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Rearrangement of 3-aminoisoxazolo[4,5-*c*]coumarins into 2-aminooxazolo[4,5-*c*]coumarins mediated by carboxylic acid anhydrides

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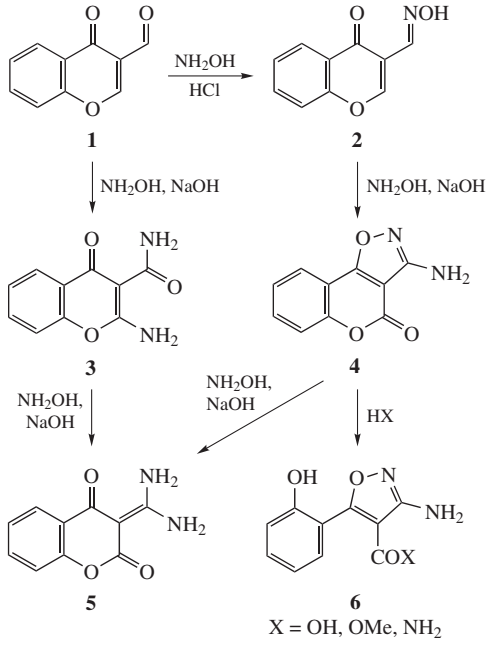
Reactions of 3-amino-4*H*-chromeno[3,4-*d*]isoxazol-4-ones with acetic and trifluoroacetic anhydrides gave the corresponding acetyl derivatives, which were rearranged into 2-amino-4*H*-chromeno[3,4-*d*][1,3]oxazol-4-ones by heating in DMSO solution.

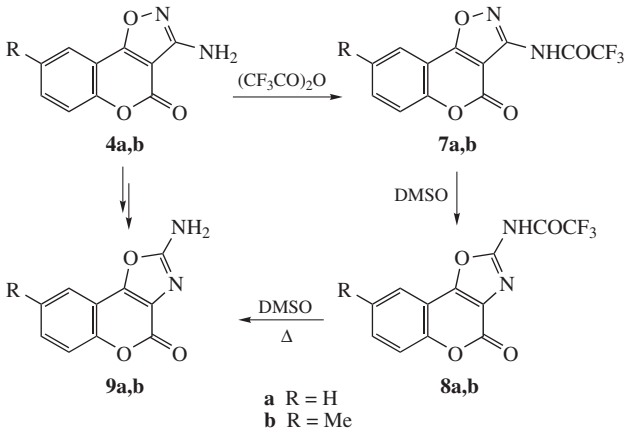
3-Formylchromone is very reactive, and its reactions with hydroxylamine give a variety of products.[1] Since the structures of these products were in doubt,[2] we have recently reinvestigated the oximation reaction of 3-formylchromone **1** and its derivatives (3-formylchromone oxime **2** and 3-cyanochromone) and found that, by varying the starting materials and reaction conditions, 2-aminochromone-3-carboxamide **3**, 3-amino-4*H*-chromeno[3,4-*d*]isoxazol-4-one **4** (3-aminoisoxazolo[4,5-*c*]coumarin), and 3-(diaminomethylene)chroman-2,4-dione **5** could be prepared in moderate to good yields.[3] The origin of compounds **3** and **4**, which are isolable intermediates under basic conditions and can be converted into **5** by treatment with an excess of hydroxylamine hydrochloride and sodium hydroxide, was explained and the overall reaction was represented as a coherent process, the final product of which is chroman-2,4-dione **5**. In addition, it was also found that the coumarin ring of 3-aminoisoxazolo[4,5-*c*]coumarin **4** can be easily opened by the action of sodium hydroxide, methanol and ammonia to give densely functionalized isoxazoles **6**[3] (Scheme 1). Since coumarins with 3,4-heterocyclic fused ring systems serve as useful synthetic intermediates and key compounds for drug design,[4] it is reasonable to expect that heterocycles like compound **4** will have significant synthetic application.



