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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7451–7454

Synthesis of fluorinated cyclic *s-trans* vinylogous acid and amide ester derivatives

Cosmas O. Okoro,* Olugbeminiyi O. Fadeyi, Patrice L. Jackson, Rhonda L. Richmond and Takeisha Farmer

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

Received 6 June 2006; revised 11 August 2006; accepted 14 August 2006

Abstract—A two-step procedure for the preparation of ethyl 4-amino-2-oxo-6-(trifluoromethyl)cyclohex-3-ene-1-carboxylate (enaminone) and methyl 4-hydroxy-2-oxo-6-(trifluoromethyl)cyclohex-3-ene-1-carboxylate (vinylogous acid) has been accomplished, using reactive Michael acceptors under basic condition. In addition, acyclic trifluoromethylated ester derivatives were isolated as competing by-products. The above compounds represent novel synthetically useful trifluoromethyl building blocks.

The high electronegativity and lipophilicity of trifluoromethyl moiety make trifluoromethylated molecules attractive, especially for biological applications. These include Efavirez (Anti-HIV),[1] Celecoxib (anti-arthritic),[2] Flutamide, Nilutamide (Prostatic cancer treatment),[3] Fluphenazine (Antipsychotic),[4] Tolrestat (Aldose reductive inhibitor),[5] and Fluoxetine (Antidepressant).[6] In addition, most trifluoromethyl substituted compounds have relatively low toxicity and high stability compared to the monofluoromethyl and difluoromethyl analogs.[7] Despite the interest in trifluoromethylated molecules, methods for their synthesis remain scarce. Thus the development of new methods for their synthesis is in continuous demand. The most general preparative route to trifluoromethylated compounds appear to be by direct introduction of a nucleophilic trifluoromethyl anion onto the desired molecules. Unfortunately, the above approach is somewhat inefficient, because reagents that would stabilize the unstable trifluoromethyl anion[8] are not readily available.

Recently, we have become interested in the synthesis of fluorinated analogs of biologically active compounds. Cyclic vinylogous acids and amides are useful intermediates in organic synthesis as synthons for the design of biologically active compounds, functionally interesting heterocyclic compounds,[9] and efficient building blocks for the synthesis of natural products.[10]

Some examples of biologically active compounds that contain the vinylogous acid and amide moieties are shown in Scheme 1. They include antibacterial[11] **1**, anticonvulsant[12] **2**, K_{ATP} channel openers[13] **3**, antitumor agent[14] **4**, hydroxyphenylpyruvate dioxygenase (4-HPPD) inhibitor[15] **5**, dopamine autoreceptor agonists,[16] acetyl cholinesterase inhibitors,[17] antiparasitic,[18] and oxytocin antagonists.[19]

Although the literature is replete with several reports of the synthesis of acyclic vinylogous acids and amides, the more stable cyclic *s-trans* analogs are less studied. We are particularly interested in the synthesis of new and conformationally-restricted analogs containing a trifluoromethyl group on a cycloalkenone ring. Herein, we delineate our efforts in the synthesis of trifluoromethylated vinylogous acid and amide using ethyl 4,4,4-trifluorocrotonate **7b** and trifluorocrotonitrile **7a**, respectively. The reaction of the above acceptors with methyl and ethyl acetoacetates **6** in base provided the hitherto unreported trifluoromethylated cyclic *s-trans* vinylogous acids **9** and amides **8**.

The enolate generated by treatment of commercially available β-keto-ester **6** with freshly prepared sodium alkoxide was allowed to react with **7a** and **7b**, respectively, to obtain trifluoromethylated cyclohexenone **8**–**9**, as *s-trans* isomer[20] (Scheme 2). The reaction was judged to be complete in 6–18 h by TLC and GC/MS.

