Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6297–6300

Stereoselective hetero-Diels–Alder reaction of 3-(trifluoroacetyl)chromones with cyclic enol ethers: synthesis of 3-aroyl-2-(trifluoromethyl)pyridines with ω-hydroxyalkyl groups

Vyacheslav Ya. Sosnovskikh,[a,*] Roman A. Irgashev,[a] Igor A. Khalymbadzha[a] and Pavel A. Slepukhin[b]

[a]*Department of Chemistry, Ural State University, 620083 Ekaterinburg, Russian Federation*
[b]*Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620041 Ekaterinburg, Russian Federation*

Received 26 May 2007; revised 26 June 2007; accepted 5 July 2007
Available online 30 July 2007

Abstract—3-(Trifluoroacetyl)chromones undergo heterodiene cycloaddition to 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under mild conditions, producing novel fused pyrans with high stereoselectivity and in good yields. These pyrans were transformed into functionalized pyridines on treatment with ammonium acetate in ethanol. The structures of the *endo*-cycloadducts were established by ^{1}H NMR spectroscopy and X-ray diffraction analysis.

It is known that 3-acylchromones **1** and trifluoroacetylated ethers **2** on reaction with alkyl vinyl ethers can act as heterodienes in an inverse-electron-demand Diels–Alder reaction.[1] However, cycloaddition involving these substrates often requires prolonged heating and occurs with low stereoselectivity affording mixtures of *endo*- and *exo*-adducts with the former predominating.[2,3] For example, the reaction of 3-formylchromone **1** (R = H) with 3,4-dihydro-2*H*-pyran was carried out in a sealed tube at 115 °C for 5 days to give tetracyclic system **3** as a mixture of two stereoisomers in approximately equal amounts in 40% yield.[2] A similar reaction between 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **2** (R = Et) and 2,3-dihydrofuran at 80 °C for 30 h afforded a diastereomeric mixture of tetrahydrofuropyran **4** in 68% yield.[3] Published data on the participation of 3-(trifluoroacetyl)chromones **5**, whose structure combines the chromone system and trifluoroacetyl substituent, in hetero-Diels–Alder reactions are lacking (Fig. 1).

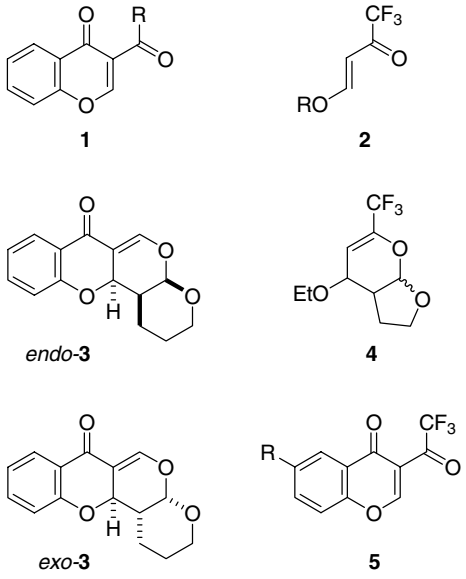
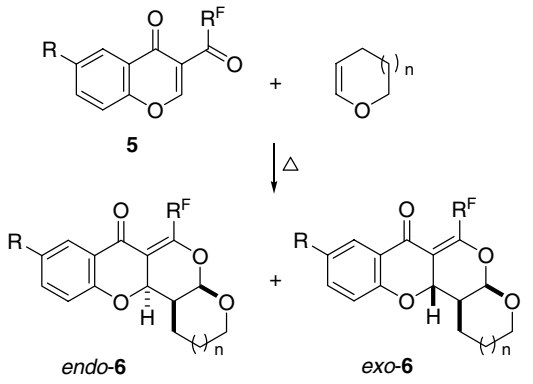


Figure 1.

