Highly diastereoselective 1,3-dipolar cycloaddition of nonstabilized azomethine ylides to 3-nitro-2-trihalomethyl-2H-chromenes: synthesis of 1-benzopyrano[3,4-c]pyrrolidines


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ARTICLE INFO

Article history:
Received 17 May 2013
Received in revised form 8 July 2013
Accepted 22 July 2013
Available online 31 July 2013

Keywords:
3-Nitro-2H-chromenes
Nonstabilized azomethine ylides
1,3-Dipolar cycloaddition
1-Benzopyrano[3,4-c]pyrrolidines

ABSTRACT

Reactions of 3-nitro-2-trifluoro(trichloro)methyl-2H-chromenes, including 2-unsubstituted derivatives, with N-alkyl-α-amino acids (sarcosine, proline) and paraformaldehyde proceed diastereoselectively to give 1-benzopyrano[3,4-c]pyrrolidines in good yields as a result of a 1,3-dipolar cycloaddition of the intermediate nonstabilized azomethine ylide at the Δ3-bond of the chromene system.

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1. Introduction

1,3-Dipolar cycloaddition is one of the most important methods for the synthesis of five-membered heterocycles. The high regio- and stereoselectivity typical of these reactions make them an indispensable tool for synthesizing natural molecules with a few chiral centers. In particular, azomethine ylides derived from readily available N-alkyl-α-amino acids and carbonyl compounds enable one-step syntheses of substituted pyrrolidines that are of considerable interest as compounds with a broad spectrum of bioactivity. On the other hand, chromane derivatives are widespread in the plant world and also possess valuable biological and pharmacological properties. In view of this, combining benzopyran and pyrrolidine moieties in a single molecule seems a synthetic task of current interest. cis-Benzopyranopyrrolidine I is an antagonist of 5-HT2C receptors with respect to 5-HT2A, whereas its more complex derivative II (Fiduxosin) is an α1 adrenoreceptor antagonist and shows an α1a/α1b selectivity for adrenoreceptors; it was suggested as a promising pharmaceutical agent for the treatment of benign prostatic hyperplasia (Fig. 1).

The key stage in the synthesis of benzopyranopyrrolidines is the cycloaddition of nonstabilized azomethine ylides to coumarins and 2H-chromenes, however, information about such reactions in the 2H-chromenes series is quite limited. It is only known that 2-aryl-3-nitro-2H-chromenes react with azomethine ylides at reflux in toluene for several hours to give the corresponding 4-aryl-3a-nitrobenzopyrano[3,4-c]pyrrolidines. Taking into account the literature data, we envisaged that introduction of such powerful electron-withdrawing substituents as CF3 and CCl3 groups into the 2-position of 3-nitro-2H-chromenes would increase their reactivity toward 1,3-dipolar cycloaddition with various 1,3-dipoles and open up a broad synthetic scope of these important oxygen-containing heterocycles. Of particular interest is the fact that introduction of a trifluoromethyl group into bioactive molecules can have profound and unexpected results on biological activity and reactivity of the...
derived fluorinated compounds. As a consequence, exploitation of an efficient method for the synthesis of these compounds is highly desirable.

2. Results and discussion

3-Nitro-2-trihalomethyl-2H-chromenes 1 (X = F, Cl), prepared by tandem condensation of the appropriate salicylaldehydes with 3,3,3-trifluoro(trichloro)-1-nitropropenes, have not received much attention despite their potential interest as CF3- and CCl3-building blocks in organic synthesis for the construction of trihalomethyl-containing heterocycles. The majority of the reactions with these compounds are nucleophilic additions at the 4-position leading to various types of 4-substituted chromenes. Most pertinent to the present research is the hetero-Diels–Alder reaction of 3-nitro-2-trihalomethyl-2H-chromenes 1 with electron-rich dienophiles, such as ethyl vinyl ether and 2,3-dihydrofuran, providing a straightforward route to the cyclic nitronates. However, examples of the participation of chromones 1 in any 1,3-dipolar cycloaddition reactions are lacking, a fact prompting us to investigate their reaction with the nonstabilized azomethine ylide derived from N-alkyl-x-amino acids (sarcosine, proline) and paraformaldehyde, and elucidate the effects of different 3-nitro-2H-chromenes on the occurrence and stereoselectivity of cycloaddition reactions compared to those of 2-aryl-3-nitro-2H-chromenes.

