# A Concise Synthesis of Trifluoromethylated Cyclohexenones: A One-Pot, Five-Step Domino Reaction

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β-Trifluoromethylated aromatic enones can undergo, in one pot, a five-step domino process leading, with good yields, to 5-trifluoromethylated cyclohexenones that constitute valuable functionalized fluorinated building-blocks.



## Introduction

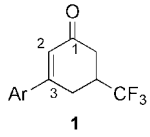
It is well known that, because of the intrinsic properties of the fluorine atom, fluorinated compounds exhibit specific and unique properties.[1] Such particularities are of huge interest and find a wide range of applications.[2] Consequently, the number of new organofluorine products that appear each year is growing steadily.[3]

Among them, trifluoromethylated-substituted molecules are of great interest in various fields of applications. For instance, the high lipophilicity brought by the $CF_3$ moiety confers a better bioavailability to the molecules bearing this group.[1b,4] Thus, such trifluoromethylated molecules find outstanding applications in the pharmaceutical field,[5] as illustrated by Efavirenz (anti-HIV)[6] and Celecoxib (anti-arthritic),[7] two recent drugs used in the treatment of human diseases.

However, despite this growing interest in trifluoromethylated substrates, methods for obtaining them are still scarce, and the development of new fluorinated building-blocks is always required.

In our search for the synthesis of fluorinated analogs of bioactive compounds, we were interested in the synthesis of trifluoromethylated cyclitols with the aim of improving their biological properties.[8] The retrosynthetic strategy started from trifluoromethylated cyclohexenones (Figure 1), all the more so, since such compounds also constitute valuable fluorinated building-blocks for other syntheses.[9]

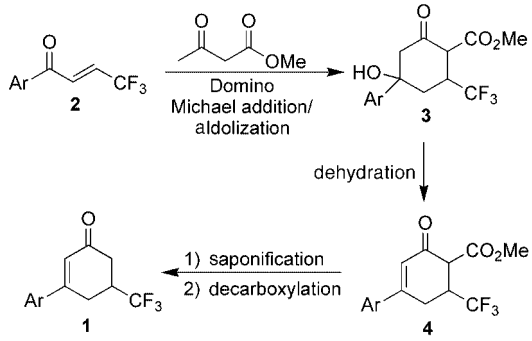
To the best of our knowledge, the sole syntheses described in the literature involve Diels–Alder reactions with trifluoropropenes[10a] or β-trifluoromethylated acrylate,[10b] and, usually, the resulting compounds do not bear any substituents at position 3.




**1**

Figure 1. Trifluoromethylated cyclohexenones.

Since we previously described an easy and rapid synthesis of β-trifluoromethylated enones,[11] we started from them to prepare the expected cyclohexenones, through a Michael addition/aldolization/dehydration domino sequence followed by saponification and decarboxylation (Scheme 1).




Scheme 1. Synthesis of **1** starting from **2**.

This strategy has been applied to **2a** (Scheme 2). In the first step, an organic base and $CH_2Cl_2$ (as solvent) have been preferred to more conventional conditions (EtONa in EtOH).

It should be noted that a catalytic amount of DBU was sufficient to consume **2a** completely within 5 h at room temperature. More surprisingly, the expected products **3a** or **4a** were not obtained, and the only product, formed in a good yield, was the cyclohexenone **1a**.

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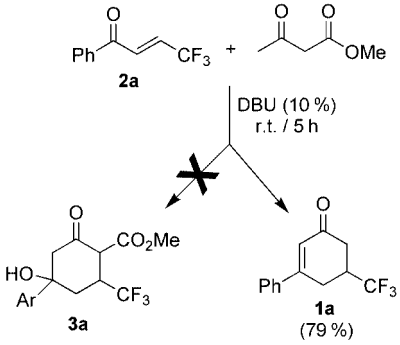
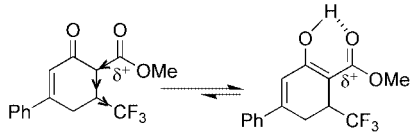



Scheme 2. Reaction of 2**a** with methyl acetoacetate.