In continuation of our studies on the chemical properties of 3-(polyfluoroacyl)chromones **5**, which turned out to be highly reactive R^F-containing substrates in reactions with mono- and dinucleophiles,[4] we decided to investigate their reaction with cyclic vinyl ethers, namely, 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran. It was of interest to elucidate the effects of structural features of chromones **5** on the occurrence and stereoselectivity

Keywords: 3-(Trifluoroacetyl)chromones; Cyclic enol ethers; Hetero-Diels–Alder reaction; Fused pyrans; Pyridines.
* Corresponding author. Fax: +7 343 261 59 78; e-mail: vyacheslav.sosnovskikh@usu.ru

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.010



Scheme 1.

of [4+2] cycloadditions compared to those of nonfluorinated chromones **1** and linear analogs **2**.

We found that chromones **5** reacted with 3,4-dihydro-2*H*-pyran (10 equiv) without solvent at 85 °C for 4 h (with **5a**–**c**) or at ~20 °C for 2 days (with **5d**) and gave cycloadducts **6a**–**d** in 42–78% yields (Scheme 1, Table 1).[5] Unlike cycloaddition reactions involving 3-formylchromone **1** and trifluoromethyl ketone **2** that occur under more drastic conditions and with low stereoselectivity,[2,3] compounds **6a**–**d** were formed almost exclusively as the *endo*-isomers with cis–cis-arrangement of the H-12a, H-12b, and H-4a atoms (for X-ray diffraction data, see below). The appearance of *exo*-adducts in 3–4% (^{1}H NMR spectral data) was observed only in the case of the more reactive chromones **5c**,**d** with electron-withdrawing substituents at C-6 of the aromatic ring. Interestingly, replacement of the trifluoromethyl group with difluoromethyl had no effect on the *endo*-selectivity (cf. **6a** and **6e**), however, the absence of the R^F group decreases *endo*-selectivity considerably (cf. **6d** and **6f**). 3-(2,2,3,3-Tetrafluoropropanoyl)chromone did not react with 3,4-dihydro-2*H*-pyran due to steric repulsion between the bulky $H(CF_2)_2$ group and the chromone carbonyl oxygen in the planar *s*-cis-conformation required for cycloaddition. The results obtained for 3,4-dihydro-2*H*-pyran show that the electron-withdrawing CF_3 and CF_2H groups in chromones **5** favor both the rate and stereoselectivity of heterodiene cycloaddition. The reactions of chromones **5a,b** with 2,3-dihydrofuran occurred under milder conditions (50 °C, 4 h) but with lower *endo*-selectivity. In this case, the ratio of the *endo*- and *exo*-cycloadducts **6g**,**h** was 7:3.

It is commonly known that *exo*-isomers are thermodynamically more stable due to the anomeric effect,[2,6,7] however, our attempts to isomerize *endo*-**6c** to *exo*-**6c** by refluxing for 3–4 h in diethyl ether in the presence of CF_3CO_2H or in ethanol with piperidine and acetic acid failed. In all cases, *endo*-**6c** was returned in a decreased amount due to partial retro-cycloaddition.[7] At the same time, when ethanol was replaced by pinacoline, we obtained a mixture of composition *endo*-**6c**:*exo*-**6c** = 66:34, which made it possible to obtain a qualitative ^{1}H NMR spectrum of *exo*-**6c**. Epimerization at C-12a proceeds, most likely, through the 1,4-addition of a piperidine molecule followed by pyrone ring opening to form an intermediate, which can recyclize to give either configuration at this atom.