Herein, we have found that treatment of 3-nitro-2-trihalomethyl-2H-chromenes 1a–h with the azomethine ylide generated in situ from sarcosine and paraformaldehyde in refluxing toluene for 5–10 min with azotropic removal of water affords the desired benzopyran[3,4-d]pyrrolidines 2a–h in high yields (77–97%), which were isolated as free bases by crystallization from dichloromethane/hexane. This indicates that the presence of an electron-withdrawing trihalomethyl group at the 2-position increases the dipolarophilic reactivity of the 2-CX3-chromenes 1a–h toward the azomethine ylide, and makes these compounds more reactive than non-halogenated 3-nitro-2H-chromenes. As is the case of cycloaddition reactions involving 2-aryl-3-nitro-2H-chromenes, compounds 2a–h were formed mainly as the cis-isomers in relation to the nitro and trihalomethyl groups at C-3a and C-4. The synchrotron of the reactions of nonstabilized azomethine ylides with alkenes results in the cis-fusion of the new pyrrolidine ring. The appearance of the trans-adducts 2a–h (3–30% according to the 1H NMR data) was observed only in the crude products. Thus, the ready accessibility and high reactivity of CX3-chromenes 1a–h have made them useful substrates for constructing biologically and medicinally important products (Scheme 1).

The structures of compounds 2a–h were determined by elemental analysis (as their oxalates 3a–h, which were obtained in almost quantitative yield in acetone) and by comparison of their IR, 1H, and 13C NMR spectra with data for related benzopyranopyrrolidines. Selected 1H NMR spectral data for compounds 2 and 3 as well as 5 and 6, which confirm the structure, are collected in Table 1. The 1H NMR spectra of cis-pyrrolidines 2 in CDCl3 contain the following characteristic signals: a triplet or a doublet of doublets of the H-1' proton at δ 2.2–2.6 ppm (J = 9.0–11.0 Hz), which is subjected to the shielding effect of the benzene moiety in the cis-position; a triplet or a doublet of doublets of H-1' at δ 3.5–3.8 ppm (J = 7.7–9.0 Hz); doublets of geminal protons H-3' and H-9' at δ 2.7–3.0 and 4.0–4.5 ppm (J = 11.9–12.2 Hz); a triplet or a doublet of doublets of the H-9b benzyl proton at δ 4.0–4.2 ppm (J = 7.5–10.5 Hz). In the case of trans-pyrrolidines 2, the strongly shielded proton H-1' at δ 1.8–2.0 ppm and strongly deshielded proton H-4 at δ 4.8–5.2 ppm (this atom exists in the cis-position toward the NO2 group) were observed as a consequence of the configuration change at C-4.

Significant variations are observed in the chemical shifts of H-4 on going from bases cis-pyrrolidines 2 (δ 4.3–4.6 ppm in CDCl3) to their oxalates 3 (δ 5.2–5.7 ppm in DMSO-d6). All signals in the 1H and 13C NMR spectra of compounds 2 and 3 were assigned on the basis of 2D 1H–13C HSQC and HMBC experiments for 2b, 3d, and 3h. Moreover, the stereochemistry of 2b was unambiguously confirmed by X-ray single crystal analysis (Fig. 2).

In addition to sarcosine, proline was briefly examined in the reaction. Cycloaddition of the azomethine ylide derived from proline and paraformaldehyde with chromenes 1a,b,f and 3-nitro-2-phenyl-2H-chromene (1i) occurred in a similar way to give compounds 4a–d, which were isolated from a mixture of regio- and stereoisomers in low yields (11–34%). Obviously, in contrast to the azomethine ylide from sarcosine, this cycloaddition was less selective. Only the indicated diastereomer could be separated by re-crystallization of the mixture from diethyl ether and hexane, however, product 4c was obtained as a 68:32 mixture of 4c with its minor isomer, the structure of which was not determined (Scheme 2).

The relative stereochemistry in cycloadducts 4b and 4d was established by 2D 1H–1H NOESY experiments. The most important proof of their stereochemistry was the NOE enhancements indicated with arrows in Fig. 3. All signals in the 1H and 13C NMR spectra of compounds 4 were assigned on the basis of 2D 1H–1H COSY, 1H–13C HSQC, and HMBC experiments of 4b,d. The doublet of doublets or triplet of the H-11a benzyl proton in compounds 4a–d allows us to rule out the alternative regioisomeric structure, in which the benzyl proton should interact with only one vicinal proton. It is necessary to be mentioned that in the case of chromenes 1a,e, sarcosine, and benzaldehyde the reaction led to a mixture of starting materials and unidentified products.

