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The first application of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones in a three-component condensation protocol for the synthesis of 3-acyl-4-aryl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones

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ABSTRACT

The one-pot, simple and efficient three-component condensation protocol for the preparation of a series of twenty-five new 3-acyl-4-aryl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones, where aryl = Ph, 4-tolyl, 4-ClPh, 4-NO_2Ph and 4-CHOPh, and acyl = Ac, Bz, 4-FBz, furan-2-oyl, thien-2-oyl and naphth-1-oyl, employing 1,3-cyclohexanedione, five aryl aldehydes and for the first time, six 4-alkyl(aryl/heteroaryl)-4-methoxy-1,1,1-trifluoroalk-3-en-2-ones, is described. Yields in 15–75% were obtained when the MCRs were performed in the presence of a catalytic amount of triethylamine (25 mol%) and in ethanol as solvent under reflux for 16 h. A representative X-ray diffraction data for 3-acetyl-4-phenyl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one is also showed.

1. Introduction

The development of multicomponent reactions (MCRs) is nowadays of great importance in synthetic organic chemistry, since they offer one-pot combinations of two or more components in one step, allowing the formation of molecules with more complex structures [1]. In addition, the design of MCRs to produce elaborate active compounds has become an important area of research in combinatorial and medicinal chemistry [2]. This approach holds a number of advantages over conventional methodologies, such as flexibility, convergence, simple starting materials and products in high yield [3].

On another vein, due to their unique physical, chemical, and biological properties, fluorine-containing compounds have attracted much attention in the field of biological and material science. Specifically, trifluoromethyl substituted heterocyles are becoming increasingly important for the development of new agrochemicals and medications [4–6]. Among many useful reactions, the introduction of a trifluoromethyl group has received great attention in the literature [7], where methyl fluorosulfonyldifluoroacetate (MFSDA), as a convenient-to-handle liquid reagent, has allowed the synthesis of a variety of CF_3-containing compounds including aryl, heteroaryl, vinyl, benzyl and allyl halides in good yields and under mild conditions.

However, one of the best methods to introduce a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This approach relies on the trifluoroacetylation of enolethers or acetals to give, in one-step and good yields, 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones which have proven to be useful building blocks for the regioselective synthesis of numerous trifluoromethyl substituted heterocycles [8].

Funcionalized chromenes and benzopyrans are an important class of compounds which have received considerable attention due to their wide range biological and pharmacological activities such as spasmolytic, diuretic, anti-coagulant, anti-cancer, and anti-anaphylactic [9]. Furthermore, they can be employed as pigments, photoactive materials and utilized as biodegradable agrochemicals, as well as, constituent of the structural unit of a series of natural products [10,11]. Many methods have been introduced for the synthesis of these compounds, such as, from aromatic aldehydes and cyclohexane-1,3-diones [11], α,β-unsaturated

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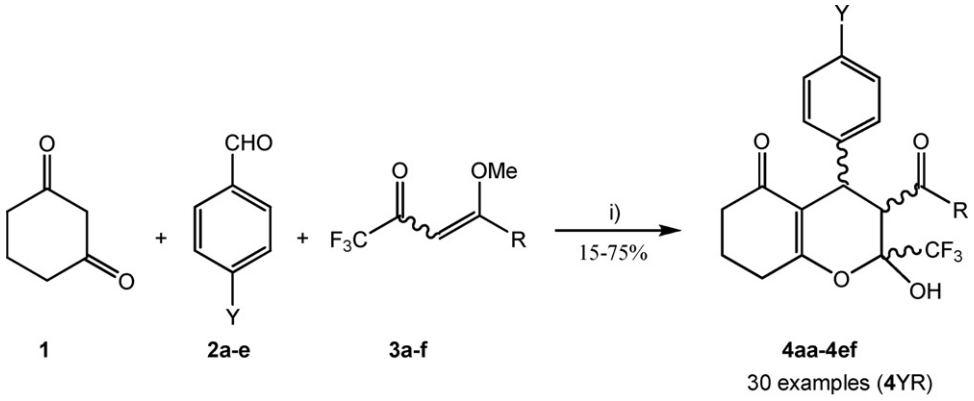


2	a	b	c	d	e
Y	H	Me	Cl	NO_2	CHO

3	a	b	c	d	e	f
R	Me	Ph	4-FPh	2- Furyl	2-Thienyl	1-Naphthyl

Scheme 1. Reaction conditions: (i) ethanol, Et_3N (25 mol%), reflux,16 h.

aldehydes and cyclohexane-1,3-diones in the presence of a catalytic amount of diarylprolinol silyl ether [12], organocatalytic enantioselective addition of five-, six- and seven-membered 1,3-cycloalkanediones to α,β-unsatured aldehydes [13], Michael reaction of β,γ-unsatured α-ketoesteres with cyclic 1,3-diketones [14] and from a one-pot three-component reaction of 1,3-cyclohexanedione with aryl aldehydes and 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione in the presence of a catalytic amount of triethylamine [3].

