenylmethyl)]-1*H*-pyrazole **3e** was conducted according to the literature [14]. We performed the reaction by using pyrazole **2e** and iodine at a 1:2 molar ratio in methanol under reflux for 2 h. For this reaction time, it was not possible to obtain compound **3e**, and only the starting material was recovered. However, when the reaction was performed increasing the reaction time from 2 h to 8 h, the products **3e** was obtained as a yellow solid in 6 h and at an optimal 72% yield (Scheme 2).

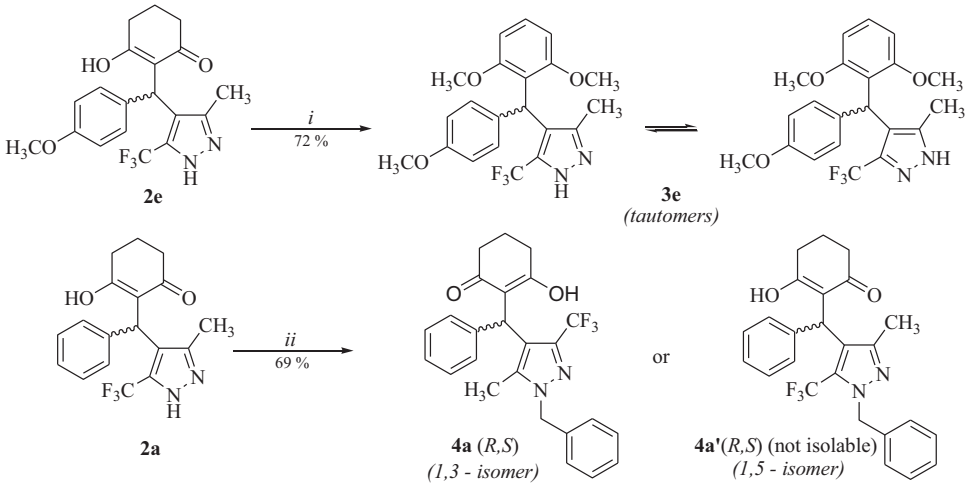
Since the compounds **2a**–**f** were obtained as NH-tautomers, we decided to investigate a possible derivatization by employing an alkylation reaction using benzyl chloride as the alkylating reagent in order to study the chemical behavior for both tautomers. This reaction should furnish one or two isomers, namely, 1,3- and/or 1,5-isomers. Both are related to the benzyl and the CF_3 substituents attached to the specific positions of the pyrazole ring. The alkylation reaction was performed using 2-[(3(5)-trifluoromethyl-5(3)-methyl-1*H*-pyrazol-4-yl)phenylmethyl]-3-hydroxycyclohex-2-en-1-one (**2a**) in the presence of a strong base (NaH) and benzyl chloride in DMF as solvent. After 24 h at room temperature, we isolated (by easy purification) the product **4a** as yellow oil at 69% yield (Scheme 2). The subsequent NMR and DFT calculation studies revealed that the alkylation reaction was regioselective and it furnished **4a** exclusively as a pure 1,3-regioisomer.

Before any structural analysis by NMR, it is important to note that compounds **2a**–**f** could present two simultaneous tautomerism processes involving rapid site proton exchange of the =N–NH (pyrazole ring) and of the O=C–C=C–OH/O=C–CH_2–C=O (1,3-cyclohexanodione) moieties, but pyrazole **3e** can shows only two tautomers due to the =N–NH. On the contrary, the *N*-benzyl substituted pyrazole **4** showed only the ketoenol form (O=C–C=C–OH fragment) for the 1,3-cyclohexanodione ring at the unique isolated isomer (1,3-isomer).

Subsequently, a complete analysis of the NMR spectra of the new pyrazoles **2a**–**f**, **3** and **4** was achieved also by comparison with reported chemical shifts for pyrazoles [26].

Pyrazoles **2** and **3** were characterized by ^{1}H NMR and the spectra showed broad singlet signals in the range of δ 12.66–13.55 ppm related to the NH, and in the range of δ 5.61–5.88 ppm for the CH group linked to the C-4 of the pyrazole rings (**2**–**4**). Although the spectra were registered in DMSO-d_6, the signals related to the OH groups were not observed for compounds **2** and **4**.