Next, taking into account the broad utility of benzopyranopyrrolidines in medicinal chemistry, and the fact that the literature contains no data on reactions of 2-unsubstituted 2H-chromenes with nonstabilized azomethine ylides, we studied the reaction of 3-cyano- and 3-methoxycarbonyl-2H-chromenes 1j,k with sarcosine and paraformaldehyde. It was found that reactivity of these compounds in benzene gave benzopyranol[3,4-c]pyrrolidines 5a,b, which were isolated as hydrochlorides in high yields (76–83%). The desired products precipitate upon neutralization of the reaction mixtures with HCl, prepared in situ from AcCl and i-PrOH, and a simple filtration provides analytically pure material. In
contrast, the reaction of 3-formyl-2H-chromene (11) under the conditions described above afforded a 2.8:1 mixture of cycloadducts 5c and 6, respectively, which were not obtained as pure (Scheme 3).

3. Conclusion

In conclusion, the use of 3-nitro-2-trihalomethyl-2H-chromenes, including 2-unsubstituted derivatives, in 1,3-dipolar cycloadditions of nonstabilized azomethine ylides allows the

Table 1

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<th>Compd</th>
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<td>2h</td>
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**Fig. 2.** X-ray crystal structure of cis-2b (ORTEP drawing, 50% probability level).

Fig. 3. NOE connectivities in compounds 4b and 4d.

**Scheme 3.**

1a, b, f, i

1j-l

4a: R = CF₃, R' = H (17%)
4b: R = CF₃, R' = Br (15%)
4c: R = CCl₃, R' = Br (11%)
4d: R = Ph, R' = H (34%)

**Scheme 2.**

3. Conclusion

In conclusion, the use of 3-nitro-2-trihalomethyl-2H-chromenes, including 2-unsubstituted derivatives, in 1,3-dipolar cycloadditions of nonstabilized azomethine ylides allows the
construction of biologically interesting 1-benzopyrano[3,4-c]pyrrolidines in one pot three-component reaction.

4. Experimental

4.1. General

NMR spectra were recorded on Bruker DRX-400 (1H—400 MHz, 19F—376 MHz) and AVANCE-500 (1H—500 MHz, 13C—126 MHz) spectrometers in DMSO-d6 and CDCl3 with TMS and C6D6 as internal standards, respectively. IR spectra were recorded on a Perkin—Elmer Spectrum BX-II instrument as KBr discs. Elemental analysis was performed on Perkin—Elmer CHN PE 2400. All solvents used were dried and distilled per standard procedures. Melting points were determined without correction. The starting 3-nitrochromenes 1a–h were prepared according to described procedures.10

4.2. General procedure for the preparation of benzopyran [3,4-c]pyrrolidines (2a–h)

A mixture of sarcosine (0.23 g, 2.6 mmol), paraformaldehyde (0.19 g, 6.0 mmol), and the corresponding 3-nitrochromene (1.0 mmol) was heated under reflux in toluene (15 mL) with a Dean—Stark trap for 5–10 min. After that the mixture was concentrated under reduced pressure and the solid formed was washed with dichloromethane/hexane (1:2) to give crude product as a mixture of two diastereomers 2 and 3. cis-Isomers 2a–h were prepared after simple recrystallization from dichloromethane/ hexane (1:2) as a colorless powder. Elemental analyses for bases 2a–h were performed for their oxalates 3a–h.

4.2.1. (3aS,4S,9bR)-2-Methyl-3a-nitro-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole (2a). Yield 97%, mp 76–77 °C; IR (KBr): v=1585, 1548, 1497, 1457, 1397, 1374, 1338 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ = 2.38 (3H, Me), 2.45 (t, 1H, H-1, J = 8.7 Hz), 2.81 (d, 1H, H-3, J = 12.2 Hz), 3.55 (t, 1H, H-1’, J = 8.7 Hz), 4.02 (d, 1H, H-3’, J = 12.2 Hz), 4.05 (t, 1H, H-9, J = 8.7 Hz), 4.43 (q, 1H, H-4, J = 5.5 Hz), 7.05–7.12 (m, 2H, H-6, H-8), 7.15 (d, 1H, H-9, J = 7.0 Hz), 7.24 (t, 1H, H-7, J = 7.7 Hz); 13C NMR (470.5 MHz, CDCl3): δ = 2a (90%) 89.3 (d, CF3, J = 6.3 Hz); 13C NMR (126 MHz, CDCl3): δ = 41.1 (Me), 44.0 (C-9b), 62.4 (q, C-3, JCF = 2.3 Hz), 62.4 (C-1), 76.0 (q, C-4, JCF = 32.4 Hz), 91.2 (C-3a), 117.5 (C-6), 122.3 (C-9a), 122.2 (q, CF3, JCF = 282.9 Hz), 123.7 (C-8), 128.2 (C-9), 128.4 (C-7), 151.7 (C-5a).

