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Wentao Gao*, Rui Liu and Yang Li

Synthesis of novel trifluoromethyl-containing heterocycle-fused troponoid compounds

Abstract: A facile synthesis of novel trifluoromethyl-containing pyrano-, pyrazolo- and isoxazolo-fused tropone compounds **4a,b**, **5a,b**, and **6a,b**, respectively, by cyclizations of (*E*)-3-[3-(trifluoromethylphenyl)acryloyl] tropolones **3a,b** is described. The substrates **3a,b** were prepared by Claisen-Schmidt condensation reaction of 3-acetyltropolone (**1**) with 3- or 4-(trifluoromethyl)benzaldehydes **2a,b**.

Keywords: aromatic hydrazine; Claisen-Schmidt condensation; cyclization; hydroxylamine hydrochloride; trifluoromethyl; tropone.

***Corresponding author: Wentao Gao,** Institute of Superfine Chemicals, Bohai University, Keji Street, Jinzhou, 121000, P. R. China, e-mail: bhuzh@163.com
Rui Liu: Institute of Superfine Chemicals, Bohai University, Keji Street, Jinzhou, 121000, P. R. China
Yang Li: Institute of Superfine Chemicals, Bohai University, Keji Street, Jinzhou, 121000, P. R. China

Introduction

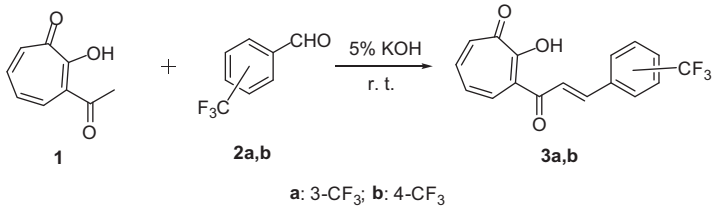
It is well known that the introduction of a trifluoromethyl group into bioactive organic molecules strongly affects their unique features such as polarity and lipid solubility (Asahina et al., 2005; Liu et al., 2008; Chowdhury et al., 2009; Feng et al., 2010). A large volume of synthetic work on this subject has been published (Donohue et al., 2002; Sloop et al., 2002; Loska et al., 2007; Shaaban 2008).

By contrast, troponoid-based compounds, especially heterocycle-fused troponoids, exhibit potent biological and pharmacological activities such as antiviral (Nakazawa et al., 2012), antifungal (Angawi et al., 2003) and antimalarial (Seephonkai et al., 2001) activities. In particular, a new heterocycle-fused troponoid, namely cordytropolone, discovered in the culture broth of *Cordyceps* sp. BCC 1681, shows promise to be developed into a new antimalarial drug (Seephonkai et al., 2001). The troponoid moiety is an important structural part of other biologically important molecules in the area of drug discovery (Cavazza et al., 2000; Isakovic et al., 2001; Nair et al., 2006). Therefore, the interesting and remarkable bioactivity surrounding the troponoid moiety continues to be a vector in the development of novel and interesting types of new drug candidates (Baldwin et al., 2003; Mori et al., 2003; Wahlström et al., 2004). In recent years, our group has synthesized a number of novel substituted or fused troponoid compounds (Gao et al., 1989, 2009, 2010a,b, 2012; Gao and Zheng, 2000; Li and Gao, 2010; Li et al., 2009, 2012a,b). Building upon this evolving expertise and diversifying our work on the synthesis of new troponoid compounds, we would like to report, herein, the synthesis of a series of novel trifluoromethyl-containing bicyclic heterocycle-fused troponoid compounds.

Results and discussion

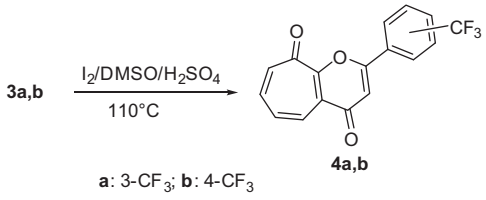
The Claisen-Schmidt condensation of 3-acetyltropolone (**1**) with 3- or 4-(trifluoromethyl)benzaldehyde according to our previously published methodology (Li et al., 2009; Chang et al., 2010) furnished the respective (*E*)-3-(3-(trifluoromethylphenyl)acryloyl)tropone **3a,b** in high yield (Scheme 1). These compounds served as precursors for the construction of the desired trifluoromethyl-containing bicyclic heterocycle-fused troponoid skeleton.