As a general characteristic for ^{13}C NMR, the CF_3 carbons resonated as quartets near δ 122 ppm with $^1J_{CF}$ near 269 Hz. The C–CF_3 carbons also resonated as quartets but near δ 139 ppm with $^2J_{CF}$ near 34 Hz. The C-4 carbons presented signals as singlets near δ



Scheme 2. Aromatization and *N*-alkylation reaction of 3,4-substituted-3(5)-trifluoromethyl-1*H*-pyrazoles. Reagents and conditions: (i) I_2 (2 equiv.), MeOH, reflux, 6 h; (ii) BnCl, NaH, DMF, r.t., 24 h.

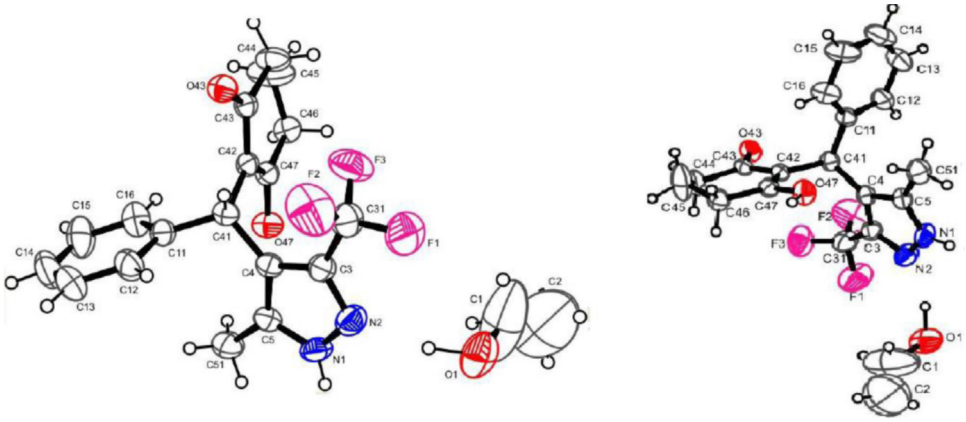


Fig. 3. ORTEP of 2-[(3-trifluoromethyl-5-methyl-1*H*-pyrazol-4-yl)phenylmethyl]-3-hydroxycyclohex-2-en-1-one (**2a**).

116 ppm. For compound **3**, a 4-[(2,6-dimethoxyphenyl)-(4-methoxyphenylmethyl)]-substituted 1*H*-pyrazole, the C-4 resonated around δ 5 ppm further downfield at δ 120.8 ppm. The substituent attached to the C-4 presented signals for tertiary CH in the range of δ 31.3–35.3 ppm. The C=O, C=C–OH, and =C–OH carbons of the 3-hydroxy-cyclohex-2-en-1-one moiety resonated as singlets in the range of δ 184.5–197.6 ppm, δ 172.1–184.9 ppm, and δ 113.8–117 ppm, respectively. It is interesting to note that due to the rapid site proton exchange at the O=C–C=C–OH fragment, the ketoenol carbons appeared only as broad singlets of compounds **2a**,**b**, **2d**, **2f,** and **4** and did not show signals for **2c** and **2e**.

Finally, ^{19}F NMR has been found to be a simple and efficient method for assigning the trifluoromethyl group position at pyrazole **4**. This compound exhibited a typical signal for a 3-(CF_3)-pyrazole isomer near δ 58.85 ppm, in contrast to the more downfield resonance of similar 5-(CF_3)-pyrazole isomers, which present signals near δ – 54.0 ppm [26]. Consequently, the 1,3- and 1,5-isomer of **4** could be easily distinguished by their ^{19}F NMR spectrum.

In addition, to determine the molecular structure of the pyrazoles of **2**, an X-ray monocrystal diffraction measurement of compound **2a** was performed and the results evaluated (Fig. 3). The crystallographic data showed that because of the possible steric effect from the two carbocyclic substituents attached to the asymmetric carbon attached to C-4 of the pyrazole ring, the trifluoromethyl group occupies a preferential position closer to the cyclohexenedione ring. Due to the ^{1}H and ^{13}C NMR similarities with **2a** data, we suggest that for other pyrazoles (**2b**, **2d**, **2f**), where *R* and *Ar* are substituents with a stronger steric effect, because *R* = phenyl, and *Ar* = 4-$NO_2C_6H_4$ and 4-$OMeC_6H_4$, the preferential spatial relationship also remains similar.