The ^{1}H NMR spectra of *endo*-cycloadducts **6a**–**e** in $CDCl_3$ consist of a characteristic doublet of quartets due to the H-12a proton in the region of 5.29–5.47 ppm with $^3J = 7.0$ Hz and $^5J_{H,F} = 2.5$ Hz (for **6e**: td, $^3J_{H,H} \sim {}^5J_{H,F} = 6.4$ Hz, $^5J_{H,F} = 2.1$ Hz) and a broad singlet due to the H-4a proton at 5.52–5.60 ppm (for **6e**: br d, $J = 2.0$ Hz). In *exo*-isomers **6c**,**d** the H-12a proton appeared as a quintet at 4.56–4.70 ppm with $J = 2.0$ Hz, and H-4a occurred as a doublet at 5.41–5.44 ppm with $J = 2.4$ Hz, that is, in the *endo*-isomers these protons are more deshielded than in the *exo*-isomers. Since a similar regularity is retained for *endo*- and *exo*-adducts **6f**–**h**, it can be assumed that the chemical shifts of H-12a and H-4a have diagnostic value in this series of

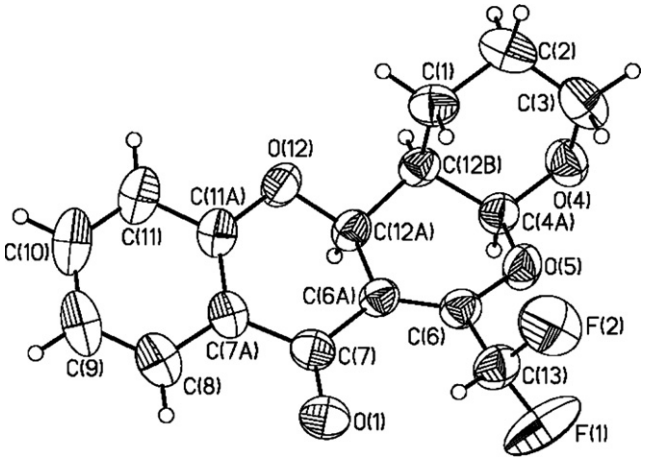
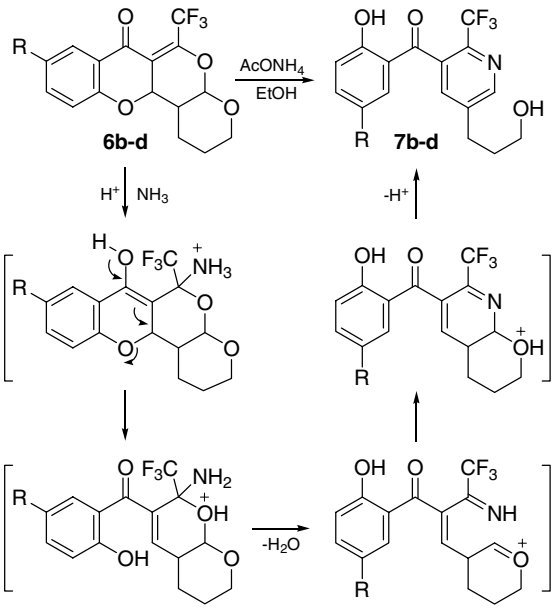


Figure 2. X-ray crystal structure of *endo*-cycloadduct **6e** (thermal ellipsoids at 50% probability).

Table 1. Synthesis of fused pyrans **6a**–**h** by reaction of chromones **5a**–**f** with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran

Chromone	Adduct	R^F	R	n	Ratio of *endo*/*exo*	Yield (%)	Mp (°C)
5a	**6a**	CF_3	H	1	100:0	42	198–199
5b	**6b**	CF_3	Me	1	100:0	51	208–209
5c	**6c**	CF_3	Cl	1	97:3	73	202–203
5d	**6d**	CF_3	NO_2	1	96:4	78	174–175
5e	**6e**	CF_2H	H	1	100:0	52	216–217
5f	**6f**	H	NO_2	1	55:45	62	195–196
5a	**6g**	CF_3	H	0	70:30	69	141–143
5b	**6h**	CF_3	Me	0	69:31	68	147–149



Scheme 2.

compounds and, hence, the assignment of the signals in the ^{1}H NMR spectra of fused pyrans *endo*-**3** and *exo*-**3**, as previously reported,[2] should be reversed.

