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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 7351–7354

Novel chemical modifications at the 4-position of chromones. Synthesis and reactivity of 4*H*-chromene-4-spiro-5′-isoxazolines and related compounds

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Received 14 June 2004; revised 22 July 2004; accepted 30 July 2004
Available online 19 August 2004

Abstract—Reactions of chromones with dilithiooximes proceed via nucleophilic 1,2-addition to give, on acidification, 4*H*-chromene-4-spiro-5′-isoxazoline derivatives in high yields. On treatment with concentrated H_2SO_4 the isoxazoline ring of this novel spiroannulated heterocyclic system opens to give α,β-unsaturated oximes, which undergo nitrosation, bromination, and the Beckmann rearrangement to the corresponding spiroisoxazolines and α,β-unsaturated amides, respectively. The latter can be obtained directly by the Beckmann rearrangement of 4*H*-chromene-4-spiro-5′-isoxazolines.

It is well known that chromones (4*H*-chromen-4-ones) are widespread in the plant kingdom in a variety of forms and are the parent compounds of important flower and fruit pigments.[1] Many natural and synthetic chromone derivatives have unique biological and pharmacological activities, including antiviral,[2] antiallergic,[3] and neuroleptic[4] activity. Since their reactivity towards nucleophiles provides a useful route to the preparation of a variety of rearranged products and new heterocyclic systems, their versatility as reactive intermediates is well documented in the literature.[1,5] Chromones are usually readily ring-opened via nucleophilic attack at the 2-position.[1,5] We have recently shown,[5a] however, that the presence of a 2-polyfluoroalkyl group appreciably increases the reactivity of the pyrone ring towards *N*-, *S*- and *C*-nucleophiles, and in certain cases facilitates 1,4-nucleophilic ring addition rather than ring fission. Thus, interaction of 2-trifluoromethylchromones with (trifluoromethyl)trimethylsilane (Ruppert's reagent) and lithium enolates derived from acetophenones gave 2,2-bis(trifluoromethyl)chroman-4-ones[6] and 2-trifluoromethyl-2-phenacylchroman-4-ones,[7] respectively. Here, we wish to report that, in contrast to acetophenone enolates, condensation of 2-trifluoromethylchromones with dilithiooximes proceeds via nucleophilic 1,2-addition and can be employed to obtain 4*H*-chromene-4-spiro-5′-isoxazoline derivatives. These compounds represent a novel spiroannulated heterocyclic system with some unexpected chemical properties.

1,4-Dianions generated from ketoximes having an α-hydrogen are useful intermediates in organic synthesis. The condensation of oxime dianions with various electrophilic substrates, such as carboxylic esters,[8] amides,[9] ketones and α,β-unsaturated ketones,[10] provides regiocontrolled access to β-keto and β-hydroxy oximes, which undergo cyclodehydration to form isoxazoles and 2-isoxazolines. However, the action of dilithiooximes on chromones has, to our knowledge, hitherto not been investigated.

We have found that reaction of acetophenone *E*-oxime[11] with 2.2 equiv of lithium diisopropylamide in ether at 0 °C followed by the addition of 2-trifluoromethylchromones (−20 °C → rt, 2 h) and careful treatment of the resulting mixture with water leads to the formation of β-hydroxy oximes **1a**,**b** in good yields. Note that oximes **1a**,**b** cyclize to spiroisoxazolines **2a**,**b** so readily that

Keywords: Chromones; Dilithiooximes; 4*H*-Chromene-4-spiro-5′-isoxazolines; α,β-Unsaturated oximes; Beckmann rearrangement; Nitrosation; Bromination.
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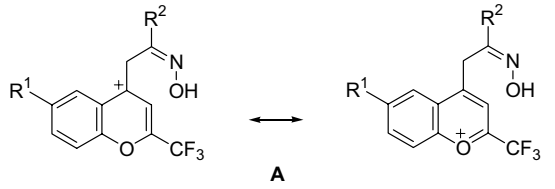
doi:10.1016/j.tetlet.2004.07.158

mixtures of **1** and **2** were obtained on attempted quenching under mildly acidic conditions. Cyclization could be completed by simple addition of aqueous hydrochloric acid to the strongly basic mixture after the condensation step. In the case of aliphatic oximes, the intermediate β-hydroxy oximes **1c**,**d** were, without isolation, subjected to acidic hydrolysis to give spiroisoxazolines **2c**,**d** in 64% and 22% yields, respectively. This reaction is a novel C–C bond forming reaction at the 4-position of the chromone system to give the 4*H*-chromene-4-spiro-5′-isoxazolines **2**[12] (Scheme 1).

