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Synthesis of 5-(trifluoromethyl)cyclohexane-1,3-dione and 3-amino-5-(trifluoromethyl)cyclohex-2-en-1-one: new trifluoromethyl building block

Olugbeminiyi O. Fadeyi, Cosmas O. Okoro *

Department of Chemistry, Tennessee State University, 3500 John A. Merritt Blvd., Nashville, TN 37209-1561, USA

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ABSTRACT

A simple synthesis of 5-(trifluoromethyl)cyclohexane-1,3-dione and 3-amino-5-(trifluoromethyl)cyclohex-2-en-1-one from the sodium salt of methyl or ethyl-4-hydroxy-2-oxo-6-(trifluoromethyl)cyclohex-3-en-1-oate is demonstrated. The compounds represent highly functionalized reactive intermediates for the synthesis of organic and heterocyclic compounds containing a trifluoromethyl group.

Fluorine-building blocks are important because of their extensive use in the synthesis of drugs covering a wide variety of therapeutic areas. A fluorine atom is similar in size to a hydrogen atom. Therefore, the replacement of hydrogen by fluorine is expected not to cause any significant alteration in molecular geometry and shape.[1] The high electronegativity of fluorine has a major effect on the electronic properties of the basic molecules. On a molecular level this allows for the inhibition of some metabolic pathways, including the modulation of membrane permeability, as well as electrostatic interactions with the target site.[2] From a physiological standpoint, better bioavailability and enhanced selectivity for the target site can be achieved. In addition, a much lower dose of a fluorinated drug is often needed in some cases, compared to the unfluorinated ones. We are particularly interested in trifluoromethyl-containing pharmaceuticals, since they are present in many commercially available drugs. In medicinal chemistry, the trifluoromethyl group is similar in size to a chloro-group and can often be used interchangeably, without loss in biological activity. Although, several trifluoromethyl building blocks are commercially available, many of them are expensive. Therefore, several laboratories are engaged in the synthesis of these important trifluoromethyl 'carrier reagents'.[3–8] For example, the trifluoromethyl group has been successfully used as a probe for the hydrophobic binding site in human thymidylate synthase.[9] As a strong electron-withdrawing group at the 3 position of tetrahydroisoquinoline (THIQ), Grunewald and co-workers reported that the trifluoromethyl group decreased the affinity of THIQ for the α_2-adrenoceptor versus human phenylethanolamine N-methyltransferase (hPNMT).[10]

The non-fluorinated 3-aminocyclohexenone, a cyclic enaminone and 1,3-cyclohexandione constitute interesting building blocks for further functionalization by various reactions. Indeed such substrates are well-known synthons in the synthesis of complex natural product. Consequently, such trifluoromethylated cyclic compounds should constitute very effective building blocks as starting material in the synthesis of fluorinated molecules.

Presently, there are few reports of compounds containing the trifluoromethyl group on a cycloalkyl or heterocyclic rings. Some of these include 3-phenyl-5-(trifluoromethyl) cyclohex-2-en-1-one,[11] 3-trifluoromethyl THIQ,[10] and 2-trifluoromethyl-1-(substituted phenyl)-4-(1*H*) quinolones.[12]

In a previous Letter, we reported the synthesis of fluorinated cyclic *s-trans* vinylogous acid and amide ester derivatives,[13] which was accompanied by unexpected by-products **1** and **2**.

We undertook an in-depth study of the above reaction in order to establish the mechanism underpinning the formation of the by-product.

Reaction of keto-ester **3** with Michael acceptor **4** in the presence of sodium alkoxide in refluxing alcohol afforded the sodium salt of methyl or ethyl-4-hydroxy-2-oxo-6-(trifluoromethyl)cyclohex-3-en-1-oate **5** and the diester **1** (Scheme 1).[14]

Our studies led us to propose the plausible mechanism for the formation of **1**. The mechanism appears to involve the intermediate Michael adducts **6**, in which the keto-carbonyl carbon of the intermediate undergoes a nucleophilic attack by a methoxide or

* Corresponding author. Tel.: +1 615 963 5332; fax: +1 615 963 5326.
E-mail address: cokoro@tnstate.edu (C. O. Okoro).