Scheme 1

In continuation of our studies on the chemical properties of 3-aminoisoxazolo[4,5-*c*]coumarin **4**, which is highly reactive with nucleophiles, we investigated its reactions with electrophilic reagents, such as carboxylic acid anhydrides. We found that isoxazolocoumarins **4a**,**b**, prepared from chromones **2** as previously reported,[3] easily reacted with an excess of trifluoroacetic anhydride (3 equiv.) in benzene affording trifluoroacetyl derivatives **7a**,**b** in 81–87% yields, which spontaneously rearrange into isomeric compounds on dissolution and storage in DMSO-d^6 at room temperature. The rearranged products were identified as oxazolo[4,5-*c*]coumarins **8a**,**b** based on the ^{13}C NMR spectra. In the case of **7a**, the reaction progress was monitored by ^{19}F NMR spectroscopy (the signal of CF_3 appeared as a singlet at 88.4 ppm for **7a** or 88.5 ppm for **8a**). After 28 h, the spectrum showed the ratio **7a**:**8a** = 78:22; after 8 days, 57:43, while product **8a** was the predominant species (74%) in a mixture with starting material **7a** (24%) and trifluoroacetic acid (2%) after three weeks. On heating in DMSO at 90 °C for 5 h, compounds **7a**,**b** gave hitherto unknown 2-amino-4*H*-chromeno-[3,4-*d*]oxazol-4-ones **9a**,**b** (2-aminooxazolo[4,5-*c*]coumarins) in high yields as the ring rearrangement products with concomitant loss of the trifluoroacetyl group; no trace amounts of trifluoroacetylated oxazoles **8a**,**b** have been detected (Scheme 2).

Next, taking into account the above results, we tried to detect an analogous ring isomerization under the action of acetic anhydride. The reaction of **4a**,**b** with acetic anhydride in the

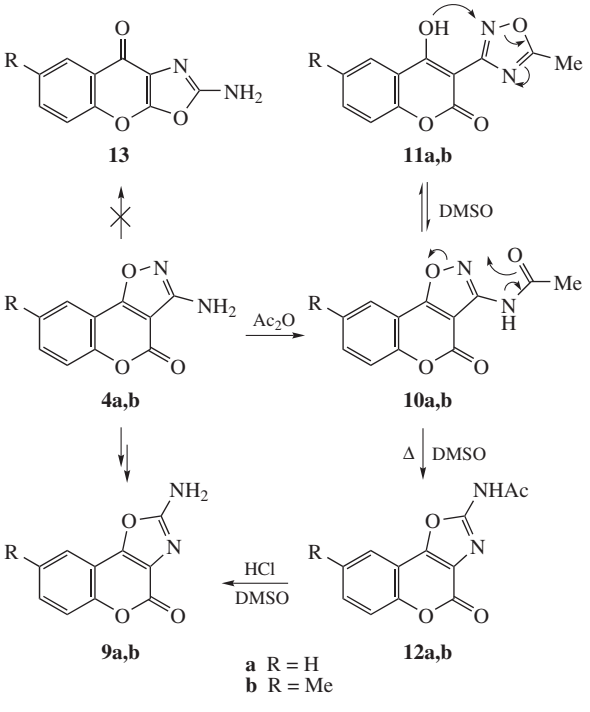


Scheme 2

presence of a catalytic amount of conc. H_2SO_4 gave acetyl derivatives **10a**,**b** (75–98% yields), which exist in DMSO-d^6 solution as a mixture with 5-methyl-1,2,4-oxadiazoles **11a**,**b**. The **10** → **11** transformation is an equilibrium process, the position of which is solvent dependent (**10a**,**b**:**11a**,**b** = 42–45:58–55 in DMSO-d^6 and **10a**:**11a** = 32:68 in DMF-d^7; the ratio of the products was determined by the integration of signals in the ^{1}H NMR spectra). This result is not surprising since the base-catalyzed interconversion between 3-acetyl(benzoyl)aminobenzisoxaloles and 5-methyl(phenyl)-3-(2-hydroxyphenyl)-1,2,4-oxadiazoles, where the equilibrium composition depends on the base and the nature of the substituent, has already been described.[5] The observed conversion is a mononuclear heterocyclic rearrangement recognized by Boulton and Katritzky[6] and developed by Vivona and Spinelli.[7] Nevertheless, when compounds **10a**,**b** were heated in DMSO at 90–95 °C for 1.5–2 h, 2-acetamidooxazolo[4,5-*c*]coumarins **12a**,**b** were obtained in good yields (56–67%).† In this case, deacetylation does not proceed and oxazoles **9a**,**b** can be prepared from **12a**,**b** by hydrochloric acid hydrolysis (Scheme 3). The possibility that the product could be oxazolo[5,4-*b*]chromone **13** was considered unlikely because the IR spectra showed absorption bands at 1730–1760 cm^{-1}, typical of the carbonyl group in coumarins[8] (the chromone carbonyl band is usually near 1660 cm^{-1}).