4.2.2. (3aS,4S,9bR)-8-Bromo-2-methyl-3a-nitro-4-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole (2b). Yield 93%, mp 111–112 °C; IR (KBr): v=1552, 1482, 1463, 1409, 1388, 1350, 1333 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ = 2.38 (3H, Me), 2.48 (t, 1H, H-1, J = 8.7 Hz), 2.85 (d, 1H, H-3, J = 11.8 Hz), 3.50 (t, 1H, H-1, J = 8.7 Hz), 3.97 (d, 1H, H-3, J = 11.8 Hz), 4.02 (t, 1H, H-9, J = 8.1 Hz), 4.43 (q, 1H, H-4, J = 5.7 Hz), 6.98 (d, 1H, H-6, J = 8.8 Hz), 7.29 (d, 1H, H-9, J = 1.9 Hz), 7.35 (d, 1H, H-7, J = 8.8 Hz), 1.97 (Hz); 19F NMR (376 MHz, CDCl3): δ = 2b (80%) 89.4 (d, CF3, J = 2.0 Hz); 2b (20%) 88.7 (d, CF3, J = 6.2 Hz); 13C NMR (126 MHz, CDCl3): δ = 41.0 (Me), 43.7 (C-9b), 62.2 (C-1), 62.2 (C-3, JCF = 2.4 Hz), 75.9 (q, C-4, JCF = 32.5 Hz), 90.6 (C-3a), 116.1 (C-8), 119.3 (C-6), 122.0 (q, CF3, JCF = 283.0 Hz), 124.2 (C-9a), 130.9 (C-7), 131.4 (C-6), 150.7 (C-5a).

4.3. General procedure for the preparation of benzopyrano [3,4-c]pyrrolidines oxalates (3a–h)

Anhydrous oxalic acid (0.10 g, 11.1 mmol) dissolved in hot acetonitrile (10 mL) was added with stirring to the solution of the corresponding benzopyran [3,4-c]pyrrolidines (2a–h) in acetonitrile (0.5 mL) and the solid formed was filtered off and washed with dry acetonitrile to give compounds 3 as a white powder.
4.4. Compounds 4a–d

4.4.1. (6S,6aS,6bS,11aR)-6a-Nitro-6-(trifluoromethyl)-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-alpyrrole (4a). This compound was prepared from 3-nitro-2-(trifluoromethyl)-2H-chromene (1a), proline, and parafarnaldehyde according to the described procedure for compounds 2. Yield 17%, mp 136–137 °C, colorless needles; IR (KB): v = 1587, 1549, 1490, 1458, 1376 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ = 1.49–3.12 (m, 6H, CH₂), 3.30 (dd, 1H, H-11, J = 10.7, 5.0 Hz), 3.59 (dd, 1H, H-11, J = 10.7, 7.3 Hz), 4.20 (t, 1H, H-7a, J = 4.7 Hz), 4.27 (t, 1H, H-11a, J = 6.1 Hz), 4.88 (q, 1H, H-6, J = 6.5 Hz), 7.00 (d, 1H, H-4, J = 8.4 Hz), 7.04–7.11 (m, 2H, H-2, H-3), 7.20 (d, 1H, H-1, J = 7.1 Hz); 13C NMR (376 MHz, CDCl₃): δ = 94.0 (m, 4C), 54.80 (s, 4H, CO₂H); 37.02 (s, H-2), 3.63; N, 8.49. Calcd for C₂₁H₂₁N₃O₈ (CO₂H)₂: C, 54.88; H, 4.61; N, 8.53.