In order to clarify whether the *N*-benzylation reaction of the pyrazole **2a** conducted for the 1,3- or the 1,5-pyrazole isomer, a CI (positive mode) mass spectrum of pyrazole **4a** was recorded and investigated (Fig. 4). The spectrum was then characterized by some prominent fragment ions. The presence of a signal at *m/z* 469 refers to a typical characteristic of this spectrometric technique [M+29] and the signal at *m/z* 441 $[C_{25}H_{23}F_3N_2O_2]^+$ (43%) corresponds to the appearance of the molecular ion [M+1]. In agreement to the literature data [18a], the signal at *m/z* 421 $[C_{25}H_{20}F_3N_2O^+]$ (29%) can refer to a simple loss of H_3O (H_2O + H). The appearance of another signal at *m/z* 329 (47%) refers to the characteristic fragmentation of a typical 1,3-substituted-pyrazole, where a loss of CF_3CN results in a [M–CF_3CN] fragment, which is a fundamental characteristic for a 1,3-pyrazole isomer [18b]. The fragment ion (*m/z* 329) can further undergo a loss of benzyl, to furnish a fragment

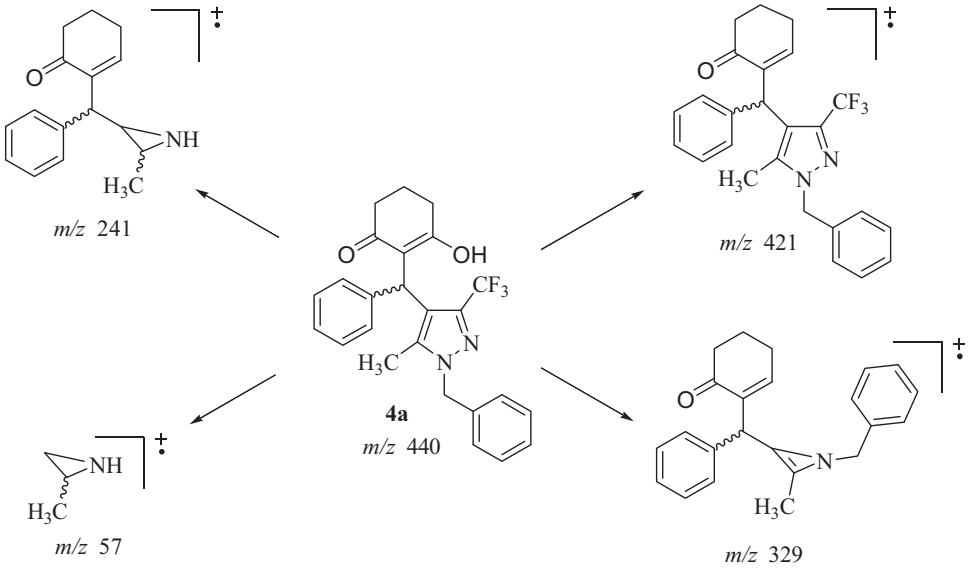


Fig. 4. Prominent fragment ions of compound **4a**.

Table 1
Relative energies of isomers[a] for compounds **4a** and **4a′** at B3LYP/cc-pVDZ level of theory.

Entry	Enantiomers	1,3-Isomer (**4a**)		1,5-Isomer (**4a′**)	
		(OH···CF_3)	(OH···CH_3)	(OH···CF_3)	(OH···CH_3)
1	*R*	0.36	3.85	5.27	3.91
2	*S*	0.00	1.53	3.75	3.04

[a] ΔE (kcal/mol) related to the stablest 1,3(*S*) isomer.

ion $[C_{16}H_{19}NO]^+$ at *m/z* 241 (100%) – this was also found in the mass spectrum as the more stable fragment. Moreover, the formation and presence of a fragment ion $[C_3H_6N]^+$ at *m/z* 57 (36%) proves the existence of a stable aziridinium ion, which should also result from an initial CF_3CN loss. Thus, these results suggest that the CF_3 group is definitively linked to the 3-position of the pyrazole ring and not to the 5-position. Other complementary MS fragments from this compound are given in the experimental part.