This result led us to suppose that the five envisaged reactions occurred in a base-catalyzed domino process. The more astonishing fact is that decarboxylation took place at room temperature. Thus, the following mechanism can be proposed to explain this reaction cascade (Scheme 3).

It appears clearly that a catalytic amount of base is only needed since its conjugated acid (DBU-H$^+$) reprotonates the subsequent anions, regenerating DBU. Saponification is certainly realized in the medium by the HO$^-$ anion which was released during the $E_1cb$ dehydration step. Decarboxylation can be then facilitated, even at room temperature, through the six-membered ring transition-state assisted by DBU-H$^+$.

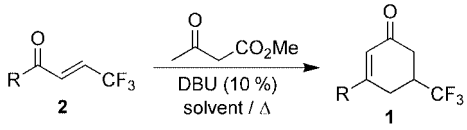
The influence of fluorine atoms in such reactions is not yet clear. Probably, the strong electron-withdrawing character of the $CF_3$ moiety activates the carboxyl group and, then, favors saponification. The presence of the $CF_3$ group could also displace the keto–enol equilibrium towards the enol form which is able to activate the carboxyl function by hydrogen bonding (Scheme 4). Nevertheless, such an assumption must be confirmed and ab initio calculations are planned.




Scheme 4. Possible activation by the $CF_3$ moiety.

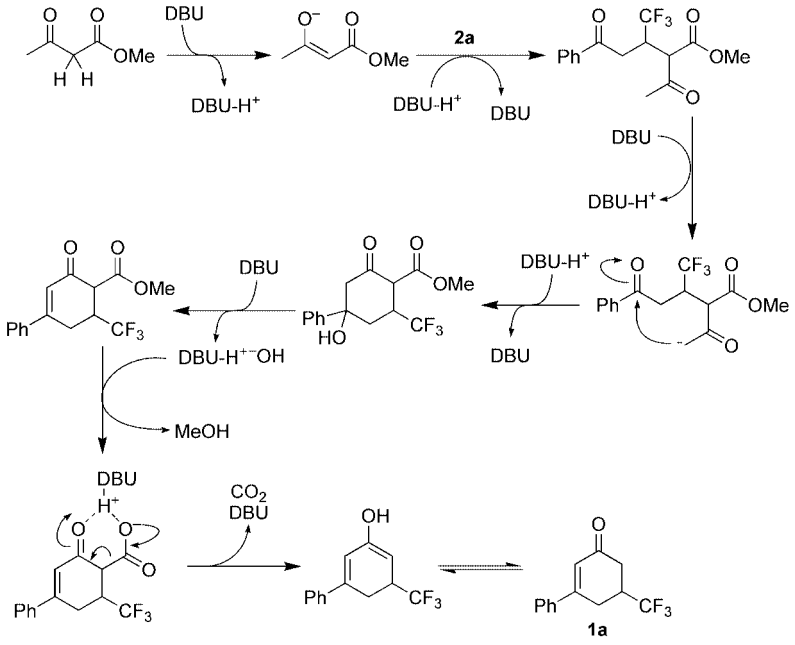
The yield of the overall reaction can be increased at higher temperatures (Table 1, entries 1–3); heating certainly improves the decarboxylation step that should logically be the rate-determining step.

Table 1. Synthesis of **1**.




| Entry | **2** | Solvent/$T$ [°C] | $t$ | **1**[a] [%] |
|---|---|---|---|---|
| 1 | **2a** | $CH_2Cl_2$/room temp. | 5 h | **1a**: 60 (79) |
| 2 | **2a** | $CH_2Cl_2$/50 | 5 h | **1a**: 60 (90) |
| 3 | **2a** | Toluene/110 | 5 h | **1a**: 70 (99) |
| 4 | **2b** | Toluene/110 | 5 h | **1b**: 61 (95) |
| 5 | **2c** | $CH_2Cl_2$/room temp. | 2d | **1c**: (35) |
| 6 | **2c** | $CH_2Cl_2$/50 | 2d | **1c**: (45) |
| 7 | **2c** | Toluene/110 | 2d | **1c**: 55 (77) |
| 8 | **2d** | Toluene/110 | 7d | **1d**: 65 (80) |

[a] Isolated yields. In parentheses, crude yields determined by $^{19}F$ NMR spectroscopy with standard $PhOCF_3$.