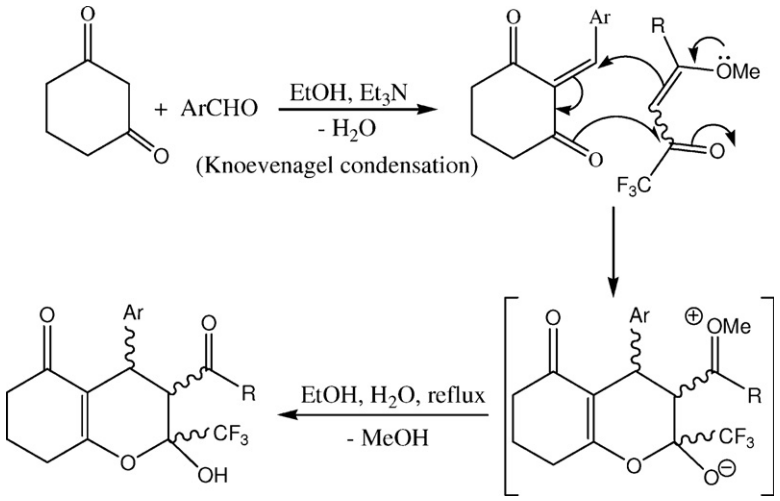
Although some similar compounds already have been described, so far, the employment of 4-methoxy-1,1,1-trifluoro-3-alken-2-ones by a three-component condensation reaction to obtain trifluoromethyl substituted 2-hydroxy-2*H*-chromenones was not yet reported.

Thus, the aim of this work is to report a facile and efficient synthesis of 2-trifluoromethyl-2*H*-chromenones using MCR methodology, which employs as starting materials 1,3-cyclohexanedione, aryl aldehydes (five examples) and 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (six examples) to show a new chemical behavior of this trifluoromethylated building block, in a [4+2] cyclocondensation reaction, and a new method to introduce the trifluoromethyl group into molecules that are of great interest to organic and medicinal chemists.

2. Results and discussion

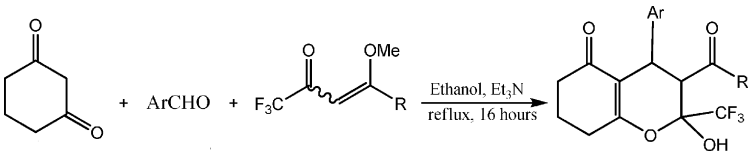
4-Methoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**3a**–**f**) are readily available CCC synthetic blocks and were prepared from trifluoroacetylation reactions of commercially available *iso*-propenyl methyl ether (for **3a**) or generated *in situ* of the respective aryl- (for **3b**–**c, 3f**) or heteroaryl (for **3d**–**e**) methyl ketone acetals with trifluoroacetic anhydride, respectively, in the presence of pyridine, as described in the literature [15].

We initially examined the MCR involving 4-methoxy-1,1,1-trifluoropent-3-en-2-one (**3a**), benzaldehyde (**2a**) and 1,3-cyclohexanedione in ethanol as solvent in the absence of a base employing stirring from 2 to 24 h at room temperature under reflux. Under this reaction condition, no precipitation products were observed in the course of the reaction, nor were any products identified by ^{1}H NMR experiments. Although some organic bases and polar protic or aprotic solvents were tested, the best conditions for the consumption of the starting materials to form **4aa** were only when the reactions were carried out in the presence of a catalytic amount of triethylamine or pyridine under refluxing ethanol. The experiments also showed that 25–30 mol% of catalyst was necessary to complete the reaction after 16 h under reflux and higher amounts of catalyst (up to 60 mol% of triethylamine or



Scheme 2. A plausible mechanism for formation of chromenones **4**.

Table 1
Regioselective multicomponent reaction for the synthesis of 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones.



