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Mendeleev Commun., 2011, **21**, 110–111
Mendeleev Communications

Reactions of 3-aminoisoxazolo[4,5-*c*]coumarin with benzoyl chloride: the first example of a preparative 1,2,4-oxadiazole–oxazole rearrangement

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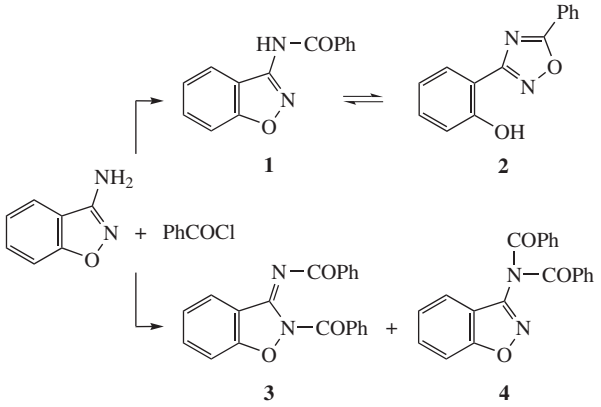
DOI: 10.1016/j.mencom.2011.03.019

Depending on conditions, reaction of 3-amino-4*H*-chromeno[3,4-*d*]isoxazol-4-one with benzoyl chloride gives 4-hydroxy- and/or 4-benzoyloxy-3-(5-phenyl-1,2,4-oxadiazol-3-yl)coumarins, which are rearranged into 2-benzamido-4*H*-chromeno[3,4-*d*]oxazol-4-one by heating in DMSO.

Unlike the reaction of 3-amino-5-methylisoxazole with aroyl chlorides giving the expected 3-aroylamino-5-methylisoxazoles,[1] information on the reactions of 3-aminobenzisoxazole with benzoyl chloride is rather contradictory. It has been reported previously[2] (without the procedure details) that this reaction gives 3-benzoylaminobenzisoxazole **1** in 65% yield; in the presence of bases, such as sodium ethoxide or sodium hydroxide, compound **1** exists in equilibrium with 3-(2-hydroxyphenyl)-5-phenyl-1,2,4-oxadiazole **2** (the Boulton–Katritzky rearrangement[3]). On the other hand, it was recently[4] shown that treatment of 3-aminobenzisoxazole with benzoyl chloride in the presence of triethylamine in dichloromethane afforded compound **1** in only 2% yield, whereas dibenzoylated derivatives **3** (38%) and **4** (17%) were the major products (Scheme 1).



Scheme 1

In this work we studied the reaction of 3-amino-4*H*-chromeno[3,4-*d*]isoxazol-4-one **5** with excess of benzoyl chloride (5.6 equiv., 90 °C, 4 h) in the absence of a solvent and found that the initial N-benzoylation, which results in 3-benzoylamino-4*H*-chromeno[3,4-*d*]isoxazol-4-one **6**, is accompanied by the Boulton–Katritzky rearrangement of the isoxazole ring into a 1,2,4-oxadiazole ring (Scheme 2). The thus forming product is 4-hydroxy-3-(5-phenyl-1,2,4-oxadiazol-3-yl)coumarin **7**, which is more thermodynamically stable than compound **6** due to conjugation with the phenyl substituent. The rearrangement occurs incompletely under these conditions, and the products **6** and **7** were isolated as 26 : 74 mixture (^{1}H NMR spectroscopic data). However, addition of one drop of concentrated H_2SO_4 accelerated the process considerably and furnished individual compound **7** (30 min, yield 51%). If sulfuric acid is replaced by pyridine, deeper benzoylation occurs to give 4-benzoyloxy-3-(5-phenyl-1,2,4-oxadiazol-3-yl)coumarin **8** (yield 76%).† Compounds **7** and **8** are rearranged almost quantitatively on heating in DMSO (90 °C, 3–4 h) to produce 2-benzoylamino-4*H*-chromeno[3,4-*d*]oxazol-4-one **9** (Scheme 2).‡

