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Highly regio- and stereoselective addition of ethyl 3-aminobut-2-enoates to 2-substituted 3-nitro-2*H*-chromenes

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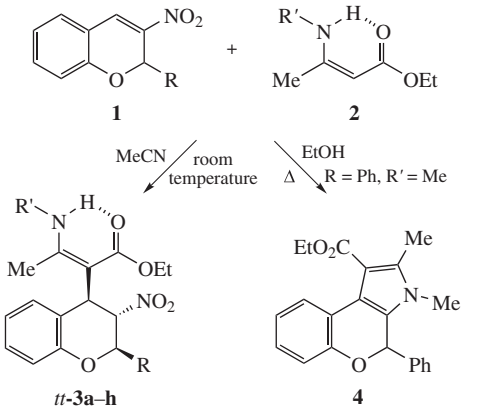
Ethyl 3-aminobut-2-enoates MeC(NHR)=CHCO$_2$Et (R = H, Me, Bn) whose reaction site is C(2) atom add to 2-R-3-nitro-2*H*-chromenes at their C(4) atom to give the corresponding *trans*,*trans*-2,3,4-trisubstituted chromanes. Analogous substrates MeC(NR$_2$)=CHCO$_2$Et (NR$_2$ is piperidin-1-yl or morpholin-4-yl) react by their C(4) methyl group to afford *cis*,*trans*-2,3,4-trisubstituted chromanes. The stereochemistry of the products was established by X-ray diffraction analysis.

2*H*-Chromene (2*H*-1-benzopyran) and its derivatives being an important class of oxygen-containing heterocyclic compounds that are widespread in the plant world[1] show various types of biological activity and can serve as starting compounds in syntheses of more complex molecules.[2] In this respect, 3-nitro-2*H*-chromenes, that are related to conjugated nitroalkenes, are of particular interest.[3] The reactions of 3-nitro-2*H*-chromenes with C-, N- and S-nucleophiles, which occur at the activated double bond and give various chromane derivatives, have been studied in sufficient detail.[4] However, reactions of these compounds with push-pull enamines have nearly not been covered. Only one paper is known[5] reporting the reaction of 2-aryl-3-nitro-2*H*-chromenes with methyl ester of β-methylaminocrotonic acid to give mixtures of the addition product and the corresponding pyrrole formed from it by the Grob reaction. Here, we have studied the reactions of 2-trifluoromethyl-, 2-trichloromethyl- and 2-phenyl-3-nitro-2*H*-chromenes with ethyl 3-aminobut-2-enoates MeC(NR^{1}R^2)=CHCO$_2$Et derived from ethyl acetoacetate and amino compounds such as ammonia, methyl- and benzylamines, morpholine and piperidine, and shown that transition from primary and secondary enamines to tertiary ones results in changes in both the regio- and stereochemistry of the addition product.

It has been found that 3-nitrochromenes **1** smoothly react in acetonitrile at ~20 °C with enamines **2** bearing primary or secondary amino groups (Scheme 1). The reaction takes two days and gives Michael C-adducts **3a**–**h** as colourless crystals in 37–83% yields. The structures of the latter were determined by elemental analyses, IR, ^{1}H, ^{19}F NMR spectroscopy and X-ray diffraction data.† The addition occurred at the chromene C-4 atom without elimination of the nitro group and with involvement of the most nucleophilic enamine α-C atom to give only one *trans*,*trans*-diastereomer (*tt*) with *Z*-configuration of the double bond stabilised by an intramolecular hydrogen bond. All the three bulky substituents in the benzopyran system occupy equatorial positions, as indicated by the high coupling constants between the H-2, H-3 and H-4 protons located in axial positions ($^3J_{H\text{-}2,H\text{-}3}$ 7.9–10.1 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 10.1–10.8 Hz in CDCl$_3$). The stereo-



a R = CF$_3$, R′ = H (83%)
b R = CF$_3$, R′ = Me (38%)
c R = CF$_3$, R′ = Bn (70%)
d R = CCl$_3$, R′ = H (58%)
e R = CCl$_3$, R′ = Me (76%)
f R = CCl$_3$, R′ = Bn (73%)
g R = Ph, R′ = Me (64%)
h R = Ph, R′ = Bn (37%)

Scheme 1

† NMR spectra were recorded for solutions of compounds in CDCl$_3$ at 400 or 500 MHz for ^{1}H and 376 MHz for ^{19}F.

