Synthesis of 5-(trifluoromethyl)-5H-chromeno[3,4-b]pyridines from 3-nitro-2-(trifluoromethyl)-2H-chromenes and aminoenones derived from acetylacetone and cyclic amines


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Reactions of 3-nitro-2H-chromenes with aminoenones derived from acetylacetone and cyclic amines proceed diastereoselectively to give functionalized 2,3,4-trisubstituted chromanes as a result of nucleophilic addition of the vinylogous β-methyl group at the C-4 atom of the chromene system. From these compounds, under acidic conditions, 5-(trifluoromethyl)-5H-chromeno[3,4-b]pyridines and 4-acetoacetoxy-3-nitro-2-(trichloromethyl)chromanes, depending on the substituent at the 2-position, were obtained in moderate to good yields.

Many derivatives of chromane (3,4-dihydro-2H-1-benzopyran) and 2H-chromene (2H-1-benzopyran) are natural compounds that are widely abundant in the plant kingdom. Some of these, as well as a series of synthetic 2H-chromenes, have found use as pesticides and promising drugs. 3-Nitro-2H-chromenes, as conjugated nitroolefins, possess unique chemical reactivity in both nucleophilic and cycloaddition reactions because of their reactive double bond. As a result, these compounds have attracted attention as excellent building blocks for the preparation of various more complex heterocyclic compounds. In particular, 3-nitro-2H-chromenes react with diverse C-, N-, S-, and P-nucleophiles to give a wide range of substituted and fused chromanes. Recently, the reactions of 2-aryl-3-nitro-2H-chromenes with α,α-dicyanoolefins in the presence of triethylamine, leading to the preparation of 6-aryl-6H-dibenzo[b,d]pyran derivatives, were reported. At the same time, to the best of our knowledge, very little information is available on the reactions of 3-nitro-2H-chromenes with push–pull enamines. It has been reported that 2-aryl-3-nitro-2H-chromenes react with methyl β-methylaminocrotonate to give mixtures of the addition product, methyl 3-methylamino-2-(2-aryl-3-nitrochroman-4-yl)-2-butenoate, and 1-benzopyrano[3,4-b]pyrrole, formed via the Grob cyclization, whereas their reactions with ethyl β-morpholino- and 4-piperidinopent-3-en-2-ones in dry acetonitrile at room temperature for 2–48 h resulted in the stereoselective formation of 2,3,4-trisubstituted chromanes 2a–i in 42%–83% yields as single diastereomeric products with cis–trans-configuration (JH12,13 = 1.5 Hz) at the C(2)–C(3) and C(3)–C(4) bonds, respectively, and with E-configuration at the double bond (Scheme 1, Table 1). The stereochemistry of the products was confirmed by an X-ray diffraction study of crystals of 2a (Fig. 1).
The reaction time varied according to the nature of the chromene molecule. In general, 2-CF₃-chromenes were more reactive than 2-CCl₃- and 2-Ph-chromenes; conjugate addition of an enamine to a CF₃-chromene containing an electron-donating MeO group required a longer period of time for completion of the reaction, while electron-withdrawing groups (Br, NO₂) required relatively short reaction times. Addition of push–pull enamines at the vinyl-

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Figure 1. X-ray crystal structure of cis-trans-2a (ORTEP drawing, 50% probability level).

ogous β-Me group possibly results from the E-configuration of the starting enamines, which hinders the approach of the α-C atom to the activated double bond of the chromene system.

Next we examined the acid hydrolysis of enaminoketones 2a–i in aqueous ethanol at reflux in the presence of concentrated HCl. As expected, hydrolysis of compounds 2f–i successfully removed the amino function to give interesting acetoacetyl derivatives 3f, g, and i as a mixture of keto-enol tautomers 3 and 3’ in 56%–66% yields, with the same configuration (9%–31% of diketo form 3’). As for the 2-CF₃-chromanes 2a–e, there was a marked difference in their reactivity toward acid hydrolysis. Under the same conditions, instead of the corresponding acetoacetyl derivatives 3, we obtained 5-(trifluoromethyl)-5H-chromeno[3,4-b]pyridines 4a, c–e in 33%–46% isolated yields (Scheme 1, Table 1). The structures of compounds 3 and 4 were established by IR, 1H, 19F, and 13C NMR spectroscopy as well as by elemental analysis.