30 examples

Entry	Ar	*R*	Product	Mp (°C)	Yield (%)[b]
1	C_6H_5 (**2a**)	CH_3 (**3a**)	**4aa**	175–176 (203–204)[c]	45 (53)[c]
2	C_6H_5 (**2a**)	C_6H_5 (**3b**)	**4ab**	187–189	54
3	C_6H_5 (**2a**)	4-FC_6H_4 (**3c**)	**4ac**	173–175	60
4	C_6H_5 (**2a**)	2-Furyl (**3d**)	**4ad**	190–191	47
5	C_6H_5 (**2a**)	2-Thienyl (**3e**)	**4ae**	187–189 (222–223)[c]	50 (68)[c]
6	C_6H_5 (**2a**)	1-Naphthyl (**3f**)	**4af**	199–200	12
7	4-$CH_3C_6H_4$ (**2b**)	CH_3 (**3a**)	**4ba**	172–174	60
8	4-$CH_3C_6H_4$ (**2b**)	C_6H_5 (**3b**)	**4bb**	176–178	64
9	4-$CH_3C_6H_4$ (**2b**)	4-FC_6H_4 (**3c**)	**4bc**	202–203	58
10	4-$CH_3C_6H_4$ (**2b**)	2-Furyl (**3d**)	**4bd**	194–196	65
11	4-$CH_3C_6H_4$ (**2b**)	2-Thienyl (**3e**)	**4be**	187–189 (216–218)[c]	63 (88)[c]
12	4-$CH_3C_6H_4$ (**2b**)	1-Naphthyl (**3f**)	**4bf**	198–200	18
13	4-ClC_6H_4 (**2c**)	CH_3 (**3a**)	**4ca**	184–186	66
14	4-ClC_6H_4 (**2c**)	C_6H_5 (**3b**)	**4cb**	189–191	75
15	4-ClC_6H_4 (**2c**)	4-FC_6H_4 (**3c**)	**4cc**	187–189	68
16	4-ClC_6H_4 (**2c**)	2-Furyl (**3d**)	**4cd**	189–191	64
17	4-ClC_6H_4 (**2c**)	2-Thienyl (**3e**)	**4ce**	181–183 (224–225)[c]	71 (60)[c]
18	4-ClC_6H_4 (**2c**)	1-Naphthyl (**3f**)	**4cf**	199–201	22
19	4-$NO_2C_6H_4$ (**2d**)	CH_3 (**3a**)	**4da**	194–196	53
20	4-$NO_2C_6H_4$ (**2d**)	C_6H_5 (**3b**)	**4db**	182–184	65
21	4-$NO_2C_6H_4$ (**2d**)	4-FC_6H_4 (**3c**)	**4dc**	177–179	51
22	4-$NO_2C_6H_4$ (**2d**)	2-Furyl (**3d**)	**4dd**	209–211	49
23	4-$NO_2C_6H_4$ (**2d**)	2-Thienyl (**3e**)	**4de**	205–207 (230–231)[c]	57 (66)[c]
24	4-$NO_2C_6H_4$ (**2d**)	1-Naphthyl (**3f**)	**4df**	206–208	16
25	4-$CHOC_6H_4$ (**2e**)	CH_3 (**3a**)	**4ea**	194–196	41
26	4-$CHOC_6H_4$ (**2e**)	C_6H_5 (**3b**)	**4eb**	182–184	43
27	4-$CHOC_6H_4$ (**2e**)	4-FC_6H_4 (**3c**)	**4ec**	182–184	45
28	4-$CHOC_6H_4$ (**2e**)	2-Furyl (**3d**)	**4ed**	202–204	60
29	4-$CHOC_6H_4$ (**2e**)	2-Thienyl (**3e**)	**4ee**	198–200	52
30	4-$CHOC_6H_4$ (**2e**)	1-Naphthyl (**3f**)	**4ef**	189–191	15

[a] Molar ratio **1**:**2a**–**e**:**3a**–**f** = 1:1:1.
[b] Yield of isolated.
[c] Yields and melting points from Ref. [3].

pyridine) did not improve the obtainment of **4aa**. Encouraged by this result, we then employed this reaction as a template to optimize the reaction conditions. According to Song et al. [3], when the reaction started from 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione, as the 1,3-dicarbonyl acyclic precursor, 2–24 h were necessary to finish the reaction resulting in 36–88% yield and depending on the aryl aldehyde substituent. In the present study, 16 h were determined as the optimal reaction time for all ketones **3** and aldehydes **2** precursors (Scheme 1).

Subsequently, we synthesized a series of thirty trifluoromethyl substituted 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one derivatives (**4aa**–**ef**), where five chromenones are known-compounds [3], named **4aa**, **4ae**, **4be**, **4ce** and **4de**, by a three-component protocol employing a 1,3-dicarbonyl cyclic compound (1,3-cyclohexanedione), five aryl aldehydes (**2a**–**e**) containing electron-withdrawing and electron-donating groups and six 4-alkyl-, 4-aryl- and 4-heteroaryl-substituted 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (**3a**–**f**).