Keywords: Trifluoromethyl; Cyclic enaminone; *s-trans*; MOPAC; Vinylogous; Michael acceptors.
* Corresponding author. Tel.: +1 615 963 5332; fax: +1 615 963 5326; e-mail: cokoro@tnstate.edu

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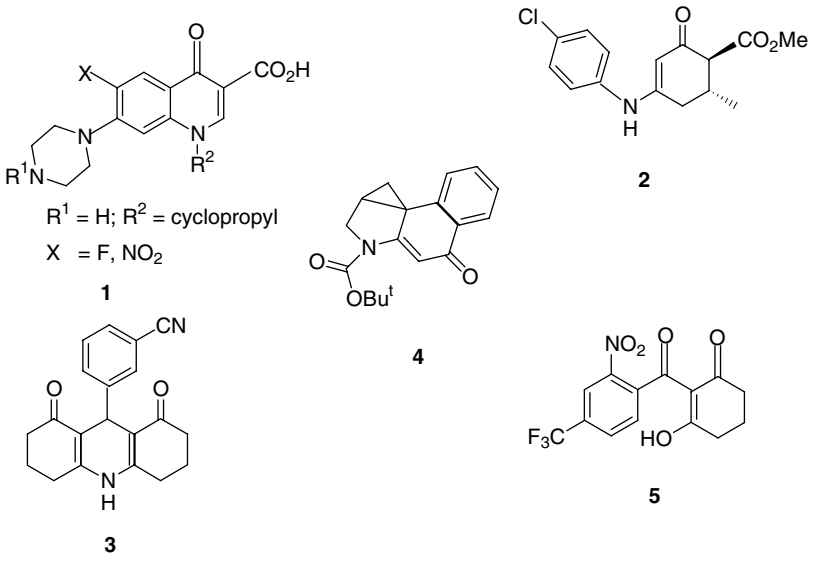
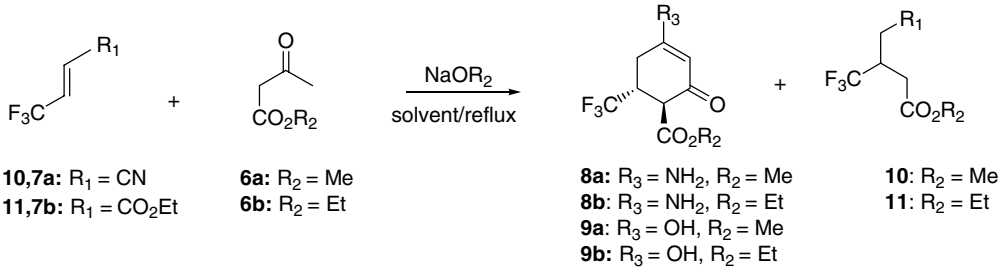
doi:10.1016/j.tetlet.2006.08.046



Scheme 1.



Scheme 2.

The reaction conditions and product yields are summarized in Table 1.

In using 4,4,4-trifluorocrotonitrile **7a** and ethyl 4,4,4-trifluorocrotonate **7b**, it was noted that the reaction time was significantly longer than that obtained when using a nonfluorinated prototype, as reported by Scott and Friary.[21] In order to explain the longer reaction time prior to optimization of the reaction, we performed MOPAC[22] calculations on **7a** and **7b**, along with its nonfluorinated prototypes **7c** and **7d** (Fig. 1).

Significantly lower LUMO energies for **7a** and **7b** were recorded. On the other hand, the nonfluorinated prototypes **7c** and **7d** showed much higher LUMO energies, (Fig. 1), which could explain the higher reactivity of **7a** and **7b**.

Therefore, the Michael addition step proceeds at a faster rate due to the higher reactivity of **7a** and **7b**. Thus, the prolonged reaction time may be due to the presence of strongly electron-withdrawing groups on the intermediate leading to the cyclized adducts. This could account for the low yield of **8** (entries 1 and 2).

The use of anhydrous ethanol or methanol was found to favor the yield of cyclic vinylogous acid **9** (entries 7 and 8), over dichloromethane, which gave lower yield of cyclic vinylogous amide **8** (entries 3 and 4). In order to improve the yield of compound **9**, and to minimize extensive purification, the sodium salt of **9** was first isolated and then acidified to give cyclohexanecarboxylate in better yield. The reaction of **7b** gave mixtures of products containing fluorinated cyclohexanecarboxylate **9**. Due to transesterification reaction, **9b** was formed along with **9a**, as shown in entry 7 of Table 1; this was also observed previously by Foster et al. while using **7d** as a Michael acceptor.[23] Purification of this mixture by column chromatography gave a single pure product assigned as compound **9** by NMR and GC/MS. However, in the case of **7a** the fluorinated cyclohexenecarboxylate **8** was obtained as two isomers which could not be separated by column chromatography (see spectral analyzes in the reference section).