These results indicate that the nature of the substituent at the 2-position influences the course of the acid-catalyzed hydrolysis of 2, which in the case of a CF₃ group took an unexpected direction compared with the reaction of nonfluorinated chromanes. It is important to note that this new cyclization process tolerates both electron-donating (MeO) and electron-withdrawing (Br, NO₂) substituents on the benzene ring. Moreover, unlike previously known approaches for the synthesis of quinolines from nitro derivatives, this reaction does not require any reducing agent or chromatographic purification of the final products, and thereby greatly facilitates the preparation of the target chromenopyridines 4.

We can assume that cyclization of 2 into 4 was possible due to the high C–H acidity of the H-2 in aci-form A, which could be easily abstracted by the base to form B (nitro–N-hydroxyamine prototropic tautomeric equilibria through a [1,4]-H shift), followed by dehydration of intermediate C into the corresponding α-nitrosoalkene C. Intramolecular nucleophilic attack of the side-chain enol on the nitroso group followed by dehydration results in the intermediate D, which undergoes a double [1,3]-H shift to give chromenopyridines 4 (Scheme 2). The lack of such reactivity in the case of compounds 2f–i was apparently due to the lower acidity of the H-2 proton. It should be noted that a similar [1,4]-H shift has been previously observed by us in the spontaneous ring-contraction–rearrangement of CF₃-containing 1,2-oxazine N-oxides into 1-pyrroline N-oxides.

The main information for the characterization of compounds 4 was obtained from the 1H NMR spectra, which showed no methylene signal, a result consistent with the pyridine structure. The most downfield shifted signal was assigned to the hydroxyl proton, which appeared as a singlet at δ 12.0 in CDCl₃, the singlet
at δ 7.58–7.77 was due to the resonance of the pyridine H-1 proton; assignment of all the signals was achieved for 2D 1H–13C HMQC, and HMBC experiments. In the 2D 1H-13C HMBC spectrum of 4c, a signal was observed at δ 316.9 from liquid NH3, indicating that the N was present in a pyridine ring.16 In addition, the CF3 group in the 19F NMR spectra of chromenopyridines 4 manifested itself as a doublet at δ 85.0–8.55 (J = 7.0–7.3 Hz).

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References and notes


10. General procedure for the synthesis of chromanes 2. A mixture of chromone 1 (1.0 mmol) and (E)-4-morpholinopiperidine/penic 3-en-2-one (0.17 g, 1.0 mmol) in dry MeCN was stirred at room temperature for several hours (Table 1). The solid that formed was filtered and recrystallized from CH2Cl2/hexane (1:2) to give compound 2 as a white powder.

11. X-ray diffraction study of compound 2a. Diffraction data were collected at 295 K on a Xcalibur 3 automatic single-crystal diffractometer (graphite monochromated MoKα, co-scan). The structure was solved by direct method and refined by the full-matrix least-squares method using the SHELX-97 program package.17 The H atoms were located geometrically using the riding model. Crystal data for 2a: C20H20F4NO4: M(R) = 412.40, monoclinic crystals, space group C2/c, a = 19.972(2), b = 10.108(1) Å, c = 20.1833(19) Å, (1-x, 1+y, 1-z); d = 90.00, μ = 96.442(1) μ; V = 4050.26(6) Å3, Z = 8, dcalc = 1.335 g/cm3, μ = 0.11 mm−1, F(000) = 1728. Crystallographic data for compound 2a (CCDC 924323) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

12. General procedure for the synthesis of compounds 3 and 4. The corresponding chromone 2 (1.0 mmol) was refluxed in a mixture of EtOH (4 ml) and H2O (2 ml), and conc. HCl (0.2 ml) with vigorous stirring for 6 h. The reaction mixture was cooled to room temperature and the solid that formed was filtered, washed with H2O (2 × 1 ml), dried at 70°C, and recrystallized from CH2Cl2/hexane (1:2) for 3a, a white powder or MeOH for 4c, colorless needles.

13. 1-(3-Nitro-4-morpholinopyridin-5-yl)thiophene (91%); 1H NMR (400 MHz, CDCl3): δ 8.82 (s, 1H), 7.84 (d, 1H, H-5, J = 8.9 Hz), 7.48 (dd, 1H, H-8, J = 11.2, 7.9 Hz), 7.35 (s, 1H, H-9), 7.31 (d, 1H, H-10, J = 8.9 Hz), 6.88 (d, 1H, H-11, J = 8.9 Hz), 4.11 (s, 4H, N(CH3)2) 2.52, (d, 2H, 1H, H-5, J = 8.9 Hz), 3.86 (s, 3H, OCH3).

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