With the aim of determining the stablest structure from all possible isomers for the compounds of **4**, we simulated all structural possibilities for obtaining the stablest isomer (1,3 or 1,5), the *R* and *S* configurations for the substituent attached to C-4, and the position of the hydroxy group (cyclohexendione) related to the CF_3 or CH_3 group. All geometries were verified as minima on the potential energy by calculating the Hessian matrices using harmonic frequency calculations. The theoretical calculations were done using the Gaussian 09 package of programs [19] and the density functional theory calculations were performed for the possible isomers in compounds **4a** and **4a′** at the B3LYP/cc-pVDZ level of theory.

The DFT calculations presented in Table 1 clearly show that isomer 1,3 (column 1) is stabler than isomer 1,5 (column 2), in addition to showing that the *S* enantiomer (entry 2) is more stable than the *R* enantiomer (entry 1). The theoretical calculations also revealed that the hydroxyl group stabilizes the molecular geometries nearer the CF_3 than the CH_3 group (Fig. 5). Therefore, we concluded that isomer 1,3 with the *S* configuration for the group attached to the C-4 of the pyrazole ring, which presents the OH substituent near the CF_3 group, is the stablest structure. Distances for the hydroxyl oxygen and the hydrogen atom to the fluorine atoms of the CF_3 substituent were found to be 310 pm and 230 pm, respectively. These distances are highly consistent with a H-F intramolecular bridge [20] stabilizing the molecule and enabling the isolation of only the structure assigned as **4a**.

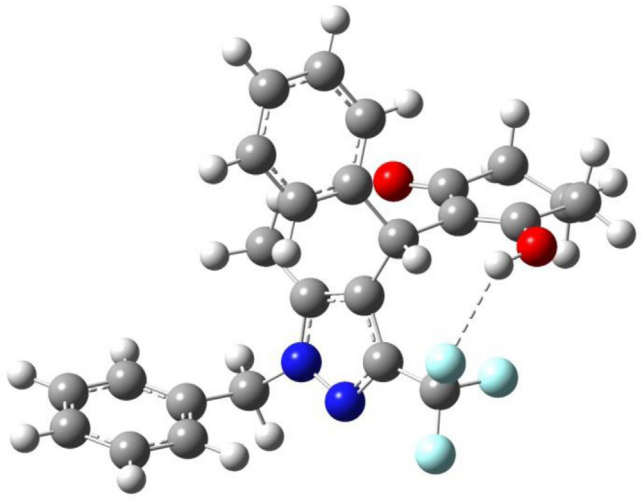


Fig. 5. Molecular structure of (*S*)-2-[(1-benzyl-5-trifluoromethyl-3-methyl-1*H*-pyrazol-4-yl)phenylmethyl]-3-hydroxycyclohex-2-en-1-one (**4a**) from DFT calculations.

3. Conclusion

In this work we developed a simple and convenient new one-pot procedure to obtain novel 2,3,4-trisubstituted-1*H*-pyrazoles (**2**) by a ring rearrangement ANRORC type reaction of specific chromenones with hydrazine. The chemical structure of a racemic mixture of pyrazole tautomers **2a–f** was verified by an oxidative process and in addition by an alkylation reaction, which furnished pyrazoles **3e** and **4a**, respectively, both at good yields. To demonstrate the importance of the analytical methods in organic synthesis, the structure of compounds **2–4** was determined with the aid and simultaneous application of ^1H, ^{13}C and ^{19}F NMR, X-ray crystal diffraction, mass spectrometry, and DFT calculation techniques. The preferential geometry, including a conclusion about the configuration and isomerism of tetra-substituted pyrazoles **4**, could only be demonstrated by employing a DFT calculation.