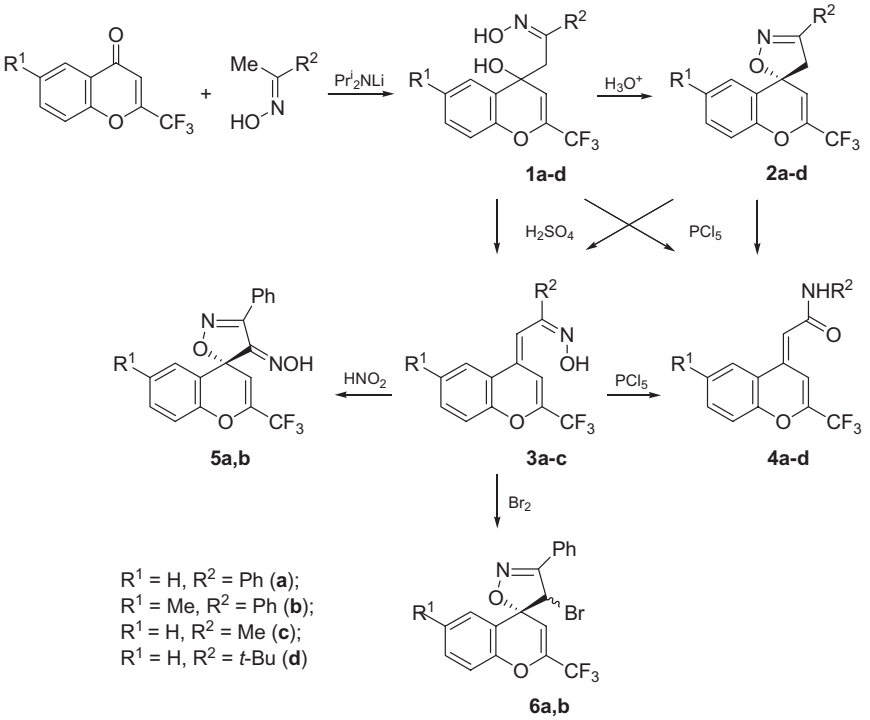
On treatment of compounds **2a**–**c** with concentrated sulfuric acid for 20 min at room temperature, followed by aqueous work-up, the isoxazoline ring opens to give α,β-enoximes **3a**–**c** in 45–85% yields.[13] This result is rather unexpected and represents a specific property of the chromene-4-spiro-5′-isoxazoline system because only base-induced ring-opening reactions have been reported for 2-isoxazolines.[14] Most likely, the initial intermediate in the sulfuric acid ring-opening of **2** is the aromatic benzopyrylium salt **A**, which then undergoes deprotonation to give **3**. Apparently, the conversion of **1a**,**b** to **3a**,**b** under the same reaction conditions also proceeds via the intermediate cation **A** and its deprotonation to the enoxime moiety (Scheme 2).

The *E*-configuration of the *exo* C=C double bond has been proved by the 2D NOESY spectrum of compound **3a**, which displayed cross peaks between the resonances of the =CH (δ 6.79) and the aromatic H-5 (δ 7.86) protons. The configuration with the hydroxyl *anti* to the phenyl group was anticipated for oximes **1** and **3** on the basis that the geometry of the starting oxime is



Scheme 2.