Synthesis of compounds **3** *and* **6** (*general procedure*). A mixture of the corresponding chromene **1** (1 mmol) and enamine **2** (1 mmol) was kept in dry acetonitrile (0.2 ml) for several hours at ~20 °C. The precipitate was filtered off and recrystallized from dichloromethane–hexane (1 : 2).

Ethyl (2*S**,3*S**,4*S**)-(*Z*)-*3-amino-2-[3-nitro-2-(trifluoromethyl)-3,4-dihydro-2*H*-chromen-4-yl]-2-butenoate* **3a**. Yield 0.33 g (83%), mp 162–163 °C (decomp.), colourless prisms. IR (KBr, ν/cm^{-1}): 3403, 3315, 3328, 1652, 1633, 1570, 1555, 1529, 1484, 1455, 1371. ^{1}H NMR (500 MHz, CDCl$_3$) δ: 0.83 (t, 3H, Me, *J* 7.1 Hz), 2.05 (s, 3H, Me), 3.87 (dq, 1H, OC*H*H, *J* 10.7 and 7.1 Hz), 3.94 (dq, 1H, OCH*H*, *J* 10.7 and 7.1 Hz), 4.56 (d, 1H, H-4, *J* 10.4 Hz), 4.7–4.9 (br. s, 1H, N*H*H), 4.87 (dq, 1H, H-2, *J* 10.3 and 5.3 Hz), 5.53 (t, 1H, H-3, *J* 10.3 Hz), 6.96 (td, 1H, H-6, *J* 7.5 and 1.1 Hz), 6.97 (d, 1H, H-8, *J* 7.8 Hz), 7.03 (dt, 1H, H-5, *J* 8.0 and 1.3 Hz), 7.17 (dddd, 1H, H-7, *J* 8.3, 7.2, 1.7 and 0.9 Hz), 9.0 (br. s, 1H, NH*H*). ^{19}F NMR (471 MHz, CDCl$_3$) δ: 84.5 (d, CF$_3$, *J* 5.3 Hz). Found (%): C, 51.19; H, 4.54; N, 7.58. Calc. for C$_{16}$H$_{17}$F$_3$N$_2$O$_5$ (%): C, 51.34; H, 4.58; N, 7.48.

*Ethyl 2,3-dimethyl-4-phenyl-3,4-dihydrochromeno[3,4-*b*]pyrrole-1-carboxylate* **4**. A mixture of 3-nitro-2-phenyl-2*H*-chromene (0.25 g, 1.0 mmol) and ethyl β-methylaminocrotonate (0.14 g, 1.0 mmol) in ethanol (2 ml) was refluxed for 6 h. After that, the mixture was concentrated under reduced pressure and the remaining oil was purified by flash chromatography on silica gel (eluent – chloroform). The solid that formed was recrystallized from dichloromethane–hexane (1 : 2). Yield 0.17 g (48%), mp 143–144 °C, white powder. IR (KBr, ν/cm^{-1}): 1693, 1521, 1496, 1467, 1442, 1414. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.42 (t, 3H, Me, *J* 7.1 Hz), 2.52 (s, 3H, Me-2), 3.26 (s, 3H, NMe), 4.37 (dq, 1H, OC*H*H, *J* 10.7 and 7.1 Hz), 4.41 (dq, 1H, OCH*H*, *J* 10.7 and 7.1 Hz), 6.28 (s, 1H, H-4), 6.77 (dd, 1H, H-6, *J* 7.8 and 1.4 Hz), 6.92 (td, 1H, H-8, *J* 7.8 and 1.4 Hz), 6.97 (td, 1H, H-7, *J* 7.5 and 1.7 Hz), 7.17–7.22 (m, 2H, Ph), 7.24–7.29 (m, 3H, Ph), 8.14 (dd, 1H, H-9, *J* 7.5 and 1.7 Hz). Found (%): C, 74.12; H, 5.92; N, 3.88. Calc. for C$_{22}$H$_{21}$NO$_3$·0.5H$_2$O (%): C, 74.14; H, 6.22; N, 3.93.