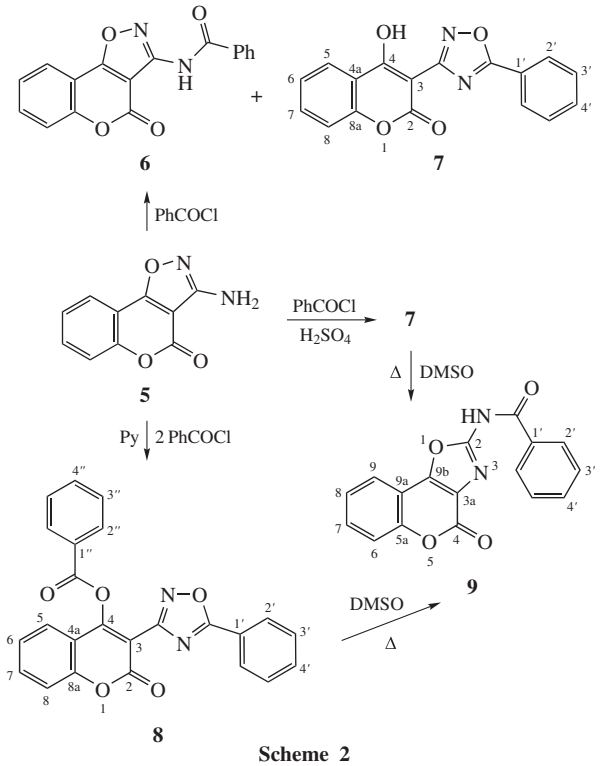
It is important to note that the **7**(**8**) → **9** transformation is the first example of preparative 1,2,4-oxadiazole–oxazole rearrangement, since the previously studied 3-acetonyl-5-aryl-1,2,4-oxadiazoles are characterised by the Boulton–Katritzky rearrangement into 3-aroylamino-5-methylisoxazoles, whereas 2-aroylamino-5-methyloxazoles were formed in insignificant amounts.[5] Although the rearrangement of the isoxazole **5** *N*-acetyl derivative, 3-acetylamino-4*H*-chromeno[3,4-*d*]isoxazol-4-one, into 2-acetylamino-4*H*-chromeno[3,4-*d*]oxazol-4-one recently discovered by us occurs *via* 4-hydroxy-3-(5-methyl-1,2,4-oxadiazol-3-yl)coumarin, we failed to isolate it in pure form due to its lower stability.[6] We obtained the parent compound of this series, 2-amino-4*H*-chromeno[3,4-*d*]oxazol-4-one, from a trifluoroacetyl derivative of isoxazole **5** by the isoxazole–oxazole rearrangement,[6] the mechanism of which has been studied in detail.[5] Based on the data reported in ref. 5, it may be assumed that DMSO acts as the Lewis base in the **7** → **9** conversion by deprotonating the 4-hydroxycoumarin ring to the anionic form, which then undergoes recyclisation *via* azirin and carbodiimide to give fused oxazole **9** (Scheme 3).

The structures of compounds **7**–**9** were confirmed by ^{1}H and ^{13}C NMR spectroscopic data; assignment of all signals was

† *4-Hydroxy-3-(5-phenyl-1,2,4-oxadiazol-3-yl)-*2H*-chromen-2-one* **7**. A suspension of **5** (200 mg, 1.0 mmol) in benzoyl chloride (1.8 g, 12.8 mmol) was heated to dissolve the substance, followed by addition of one drop of conc. H_2SO_4. The resulting mixture was kept at room temperature for 30 min and diluted with diethyl ether (8 ml). The solid obtained was filtered off, washed with diethyl ether, and recrystallized from butanol–ethanol (8:2). Yield, 150 mg (51%); mp 192–194 °C, colourless powder.

*4-Benzoyloxy-3-(5-phenyl-1,2,4-oxadiazol-3-yl)-*2H*-chromen-2-one* **8**. To a suspension of **5** (260 mg, 1.3 mmol) in benzoyl chloride (0.9 g, 6.4 mmol), pyridine (240 mg, 3.0 mmol) was added. The resulting reaction mixture was heated at 90 °C for 2 h and diluted with toluene (4 ml). Then, the mixture was heated for another 6 h and kept at room temperature. The solid obtained was filtered off, washed with toluene, ethanol, and water. Yield, 400 mg (76%); mp 228–230 °C, colourless powder.

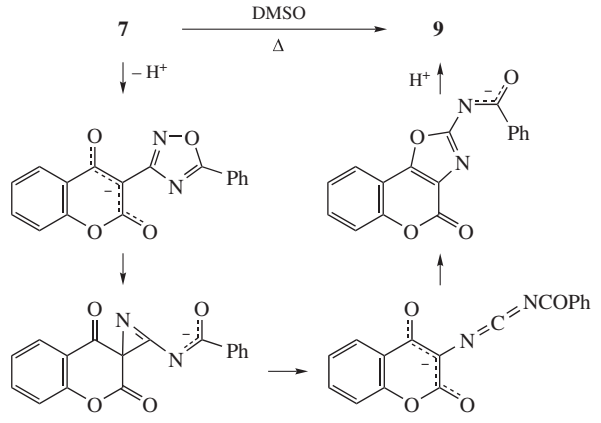
For spectral characteristics and elemental analyses of compounds **7** and **8**, see Online Supplementary Materials.