retained[9b,15] and is substantiated by the products of the Beckmann rearrangement, which proceeds by intramolecular migration of the group *anti* to the departing OH group.[16] Indeed, phosphorus pentachloride, in diethyl ether at room temperature, rearranged oximes **1a**,**b** and **3a**–**c** in high yield to amides **4a**–**c**, and hence compounds **1** and **3** presumably exist with the R^2 group *anti* to the N–O bond. This reaction is not limited to **1** and **3**, but occurs readily with spiroisoxazolines **2a**–**d**, which may be regarded as latent oxime forms. To the best of our knowledge, this is the first example of the Beckmann rearrangement with participation of an isoxazoline ring and without isolation of the corresponding α,β-unsaturated oxime. Note that compound **2d** did not convert into **3d** under the action of sulfuric acid, and hence the Beckmann rearrangement occurs at the benzopyrylium cation **A** stage. The stereochemistry and assignment of the H-3 and =CH protons of amides **4** were determined with the 2D NOESY and 2D HSQC spectra of **4c**.[17] The characteristic feature of the ^{1}H NMR spectra of amides **4** is the unusually downfield signal of the H-3 proton (δ 8.42–8.49). Such strong deshielding of the H-3 atom, which is usually manifested at 6–7 ppm, is a result of



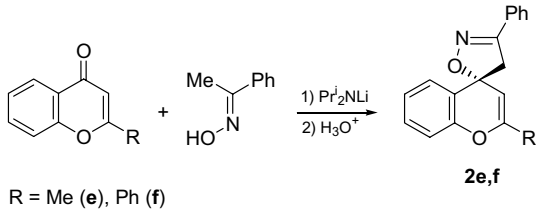
Scheme 1.

the conformation in which the amide carbonyl is situated near H-3 and deshields this atom.

Further transformations are also possible for α,β-enoximes **3**. Nitrosation of these compounds using $NaNO_2$ in dilute HCl afforded oximinoisoxazolines **5a**,**b** in 78% and 59% yields, respectively. Formation of **5** from **3** may occur via electrophilic attack at the α-position of **3** by the nitrosonium cation. The resulting cationic species then undergoes nucleophilic attack by the hydroxyl group to give the 4-nitrosoisoxazoline which exists in the oxime form. Nitrosation of α,β-unsaturated oximes with nitrous acid has been described previously, however, the products were 3,5,5-trimethylpyrazolenine 1,2-dioxide (from mesityl oxide oxime),[18] 3,4-diazacyclopentadienone 3,4-dioxides (from β-alkyl or aryl α,β-unsaturated oximes),[19] and 1-hydroxypyrazole 2-oxides (from α-substituted α,β-unsaturated oximes),[20] which arise from initial attack at the oxime nitrogen atom by the nitrosonium cation. Bromination of oximes **3a**,**b** was accomplished in CCl_4 with bromine at room temperature. The reaction was rapid and gave 4-bromoisoxazolines **6a**,**b** as a mixture of two diastereomers in 89–92% yields (92:8 for **6a** and 96:4 for **6b**). The relative ease with which electrophilic attack towards the α-C atom of the *exo*-double bond occurs may be due to the intermediate benzopyrylium cation **A** and the neighboring-group participation of the oxime hydroxyl group, which is *syn* to the C=C bond.

Finally, in attempting to ascertain if related chromones can participate in this reaction, we found that 2-methylchromone reacts with acetophenone oxime in the presence of lithium diisopropylamide to give the corresponding spiroisoxazoline **2e** in a remarkable 97% yield, in spite of the known susceptibility of the 2-methyl group to deprotonation by basic reagents.[21] Flavone was similarly converted in 65% yield to compound **2f**. However, in the case of chromone, the reaction mixture almost immediately becomes dark-red and resinifies under the same conditions, since the absence of a substituent allows the base relatively free access to the 2-position and consequently to nucleophilic attack and other ring-opening reactions.[22] (Scheme 3).

In summary, we have developed a simple and practical access to 4*H*-chromene-4-spiro-5′-isoxazolines, which can be easily converted to other chromone derivatives possessing a variety of functionalities. Further studies on the synthetic application of spiroannulated isoxazolines are now in progress.



R = Me (**e**), Ph (**f**)

2e,f

Scheme 3.

Acknowledgements

This work was financially supported by the Russian Foundation for Basic Research (Grant 02-03-32706) and by the U.S. Civilian Research and Development Foundation and Russian Federation Ministry of Education (Grants EK-005-X1 and Y1-005-04).