Our recent work has shown that the I_2/DMSO/H_2SO_4 system is an efficient reagent for intramolecular oxidative cyclization of 3-cinnamoyltropolones (Gao et al., 2009; Li et al., 2009). In this work, this approach was extended on the oxidative cyclization of trifluoromethyl-substituted tropolones **3a** and **3b** (Scheme 2). After usual workup followed by purification of crude products by crystallization from 1,4-dioxane, the desired flavone-like products **4a** and **4b** were obtained in yields of 66% and 68%, respectively. In this reaction, to ensure precipitation of the product directly from the reaction mixture, a minimal amount of DMSO was used. Oxidative cyclization was also attempted using the DMSO-I_2 reagent system in the absence of concentrated H_2SO_4, according to the literature method by Lokhande et al. (2005). This reaction produced products **4a,b** in low yields.

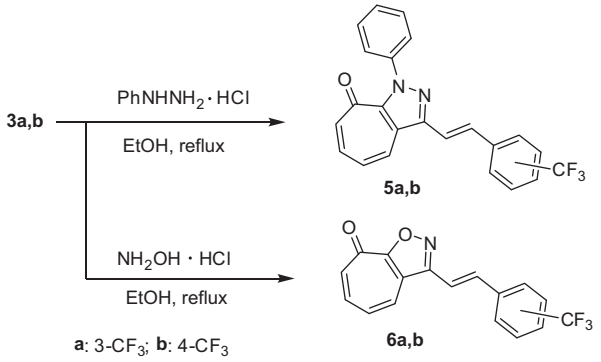


Scheme 1

Isoxazoles and pyrazoles are important classes of biologically active heterocycles, being readily applied to drug design, and have a rich chemistry because of their easy reductive cleavage and susceptibility to ring transformations (Nakamura et al., 2003; Penning et al., 2006). In this work, the synthesis of trifluoromethyl-substituted isoxazolo- and pyrazolo-fused troponoids was accomplished by cyclization of **3a,b** with bifunctional agents (Scheme 3). The methodology has been used by us previously for the synthesis of related compounds (Gao et al., 1989, 2010a, 2012; Li and Gao 2010; Li et al., 2012a,b). Thus, the treatment of tropolones **3a,b** with phenylhydrazine hydrochloride or hydroxylamine hydrochloride in refluxing ethanol under reflux conditions furnished the respective products **5a,b** and **6a,b** in acceptable yields of 54–62%.



Scheme 2



Scheme 3

Conclusion

The construction of a series of novel trifluoromethyl-containing pyrano-, pyrazolo- and isoxazolo-fused bicyclic tropones compounds was achieved.

Experimental

All reagents were obtained from Fluka and used without purification. Melting points were determined by using WRS-1B melting points apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer at 400 MHz. Electrospray ionization (ESI) mass spectra were determined using an MSD VL ESI1 spectrometer. Elemental analysis was performed using an Elementar Vario EL-III element analyzer. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel GF254 using ethyl acetate/petroleum ether (1:4) as eluent.

Preparation of 3-(3-(trifluoromethylphenyl) acryloyl)tropolones 3a,b

An aqueous solution of 5% KOH (5 mL) was added dropwise to a stirred solution of 3-acetyltropolone (**1**, 1 mmol, 164 mg) and 1.5 equimolar amount of 3- or 4-(trifluoromethyl)benzaldehyde (**2a,b**, 1.5 mmol, 261 mg) in 50% aqueous methanol (5 mL). The mixture was stirred at room temperature for 24 h and then quenched by addition of water (5 mL) and acidified with 1 M HCl. The resultant precipitate of **3a,b** was collected by filtration, washed with water, dried and crystallized from methanol.