Scheme 3. Mechanism for the formation of **1a**.

Other cyclohexenones (**1b–d**) have been synthesized in the same way, starting from various β-trifluoromethylated enones **2b–d** (Figure 2 and Figure 3, Table 1).

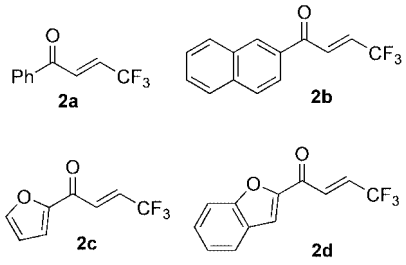



Figure 2. β-Trifluoromethylated enones.

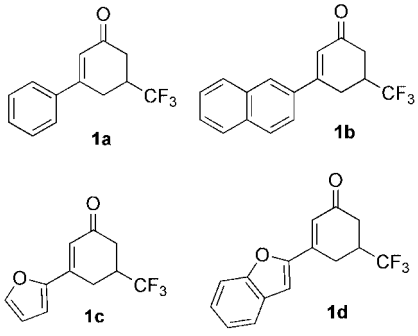
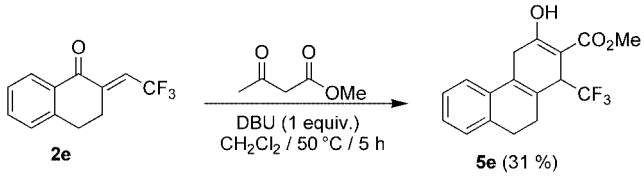



Figure 3. 5-Trifluoromethylated cyclohexenones.

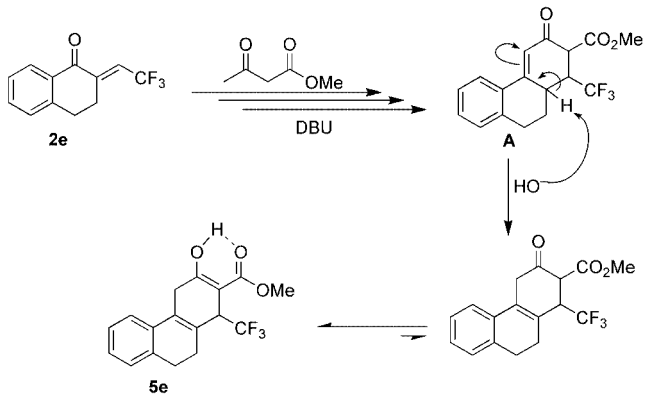
The reactions generally gave good yields, though in the case of heteroaromatic enones (**2c**,**d**), longer reaction times were required. In these latter cases, analyses of the reaction mixtures have shown that the Michael reaction (first step) was rapid (detection of the rapid formation of a 50:50 mixture of the two diastereomers of the Michael adduct with **2c**, which disappear to form **1c)** whereas the aldolization step was the limiting step, essentially because of the lower reactivity of the carbonyl function in **2c**,**d**.

However, when the reaction was carried out with enone **2e**, arising from tetralone, the expected cyclohexenone was not obtained. Furthermore, this reaction was not as clean as the previous ones and required 1 equiv. of DBU for a total conversion of **2e**. Nevertheless, **5e** was formed as the major product (Scheme 4 and Scheme 5).




Scheme 5. Reaction of **2e**.

This product (**5e**) was only obtained at 50 °C, since heating to 110 °C led to a complex mixture. The enol form is the only detected tautomer, certainly because of the increased acidity of the hydrogen atom in the α position to $CO_2Me$, due to the $CF_3$ group, and because of the stabilization by an H bond with the carboxyl moiety. The formation of such compounds can be rationalized as shown in Scheme 6.