All of the signals in the ^{1}H and ^{13}C NMR spectra of compounds **9**–**12** were assigned on the basis of 2D ^{1}H–^{13}C HSQC, ^{1}H–^{15}N HMQC, and HMBC experiments. The significant ^{13}C NMR chemical shifts compiled in Figure 1 suggest differences in the regiochemistry at the C^{3a} and C^{9b} atoms of **10b** and **12b**, and a comparison of these chemical shifts with the data reported for related systems[9] confirms the validity of the structures. Besides the signals expected for the aromatic protons, the ^{1}H NMR spectra of **12a**,**b** showed a characteristic singlet due to the amidic proton at 12.0 ppm; the amino group of oxazoles **9a**,**b** appeared as a singlet at 7.8 ppm. The simplest way to distinguish between isomers **4** and **9** is the ^{1}H chemical shift of the amino group in DMSO-d^6: the NH_2 protons of oxazoles **9** constantly resonate at ~1.4 ppm downfield.

To confirm the conclusion about the structures of **10** and **11**, we carried out additionally a 2D ^{1}H–^{15}N HMBC experiment for



Scheme 3

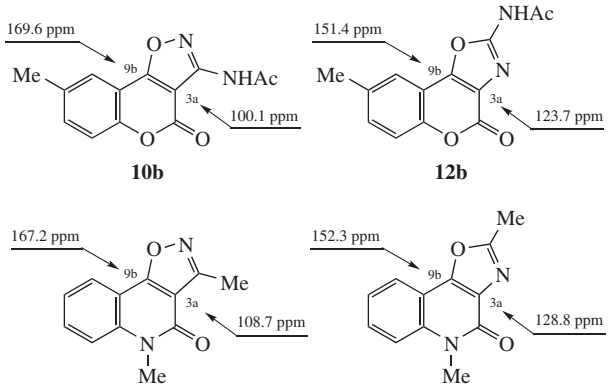


Figure 1 Comparison of the selective ^{13}C chemical shifts of isoxazole **10b** and oxazole **12b** with the data reported for related fused 2-quinolones.[9]

† NMR spectra were recorded for DMSO-d_6 solutions of compounds at 400 MHz for 1H, 100 MHz for 13C and 40 MHz for 15N.

*3-Amino-8-methyl-4*H*-chromeno[3,4-*d*]isoxazol-4-one* **4b**. This compound was prepared from 3-formyl-6-methylchromone oxime according to the procedure described previously for **4a**.[3] Yield, 46%; mp 248–250 °C. ^{1}H NMR, δ: 2.42 (s, 3H, Me), 6.42 (s, 2H, NH_2), 7.46 (d, 1H, H-6, *J* 8.6 Hz), 7.58 (ddq, 1H, H-7, *J* 8.6, 2.1 and 0.5 Hz), 7.78 (br. d, 1H, H-9, *J* 2.0 Hz). ^{13}C NMR, δ: 20.19 (Me), 97.10 (C^{3a}), 110.23 (C^{9a}), 117.06 (C^6), 121.88 (C^9), 134.59 (C^8), 134.70 (C^7), 151.81 (C^{5a}), 156.52 (C$^{3/4}$), 160.50 (C$^{4/3}$), 168.72 (C^{9b}). IR (KBr, ν/cm^{-1}): 3474, 3433, 3368, 3315, 3205, 1737, 1649, 1620, 1577, 1526, 1470. Found (%): C, 61.07; H, 3.76; N, 12.63. Calc. for $C_{11}H_8N_2O_3$ (%): C, 61.11; H, 3.73; N, 12.96.