4. Experimental

4.1. Analytical equipment's and procedures

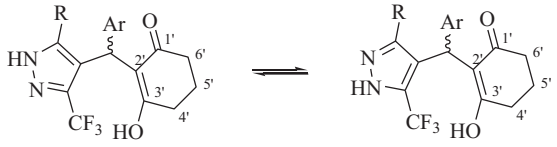
Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers, without further purification. The melting points were determined using coverslips on a Microquímica MQAPF–302 apparatus and are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were acquired on a Bruker DPX 200 spectrometer (^1H at 200.13 MHz) and Bruker DPX 400 (^{13}C at 100.32 MHz and ^{19}F at 376.3 MHz) spectrometer, using 5 mm sample tubes, 298 K, and a digital resolution of ±0.01 ppm, in DMSO-d_6 or $CDCl_3$, with TMS as the internal reference (^1H and ^{13}C) or hexafluorobenzene as the external reference (^{19}F). Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. Mass spectra were registered in an Agilent 6460 Triple Quad LC/MS connected to a 1200 series LC and equipped with a solvent degasser, binary pump, column oven, and auto-sampler. The CHN elemental analyses were performed on a Perkin–Elmer 2400 CHN elemental analyzer (University of São Paulo, Brazil) and the high resolution mass spectrometry was performed using an Agilent-QTOF 6530 spectrometer (Santa Maria Federal University, Brazil) and Bruker Daltonics MicrOTOF (University of São Paulo, Brazil). The diffraction measurements were done by graphite-monochromatized Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer [21]. The structure of **2a** was solved with direct methods using the SHELXS-97 program [22], and refined on F^2 by full-matrix least-squares using the SHELXL-97 package [23]. The absorption correction was done by Gaussian methods [24]. Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3) and 0.93 Å (aromatic CH), using a riding model. The hydrogen isotropic thermal parameters were kept at Uiso(H) = χUeq (carrier C atom), with χ = 1.5 for the methyl groups and χ = 1.2 for the other groups. The valence angles C–C–H and H–C–H of the methyl groups were set to 109.5° and the H atoms were allowed to rotate around the C–C bond. The molecular graph was prepared using ORTEP-3 for Windows [25].

4.2. Synthesis

Compounds **1a–f** were obtained from a multi-component reaction (MCR) involving 1,3-cyclohexanedione, aryl aldehydes, 4-(alkyl/aryl/heteroaryl)substituted 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones and triethylamine [13].

*4.2.1. General procedure for the synthesis of 3-hydroxy-2-[(3(5)-(methyl/phenyl)-5(3)-(trifluoromethyl)-1H-pyrazol-4-yl)arylmethyl]cyclohex-2-en-1-ones (**2a–f**)*

Hydrazine monohydrate (2 mmol, 100 mg) was added at room temperature to a solution of 3-acyl-2-trifluoromethyl-2*H*-chromenones **1a–f** (1 mmol) stirred in ethanol (10–15 mL). The mixture was then boiled under reflux for 16 h. The solvent was slowly evaporated under reduced pressure. The resulting red solid product was dried in a desiccator under reduced pressure over P_2O_5 and this furnished pyrazoles **2a–f** at 63–90% yields without purification at a high degree of purity according to HRMS analysis data.



*4.2.1.1. 3-Hydroxy-2-[(3(5)-methyl-5(3)-(trifluoromethyl)-1H-pyrazol-4-yl)phenylmethyl]cyclohex-2-en-1-one (**2a**): yellow solid, yield 78%, mp. 234–236 °C.* ^{1}H NMR (DMSO-d_6): δ = 12.66 (s, 1H, NH), 7.22 (t, *J* = 7 Hz, 2H, Ph), 7.12 (t, *J* = 7 Hz, 1H, Ph), 7.04 (d, *J* = 8 Hz, 2H, Ph), 5.69 (s, 1H, CH), 2.38–2.25 (m, 4H, H4′, H6′), 1.86–1.79 (m, 2H, H5′), 1.55 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 195.7 (C1′), 172.6 (C3′), 141.6 (Ph), 139.6 (C3/C5), 138.9 (q, *J* = 30 Hz, C5/C3), 127.9, 127.5, 123.7 (Ph), 122.3 (q, *J* = 269 Hz, CF_3), 116.9 (C4), 115.0 (C2′), 36.4 (C6′), 33.6 (CH), 29.4 (C4′), 20.2 (C5′), 10.3 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) 350 (100), 310 (80), 279 (30), 226 (35), 199 (15).