A plausible and simplified mechanism for the multicomponent synthesis of chromenones **4** using triethylamine in ethanol at reflux is proposed in Scheme 2. One of the most general mixed aldol condensation reactions involves the use of aromatic aldehydes with 1,3-diketones. Aromatic aldehydes are incapable of enolization and cannot function as the nucleophilic component. Dehydration is especially favorable because the resulting enone is conjugated with the aromatic ring. Moreover, there are numerous examples of both acid- and base-catalyzed mixed aldol condensations involving aromatic aldehydes. On the other hand, the nucleophilic proprieties of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one were studied in much more detail in the diacylation reactions of alkyl vinyl ethers [23a], [2+3] dipolar cycloaddition involving nitrones [23b] and α-halogenation [23c], but the reactions of fluorinated enones **3** with electrophiles, as demonstrated in the present work, have not been yet reported. Thus, in our case, we think that triethylamine is sufficiently basic to promote a Knoevenagel condensation of the aromatic aldehyde (**2**) with one molecule of 1,3-hexanedione to give the dehydrated Knoevenagel product. The subsequent Michael addition of the 4-methoxy-1,1,1-trifluoroalk-3-en-2-one (**3**) to the Knoevenagel product, in a [4+2] cyclocondensation reaction type, with subsequent water addition to the exocyclic oxymethylated carbon and followed by the hydrolysis of the hemiacetal function, allowed

the isolation of the chromenones **4**. However, the exact sequence of intermediates is difficult to determine since many of the steps are, expected, in equilibrium.

As a result, twenty-five chromen-5(6*H*)-ones **4** were obtained in satisfactory to good yields (41–75%), but poor yields (15–22%) were verified for the synthesis of five 3-(naphth-1-oyl) derivatives (**4af**–**ef**), although the reaction time was prolonged up to 48 h under reflux. Even so, many times no precipitated products were observed in the reaction mixture and a more laborious reaction work-up was necessary after the end of the reaction. For all other compounds, the products precipitated in the course of the reaction and after the reaction time, the desired compounds were filtered, washed with cold ethanol and air-dried. Subsequently, a recrystallization from ethanol/ethylacetate (2:1) and drying in a desiccator under reduced pressure over P_2O_5, furnished **4** in high purity (elemental analysis). The summary of the results of all reactions and the melting point with the literature data for known compounds are shown in Table 1.

With the exception of 3-(naphth-1-oyl) derivatives (**4af**–**ef**), it was also observed that the reaction yields were not very sensitive to the presence, or lack, of a *Y*-substituent at the *para*-position of the aryl aldehydes, nor to the *R*-substituent effect of the vinyl ketones **3**. The electronic and steric effects of the aryl substituents from the aldehydes **2** and the naphthyl group of the trifluoromethylated enone **3** in the cyclocondensation reaction step, after the Knoevenagel condensation step, make the approach between the two molecules difficult. This is the probable explanation for the poor yields in the synthesis of 3-(naphth-1-oyl) derivatives (**4af**–**ef**).

It is also noteworthy that a great difference between the melting points has been reported [3] and the same was found for the compounds synthesized by us in the present study, i.e., **4aa** (28 °C), **4ae** (35 °C), **4be** (29 °C), **4ce** (43 °C) and for **4de** (25 °C). Although the physical data of these five molecules were reported [3], the melting point differences obliged us to perform a complete structural re-investigation, to include ^{13}C NMR and MS experiments, as well as an X-ray diffraction measurement for **4aa**, and a CHN microanalysis to verify their purity.

Compounds **4** are constituted by a 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one ring which is the core of the structure and it has four main substituents attached: a hydroxyl and a trifluoromethyl group at the C2-position and an acyl and an aryl substituent at the C3- and C4-positions, respectively. The structures of compounds **4** were deduced from ^1H and ^{13}C NMR uni- and bi-dimensional experiments, in DMSO-d_6 as solvent (COSY, HSQC, HMBC and DEPT 135), MS, IR and by comparison with NMR data of other 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones previously synthesized [3], and the purity grade was proven by CHN elemental analysis.

From the described reaction (Scheme 1), compounds **4** show three stereocenters and eight stereoisomers would be expected, among these, four pairs of enantiomers. If four pairs of enantiomers were formed both ^1H and ^{13}C NMR spectra should show four sets of signals. However, the NMR spectra showed only one set of signals, which indicates that only one pair of enantiomers was obtained.

Most of the compounds **4** (24 examples) showed an important feature in the ^1H NMR spectra, in DMSO-d_6. The methyne protons (H3, H4) are shown as a typical AX system as two doublets, in which, one of them is on average at δ 4.22 ppm (H3) and the other at δ 3.87 ppm (H4), with a vicinal coupling constant $^3J_{HH}$ = 12 Hz, indicating a typical *trans*-axial configuration of these two hydrogen atoms. However, the ^1H NMR spectra showed signals for H3 and H4 for four 3-(4-fluorobenzoyl) substituted chromenones (**4ac**, **4bc**, **4dc** and **4ec**; Y = H, Me, NO_2 and CHO) and for two 3-benzoyl substituted (**4db** and **4eb**; Y = NO_2 and CHO) as one unique and broad peak in the range of δ 4.3 ppm, corresponding to a typical AB system.