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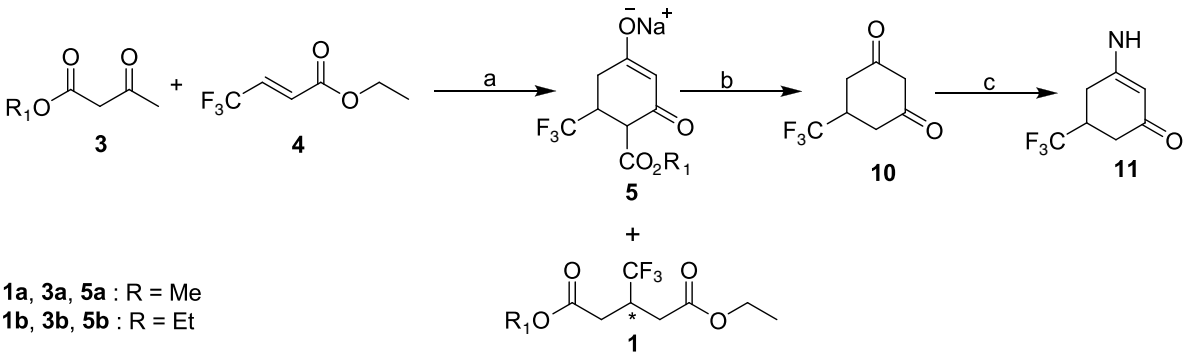


Scheme 1. Synthesis of highly functionalized fluorinated building blocks **1**, **10**, and **11**.[14] Reagents and conditions: (a) base, solvent, reflux. 7 h; (b) 5 M NaOH, H_2O, Heat, 1 h; (c) $NH_4(OAc)$, xylene, reflux, 3 h.

ethoxide ion to give a tetrahedral intermediate that collapses to give the ester **1** with the loss of methyl or ethyl acetate (Scheme 2).

It should be noted that when Michael acceptor **7** is used, ethyl-3-(cyanomethyl)-4,4,4-trifluorobutanoate**8** was formed along with desired product enaminone **9** (Scheme 3).[13]

Its formation is presumed to occur via earlier proposed mechanism (Scheme 2).

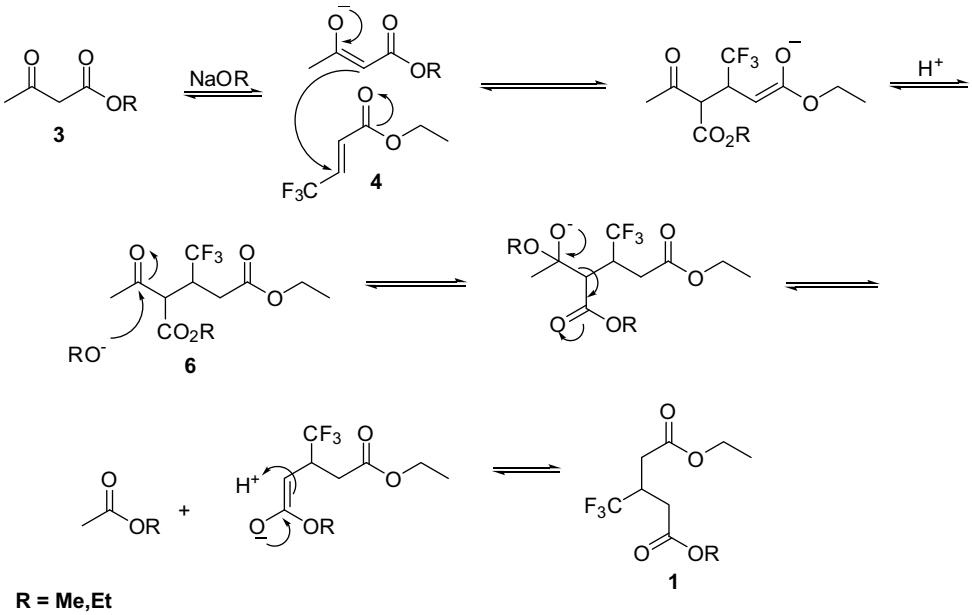
No by-product was observed when *tert*-butoxide, a stronger base and poorer nucleophile, was used. In addition, higher yield of the desired product was obtained compared to methoxide and ethoxide, respectively (Table 1).[14]

It should be mentioned that when excess alcohol is used in the presence of alkoxide, better yield of the desired product was observed, along with the by-product. The presence of excess alcohol presumably decreased the nucleophilicity of the alkoxide. However, since the reactive site of the intermediate is highly electrophilic (Fig. 1), the formation of the by-product is unavoidable when methoxide or ethoxide is used as base.