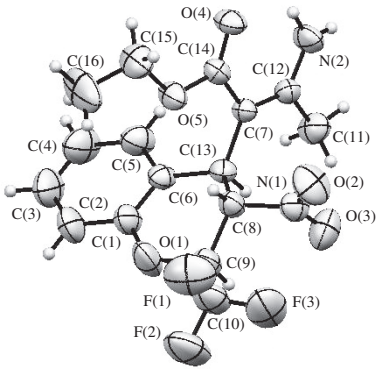
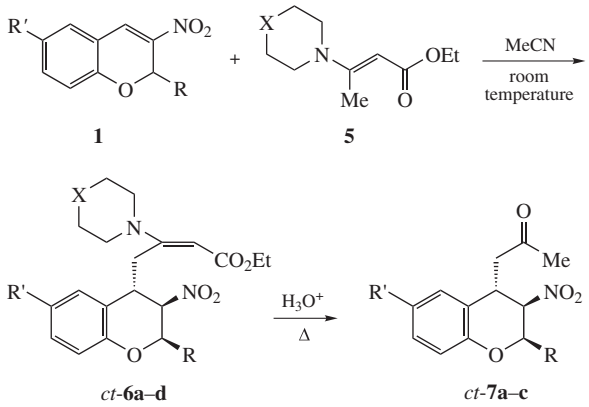


Figure 1 Molecular structure of chromane *tt*-**3a** (thermal ellipsoids at 50% probability level).

chemistry of compound **3a** was ultimately proven by X-ray diffraction study (Figure 1).‡



a R = CF_3, R′ = H, X = O (79%)
b R = CCl_3, R′ = Br, X = O (56%)
c R = CCl_3, R′ = H, X = CH_2 (54%)
d R = Ph, R′ = H, X = O (63%)

a R = CF_3 (44%)
b R = CCl_3 (56%)
c R = Ph (82%)

Scheme 2

Refluxing of 2-phenyl-3-nitro-2*H*-chromene with methyl β-methylaminocrotonate in ethanol resulted in chromeno[3,4-*b*]-pyrrole **4** in 48% yield,† which agrees with literature data,[5] but the reaction with methyl β-benzylaminocrotonate under the same conditions ceased at the stage of adduct **3h**. In the case of 2-trifluoromethyl- and 2-trichloromethyl-3-nitro-2*H*-chromenes, the reaction always gave only adducts **3**, irrespective of the solvent, whereas formation of chromenopyrroles was not observed at all.

It is interesting that on moving from primary and secondary *Z*-enamines **2**, which are stabilised by an intramolecular hydrogen bond, to tertiary *E*-enamines **5** obtained from ethyl acetoacetate and morpholine or piperidine, the reaction with nitrochromenes **1** under the same conditions occurred differently to afford ethyl 3-amino-4-(3-nitrochroman-4-yl)-2-butenoates **6a–d** in 41–79% yields (Scheme 2).† In this case, the reaction site of enamines **5** was the vinylogous β-Me group, whereas products **6** are formed as one *cis*,*trans*-diastereomer (*ct*) ($^3J_{H\text{-}2,H\text{-}3} \approx {}^3J_{H\text{-}3,H\text{-}4} \approx$ ≈ 1.5 Hz) with *E*-configuration of the double bond. This can be explained by the *E*-configuration of enamines **5** and, hence, steric constraints at the α-C atom. Note that enamines **5** react with α-(trichloroethylidene)nitroalkanes in a similar way.[6] The stereochemistry of product **6b** was confirmed by an X-ray diffraction study (Figure 2).‡ The CF_3 group in the ^{19}F NMR spectra of trifluoromethylated chromanes **3** and **6** in $CDCl_3$ manifests itself as a doublet at δ 84.5 (*J* 5.2 Hz) and 86.7 (*J* 6.0 Hz), respectively.