The $^{13}C\{^1H\}$NMR spectra exhibited only one set of peaks for chromenones **4**, despite the fact that three stereogenic carbons are present in each molecule. Due to the presence of the CF_3 group, the C-2 carbon presented a characteristic quartet at δ 94.6 ppm with $^2J_{CF}$ = 33 Hz. Also, the CF_3 group showed a typical quartet at δ 121.7 ppm with $^1J_{CF}$ = 287 Hz and the *endo*-cyclic carbonyl carbon C-5 showed NMR signals in the range of δ 194.9 ppm. Due to the substituent effects on the structures of **4**, the *exo*-cyclic carbonyl carbon attached to C-3 revealed signals from δ 182.2 to 204.1 ppm ($\Delta\delta$ = 21.9 ppm), the C-3 from δ 47.7 to 58.3 ppm ($\Delta\delta$ = 10.6 ppm) and C-4, which is attached to the *p*-substituted aryl moiety derived from the aldehyde precursors, showed signals in the narrow range of δ 27.6–28.2 ppm ($\Delta\delta$ = 0.6 ppm).

Complementarily, the X-ray diffraction measurement was carried out for compound **4aa** (Fig. 1) [16] proving that H3 and H4 are situated *trans* to each other, as are the substituents attached to these carbons. The X-ray data demonstrated that the proton attached to oxygen O21 of hydroxyl group presents, according to the literature [22], a possible intramolecular H-bond with the oxygen O32 of the carbonyl group [*D*(O32···H21) = 2.224 Å and (O32···O21) = 3.019 Å].

Thus, the X-ray diffraction and the NMR data confirmed that only one pair of enantiomers was obtained. Since the cyclization reaction is essentially driven by thermodynamic factors where the position of the substituents will depend on the steric factors, as well as the stability of the resulting products, Fig. 1 represents one enantiomer of the most stable possible structure for compounds **4**.

Finally, we would like to report that we are conducting studies on the reactivity of the described 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones. Preliminary results have demonstrated that chromenone **4aa** reacts with hydrazine hydrate to furnish 5-trifluoromethyl-3-methyl-4-(2-benzyl-3-hydroxycyclohex-2-enone-2-yl)-1*H*-pyrazole as an oil, by a new ring transformation reaction.

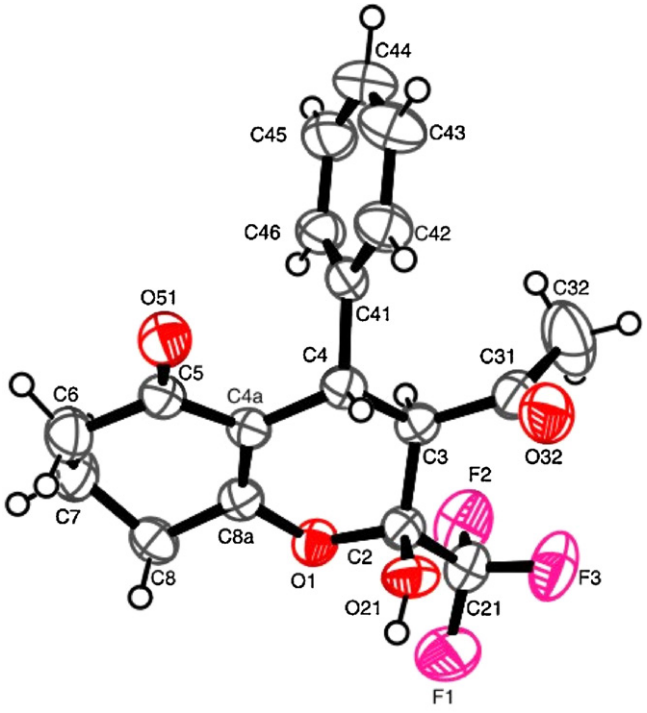
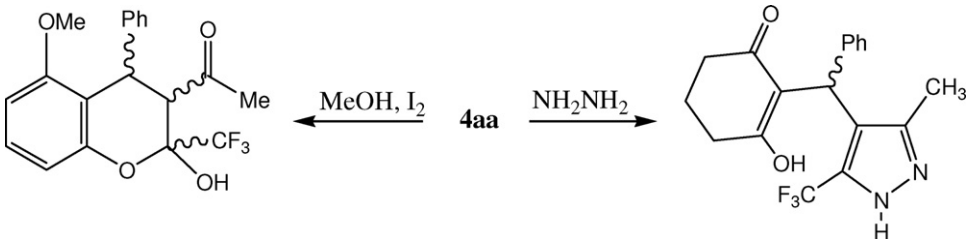


Fig. 1. A perspective view of 3-acetil-4-phenyl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-*2H*-chromen-5(6*H*)-one (**4aa**) with atoms labeled (CCDC 774510) [16]. Displacement ellipsoids are drawn at the 50% probability level.



Scheme 3. Examples of reactivity studies on chromenone **4aa**.