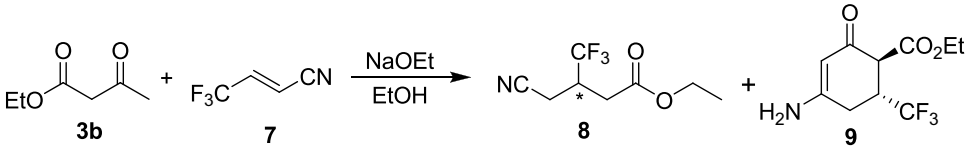
Although low yield was obtained after long reaction time when NaH or DBU was used, the by-product was not detected (Table 1).

We note that no analogous by-product was reported by other laboratories when a non-fluorinated Michael acceptor is employed. Thus the observed by-product may be unique to the strong electron-withdrawing character of the CF_3 moiety, which activates the keto-carbonyl carbon of the Michael adduct intermediate **6** (Fig. 1) and favors nucleophilic attack to this highly reactive site (Scheme 2).

We then concentrated on the removal of the ester functionality. Treatment of the sodium salt **5** with 5 M NaOH led to the dianion of methyl or ethyl-4-hydroxy-2-oxo-6-(trifluoromethyl)cyclohex-3-



Scheme 2. Proposed mechanism for the formation of fluorinated diester **1**.

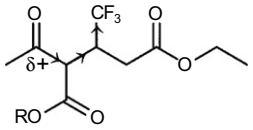


Scheme 3.[13]

Table 1
Formation of desired cyclohexandione **10** and by-product pentanedioate **1**

Keto-ester	Base (equiv)	Solvent	Yield[b] (%)	
			1	**10**
1a	MeONa (1.0 equiv)	MeOH	28[a] **1a**	20
1b	EtONa (1.0 equiv)	EtOH	39 **1b**	26
1a	^{t}-BuONa (1.0 equiv)	^{t}-BuOH	0	45
1a	NaH (1.2 equiv)	THF	0	5.6
1a	DBU (10%)	CH_2Cl_2	0	9.2
1a	DBU (10%)	Toluene	0	12

[a] Due to transesterification caused by ethoxide ion, **1b** was formed in 7% yield.
[b] Isolated yields.



6

R= Me, Et

Figure 1. Possible activation by the CF_3 moiety.

en-1-oate, followed by heating in water gave moderate yield of 5-(trifluoromethyl)cyclohexane-1,3-dione **10** as stable white solids (Scheme 1).[14]

We note that attempted hydrolysis and decarboxylation under strong acid or strong base conditions, including the use of lithium hydroxide in tetrahydrofuran, led to ring-opened product. The resulting 5-(trifluoromethyl)cyclohexane-1,3-dione was easily converted to 3-amino-5-trifluoromethyl)cyclohex-2-en-1-one via azeotropic removal of water using a dean Stark trap (Scheme 1), as reported by Manfredini and co-workers.[15,16]

In summary, two six-membered trifluoromethyl building blocks have been prepared as novel synthetically useful intermediates. The use of these compounds for the synthesis of various heterocycles, including anticancer and anticonvulsant agents is in progress and will be reported in specialized journals.