4.4.2. (6S,6aS,6bS,11aR)-2-Bromo-6a-nitro-6-(trifluoromethyl)-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-alpyrrole (4b). This compound was prepared from 6-bromo-3-nitro-2-(trifluoromethyl)-2H-chromene (1b), proline, and parafarnaldehyde according to the described procedure for compounds 2. Yield 15%, mp 132–133 °C,
4.4.3. $\left[65 \cdot \text{so}^{1} \text{b}, 
{\text{6s}}, 11 \text{ar}^{4} \text{b}\right]-2$-Bromo-6a-nitro-6-(trichloromethyl)-6,6b,6,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizine (4e). This compound was prepared from 3-bromo-2-nitro-3-(trichloromethyl)-2H-chromene (1f), proline, and paraformaldehyde according to the described procedure. 

4.4.4. $\left[66 \cdot \text{so}^{1} \text{b}, 
{\text{6s}}, 8,9,11,11a\right]$-octahydrochromeno[3,4-a]pyrrolizine (4d). This compound was prepared from 3-nitro-2-phenyl-2H-chromene (1l), proline, and paraformaldehyde according to the described procedure as a base and purified by recrystallization from hexane:ether. Yield 32%, mp 120–121°C, yellow crystals; IR (KBr): v = 1658, 1591, 1493, 1457, 1374 cm$^{-1}$; 1H NMR (500 MHz, CDCl$_3$); δ = 1.00 (dd, 1H, H-7$^*$, J = 1.6, 12.8 Hz), 3.20 (s, 3H, CH$_3$), 3.45 (t, 1H, H-8, J = 6.6 Hz), 2.01 (dd, 1H, H$^*$-8', J = 2.4, 9.2 Hz), 1.67 (m, 2H, H-9), 4.20 (t, 1H, H-11, J = 7.5 Hz), 7.08 (d, 1H, H-4, J$^*$ = 2.0 Hz), minor isomer $\delta$ = 1.90–2.05 (s, 4H, CH$_2$), 2.78 (t, 1H, H-11, J = 8.5 Hz), 2.48 (dd, 1H, H-7, J$^*$ = 9.7, 11.0 Hz), 3.28 (s, 1H, H-9, J = 6.6 Hz), 3.47 (t, 1H, H-11, J = 7.5 Hz), 4.61 (t, 1H, H$^*$-8', J = 7.5 Hz), 7.02 (d, 1H, H-4, J$^*$ = 8.6 Hz), 7.19–7.22 (m, 1H, H-1), 7.34–7.39 (m, 1H, H-3). Found: C 39.38; H 3.13; N 6.09. Calcd for C$_{13}$H$_2$BrCl$_2$N$_2$O$_3$: C 59.69; H 3.09; N 6.14.

4.5. Compounds 5a,b

4.5.1. $\left[3a \cdot \text{ar}^{1} \text{b}, 
{\text{9b}}\right]$-2-Methyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole-3a-carbonitrile (5a). This compound was prepared as a yellow oil from 3-cyano-2H-chromene (1j), sarcosine, and paraformaldehyde according to the described procedure.

4.6. X-ray diffraction study of compound 2b

Intensities of reflections were measured on an automated four-circle Xcalibur 3 diffractometer (Oxford Diffraction, Abingdon, UK; graphite monochromated Mo Kα radiation, CCD detector, θ-θ scanning). The structure was solved by a direct method using the SHEX97 package. The hydrogen atoms were located geometrically using a riding model. Nonhydrogen atoms were refined by a full-matrix least-squares method against $F^2$ within the anisotropic approximation. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 360633; e-mail: deposit@ccdc.cam.ac.uk). The CCDC deposition number for compound 2b is 925671. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/products/csd/request/.

Crystal data for 2b at 295(2) K: C$_{25}$H$_{28}$Br$_2$N$_2$O$_3$, M = 381.85, a = 7.3625(14) Å, b = 7.6363(12) Å, c = 13.950(3) Å, α = 74.399(15)°, β = 78.411(15)°, γ = 75.659(15)°, V = 724.2(2) Å$^3$, triclinic crystals space group $P$T, $Z$ = 2, $D$ = 1.748 g cm$^{-3}$, $μ$ = 2.885 mm$^{-1}$, $F(000)$ = 380, 7403 reflections measured up to $2θ_{max}$=56.6°, 3492 unique (Rint = 0.0309), which were used in all calculations. Refinement was converged at $R_w=F^2/|F|^2 = 0.0557$ (all data), $R_1=0.0324$ (1551 reflections with $I>2σ(I)$), GoF=1.001.

Acknowledgements

This work was supported financially by the Russian Foundation for Basic Research (Grants 11-03-00126 and 12-03-31036).

References and notes