In addition, **4aa** reacts with iodine in methanol under reflux, aromatizing the cyclohexanone fragment to give the respective 5-methoxy-3,4-dihydro-2*H*-chromene, but hindering dehydration. Thus the hemiacetal function at carbon-2 of the pyran ring remains (Scheme 3).

3. Conclusion

In summary, we have developed a new, simple and convenient MCR protocol of wide scope for the synthesis of trifluoromethyl substituted 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones starting from commercially available 1,3-cyclohexanedione and aryl aldehydes and, for the first time, 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones, which proved to be a useful synthetic block to attach a CF_3 group at the heterocycles.

4. Experimental

4.1. Synthesis

Unless otherwise indicated all common reagents and solvents were as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus. ^{1}H, ^{13}C and ^{19}F NMR spectra were acquired on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{19}F at 376.3 MHz) and Varian Mercury Plus 400 AS spectrometers (^{13}C at 100.60 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, 260 pt/ppm, in DMSO-d_6 as solvent, using TMS as internal reference (0.05% v/v, ^{1}H and ^{13}C) or fluorobenzene as external reference (^{19}F). 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. Samples were eluted employing a mixture of acetonitrile:water (40:60 v/v), as the mobile phase. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN Elemental Analyzer (São Paulo University-USP/Brazil). The diffraction measurements were carried out by graphite-monochromatized Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer [17]. The structure of **4aa** was solved with direct methods using SHELXS-97 program [18], and refined on F^2 by full-matrix least-squares by the SHELXL-97 package [19]. The absorption correction was performed by Gaussian methods [20]. Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3), 0.97 Å (methylene CH_2), 0.98 Å (methyne CH), 0.93 Å (aromatic CH) and 0.82 Å (OH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to *U*iso(H) = χ*U*eq (carrier C atom), with χ = 1.5 for methyl groups and χ = 1.2 otherwise. The valence angles C–C–H and H–C–H of methyl groups were set to 109.5° and the H atoms were allowed to rotate around the C–C bond. Molecular graph was prepared using ORTEP3 for Windows [21].

4.2. General procedure for the synthesis of 3-acyl-4-aryl-2-(trifluoromethyl)-2-hydroxy-3,4,7,8-tetrahydro-2H-chromen-5(6H)-ones (4)

4.2.1. General procedure

To a stirred mixture of aryl aldehydes (2.0 mmol), 1,3-ciclohexanedione (0.224 g, 2.0 mmol) and 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (2.0 mmol) in EtOH (15 mL) was added triethylamine (0.5 mmol, 50 mg) in a catalytic amount at room temperature. Immediately, the solid products started to precipitate. Then, the mixture was stirred under reflux for more 16 h. After this time, the desired products were filtered, washed with cold EtOH, air-dried and a recrystallization from ethanol/ethylacetate (2:1) and drying in a desiccator under reduced pressure over P_2O_5, furnished **4** in high purity (elemental analysis).

*4.2.1.1. 3-Acetyl-2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4,7,8-tetra-hydro-2H-chromen-5(6H)-one (**4aa**). White solid, yield 45%, mp 175–176 °C; (Lit. [3]: 203–204 °C).* ^{1}H NMR (DMSO-d_6): δ = 9.02 (s, 1H, OH), 7.09–7.25 (m, 5H, Ar), 4.00 (d, *J* = 12 Hz, 1H, H3), 2.99 (d, *J* = 12 Hz, 1H, H4), 2.62–2.50 (m, 2H, H6), 2.20–2.17 (m, 2H, H8), 1.97 (s, 3H, Ac.), 1.94–1.88 (m, 2H, H7).

^{13}C NMR (DMSO-d_6): δ = 203.9 (C=O, Ac.), 194.9 (C5), 166.3 (C8a), 141.3, 128.2, 127.2, 126.3 (Ar), 121.9 (q, $^1J_{CF}$ = 287 Hz, CF_3), 114.6 (C4a), 94.1 (q, $^2J_{CF}$ = 33 Hz, C2), 58.1 (C3), 37.4 (C6), 36.4 (s, 3H, Ac.), 29.5 (C8), 27.8 (C4), 19.4 (C7).

^{19}F NMR (DMSO-d_6): δ = −81.04 (CF_3). MS (ESI) *m*/*z*: [(M+H)$^+$, 355.2]. IR (KBr) ν_{max}: 3303, 1725, 1604, 1358, 1229, 1190, 1165, 1040, 950 cm^{-1}. Anal. Calcd. for $C_{18}H_{17}F_3O_4$ (354.11): C, 61.02; H, 4.84%. Found: C, 61.01; H, 4.78%.

