3-Methoxalylchromone—a novel versatile reagent for the regioselective purine isostere synthesis†

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The first synthesis of 3-methoxalylchromone was described. The reaction of the latter with electron-rich aminoheterocycles afforded a set of heteroannelated pyridines bearing a CO_2Me substituent located at the α-position of the pyridine core.

Purine isosteres and purine like scaffolds are of a great interest as privileged scaffolds[1] in medicinal chemistry and drug design. Functionalized derivatives of purine-like scaffolds are of considerable interest as lead structures and synthetic building blocks in medicinal and agricultural chemistry.[2–8]

On the other hand, purine- and pyridine-like scaffolds,[9] bearing a carboxylic or carbonylic function at position 2 of the purine core, are recognized to be potent inhibitors of inosine 5′-monophosphate dehydrogenase (IMPDH). IMPDH constitutes a group of enzymes which is playing a key role in the purine *de novo* biosynthesis.[10] In the last two decades, IMPDH became an important target enzyme for drug design.[9]

At the same time, derivatives of 4*H*-1-benzopyran-4-one, also known as 4*H*-chromen-4-ones or chromones, are prominent natural products possessing a wide range of interesting biological properties.[11] In addition, many natural and synthetic chromones are used as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems.[12] The synthetic utility of 2-unsubstituted 3-acylchromones **1** primarily derives from the reactivity of their three electron-deficient centers, *i.e.* carbon atoms C-2 and C-4 of the chromone moiety and the acyl group attached to carbon C-3. The majority of the known reactions of these compounds are nucleophilic additions with concomitant opening of the pyrone ring leading to various types of heterocyclic products.[13] The synthesis and chemical properties of a variety of 3-acylchromones **1** have been previously studied.

It occurred to us that 3-methoxalylchromone (**2**), a new chromone derivative containing a α-ketoester moiety, might be a versatile synthetic building block containing four electrophilic centers. To the best of our knowledge, there has been only an isolated report of a related molecule, namely 6,7-dimethoxy-3-ethoxalyl-2-methylchromone. The latter was prepared from 2-hydroxyacetophenone, diethyl oxalate and acetic anhydride.[14] The chemistry of this molecule was not studied.

It is known that 3-acylchromones **1** are available by reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)-propen-1-one with various electrophiles.[15,16] We have found that hitherto unknown 3-methoxalylchromone (**2**) can be prepared in 79% yield by reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)propen-1-one with methyl 2-chloro-2-oxoacetate (Scheme 1). The structure of **2**[17] was independently confirmed by X-ray crystal structure analysis (Fig. 1).

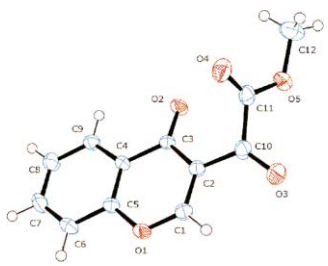
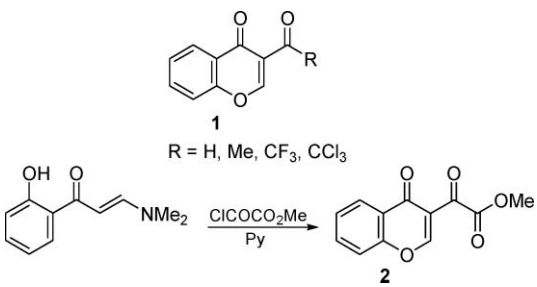


Fig. 1 Molecular structure of chromone **2**.



Scheme 1 Synthesis of 3-methoxalylchromone (**2**).

Based on the retrosynthetic analysis and on our previous expertise in cyclization reactions of electron-rich systems[18] we started a project directed towards the development of a new synthesis of ester-substituted purine isosteres starting with **2**. Continuing our research program dedicated to the design and synthesis of novel inhibitors of IMPDH and in view of the unique biological properties displayed by many fused pyridines and pyrimidine

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heterocycles containing imidazole, pyrazole and thiazole rings,[2–8] we have studied the reactions of 3-methoxalylchromone (**2**) with electron-rich aminoheterocycles **3–8** (Fig. 2). Besides the pharmacological relevance of the products, the reactions are also interesting in their own right from the viewpoint of their chemo- and regioselectivity.[19] Recently, we have reported the synthesis of a wide range of trifluoromethylated fused pyridines by reaction of 3-(trifluoroacetyl)chromone **1** (R = CF_3) with heterocyclic amines.[20]