Scheme 6. Mechanism of the formation of **5e**.

Following the previous mechanism (Scheme 3), intermediate **A** was formed after a Michael addition/aldolization/dehydration sequence and an $HO^-$ ion was released. This was expected to saponify the ester group and induce decarboxylation but, in the case of **A**, the allylic position can be deprotonated to promote the isomerisation of the double bond to give a more substituted one. Thus, the saponification was not facilitated and decarboxylation did not occur.

In conclusion, we have described a rapid and efficient route to trifluoromethylated cyclohexenones which are valuable building blocks for further syntheses. This method constitutes an interesting example of a base-catalyzed, five-step domino reaction. Although this strategy has been only applied to aromatic enones, considering the proposed mechanism, the presence of the aromatic substituent seems not to be essential. The use of such trifluoromethylated building-blocks in the syntheses of potential bioactive compounds are in progress and will be described in due course.

## Experimental Section

**General:** $CH_2Cl_2$ and toluene were dried over molecular sieves before use. Other reagents were used as received. NMR spectra were recorded with a Bruker Avance 300 instrument. $^1H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded in $CDCl_3$ at 300, 75 and 282 MHz, respectively. Chemical shifts are given in ppm relative to TMS ($^1H$, $^{13}C$) or $CFCl_3$ ($^{19}F$) as internal reference. Coupling constants are given in Hertz. Flash chromatography was performed on silica gel 60 M (0.04–0.063 mm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

**Synthesis of β-Trifluoromethylated Enones 2**: The β-trifluoromethylated enones were synthesized as described previously.[11] Compounds **2a** and **2e** have already been described.[11]

**(2E)-4,4,4-Trifluoro-1-(2-naphthyl)but-2-en-1-one (2b):** White solid. M.p. 68–70 °C. $^1H$ NMR: $\delta$ = 8.42 (s, 1 H), 7.86–8.05 (m, 4 H), 7.55–7.72 (m, 3 H), 6.90 (dq, $J$ = 15.3, $J$ = 6.8 Hz, 1 H) ppm. $^{13}C$ NMR: $\delta$ = 188.0, 136.4; 133.9, 132.8, 131.40, 131.40 (q, $J$ = 5.7 Hz), 130.5 (q, $J$ = 35.1 Hz), 130.1, 129.6, 129.4, 128.3, 127.6, 124.3, 123.1 (q, $J$ = 270.2 Hz) ppm. $^{19}F$ NMR: $\delta$ = –65.35 (dd, $J$ = 6.8, $J$ = 2.3 Hz) ppm. $C_{14}H_9F_3O$ (250): calcd. C 67.20, H 3.63; found C 67.04, H 3.72.

**(2E)-4,4,4-Trifluoro-1-(2-furyl)but-2-en-1-one (2c):** White solid. M.p. 64–66 °C. $^1H$ NMR: $\delta$ = 7.67 (dd, $J$ = 1.6, $J$ = 0.6 Hz, 1 H),

7.37 (dq, $J$ = 15.6, $J$ = 2.1 Hz, 1 H), 7.36 (dd, $J$ = 0.6, $J$ = 3.5 Hz, 1 H), 6.83 (dq, $J$ = 15.6, $J$ = 6.8 Hz, 1 H), 6.60 (dd, $J$ = 1.6, $J$ = 3.5 Hz, 1 H) ppm. $^{13}$C NMR: $\delta$ = 175.5, 152.8, 148.4, 130.8 (q, $J$ = 5.9 Hz), 130.0 (q, $J$ = 35.3 Hz), 122.9 (q, $J$ = 270.0 Hz), 120.1, 113.5 ppm. $^{19}$F NMR: $\delta$ = –65.78 (dd, $J$ = 6.8, $J$ = 2.1 Hz) ppm. $C_8H_5F_3O_2$ (190): calcd. C 50.54, H 2.65; found C 50.75, H 2.52.