3-(3-(3-(Trifluoromethyl)phenyl)acryloyl)tropolone (3a) This compound was obtained as bright yellow crystals from **2a** (3-(trifluoromethyl)benzaldehyde); yield 83%; mp 188–189°C; ^{1}H NMR ($CDCl_3$): δ 7.02–7.05 (m, 2H), 7.41 (d, 1H, *J* = 16 Hz), 7.45 (d, 1H, *J* = 8 Hz), 7.63 (d, 1H, *J* = 11 Hz), 7.81 (d, 1H, *J* = 8 Hz), 7.86–7.90 (m, 2H), 8.43 (d, 1H, *J* = 16 Hz), 8.45 (d, 1H, *J* = 11 Hz), 10.42 (s, 1H); MS: m/z 321.1 $[M+H]^+$. Anal. Calcd for $C_{17}H_{11}F_3O_3$: C, 63.75; H, 3.46. Found: C, 63.53; H, 3.31.

3-(3-(4-(Trifluoromethyl)phenyl)acryloyl)tropolone (3b) This compound was obtained as bright yellow crystals from **2b** (4-(trifluoromethyl)benzaldehyde); yield 87%; mp 209–210°C; ^{1}H NMR ($CDCl_3$): δ 7.14–7.19 (m, 1H), 7.34 (d, 1H, *J* = 16 Hz), 7.36–7.42 (m, 1H), 7.57 (d, 1H, *J* = 11 Hz), 7.63–7.66 (m, 2H), 8.19 (d, 1H, *J* = 16 Hz), 7.97–8.07 (m, 2H),

8.38 (d, 1H, J = 11 Hz), 10.39 (1H, s); MS: m/z 321.0 $[M+H]^+$. Anal. Calcd for $C_{17}H_{11}F_3O_3$: C, 63.75; H, 3.46. Found: C, 63.47; H, 3.51.

Preparation of 2-[3- or 4-(trifluoromethyl) phenyl]cyclohepta[*b*]pyran-4,9-diones (4a,b)

A mixture of compound **3a,b** (1 mmol, 320 mg), DMSO (8 mL) and 2–4 drops of concentrated H_2SO_4 was stirred at 110°C for 15 min and then treated with I_2 (0.1 mmol, 25.4 mg) and stirred for an additional 12 h. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature. The resulting precipitate of **4a,b** was collected by filtration and crystallized from 1,4-dioxane.

2-[3-(Trifluoromethyl)phenyl]cyclohepta[*b*]pyran-4,9-dione (4a) This compound was obtained as a yellowish-brown solid from **3a** (3-(3-(3-(trifluoromethyl)phenyl)acryloyl)tropolone); yield 66%; mp 203–205°C; ^{1}H NMR (DMSO-d_6): δ 7.53 (s, 1H), 7.67 (d, 1H, J = 11 Hz), 7.82–7.86 (m, 2H), 7.97 (s, 1H), 8.07 (d, 1H, J = 8 Hz), 8.32–8.40 (m, 3H); MS: m/z 318.9 $[M+H]^+$. Anal. Calcd for $C_{17}H_9F_3O_3$: C, 64.16; H, 2.85. Found: C, 63.89; H, 3.01.

2-[4-(Trifluoromethyl)phenyl]cyclohepta[*b*]pyran-4,9-dione (4b) This compound was obtained as a yellowish-brown solid from **3b** (3-(3-(4-(trifluoromethyl)phenyl)acryloyl)tropolone); yield 68%; mp 216–218°C; ^{1}H NMR (CF_3COOD): δ 7.56 (s, 1H), 7.63–7.67 (m, 2H), 7.81 (d, 1H, J = 12 Hz), 7.92 (d, 2H, J = 7 Hz), 8.26 (d, 2H, J = 7 Hz), 8.53 (d, 1H, J = 11 Hz); MS: m/z 319.1 $[M+H]^+$. Anal. Calcd for $C_{17}H_9F_3O_3$: C, 64.16; H, 2.85. Found: C, 64.43; H, 2.66.

Preparation of 1-phenyl-3-[3-(trifluoromethyl)styryl]cyclohepta[*c*]pyrazol-8(1*H*)-ones (5a,b)

A solution of **3a**,**b** (1 mmol, 320 mg) in ethanol (10 mL) was stirred and treated with phenylhydrazine hydrochloride (217 mmg, 1.5 mmol). The mixture was heated under reflux for 24 h, then cooled to room temperature and quenched with water. The resulting precipitate of **5a,b** was collected by filtration and crystallized from ethanol.