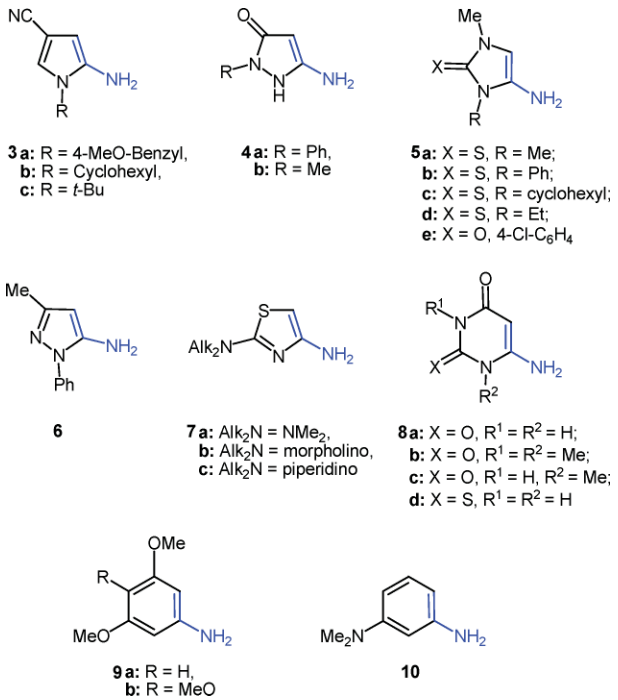


Fig. 2 Structures of the used 1,3-C,N-dinucleophiles.

We have started our investigation in this area by the study of the reaction of **2** with aminopyrroles **3a–c** in order to obtain the corresponding pyrrolo[2,3-*b*]pyridine ring system. The latter represents an important synthetic target, due to its unique pharmacological properties.[5] It was found that, compared to the analogous reactions of **1** (R = CF_3), the reaction of 3-methoxalylchromone (**2**) with amines **3** proceeded under milder conditions (AcOH, reflux 2–5 h) and with an excellent regioselectivity to give products **12a–c**. The structure of the products was confirmed by X-ray crystal structure analyses (Fig. 3). To study the scope and limitations of the methodology, we investigated the reactions of **2** with other electron-rich aminoheterocycles and anilines **4–10**.

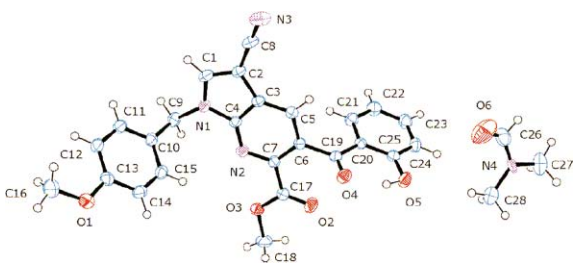
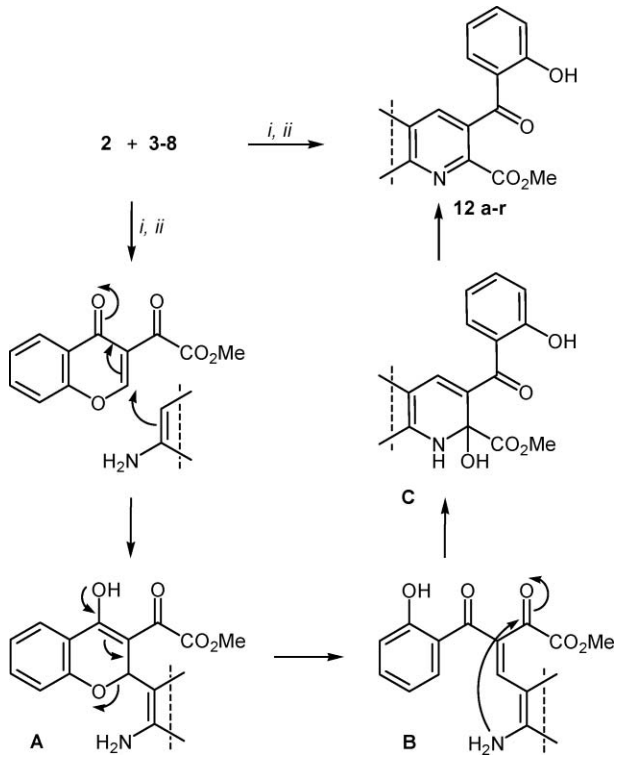


Fig. 3 Molecular structure of compounds **12a** in the form of a solvate complex with DMF.