*4.2.1.2. 3-Benzoyl-2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4,7,8-tetrahydro-2H-chromen-5(6H)-one (**4ab**). White solid, yield 54%, mp 187–189 °C.* ^{1}H NMR (DMSO-d_6): δ = 8.57 (s, 1H, OH), 7.46–7.44 (m, 3H, Ar), 7.32–7.28 (m, 2H, Ar), 7.14–7.05 (m, 4H, Ar), 6.96 (m, 1H, Ar), 4.24 (d, *J* = 12 Hz, 1H, H3), 4.19 (d, *J* = 12 Hz, 1H, H4), 2.63–2.58 (m, 2H, H6), 2.26–2.19 (m, 2H, H8), 1.98–1.95 (m, 2H, H7).

^{13}C NMR (DMSO-d_6): δ = 195.9 (C=O, Bz), 194.4 (C5), 165.8 (C8a), 141.0, 137.7, 132.7, 128.0, 127.6, 127.1, 127.0, 125.7 (Ar), 122.0 (q, $^1J_{CF}$ = 287 Hz, CF_3), 114.8 (C4a), 94.5 (q, $^2J_{CF}$ = 33 Hz, C2), 49.0 (C3), 38.3 (C6), 36.3 (C8), 27.6 (C4), 19.3 (C7).^{19}F NMR (DMSO-d_6): δ = −80.33 (CF_3). MS (ESI) *m*/*z*: [(M+H)$^+$, 417.1], [(M+Na)$^+$, 439.0], [(M+K)$^+$, 455]. IR (KBr) ν_{max}: 3344, 1683, 1608, 1359, 1243, 1186, 1160, 1001 cm^{-1}. Calcd. for $C_{23}H_{19}F_3O_4$ (416.12): C, 66.34; H, 4.60%. Found: C, 66.07; H, 4.93%.

*4.2.1.3. 3-(4-Fluorobenzoyl)-2-hydroxy-4-phenyl-2-(trifluoro-methyl)-3,4,7,8-tetrahydro-2H-chromen-5 (6H)-one (**4ac**). White solid, yield 60%, mp 173–175 °C.* ^{1}H NMR (DMSO-d_6): δ = 8.62 (s, 1H, OH), 7.99–7.95 (m, 1H, Ar), 7.59–7.55 (m, 2H, Ar), 7.13–7.11 (m, 2H, Ar), 7.09–7.01 (m, 4H, Ar), 4.27 (s, 2H, H3, H4), 2.63–2.56 (m, 2H, H6), 2.23–2.20 (m, 2H, H8), 2.04–1.95 (m, 2H, H7).

^{13}C NMR (DMSO-d_6): δ = 194.6 (C=O, Bz), 194.4 (C5), 165.9 (C8a), 164.4 (d, $^1J_{CF}$ = 253 Hz, Ar), 140.9, 133.9 (Ar), 130.1 (d, $^3J_{CF}$ = 9 Hz, Ar), 127.6, 127.2, 125.8 (Ar), 121.6 (q, $^1J_{CF}$ = 287 Hz, CF_3), 115.1 (d, $^2J_{CF}$ = 22 Hz, Ar), 114.8 (C4a), 94.6 (q, $^2J_{CF}$ = 33 Hz, C2), 49.0 (C3), 38.7 (C6), 36.3 (C8), 27.7 (C4), 19.3 (C7).

^{19}F NMR (DMSO-d_6): δ = −80.37 (CF_3), −105.0 (4-FPh). MS (ESI) m/z: [(M+H)$^+$, 435.1], [(M+Na)$^+$, 457.2]. IR (KBr) ν_{max}: 3453, 1688, 1603, 1358, 1241, 1188, 1160, 845 cm^{-1}. Anal. Calcd. for $C_{23}H_{18}F_4O_4$ (434.11): C, 63.60; H, 4.18%. Found: C, 63.70; H, 4.46%.

*4.2.1.4. 3-(Furan-2-oyl)-2-hydroxy-4-phenyl-2-(trifluoromethyl)-3,4,7,8-tetrahydro-2H-chromen-5(6H)-one (**4ad**). Yellow solid, yield 47%, mp 190–191 °C.* ^{1}H NMR (DMSO-d_6): δ = 8.55 (s, 1H, OH), 7.76–7.75 (m, 1H, Fur), 7.12–7.03 (m, 5H, Ph), 7.00–6.96 (m, 1H, Fur), 6.48–6.47 (m, 1H, Fur), 4.16 (d, J = 12 Hz, 1H, H3), 3.88 (d, J = 12 Hz, 1H, H4), 2.62–2.55 (m, 2H, H6), 2.21–2.18 (m, 2H, H8), 1.98–1.92 (m, 2H, H7).

^{13}C NMR (DMSO-d_6): δ = 195.0 (C5); 182.9 (C=O, Fur), 166.3 (C8a), 152.3 (Fur), 148.6 (Fur), 141.2, 127.8, 127.6, 126.0 (Ph), 121.8 (q, $^1J_{CF}$ = 287 Hz, CF_3), 119.5 (Fur), 115.0 (C4a), 112.6 (Fur), 94.8 (q, $^2J_{CF}$ = 33 Hz, C2), 49.5 (C3), 38.2 (C6), 36.5 (C8), 27.9 (C4), 19.6 (C7).