Scheme 2

performed based on results of 2D ^{1}H–^{13}C HSQC and HMBC experiments and by comparison of characteristic ^{1}H and ^{13}C shifts with those of similar atoms in related molecules[6] (Figure 1). The most informative cross-peaks of the 2D HMBC spectrum in DMSO-d_6 for compound **8** are as follows: H(2′,6′)/OCN, H(2″,6″)/OCO, H(5)/C(4), H(5)/C(8a), H(5)/C(7), H(7)/C(8a), H(7)/C(5), H(4″)/C(2″,6″), H(2″,6″)/C(4″).

Unfortunately, to date, all our attempts to extend the scope of this 1,2,4-oxadiazole–oxazole rearrangement failed. In fact, contrary to expectations, the stage of isoxazole **5** 4-chlorobenzoylation under sulfuric acid catalysis proved to be slower than benzoylation and resulted in a mixture of the starting isoxazole **5** (85%) and 4-hydroxy-3-[5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl]coumarin **11** (15%), whereas the reaction of **5** with 4-chlorobenzoyl chloride in the presence of pyridine led to a mixture of approximately equal amounts of compounds **10** (45%) and **11** (55%) (Scheme 4).



Scheme 3

‡ *2-Benzoylamino-4*H*-chromeno[3,4-*d*]oxazol-4-one* **9**. A solution of **7** or **8** (0.35 mmol) in DMSO (1.5 ml) was heated at 90 °C for 3–4 h. Then, the reaction mixture was diluted with water (8 ml) and the solid obtained was filtered off, washed with water, and dried. Yield, 91–98%; mp 276–277 °C (decomp.), colourless crystals.

For spectral characteristics and elemental analysis of compound **9**, see Online Supplementary Materials.

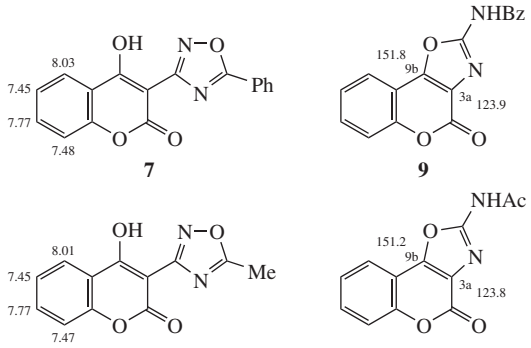
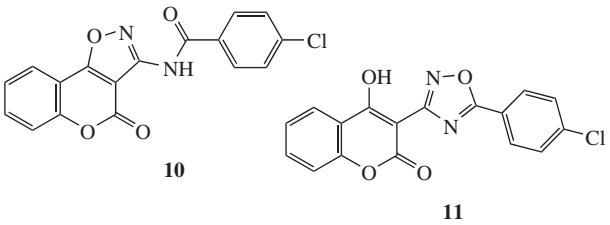


Figure 1 Comparison of the selective ^{1}H and ^{13}C chemical shifts (δ/ppm) of compounds **7** and **9** with the data reported for related molecules.[6]

Although these derivatives could not be isolated in pure form, they were reliably identified by ^{1}H NMR spectra of mixtures that contained no other admixtures. This result allows for anticipation of finding more suitable aroylation conditions.



Scheme 4

In summary, benzoylation of 3-amino-4*H*-chromeno[3,4-*d*] isoxazol-4-one **5** on treatment with benzoyl chloride is accompanied by a Boulton–Katritzky rearrangement and results in 5-phenyl-1,2,4-oxadiazoles **7** and **8** containing a 4-hydroxycoumarin moiety at the 3-position. The nearly quantitative conversion of these compounds into 2-benzamido-4*H*-chromeno-[3,4-*d*]oxazol-4-one **9** occurs under mild conditions and gives a first example of a preparative 1,2,4-oxadiazole–oxazole rearrangement. In conjuction with the pharmaceutical importance of oxazolo[4,5-*c*]coumarins, some of which possess antiallergic, antiinflammatory and central nerve depressing activities,[7] this reaction is noteworthy and will complement the published synthetic methods for the preparation of fused heterocycles incorporating a coumarin moiety.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.03.019.

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Received: 6th July 2010; Com. 10/3558