Hydrolysis of esters **6a**,**c**,**d** on refluxing in 70% ethanol in the presence of concentrated HCl is accompanied by decarboxylation to give acetonyl derivatives **7a–c** with the same configuration ($^3J_{H\text{-}2,H\text{-}3} \approx {}^3J_{H\text{-}3,H\text{-}4} \approx 2.0$ Hz). We also obtained compounds

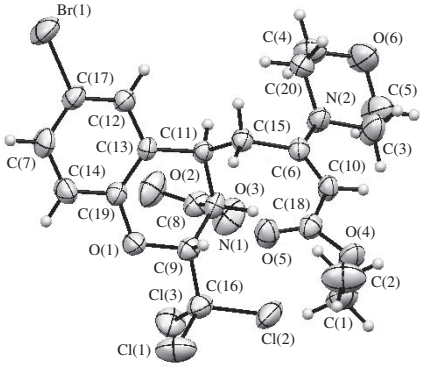


Figure 2 Molecular structure of chromane *ct*-**6b** (thermal ellipsoids at 50% probability level).

Ethyl (2S*,3R*,4S*)-(E)*-4-[6-bromo-3-nitro-2-(trichloromethyl)-3,4-dihydro-2*H*-chromen-4-yl]-3-morpholino-2-butenoate* **6b**. Yield 0.32 g (56%), mp 209–210 °C (decomp.), colourless crystals. IR (KBr, ν/cm^{-1}): 1673, 1583, 1556, 1480, 1449, 1400, 1354. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, 3H, Me, *J* 7.1 Hz), 2.85 (dd, 1H, H-4′a, *J* 15.2 and 5.4 Hz), 3.19 [dt, 2H, N(C*H*H)$_2$, *J* 12.8 and 4.9 Hz], 3.27 [dt, 2H, N(CH*H*)$_2$, *J* 12.8 and 4.8 Hz], 3.36 (dd, 1H, H-4, *J* 11.6 and 5.4 Hz), 3.73 [t, 4H, O(CH$_2$)$_2$, *J* 4.8 Hz], 4.06 (dq, 1H, OC*H*H, *J* 10.9 and 7.1 Hz), 4.10 (dq, 1H, OCH*H*, *J* 10.9 and 7.1 Hz), 4.31 (br. t, 1H, H-4′b, *J* 13.4 Hz), 5.08 (s, 1H, H-2′), 5.18 (d, 1H, H-2, *J* 1.4 Hz), 5.56 (br. s, 1H, H-3), 7.03 (d, 1H, H-8, *J* 8.8 Hz), 7.28 (d, 1H, H-5, *J* 2.2 Hz), 7.38 (dd, 1H, H-7, *J* 8.8 and 2.2 Hz). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.05 (t, 3H, Me, *J* 7.1 Hz), 2.21–2.38 [m, 5H, H-4′a, N(CH$_2$)$_2$], 3.07 [t, 4H, O(CH$_2$)$_2$, *J* 4.8 Hz], 3.12 (dd, 1H, H-4, *J* 11.4 and 5.9 Hz), 3.96–4.08 (m, 3H, H-4′b, OCH$_2$), 4.86 (s, 1H, H-2′), 5.43 (d, 1H, H-2, *J* 1.0 Hz), 5.76 (br. s, 1H, H-3), 6.69 (d, 1H, H-8, *J* 8.8 Hz), 6.96 (dd, 1H, H-7, *J* 8.8 and 2.2 Hz), 7.11 (d, 1H, H-5, *J* 2.2 Hz). Found (%): C, 41.78; H, 3.74; N, 4.95. Calc. for $C_{20}H_{22}BrCl_3N_2O_6$ (%): C, 41.95; H, 3.87; N, 4.89.