1-Phenyl-3-[3-(trifluoromethyl)styryl]cyclohepta[*c*]pyrazol-8(1*H*)-one (5a) This compound was obtained as a yellowish-brown solid from **3a** (3-(3-(3-(trifluoromethyl)phenyl)acryloyl)tropolone); yield 54%; mp 195–197°C; ^{1}H NMR (DMSO-d_6): δ 7.66–7.71 (m, 7H), 7.74 (d, 1H, J = 16 Hz), 7.91 (d, 1H, J = 11 Hz), 7.95 (d, 1H, J = 16 Hz), 7.98–8.01 (m, 3H), 8.41 (s, 1H), 8.87 (d, 1H, J = 8 Hz); MS: m/z 392.9 $[M+H]^+$. Anal. Calcd for $C_{23}H_{15}F_3N_2O$: C, 70.40; H, 3.85; N, 7.14. Found: C, 70.26; H, 4.13; N, 6.93.

1-Phenyl-3-[4-(trifluoromethyl)styryl]cyclohepta[*c*]pyrazol-8(1*H*)-one (5b) This compound was obtained as a yellowish-brown solid from **3b** (3-(3-(4-(trifluoromethyl)phenyl)acryloyl)tropolone); yield 58%; mp 204–206°C; ^{1}H NMR (DMSO-d_6): δ 6.92 (d, 1H, J = 12 Hz), 6.99–7.03 (m, 1H), 7.42–7.50 (m, 6H), 7.65 (d, 1H, J = 16 Hz), 7.76 (d, 2H, J = 8 Hz), 7.95 (d, 1H, J = 16 Hz), 8.01 (d, 2H, J = 8 Hz), 8.17 (d, 1H, J = 11 Hz); MS: m/z 393.1 $[M+H]^+$. Anal. Calcd for $C_{23}H_{15}F_3N_2O$: C, 70.40; H, 3.85; N, 7.14. Found: C, 70.22; H, 3.95; N, 7.03.

Preparation of 3-[3- or 4-(trifluoromethyl) styryl]-8*H*-cyclohepta[*d*]isoxazol-8-ones (6a,b)

A solution of tropolone **3a** or **3b** (1 mmol, 320 mg) in ethanol (10 mL) was stirred and treated with hydroxylamine hydrochloride (104 mmg, 1.5 mmol). The mixture was heated under reflux for 24 h, then cooled to room temperature and quenched with water. The resultant precipitate of **6a,b** was collected by filtration and crystallized from ethanol.

3-[3-(Trifluoromethyl)styryl]-8*H*-cyclohepta[*d*]isoxazol-8-one (6a) This compound was obtained as a yellowish-brown solid from **3a** (3-(3-(3-(trifluoromethyl)phenyl)acryloyl)tropolone); yield 62%; mp 197–199°C; ^{1}H NMR (DMSO-d_6): δ 7.12–7.25 (m, 2H), 7.28 (d, 1H, J = 16 Hz), 7.58–7.81 (m, 4H,), 8.05 (d, 1H, J = 11 Hz), 8.12–8.27 (m, 2H); MS: m/z 318.0 $[M+H]^+$. Anal. Calcd for $C_{17}H_{10}F_3NO_2$: C, 64.36; H, 3.18; N, 4.41. Found: C, 64.56; H, 3.00; N, 4.20.

3-[4-(Trifluoromethyl)styryl]-8*H*-cyclohepta[*d*]isoxazol-8-one (6b) This compound was obtained as a yellowish-brown solid from **3b** (3-(3-(4-(trifluoromethyl)phenyl)acryloyl)tropolone); yield 56%; mp 215–216°C; ^{1}H NMR (DMSO-d_6): δ 7.12–7.15 (1H, m), 7.27 (1H, d, J = 16 Hz), 7.62 (1H, d, J = 16 Hz), 7.64 (1H, d, J = 11 Hz), 7.78–7.82 (3H, m), 7.98–8.05 (3H, m); MS: m/z 318.1 $[M+H]^+$. Anal. Calcd for $C_{17}H_{10}F_3NO_2$: C, 64.36; H, 3.18; N, 4.41; Found: C, 64.15; H, 3.36; N, 4.19.

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