To confirm the relative configuration of the H-12a, H-12b, and H-4a atoms in *endo*-cycloadducts **6**, an X-ray diffraction study was carried out on crystals of **6e**. This study proved the *endo*-structure with the cis–cis-arrangement of the nodal hydrogen atoms in these compounds (Fig. 2).[8]

Cycloadducts **6** can be considered as latent 2-R^F-pyrilium cations, as they give pyridines **7b–d** in 67–80% yields on reflux with ammonium acetate in ethanol.[9] This reaction represents a new route for the synthesis of trifluoromethylated pyridines possessing an ω-hydroxyalkyl group, which are difficult to prepare by other methods. Taking into account that the salicyloyl substituent can easily be transformed via Dakin reaction into a carboxyl group,[10] this is also a method for preparing new derivatives of nicotinic acid with potential biological activity. A possible reaction pathway is presented in the Scheme 2 and includes the acid-catalyzed nucleophilic 1,4-addition of ammonia, opening of two pyran cycles, and heterocyclization to the pyridine system. As far as we are aware, only one example of a similar transformation involving the cycloadduct of 3-formylchromone and ethyl vinyl ether resulting in 3-salicyloylpyridine has been published.[11]

In conclusion, we have shown that the hetero-Diels–Alder reaction between 3-(polyfluoroacyl)chromones and cyclic enol ethers provides a short and stereoselective approach to the synthesis of R^F-containing fused pyrans, which can be considered as masked pyrilium cations with rich synthetic potential. Further studies on the synthetic application of these compounds for the preparation of novel trifluoromethylated heterocycles are now in progress.

Acknowledgments

This work was financially supported by the RFBR (Grant 06-03-32388) and CRDF (Grant BP2M05).