*2-Amino-8-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one* **9b**. This compound was prepared from **7b** by heating in DMSO at 90 °C for 5 h. Yield, 92%; mp ~320 °C (decomp.). ^{1}H NMR, δ: 2.41 (s, 3H, Me), 7.35 (dd, 1H, H-7, *J* 8.5 and 1.8 Hz), 7.40 (d, 1H, H-6, *J* 8.5 Hz), 7.45 (s, 1H, H-9), 7.76 (s, 2H, NH_2). ^{13}C NMR, δ: 20.38 (Me), 111.11 (C^{9a}), 116.57 (C^6), 119.27 (C^9), 125.20 (C^{3a}), 130.36 (C^7), 134.27 (C^8), 149.16 (C$^{5a/9b}$), 149.32 (C$^{9b/5a}$), 155.76 (C^4), 162.46 (C^2). IR (ATR, ZnSe, ν/cm^{-1}): 3337, 3117, 1727, 1667, 1634, 1566. Found (%): C, 61.05; H, 3.76; N, 12.94. Calc. for $C_{11}H_8N_2O_3$ (%): C, 61.11; H, 3.73; N, 12.96.

*3-Acetamido-8-methyl-4*H*-chromeno[3,4-*d*]isoxazol-4-one* **10b** *and 4-hydroxy-6-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)-2*H*-chromen-2-one* **11b**. A mixture of **4b** (600 mg, 2.78 mmol) in acetic anhydride (4 ml) was heated under reflux, and one drop of conc. H_2SO_4 was added. The resulting reaction mixture was kept at room temperature for a day and the solid obtained at standing was filtered off, washed with diethyl ether, and dried. Yield, 98%; mp 203–204 °C. ^{1}H NMR, δ: (**10b**, 45%) 2.18 (s, 3H, Me), 2.44 (s, 3H, Me), 7.51 (d, 1H, H-6, *J* 8.5 Hz), 7.64 (ddq, 1H, H-7, *J* 8.5, 2.2 and 0.6 Hz), 7.90 (br. d, 1H, H-9, *J* 2.0 Hz), 10.55 (s, 1H, NH); (**11b**, 55%) 2.42 (s, 3H, Me), 2.72 (s, 3H, Me), 7.37 (d, 1H, H-8, *J* 8.5 Hz), 7.58 (ddq, 1H, H-7, *J* 8.5, 2.0 and 0.6 Hz), 7.80 (br. d, 1H, H-5, *J* 1.9 Hz). ^{13}C NMR, δ: (**10b**) 20.19 (8-Me), 23.05 (Me), 100.06 (C^{3a}), 109.76 (C^{9a}), 117.08 (C^6), 122.04 (C^9), 134.93 (C^8), 135.23 (C^7), 151.76 (C^{5a}), 155.21 (C^3), 158.84 (C^4), 168.53 (NCO), 169.64 (C^{9b}); (**11b**) 11.94 (Me), 20.33 (6-Me), 91.66 (C^3), 114.94 (C^{4a}), 116.37 (C^8), 123.72 (C^5), 133.77 (C^6), 135.06 (C^7), 151.21 (C^{8a}), 154.61 (C^2), 162.72 (C$^{3'}$), 166.22 (C^4), 176.30 (C$^{5'}$). ^{15}N NMR, δ: (**10b**) 116.8 (NH); (**11b**) 236.7 (N$^{4'}$). IR (ATR, ZnSe, ν/cm^{-1}): 1728, 1706, 1623, 1569, 1505, 1488. Found (%): C, 60.54; H, 3.98; N, 10.86. Calc. for $C_{13}H_{10}N_2O_4$ (%): C, 60.47; H, 3.90; N, 10.85.

*2-Acetamido-8-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one* **12b**. A solution of **10b** (200 mg, 0.77 mmol) in DMSO (2 ml) was heated at 90–95 °C for 1.5–2 h. Then, the reaction mixture was diluted with water (8 ml) and the solid obtained was filtered off, washed with water and recrystallized from butanol–xylene. Yield, 56%; mp 282–283 °C. ^{1}H NMR, δ: 2.22 (s, 3H, Me), 2.43 (s, 3H, 8-Me), 7.46 (s, 2H, H-6, H-7), 7.55 (s, 1H, H-9), 11.96 (s, 1H, NH). ^{13}C NMR, δ: 20.30 (8-Me), 23.67 (Me), 110.64 (C^{9a}), 116.93 (C^6), 120.18 (C^9), 123.73 (C^{3a}), 132.05 (C^7), 134.72 (C^8), 150.14 (C^{5a}), 151.35 (C^{9b}), 154.60 (C$^{2/4}$), 155.38 (C$^{4/2}$), 167.95 (NCO). ^{15}N NMR, δ: 128.9 (NH). IR (ATR, ZnSe, ν/cm^{-1}): 3217, 3055, 1752, 1723, 1608, 1587, 1519, 1495. Found (%): C, 60.40; H, 3.85; N, 10.73. Calc. for $C_{13}H_{10}N_2O_4$ (%): C, 60.47; H, 3.90; N, 10.85.