Acknowledgments

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14. *Procedure for 5-(trifluoromethyl)cyclohexane-1,3-dione* **10**: Keto-ester **3** (1 mmol) was added to a mixture of sodium alkoxide freshly prepared from sodium metal (1 mmol) in 3 ml of absolute dry alcohol. The mixture was stirred for 40 min; 4,4,4-trifluoromethyl crotonate **4** (1 mmol) was added dropwise, and the mixture was stirred for additional 15 min at room temperature. The mixture was refluxed for 6–8 h. The mixture was evaporated and the sodium salt was dissolved in 10 ml of water, which was extracted with CH_2Cl_2 (5 × 10 ml). Into the aqueous layer was added 2 ml of 5 M NaOH. The mixture was refluxed for 1 h and allowed to cool to room temperature. The cooled mixture was acidified with 2 M H_2SO_4 and then extracted with EtOAc, the combined organic layer was dried over anhydrous $MgSO_4$ and solvent removed under reduced pressure to give white solid, which was recrystallized from EtOAc/Hexane to give **10** as white solid. Mp: 140–142 °C; IR (*nujol*): 2922, 2720, 1716, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.25 (m, 1H), 2.36–2.391 (d, 4H), 3.42 (s, 2H), 5.23 (s, 1H). EIMS *m*/*z*; 42 (100%), 69 (40%), 123 (20%), 152 (90%), 180 (12.5%), (M^+). Elemental analysis ($C_7H_7F_3O_2$), Mw: 180.12; calcd: C (46.68), H (3.92). Found: C (46.86), H (3.96).
Spectral analysis of by-products: Compound **1a**, *1-Ethyl-5-methyl 3-(trifluoromethyl)-pentanedioate*: Colorless oil. Bp: 88.7 °C; IR (*nujol*): 2957.56, 2925.18, 2853.77, 1748.53, 1440.22 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, t, *J* = 7.01 Hz), 2.45 (2H, dd, *J* = 16.2, 7.49 Hz), 2.57 (2H, dd, *J* = 16.2, 5.79 Hz), 3.20 (1H, m), 3.6 (3H, s), 4.01 (2H, q, *J* = 7.01 Hz). EIMS *m*/*z*; 42 (17%), 123 (19%), 169 (68%), 197 (100%), 211 (30%) 242 (60%) (M^+). Elemental analysis ($C_9H_{13}F_3O_4$), Mw: 242.19; calcd: C (44.63), H (5.41). Found: C (45.11), H (5.77).
Compound **1b**, *Diethyl-3-(trifluoromethyl)-pentanedioate*: Colorless oil. Bp: 95.1 °C; IR (*nujol*): 2970.22, 2949.35, 2922.06, 2862.71 1745.39, 1451.13 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, *J* = 7.12 Hz), 2.50 (2H, dd, *J* = 16.3, 7.52 Hz), 2.62 (2H, dd, *J* = 16.3, 5.8 Hz), 3.30 (1H, m), 4.12 (4H, q, *J* = 7.11 Hz). EIMS *m*/*z*; 42 (10%), 115 (9%), 182 (22%), 210 (9%), 211 (100%), 256 (12%) (M^+). Mw: 256.22. HRMS[17]
Compound **8**, *Ethyl-3-(cyanomethyl)-4,4,4-trifluorobutanoate*: Yellow oil; IR (*nujol*): 2957.56, 2925.18, 2853.77, 1748.53,1440.22 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, *J* = 7.9 Hz) 2.5 (2H, dd, *J* = 16.8, 8.1 Hz), 2.7 (2H, dd, *J* = 16.8, 6.2 Hz), 3.4 (1H, m), 4.14 (2H, q, *J* = 7.9 Hz). EIMS *m*/*z*; 42 (7%), 123 (20%), 169 (18%), 209 (100%) (M^+).
Elemental analysis ($C_8H_{10}F_3NO_2$), Mw: 209.16; calcd: C (45.94), H (4.82), N (6.70). Found: C (46.33), H (4.75), N (6.49).
15. *Procedure for 3-amino-5-(trifluoromethyl)cyclohex-2-en-1-one***11**: 5-trifluoromethyl-cyclohex-1,3-dione **10** (1 mmol) and ammonium acetate (1 mmol) in 10 ml of xylene was refluxed with the separation of water using a Dean Stark trap. After about 3 h the reaction was cooled and evaporated to give yellow oil. Recrystallizations with xylene afforded **11** in 89% yield as yellow solid. Mp: 160–162 °C; IR (*nujol*) 3289, 3195, 1659, 1459 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27 (m, 1H), 2.36–2.391 (d, 4H), 5.01 (s, 1H), 6.9 (br s, 2H). EIMS *m*/*z*; 42 (27%), 82 (100%), 162 (12.5%), 178 (85%), 179 (27%), (M^+).
Elemental analysis ($C_7H_8F_3NO$), Mw: 179.14; calcd: C (46.93), H (4.50), N (7.82). Found: C (47.40), H (4.45), N (7.41).
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