HRMS Calc. for $C_{18}H_{17}F_3N_2O_2$: 351.1279. Found: 351.1275.

*4.2.1.2. 3-Hydroxy-2-[(5(3)-(trifluoromethyl)-3(5)-phenyl-1H-pyrazol-4-yl)phenylmethyl]cyclohex-2-en-1-one (**2b**): yellow solid, yield 80%, mp. 136–137 °C.* ^{1}H NMR (DMSO-d_6): δ = 13.26 (s, 1H, NH), 7.19–7.12 (m, 5H, Ph), 6.93–6.88 (m, 5H, Ph), 5.67 (s, 1H, CH), 2.18–2.01 (m, 4H, H6′ e H4′), 1.69–1.60 (m, 2H, H5′).

^{13}C NMR (DMSO-d_6): δ = 193.5 (C1′), 172.1 (C3′), 147.2 (C3/C5), 142.3 (Ph), 139.0 (q, *J* = 34 Hz, C5/C3), 129.8, 129.2, 128.2, 127.0, 126.8, 124.8 (Ph), 122.1 (q, *J* = 269 Hz, CF_3), 117.9 (C4), 115.0 (C2′), 35.9 (C6′), 35.0 (CH), 29.6 (C4′), 20.4 (C5′).

MS (ESI) *m*/*z* [(M+H)$^+$, 413.2].

HRMS Calc. for $C_{23}H_{19}F_3N_2O_2$: 413.1479. Found: 413.1476.

*4.2.1.3. 3-Hydroxy-2-[(5(3)-(trifluoromethyl)-3(5)-methyl-1H-pyrazol-4-yl)-4-nitrophenylmethyl]cyclohex-2-en-1-one (**2c**): red solid, yield 90%, mp. 164–166 °C.* ^{1}H NMR (DMSO-d_6): δ = 13.01 (s, NH, 1H), 8.01 (d, *J* = 8 Hz, 2H, Ph), 7.29 (d, *J* = 8 Hz, 2H, Ph), 5.80 (s, CH, 1H), 2.43–2.29 (m, 4H, H4′, H6′), 1.92–1.79 (m, 2H, H5′), 1.17 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 151.1, 145.5 (Ph), 139.3 (C3/C5), 139.2 (q, *J* = 34 Hz, C5/C3), 129.0, 122.9 (Ph), 122.3 (q, *J* = 269 Hz, CF_3), 115.6 (C4), 114.0 (C2′), 34.0 (CH), 34.0 (C4′, C6′), 20.3 (C5′), 10.6 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) 396 (32), 378 (92), 349 (75), 326 (100), 201 (42).

HRMS Calc. for $C_{18}H_{16}F_3N_3O_4$: 396.1179. Found: 396.1177.

*4.2.1.4. 3-Hydroxy-2-[(5(3)-(trifluoromethyl)-3(5)-phenyl-1H-pyrazol-4-yl)-4-nitrophenylmethyl]cyclohex-2-en-1-one (**2d**): red solid, yield 85%, mp. 170–172 °C.* ^{1}H NMR (DMSO-d_6): δ = 13.55 (s, 1H, NH), 7.89 (d, *J* = 8 Hz, 2H, Ph), 7.24–7.17 (m, 7H, Ph), 5.77 (s, 1H, CH), 2.20–2.02 (m, 4H, H4′, H6′), 1.69–1.64 (m, 2H, H5′).

^{13}C NMR (DMSO-d_6): δ = 197.6 (C1′), 184.9 (C3′), 151.3, 145.2 (Ph), 142.7 (C3/C5), 138.9 (q, *J* = 34 Hz, C5/C3), 129.5, 129.4, 127.7, 127.1, 122.0 (Ph), 122.0 (q, *J* = 269 Hz, CF_3), 116.7 (C4), 114.6 (C2′), 35.3 (CH), 33.1 (C4′ e C6′), 19.7 (C5′).