The initial reaction of **7a** or **7b** with acetoacetic ester **6** was expected to follow the normal course of Michael addition reaction to form the intermediate **12** (Scheme 3). However, the reaction could proceed via nucleophilic acyl substitution reaction involving C-1 and C-6 carbons (route a) to give compounds, **8** and **9** after workup. On the other hand, the reaction occurred via route b to rapidly form alkyl 3-(trifluoromethyl) pentanedioate **10** and alkyl 3-(cyanomethyl)-4,4,4-trifluorobutanoate **11**, respectively.

The mechanism of the latter pathway is yet to be fully understood, however, it is presumed to involve rupture

Table 1. Reaction of Michael acceptors **7** with keto-ester **6** affording trifluoromethylated cyclohexenone **8–9**

Entry	Michael acceptor	Keto-ester	Solvent	Yield[b] (%)	Time (h)
1	**7a**	**6a**	CH_2Cl_2	37 **8a**	18
2	**7a**	**6b**	CH_2Cl_2	27 **8b**	18
3	**7a**	**6a**	MeOH	27	24
4	**7a**	**6b**	EtOH	9	24
5	**7b**	**6a**	CH_2Cl_2	33[a]	10
6	**7b**	**6b**	CH_2Cl_2	30	18
7	**7b**	**6a**	MeOH	51[a] **9a**	7
8	**7b**	**6b**	EtOH	67 **9b**	14

[a] Due to transesterification caused by ethoxide ion, **9b** was formed in 10% yield.
[b] Isolated yields.

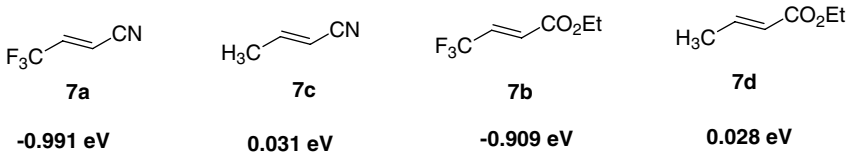
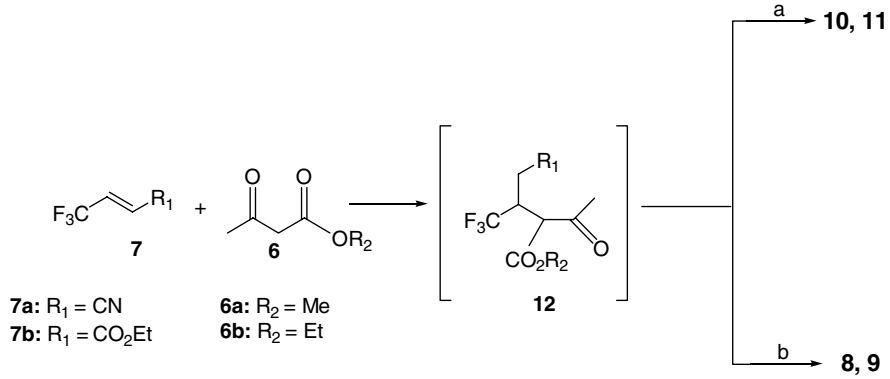


Figure 1. MOPAC calculation for fluorinated and nonfluorinated Michael acceptors **7**: LUMO energy levels are in bold.



Scheme 3.

of the adjacent carbon–carbon bond, which could be facilitated by the likely formation of resonance stabilized acylium cation.

In conclusion, trifluoromethylated cyclic *s-trans* vinylogous acids and amides have been synthesized. In addition, acyclic trifluoromethylated ester derivatives **10** and **11** were isolated as useful by-products. Further studies on the scope and synthetic applications of compounds **8–11** are in progress and will be described in due course. The above compounds provide a starting point for the creation of new knowledge in the area of fluoroorganic synthesis.

Acknowledgements

We are thankful to the US Department of Education Title III Grant, Tennessee State University for financial support.