Synthesis of compounds **7** (*general procedure*). A mixture of the corresponding chromane **6** (1.0 mmol), H_2O (1.0 ml), EtOH (4.0 ml) and concentrated HCl (0.2 ml) was refluxed for 6 h. After cooling, the solid was separated by filtering, washed with water (2×1 ml), dried and recrystallized from an appropriate solvent.

(2S*,3R*,4S*)*-1-[3-Nitro-2-(trifluoromethyl)-3,4-dihydro-2*H*-chromen-4-yl]acetone* **7a**. Yield 0.13 g (44%), mp 109–110 °C (dichloromethane–hexane, 1 : 1), white powder. IR (KBr, ν/cm^{-1}): 1719, 1585, 1564, 1490, 1375. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.23 (s, 3H, Me), 2.80 (dd, 1H, C*H*HAc, *J* 18.8 and 9.7 Hz), 3.05 (dd, 1H, CH*H*Ac, *J* 18.8 and 3.8 Hz), 3.97 (br. d, 1H, H-4, *J* 8.8 Hz), 4.52 (qd, 1H, H-2, *J* 5.9 and 2.2 Hz), 5.16 (t, 1H, H-3, *J* 2.0 Hz), 7.02 (dd, 1H, H-8, *J* 8.3 and 1.0 Hz), 7.06 (td, 1H, H-6, *J* 7.3 and 1.0 Hz), 7.13 (dd, 1H, H-5, *J* 7.7 and 1.3 Hz), 7.24 (td, 1H, H-7, *J* 7.6 and 1.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: 87.0 (d, CF_3, *J* 5.9 Hz). Found (%): C, 51.62; H, 4.03; N, 4.49. Calc. for $C_{13}H_{12}F_3NO_4$ (%): C, 51.49; H, 3.99; N, 4.62.

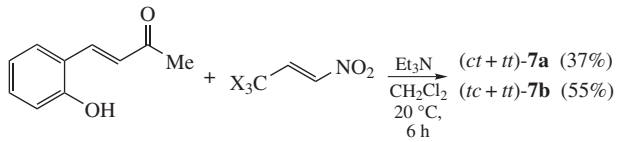
‡ *X-Ray diffraction data for* **3a** *and* **6b**.

At 295 K, the crystals of **3a** ($C_{16}H_{17}F_3N_2O_5$) are monoclinic, space group $P2_1/c$, a = 9.5731(11), b = 10.0413(9) and c = 18.4072(12) Å, β = 92.103(7)°, V = 1768.2(3) Å^3, Z = 4, d_{calc} = 1.406 g cm^{-3}, μ = 0.125 mm^{-1}, F(000) = 776.

At 295 K, the crystals of **6b** ($C_{20}H_{22}BrCl_3N_2O_6$) are monoclinic, space group $P2_1/n$, a = 12.0862(11), b = 12.0044(7) and c = 17.4391(16) Å, β = = 106.161(8)°, V = 2430.2(3) Å^3, Z = 4, d_{calc} = 1.565 g cm^{-3}, μ = 2.059 mm^{-1}, F(000) = 1160.

Diffraction data were collected on an Xcalibur 3 automatic single-crystal diffractometer (graphite-monochromated MoKα radiation, ω-scans). The structures were solved by direct methods and refined by the full-matrix least-squares method using the SHELX-97 program package.[7] The H atoms were located geometrically using the riding model.

CCDC 915041 and 915042 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.



Scheme 3

7a,**b** in a different way, *viz.*, by tandem condensation of *o*-hydroxybenzylideneacetone with (*E*)-1-nitro-3,3,3-trifluoro(trichloro)-propenes (Scheme 3). However, the reaction was less stereoselective in this case, and chromanes **7a**,**b** were formed as a mixture of two diastereomers (*ct*:*tt* = 80:20 for **7a** and *tc*:*tt* = 72:28 for **7b**).