MS (ESI) *m*/*z* [(M+H)$^+$, 458.2].

HRMS Calc. for $C_{23}H_{18}F_3N_3O_4$: 458.1279. Found: 458.1281.

*4.2.1.5. 3-Hydroxy-2-[(5(3)-(trifluoromethyl)-3(5)-methyl-1H-pyrazol-4-yl)-4-methoxyphenylmethyl]cyclohex-2-en-1-one (**2e**): yellow solid, yield 63%, mp. 127–129 °C.* ^{1}H NMR (DMSO-d_6): δ = 12.75 (s, NH, 1H), 6.95 (d, *J* = 8 Hz, 2H, Ph), 6.79 (d, *J* = 8 Hz, 2H, Ph), 5.61 (s, 1H, CH), 3.70 (s, 3H, OCH_3), 2.41–2.28 (m, 4H, H4′, H6′), 1.85–1.80 (m, 2H, H5′), 1.54 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 157.2 (Ph), 139.7 (C3/C5), 138.8 (q, *J* = 34 Hz, C5/C3), 133.6, 128.9 (Ph), 122.4 (q, *J* = 269 Hz, CF_3), 117.6 (C4), 115.4 (C2′), 113.0 (Ph), 54.8 (OCH_3), 33.0 (C4′), 32.9 (C6′), 32.8 (CH), 20.3 (C5′), 10.4 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) 380 (100), 340 (100), 309 (50), 269 (75).

HRMS Calc. for $C_{19}H_{19}F_3N_2O_3$: 381.1394. Found: 381.1389.

*4.2.1.6. 3-Hydroxy-2-[(5(3)-(trifluoromethyl)-3(5)-phenyl-1H-pyrazol-4-yl)-4-methoxyphenylmethyl]cyclohex-2-en-1-one (**2f**): yellow solid, yield 72%, mp. 120–122 °C.* ^{1}H NMR (DMSO-d_6): δ = 12.81 (s, NH, 1H), 7.20 (m, 5H, Ph), 6.82 (d, *J* = 8 Hz, 2H, Ph), 6.47 (d, *J* = 8 Hz, 2H, Ph), 5.61 (s, 1H, CH), 3.60 (s, 3H, OCH_3), 2.10–2.02 (m, 4H, H4′, H6′), 1.70–1.63 (m, 2H, H5′).

^{13}C NMR (DMSO-d_6): δ = 184.5 (C1′, C3′), 156.8 (Ph), 142.4 (C3/C5), 138.7 (q, *J* = 34 Hz, C5/C3), 134.2, 130.1, 129.4, 129.3, 127.2, 126.9, 126.2 (Ph), 122.2 (q, *J* = 269 Hz, CF_3), 115.3 (C4), 113.8 (C2′), 112.3 (Ph), 54.7 (OCH_3), 34.3 (CH), 34.3 (C4′ e C6′), 20.0 (C6′).

MS (ESI) *m*/*z* (%) 442 (71), 402 (100), 371 (26), 331 (31), 229 (21).

HRMS Calc. for $C_{24}H_{21}F_3N_2O_3$: 443.1579. Found: 443.1574.

*4.2.2. Synthesis of 3(5)-trifluoromethyl-5(3)-methyl-4-[(2,6-dimethoxyphenyl)-(4-methoxyphenylmethyl)]-1H-pyrazole (**3e**)*

A mixture of 3-hydroxy-2-[(5(3)-(trifluoromethyl)-3(5)-methyl-1*H*-pyrazol-4-yl)-4-methoxyphenylmethyl]cyclohex-2-en-1-one (**2e**) (0.198 g, 0.5 mmol) and iodine (0.126 g, 1 mmol) stirred in methanol (5 mL) was boiled under reflux for 6 h. The solvent was evaporated under pressure and the residue was taken up into dichloromethane (15 mL). The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate, and brine and then dried over Na_2SO_4. The mixture was filtered and the solvent evaporated under reduced pressure. The resulting solid product was dried in a desiccator under reduced pressure over P_2O_5 and furnished **3e** (72%) without purification as a yellow solid (mp. 109–111 °C) and at a high degree of purity according to CHN elemental analysis data.