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20. *A representative experimental procedure is as follows*: β-keto-ester **6** (1 mmol) was added to a mixture of sodium metal (1 mmol) in 3 ml of anhydrous alcohol. The reaction was stirred for 40 min at room temperature. Then, **7** (1 mmol) was added dropwise, after which the resulting mixture was allowed to stir for an additional 15 min at room temperature. Next, the reaction was heated to reflux for the time indicated in Table 1. The reaction was quenched by adding it to water (10 ml) overlaid with dichloromethane and the layers were separated. The organic fraction was dried ($MgSO_4$). Filtration and removal of the organic solvent furnished compound **10**. The aqueous layer above was acidified with 2 M sulfuric acid, and then extracted with dichloromethane (3×10 ml). The combined organic fractions were washed with brine (30 ml), dried over $MgSO_4$, and the solvents were concentrated at reduced pressure. The crude product (yellow oil) was purified by column chromatography using petroleum ether/ethyl acetate (4:1) to give **9**. The compounds **11** and **8** were similarly prepared, except that hexane/ethyl acetate (3:1) was used as eluent.
Spectral analysis: Compound **8a**, Methyl-4-amino-2-oxo-6-trifluoromethyl-cyclohex-3-en-1-oate: Yellow solid. Mp 98–100 °C (37% yield); IR (KBr): 3251, 3100, 2965, 1647, 1444, 1406, 1169 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 2.7$ (dd, $J = 9.4$ Hz, $J = 17.1$ Hz 1H), $\delta = 2.67$–2.84 (m, 2H), $\delta = 3.2$ (m, 1H), $\delta = 3.65$ (s, 3H), $\delta = 5.13$ (s, 1H), $\delta = 10.47$ (br s, NH_2). EIMS *m/z*; 109 (24%), 136 (62%), 150 (65%), 205 (100%), 237 (53%) (M^+).
Compound **8b**, Ethyl-4-amino-2-oxo-6-trifluoromethyl-cyclohex-3-en-1-oate: Yellow solid. Mp 84–86 °C (27% yield): ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 1.2$ (t, $J = 14.0$ Hz, 3H), $\delta = 2.67$ (dd, $J = 9.6$ Hz, $J = 17.2$ Hz, 1H), $\delta = 2.7$–2.8 (m, 2H), $\delta = 3.2$ (m, 1H), $\delta = 4.08$ (q, $J = 14.0$ Hz, 2H), $\delta = 5.1$(s, 1H), $\delta = 10.43$ (br s, NH_2). EIMS *m/z*; 109 (51%), 136 (95%), 150 (100%), 205 (61%), 237 (34%), 251(15%) (M^+).
Compound **9a**, Methyl-4-hydroxy-2-oxo-6-trifluoromethyl-cyclohex-3-en-1-oate: White solid. Mp 83–87 °C (51% yield); IR (KBr): 3160 (br), 3020, 1731, 1662, 1626 cm^{-1}.^1H NMR ($CDCl_3$, 600 MHz): $\delta = 2.4$–2.6 (m, 2H), $\delta = 2.8$ (d, $J = 10.9$ Hz, 1H), $\delta = 3.15$ (m, 1H), $\delta = 3.6$ (s, 3H), $\delta = 5.38$ (s, 1H), $\delta = 10.03$ (br s, 1H). EIMS *m/z*; 95 (40%), 137 (79%), 169 (100%), 178 (20%), 238 (38%) (M^+).
Compound **9b**, Ethyl-4-hydroxy-2-oxo-6-trifluoromethyl-cyclohex-3-en-1-oate: White solid. Mp 100–102 °C (67% yield): ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 1.4$ (t, $J = 13.96$ Hz, 3H), $\delta = 2.5$–2.7 (m, 2H), $\delta = 2.8$ (d, $J = 10.9$ Hz, 1H), $\delta = 3.2$ (m, 1H), $\delta = 4.03$ (q, $J = 13.96$ Hz, 2H) $\delta = 5.30$ (s, 1H), $\delta = 10.0$ (br s, 1H). EIMS *m/z*; 95 (28%), 137 (75%), 183 (100%), 207 (15%), 252 (38%) (M^+).
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