^{19}F NMR (DMSO-d_6): δ = −80.67 (CF_3). MS (ESI) m/z: [(M+H)$^+$, 407.1], [(M+Na)$^+$, 429.1]. IR (KBr) ν_{max}: 3447, 1673, 1608, 1426, 1358, 1189, 1163, 1040, 764, 732 cm^{-1}. Anal. Calcd. for $C_{21}H_{17}F_3O_5$ (406.10): C, 62.07; H, 4.22%. Found: C, 61.94; H, 4.51%.

*4.2.1.5. 2-Hydroxy-4-phenyl-3-(thien-2-oyl)-2-(trifluoromethyl)-3,4,7,8-tetrahydro-2H-chromen-5(6H)-one (**4ae**). White solid, yield 50%, mp 187–189 °C; (Lit. [3]: 222–223 °C).* ^{1}H NMR (DMSO-d_6): δ = 8.55 (s, 1H, OH), 7.80 (d, J = 5 Hz, 1H, Th), 7.41 (s, 1H, Th), 7.07–7.04 (m, 4H, Ar), 6.97–6.96 (m, 2H, Ph/Th), 4.19 (d, J = 12 Hz, 1H, H3), 3.98 (d, J = 12 Hz, 1H, H4), 2.62–2.57 (m, 2H, H6), 2.20–2.18 (m, 2H, H8), 1.97–1.95 (m, 2H, H7).

^{13}C NMR (DMSO-d_6): δ = 194.6 (C5), 188.1 (C=O, Th), 166.0 (C4a), 144.5 (Th), 140.9 (Ph), 135.7 (Th), 132.9 (Th), 128.2 (Ph), 127.6 (Th), 127.3, 125.8 (Ph), 121.7 (q, $^1J_{CF}$ = 287 Hz, CF_3), 114.9 (C4a), 94.6 (q, $^2J_{CF}$ = 33 Hz, C2), 50.9 (C3), 38.6 (C6), 36.3 (C8), 27.8 (C4), 19.4 (C7).

^{19}F NMR (DMSO-d_6): δ = −81.41 (CF_3). MS (ESI) m/z: [(M+H)$^+$, 423.0], [(M+Na)$^+$, 445.0]. IR (KBr) ν_{max}: 3420, 1659, 1609, 1361, 1259, 1189, 1163, 1020, 729, 709 cm^{-1}. Anal. Calcd. for $C_{21}H_{17}F_3O_4S$ (422.08): C, 59.71; H, 4.06%. Found: C, 59.81; H, 4.32%.

*4.2.1.6. 2-Hydroxy-3-(naphth-1-oyl)-4-phenyl-2-(trifluoromethyl)-3,4,7,8-tetrahydro-2H-chromen-5(6H)-one (**4af**). White solid, yield 12%, mp 199–200 °C.* ^{1}H NMR (DMSO-d_6): δ = 8.70 (s, 1H, OH), 8.37 (d, J = 8.0 Hz, 1H, Ar), 7.97 (d, J = 8 Hz, 1H, Ar) 7.90 (d, J = 8 Hz, 1H, Ar), 7.60–7.51 (m, 2H, Ar), 7.24–7.11 (m, 5H, Ar), 7.07–7.05 (m, 1H, Ar), 6.88 (d, J = 7 Hz, 1H, Ar), 4.37 (d, J = 12 Hz, 1H, H3), 4.17 (d, J = 12 Hz, 1H, H4), 2.64–2. 53 (m, 2H, H6), 2.25–2.22 (m, 2H, H8), 2.00–1.97 (m, 2H, H7).

^{13}C NMR (DMSO-d_6): δ = 197.0 (C=O, Naph.), 194.7 (C5), 166.0 (C8a), 141.6, 135.3, 133.0, 132.8, 129.2, 128.0, 127.9, 127.5, 127.3, 127.2, 126.2, 125.9, 125.1, 123.8 (Ar), 120.7 (q, $^1J_{CF}$ = 287 Hz, CF_3), 114.8 (C4a), 94.6 (q, $^2J_{CF}$ = 33 Hz, C2), 52.7 (C3), 38.2 (C6), 36.3 (C8), 27.7 (C4), 19.4 (C7).

^{19}F NMR (DMSO-d_6): δ = −77.0 (CF_3). MS (ESI) m/z (%): [(M+H)$^+$, 467.1], [(M+Na)$^+$, 489.1]. IR (KBr) ν_{max}: 3428, 1678, 1607, 1349, 1230, 1193, 1039, 1016, 736, 654 cm^{-1}. Anal. Calcd. for $C_{27}H_{21}F_3O_4$ (466.14): C, 69.52; H, 4.54%. Found: C, 69.09; H, 5.01%.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2010.12.011.

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