**(2E)-1-(1-Benzofuran-2-yl)-4,4,4-trifluorobut-2-en-1-one (2d):** Yellow solid. M.p. 73–75 °C. $^1$H NMR: $\delta$ = 7.73 (bdd, $J$ = 7.9, $J$ = 1.0 Hz, 1 H), 7.65 (d, $J$ = 0.8 Hz, 1 H), 7.45–7.62 (m, 3 H), 7.34 (ddd, $J$ = 7.9, $J$ = 6.9, $J$ = 1.1 Hz, 1 H), 6.94 (qd, $J$ = 6.8, $J$ = 15.6 Hz, 1 H) ppm. $^{13}$C NMR: $\delta$ = 177.5, 156.6, 152.5, 130.7 (q, $J$ = 5.5 Hz), 130.5 (q, $J$ = 35.5), 129.7, 127.3, 124.8, 124.0, 122.9 (q, $J$ = 270.2 Hz), 115.8; 112.96 ppm. $^{19}$F NMR: $\delta$ = –65.59 (dd, $J$ = 6.8, $J$ = 2.3 Hz) ppm. $C_{12}H_7F_3O_2$ (240): calcd. C 60.01, H 2.94; found C 60.12, H 3.22.

**Synthesis of Trifluoromethylated Cyclohexenones 1**: Methyl acetoacetate (110 μL, 1 mmol) was added to a solution of **2** (1 mmol) in $CH_2Cl_2$ (1 mL) [or toluene]. DBU (15 μL, 0.1 mmol) was then added, and the mixture was stirred at the required temperature. The reaction mixture was washed with brine, dried over $MgSO_4$, and the solvents evaporated in vacuo. The crude product was purified by flash chromatography.

**3-Phenyl-5-(trifluoromethyl)cyclohex-2-en-1-one (1a):** White solid. M.p. 70–72 °C. $^1$H NMR: $\delta$ = 7.42–7.57 (m, 5 H), 6.48 (s, 1 H), 2.72–3.10 (m, 4 H), 2.50 (m, 1 H) ppm. $^{13}$C NMR: $\delta$ = 195.9, 156.8, 138.0, 131.0, 129.4, 126.8 (q, $J$ = 278.5 Hz), 126.6, 125.6, 39.7 (q, $J$ = 28.4 Hz), 36.0 (q, $J$ = 2.2 Hz), 27.2 (q, $J$ = 2.7 Hz) ppm. $^{19}$F NMR: $\delta$ = –74.00 (d, $J$ = 6.9 Hz). $C_{13}H_{11}F_3O$ (240): calcd. C 65.00, H 4.62; found C 65.20, H 4.58.

**3-(2-Naphthyl)-5-(trifluoromethyl)cyclohex-2-en-1-one (1b):** White solid. M.p. 94–96 °C. $^1$H NMR: $\delta$ = 7.95 (s, 1 H), 7.80–7.91 (m, 3 H), 7.50–7.61 (m, 3 H), 6.59 (br. s, 1 H), 3.11 (d, $J$ = 13.0 Hz, 1 H), 2.71–2.99 (m, 3 H), 2.48 (dd, $J$ = 16.2, $J$ = 13.6 Hz, 1 H) ppm. $^{13}$C NMR: $\delta$ = 195.8, 156.2, 135.0, 134.6, 133.4, 129.20, 129.15, 128.1, 128.0, 127.4, 126.9 (q, $J$ = 278.7 Hz), 126.8, 125.7, 123.4, 39.7 (q, $J$ = 28.4 Hz), 36.0 (q, $J$ = 2.2 Hz), 27.0 (q, $J$ = 2.9 Hz) ppm. $^{19}$F NMR: $\delta$ = –73.86 (d, $J$ = 6.9 Hz) ppm. $C_{17}H_{13}F_3O$ (290): calcd. C 70.34, H 4.51; found C 70.27, H 4.73.