References and notes

1. (a) Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1983**, 228–229; (b) Dean, F. M.; Al-Sattar, M.; Smith, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 535–536; (c) Ghosh, C. K.; Tewari, N.; Bhattacharyya, A. *Synthesis* **1984**, 614–615; (d) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1990**, 347–350; (e) Gadhwal, S.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2827–2829.
2. Saengchantara, S. T.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 789–794.
3. Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1989**, 215–217.
4. (a) Sosnovskikh, V. Ya.; Irgashev, R. A. *Synlett* **2005**, 1164–1166; (b) Sosnovskikh, V. Ya.; Irgashev, R. A.; Barabanov, M. A. *Synthesis* **2006**, 2707–2718; (c) Sosnovskikh, V. Ya.; Irgashev, R. A. *Heteroat. Chem.* **2006**, *17*, 99–103; (d) Sosnovskikh, V. Ya.; Moshkin, V. S.; Irgashev, R. A. *Tetrahedron Lett.* **2006**, *47*, 8543–8546; (e) Sosnovskikh, V. Ya.; Irgashev, R. A. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 2208–2209 (*Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 2294–2295).
5. *9-Methyl-6-(trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one* **6b**: IR (KBr) 1685, 1634, 1615, 1582, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–2.20 (m, 4H, 1-CH_2, 2-CH_2), 2.32 (s, 3H, Me), 2.56–2.63 (m, 1H, H-12b), 3.89 (ddt, 1H, 3-C*H*H, $^2J = 11.6$ Hz, $^3J = 4.6$ Hz, $J = 1.7$ Hz), 4.03 (td, 1H, 3-CH*H*, $^2J \approx {}^3J = 11.6$ Hz, $^3J = 3.6$ Hz), 5.29 (dq, 1H, H-12a, $^3J = 7.0$ Hz, $^5J_{H,F} = 2.6$ Hz), 5.52 (br s, 1H, H-4a), 6.84 (d, 1H, H-11, $^3J = 8.4$ Hz), 7.29 (ddq, 1H, H-10, $^3J = 8.4$ Hz, $^4J = 2.3$, 0.6 Hz), 7.75 (dq, 1H, H-8, $^4J = 2.3$, 0.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 94.87 (d, CF_3, $^5J_{F,H} = 2.6$ Hz). Anal. Calcd for $C_{17}H_{15}F_3O_4$: C, 60.00; H, 4.44. Found: C, 59.99; H, 4.16.
6. Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 1133–1136.
7. Coutts, S. J.; Wallace, T. W. *Tetrahedron* **1994**, *50*, 11755–11780.
8. *Crystal data for* **6e**: $C_{16}H_{14}F_2O_4$, triclinic crystals space group $P\bar{1}$, at 295(2) K, $a = 8.2050(5)$, $b = 9.4468(6)$, $c = 10.4422(6)$ Å, $\alpha = 90.326(7)°$, $\beta = 108.959(5)°$, $\gamma = 114.490(5)°$, $V = 687.28(7)$ Å^3, $d_{calc} = 1.490$ g cm^{-3}, absorption coefficient $\mu = 0.124$ mm^{-1}, $Z = 2$. The intensities of 4064 ($R_{int} = 0.0140$) were measured on a 'Xcalibur 3' automatic four-circle diffractometer (MoK_α radiation, $\lambda = 0.71093$ Å, graphite monochromator, $\omega/2\theta$ scan, $2\theta_{max} = 52°$). The structure was solved by direct methods with the use of the SHELXTL program package.[12] Nonhydrogen atoms were refined by full-matrix least-squares procedures (with F^2) in an anisotropic approximation. The positions of hydrogen atoms were found by a difference Fourier synthesis and refined in an isotropic approximation. The final discrepancy factors $R_1 = 0.0397$, $wR_2 = 0.1016$, Goof = 1.005 for 2284 reflections with $I > 2\sigma(I)$, $R_1 = 0.0766$, $wR_2 = 0.1098$ (all data). Largest different peak and hole: 0.207 and −0.167 e Å^{-3}. Completeness to $\theta = 26.00°$ 96.0%. Deposition number CCDC 646177.
9. *3-(5-Chloro-2-hydroxybenzoyl)-5-(3-hydroxypropyl)-2-(trifluoromethyl)pyridine* **7c**: Yield 67%, mp 103–104 °C. IR (KBr) 3403, 1636, 1617, 1575, 1472 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (br s, 1H, OH), 1.92–1.99 (m,

2H, CH_2), 2.92 (t, 2H, Py-CH_2, $J = 7.7$ Hz), 3.74 (t, 2H, OCH_2, $J = 6.0$ Hz), 7.03 (d, 1H, H-6′, $^{m}J = 2.6$ Hz), 7.06 (d, 1H, H-3′, $^{o}J = 9.0$ Hz), 7.50 (dd, 1H, H-4′, $^{o}J = 9.0$ Hz, $^{m}J = 2.6$ Hz), 7.61 (d, 1H, H-4, $^{m}J = 1.5$ Hz), 8.76 (d, 1H, H-6, $^{m}J = 1.5$ Hz), 11.61 (s, 1H, OH); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 98.67 (s, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.03, 33.04, 61.29, 119.89, 120.45, 121.23 (q, CF_3, $^{1}J_{C,F} = 275.2$ Hz), 124.06, 131.60, 131.67, 135.87, 137.68, 140.72, 142.30 (q, *C*–CF_3, $^{2}J_{C,F} = 35.0$ Hz), 151.19, 161.73, 198.11. Anal. Calcd for $C_{16}H_{13}F_3NO_3$: C, 53.42; H, 3.64; N, 3.89. Found: C, 53.54; H, 3.58; N, 3.81.

10. Bodwell, G. J.; Hawco, K. M.; Satou, T. *Synlett* **2003**, 879–881.
11. Uddin, R.; Zaman, A. *Indian J. Chem.* **1995**, *34B*, 1039–1042.
12. Sheldrick, G. M. SHELX-*97 release 97-2*; University of Göttingen: Göttingen (Germany), 1998.