Thus, the reaction of 2-substituted 3-nitro-2*H*-chromenes with push-pull enamines depending on their structure, gives either *trans*,*trans*-3-amino-2-(3-nitrochroman-4-yl)-2-butenoates or *cis*,*trans*-3-amino-4-(3-nitrochroman-4-yl)-2-butenoates. The polyfunctional products described above can serve for the preparation of more complex heterocyclic compounds, including those containing CF_3 and CCl_3 groups.

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Online Supplementary Materials

Supplementary data associated with this article (characteristics of compounds *tt*-**3b**–**h**, *ct*-**6a**,**c**,**d** and *ct*-**7b**,**c**) can be found in the online version at doi:10.1016/j.mencom.2013.05.010.

References

1 G. P. Ellis, in *The Chemistry of Heterocyclic Compounds*, ed. G. P. Ellis, Wiley, New York, 1977, p. 31.

2 (*a*) W. S. Bowers, T. Ohta, J. S. Cleere and P. A. Marsella, *Science*, 1976, **193**, 542; (*b*) R. Bergmann and R. Gericke, *J. Med. Chem.*, 1990, **33**, 492; (*c*) G. Burrell, F. Cassidy, J. M. Evans, D. Lightowler and G. Stemp, *J. Med. Chem*., 1990, **33**, 3023; (*d*) R. Gericke, J. Harting, I. Lues and C. Schittenhelm, *J. Med. Chem.*, 1991, **34**, 3074.

3 (*a*) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001; (*b*) A. Yoshikoshi and M. Miyashita, *Acc. Chem. Res*., 1985, **18**, 284.

4 (*a*) V. Yu. Korotaev, V. Ya. Sosnovskikh, I. B. Kutyashev and M. I. Kodess, *Lett. Org. Chem*., 2005, **2**, 616; (*b*) V. Yu. Korotaev, V. Ya. Sosnovskikh, I. B. Kutyashev and M. I. Kodess, *Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 317 (*Izv. Akad. Nauk, Ser. Khim.*, 2006, 309); (*c*) V. Yu. Korotaev, V. Ya. Sosnovskikh, I. B. Kutyashev and M. I. Kodess, *Russ. Chem. Bull., Int. Ed*., 2006, **55**, 2020 (*Izv. Akad. Nauk, Ser. Khim.*, 2006, 1945); (*d*) V. Yu. Korotaev, I. B. Kutyashev, V. Ya. Sosnovskikh and M. I. Kodess, *Mendeleev Commun.*, 2007, **17**, 52; (*e*) V. Yu. Korotaev, V. Ya. Sosnovskikh and I. B. Kutyashev, *Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2054 (*Izv. Akad. Nauk, Ser. Khim*., 2007, 1985); (*f*) V. Yu. Korotaev, V. Ya. Sosnovskikh, M. A. Barabanov, E. S. Yasnova, M. A. Ezhikova, M. I. Kodess and P. A. Slepukhin, *Tetrahedron*, 2010, **66**, 1404; (*g*) V. Yu. Korotaev, V. Ya. Sosnovskikh, A. Yu. Barkov, P. A. Slepukhin, M. A. Ezhikova, M. I. Kodess and Yu. V. Shklyaev, *Tetrahedron*, 2011, **67**, 8685; (*h*) S. Biswas, P. R. Maulik, R. C. Gupta, M. Seth and A. P. Bhaduri, *Acta Crystallogr., Sect. C*, 1996, **52**, 1036; (*i*) C. Lin, J. Hsu, M. N. V. Sastry, H. Fang, Z. Tu, J.-T. Liu and C.-F. Yao, *Tetrahedron*, 2005, **61**, 11751.

5 R. C. Gupta, M. Seth and A. P. Bhaduri, *Indian J. Chem*., 1991, **30B**, 297.

6 V. Yu. Korotaev, A. Yu. Barkov, P. A. Slepukhin, M. I. Kodess and V. Ya. Sosnovskikh, *Tetrahedron Lett*., 2011, **52**, 5764.

7 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.

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