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12. *2-(Trifluoromethyl)-4H-chromene-4-spiro-5′-3′-phenyl- 4′, 5′-dihydroisoxazole* (**2a**). Yield 83%, mp 124–125 °C, colorless needles; (Found: C, 65.18; H, 3.43; N, 4.20. $C_{18}H_{12}F_3NO_2$ requires C, 65.26; H, 3.65; N, 4.23%); ν_{max} (Nujol) 1695 (C=C), 1615, 1595, 1585 (arom.) cm^{-1}; δ (400 MHz, $CDCl_3$) 3.57 (1H, d, J = 17.5 Hz, C*H*H), 3.78 (1H, d, J = 17.5 Hz, CH*H*), 5.95 (1H, s, =CH), 7.18 (1H, dd, ^oJ = 8.4 Hz, ^mJ = 1.1 Hz, H-8), 7.24 (1H, ddd, ^oJ = 7.9, 7.3 Hz, ^mJ = 1.1 Hz, H-6), 7.39 (1H, ddd, ^oJ = 8.4, 7.3 Hz,

^{m}J = 1.6 Hz, H-7), 7.42–7.49 (3H, m, H-3′, H-4′, H-5′), 7.52 (1H, dd, ^{o}J = 7.9 Hz, ^{m}J = 1.6 Hz, H-5), 7.68–7.73 (2H, m, H-2′, H-6′).

13. *1-Phenyl-2-[2-(trifluoromethyl)-4H-chromen-4-ylidene]ethan-1-one oxime* (**3a**). Yield 85%, mp 174–175 °C, light yellow needles; (Found: C, 65.38; H, 3.63; N, 4.22. $C_{18}H_{12}F_3NO_2$ requires C, 65.26; H, 3.65; N, 4.23%); ν_{max} (Nujol) 3200 (OH), 1675 (C=C), 1620, 1595, 1575 (arom.) cm^{-1}; δ (400 MHz, $CDCl_3$) 6.03 (1H, s, H-3), 6.79 (1H, s, =CH), 7.18 (1H, dd, ^{o}J = 8.3 Hz, ^{m}J = 1.2 Hz, H-8), 7.27 (1H, ddd, ^{o}J = 8.1, 7.3 Hz, ^{m}J = 1.2 Hz, H-6), 7.38–7.44 (4H, m, H-7, H-3′, H-4′, H-5′), 7.56–7.59 (2H, m, H-2′, H-6′), 7.86 (1H, dd, ^{o}J = 8.1 Hz, ^{m}J = 1.6 Hz, H-5), 8.0–9.0 (1H, br s, H).
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17. *N-Methyl-2-[2-(trifluoromethyl)-4H-chromen-4-ylidene]acetamide* (**4c**). Yield 89%, mp 191–192 °C, light yellow crystals; (Found: C, 57.76; H, 3.93; N, 5.19. $C_{13}H_{10}F_3NO_2$ requires C, 58.00; H, 3.74; N, 5.20%); ν_{max}(KBr) 3280 (NH), 1675 (C=O), 1630, 1595, 1560 (arom.) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.69 (3H, d, J = 4.7 Hz, Me), 6.40 (1H, s, =CH), 7.35–7.42 (2H, m, H-8, H-6), 7.56 (1H, ddd, ^{o}J = 8.4, 7.2 Hz, ^{m}J = 1.4 Hz, H-7), 7.75 (1H, dd, ^{o}J = 8.1 Hz, ^{m}J = 1.4 Hz, H-5), 8.07 (1H, q, J = 4.7 Hz, NH), 8.48 (1H, s, H-3); δ_C (100 MHz, DMSO-d_6) 25.43 (Me), 105.45 (q, $^{3}J_{C,F}$ = 4.2 Hz, C-3), 109.67 (=CH), 118.05 (C-8), 119.21 (q, $^{1}J_{C,F}$ = 271.5 Hz, CF_3), 119.25 (C-4a), 122.84 (C-5), 126.10 (C-6), 131.22 (C-4), 131.72 (C-7), 139.93 (q, $^{2}J_{C,F}$ = 36.8 Hz, C-2), 150.30 (C-8a), 166.13 (C=O).
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