a mixture of **10b** and **11b**, which exhibits a cross-peak between the Me group (δ 2.72 ppm) and the N^4 atom (δ_{N4} 236.7 ppm). In the ^1H–^{15}N HMQC spectra, showing directly bound hydrogen and nitrogen atoms, one ^{15}N atom is revealed at δ_N 116.8 ppm, which has a direct constant with the NH proton at δ 10.55 ppm; the same nitrogen atom in the ^1H–^{15}N HMBC correlated with the Me group at δ 2.18 ppm.

This ring isomerization is a well-documented photochemical,[10] thermal[11] or base-promoted reaction[12] of the isoxazole system. The observed rearrangement shows a peculiar reactivity of the isoxazolo[4,5-*c*]coumarin system of **4** and seems an unusual case of an uncatalyzed and mild isoxazole to oxazole rearrangement induced by carboxylic acid anhydrides. This result is consistent with those obtained by Padwa *et al.*,[11] who found that the dissociation energy of the O–N bond is significantly diminished when the isoxazole oxygen is conjugated with a carbonyl group (thermolysis of 4-acylisoxazoles was performed at 230–240 °C, whereas 3,4-diphenyl-5-acetylisoxazole was perfectly stable to the thermal conditions[11]). At the same time, the rearrangement of 3-aroylaminoisoxazoles[12] proceeded in the presence of Bu^{t}OK in DMF at 110–120 °C. The ability of **7** and **10** to rearrange into **8** and **12** under mild reaction conditions is presumably due to the favorable combination of 4-carbonyl and 3-acylamino groups in the isoxazole ring, which increases the acidity of the amidic proton required for rearrangement. The initial deprotonation of the very acidic NH proton in **7** or **10** under the action of DMSO probably enhanced the nucleophilicity of the neighboring nitrogen atom and promoted O–N bond cleavage. Note that the rearrangement occurs only with acylated derivatives; refluxing in DMSO left isoxazoles **4** almost unchanged. As regards the mechanistic aspects, the formation of the oxazole system could be explained by assuming the anionic promoted Boulton–Katritzky rearrangement of the isoxazole ring to the less stable 3-(4-hydroxycoumarin-3-yl)-1,2,4-oxadiazoles and their conrtaction to the azirine intermediates, followed by an anionic assisted ring expansion of the latter *via* carbodiimide to fused 2-acylaminooxazoles.[13] The driving force for this irreversible rearrangement is presumably the formation of the thermodynamically more stable 2-aminooxazole structure with an isourea fragment.

Note that only 2-alkyl- and 2-aryloxazolo[4,5-*c*]coumarins and -quinolones derived either from 3-amino-4-hydroxycoumarins[14] and -2-quinolones,[15] or by Beckmann rearrangement of the oximes of 3-acyl-4-hydroxycoumarins[8] and -2-quinolones[9] were described previously. Some of these derivatives possess antiallergic, antiinflammatory and central nerve depressing activities.[15] In conjunction with the pharmaceutical importance of fused heterocycles incorporating a coumarin moiety,[4] this simple and cheap synthesis of 2-aminooxazolo[4,5-*c*]coumarins **9** and their acetyl derivatives **12** from readily available 3-formylchromones **1** is noteworthy and will complement the published synthetic methods.

In conclusion, we found that 3-aminoisoxazolo[4,5-*c*]coumarins react with carboxylic acid anhydrides to afford the corresponding amides, which can be converted by heating in DMSO into either 2-acetamido- or 2-aminooxazole derivatives depending upon the nature of the anhydride employed for rearrangement. The resulting products, 2-aminooxazolo[4,5-*c*]coumarins, are of considerable interest as useful precursors in the synthesis of other biologically and medicinally important heterocycles.

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