**3-(2-Furyl)-5-(trifluoromethyl)cyclohex-2-en-1-one (1c):** White solid. M.p. 87–91 °C. $^1$H NMR: $\delta$ = 7.58 (d, $J$ = 1.5 Hz, 1 H), 6.83 (d, $J$ = 3.6 Hz, 1 H), 6.51–6.58 (m, 2 H), 2.82–3.04 (m, 2 H), 2.62–2.78 (m, 2 H), 2.47 (dd, $J$ = 16.5, $J$ = 13.3 Hz, 1 H) ppm. $^{13}$C NMR: $\delta$ = 195.5, 151.5, 146.1, 144.2, 126.7 (q, $J$ = 278.5 Hz), 120.9, 113.9, 113.1, 39.4 (q, $J$ = 28.5 Hz), 36.2 (q, $J$ = 2.2 Hz), 24.6 (q, $J$ = 2.9 Hz) ppm. $^{19}$F NMR: $\delta$ = –74.10 (d, $J$ = 6.9 Hz) ppm. $C_{11}H_9F_3O_2$ (230): calcd. C 57.40, H 3.94; found C 57.48, H 4.04.

**3-(1-Benzofuran-2-yl)-5-(trifluoromethyl)cyclohex-2-en-1-one (1d):** Yellow solid. M.p. 105–108 °C. $^1$H NMR: $\delta$ = 7.62 (m, 1 H), 7.51 (m, 1 H), 7.41 (m, 1 H), 7.28 (m, 1 H), 7.14 (br. s, 1 H), 6.76 (bd, $J$ = 2.2 Hz, 1 H), 2.85–3.12 (m, 2 H), 2.68–2.84 (m, 2 H), 2.51 (dd, $J$ = 13.0, $J$ = 16.5 Hz, 1 H) ppm. $^{13}$C NMR: $\delta$ = 195.53, 156.08, 152.91, 144.32, 128.44, 127.56, 126.69 (q, $J$ = 278.4 Hz), 124.06, 123.23, 122.40, 112.03, 110.02, 39.36 (q, $J$ = 28.7 Hz), 36.30 (q, $J$ = 2.1 Hz), 24.59 (q, $J$ = 3.1 Hz) ppm. $^{19}$F NMR: $\delta$ = –74.00 (d, $J$ = 7.3 Hz) ppm. $C_{15}H_{11}F_3O_2$ (280): calcd. C 64.29, H 3.96; found C 64.17, H 4.05.

**Synthesis of Methyl 3-Hydroxy-1-(trifluoromethyl)-1,4,9,10-tetrahydrophenanthrene-2-carboxylate (5e):** Methyl acetoacetate (110 μL, 1 mmol) was added to a solution of **2e** (1 mmol) in $CH_2Cl_2$ (1 mL) [or toluene]. DBU (150 μL, 1 mmol) was then added, and the mixture was stirred at 50 °C. The reaction mixture was washed with brine, dried over $MgSO_4$, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography. Yellow solid. M.p. 62–69 °C. $^1$H NMR: $\delta$ = 12.60 (br. s, 1 H), 7.21–7.32 (m, 4 H), 4.17 (m, 1 H), 3.89 (s, 3 H), 3.41 (AB system, $J$ = 21.2 Hz, 2 H), 2.85 (m, 2 H), 2.66 (m, 1 H), 2.36 (m, 1 H) ppm. $^{13}$C NMR: $\delta$ = 175.3, 171.6, 136.3, 134.0, 130.1, 128.00, 127.96, 127.5 (q, $J$ = 1.3 Hz), 127.3 (q, $J$ = 283.6 Hz), 127.1, 122.9, 93.1 (q, $J$ = 2.6 Hz), 5.3, 45.9 (q, $J$ = 28.2 Hz), 31.8, 29.3 (q, $J$ = 1.8 Hz), 28.6 ppm. $^{19}$F NMR: $\delta$ = –70.44 (d, $J$ = 8.03 Hz) ppm. $C_{17}H_{15}F_3O_3$ (324): calcd. C 62.96, H 4.66; found C 63.25, H 4.51.

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