^{1}H NMR (DMSO-d_6): δ = 7.21 (t, *J* = 8 Hz, 1H, Ph), 6.91 (d, *J* = 8 Hz, 2H, Ph), 6.79 (d, *J* = 8 Hz, 2H, Ph), 6.65 (d, *J* = 8 Hz, 2H, Ph), 6.13 (s, 1H, CH), 3.70 (s, 3H, OCH_3), 3.58 (s, 6H, OCH_3), 1.61 (s, 3H, CH_3).

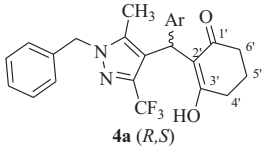
^{13}C NMR (DMSO-d_6): δ = 157.8, 157.2 (Ph), 139.6 (C3/C5, Pz), 138.9 (q, *J* = 34 Hz, C5/C3, Pz), 133.1, 128.9, 128.0 (Ph), 122.2 (q, *J* = 269 Hz, CF_3), 120.8 (C4, Pz), 117.0, 113.12, 104.7 (Ph), 55.4 (OCH_3), 54.7 (OCH_3), 33.8 (CH), 10.0 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) 406 (100), 366 (75), 337 (87).

Anal. Calc. for $C_{21}H_{21}F_3N_2O_3$ (406.15): C, 62.06; H, 5.21; N, 6.89. Found: C, 61.97, H, 5.15, N, 6.91.

*4.2.3. Synthesis of 2-[(1-benzyl-5-trifluoromethyl-3-methyl-1H-pyrazol-4-yl)phenylmethyl]-3-hydroxycyclohex-2-en-1-one (**4a**)*

To a solution of 2-[(3(5)-trifluoromethyl-5(3)-methyl-1*H*-pyrazol-4-yl)phenylmethyl]-3-hydroxycyclohex-2-en-1-one (**2a**) (0.5 mmol, 175 mg), and sodium hydride (0.9 mmol, 21 mg) stirred with anhydrous DMF (10 mL), pure benzyl chloride (0.55 mmol, 69 mg) was added at room temperature. After the addition process, the mixture was stirred for a further 24 h at room temperature. After this time, chloroform (15 mL) was added to the reaction and the organic layer was washed with distilled water (3 × 10 mL). Then, the organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The resulting brown oil was boiled in chloroform (10 mL) in the presence of active charcoal and filtered hot. After a second solvent evaporation under reduced pressure, the alkylated product **4a** (yellow oil) was isolated at 69% yield without purification and at a high degree of purity according to the CHN elemental analysis data.



4a (*R,S*)

^{1}H NMR ($CDCl_3$): δ = 7.98 (s, 1H, OH), 7.24–6.97 (m, 10H, Ph), 5.88 (s, 1H, CH), 5.01 (m, 2H, CH_2), 2.68–2.63 (m, 2H, H6′), 2.34 (bs, 2H, H4′), 2.01–1.98 (m, 2H, H5′), 1.35 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 197.2 (C1′), 172.5 (C3′), 150.6 (Ph), 150.6 (Ph), 140.6 (C3), 139.5 (q, J = 34 Hz, C5), 135.6, 128.4, 128.3, 128.1, 127.7, 126.9, 125.8 (Ph), 122.3 (q, J = 269 Hz, CF_3), 117.2 (C2′), 114.4 (C4), 69.6 ($\underline{C}H_2$Ph), 36.5 (C6′), 34.6 (C4′), 31.3 (CH), 24.9 (C5′), 10.4 (CH_3).

MS (CI+): m/z (%) 441 (M+1) (43); 421 (29); 329 (47); 241 (100); 211 (85); 221 (85); 91 (71); 69 (10); 57 (36).

Anal. Calc. for $C_{25}H_{23}F_3N_2O_2$ (440.17): C, 68.17; H, 5.26; N, 6.36. Found: C, 68.30, H, 5.25, N, 6.05.

Acknowledgements

The authors thank the Coordination for Improvement of Higher Education Personnel (CAPES) for fellowships, and the National Council for Scientific and Technological Development (CNPq) for financial support (Process numbers 303.013/2011-7 and 470.788/2010-0-Universal).

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