These reactions provided a variety of heteroannelated pyridines **12d–r** bearing a CO_2Me group located at the α-position of the pyridine core (Scheme 2, Table 1). It is worth mentioning that the best results were obtained when the reactions were carried out in acetic acid. Only 4-aminoimidazoles **5** proved to be unstable in the presence of acetic acid. Therefore, DMF/TMSCl was used as a water scavenger.



Scheme 2 *Reagents and conditions*: (i): AcOH, reflux, 2–5 h (for **3**, **4**, **6**, **7**, **8**); (ii): DMF/TMSCl, 80–100 °C (for **5**).

In all cases, ring opening of the pyrone ring takes place with subsequent annulation of the pyridine core. In fact, the cyclization of **2** with aminoheterocycles **3–8** turned out to be highly regioselective and did not result in the formation of isomeric mixtures. In case of the aromatic amines **9** and **10**, we observed (by HPLC) the formation of a complex mixture of many unidentified products as well as low quantities of two possible regioisomers (both in acetic acid or using DMF/TMSCl). Many attempts to isolate and separate these products failed.

The formation of products **12a-r** can be explained by conjugate addition of the enamine carbon atom of the aminoheterocycle to the double bond of **2** to give intermediate **A**. Subsequent pyrone ring opening delivers intermediate of type **B**. The intramolecular attack of the amino group to the carbonyl group affords intermediate **C** which undergoes elimination of water to give pyridines **12** (Scheme 2).

The structures of compounds **12a** and **12l** were confirmed by an X-ray crystal structure analysis[21] (Fig. 3 and 4), whereas the structures of the other fused pyridines were assigned on the basis of their spectroscopic features in comparison with those of **12a** and **12l**.

Finally, the hydrolysis of several representatives of **12** was conducted; these reactions were carried out in a solution of

Table 1 Synthesis of fused heterocycles **12d–r**

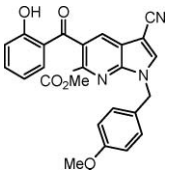
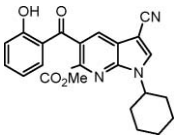
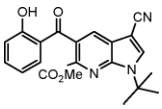
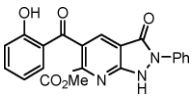
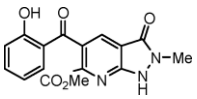
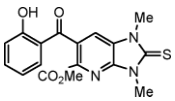
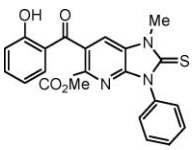
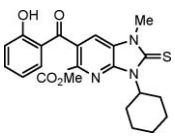
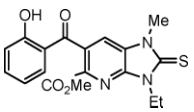
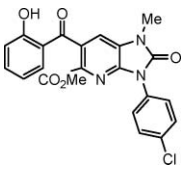
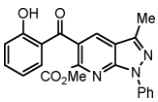
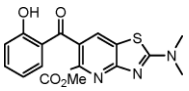
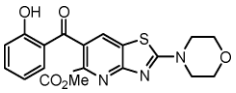
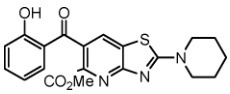
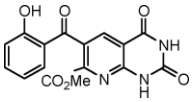
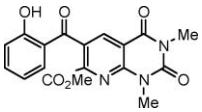
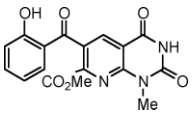
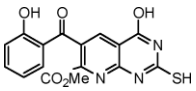
Amine		Product	% (*12*)[a]
3a	**12a**		78
3b	**12b**		75
3c	**12c**		89
4a	**12d**		57
4b	**12e**		80
5a	**12f**		71
5b	**12g**		73
5c	**12h**		64
5d	**12i**		70
5e	**12j**		69
6	**12k**		73
7a	**12l**		68

Table 1 *(Contd.)*

Amine		Product	% (*12*)[a]
7b	**12m**		71
7c	**12n**		77
8a	**12o**		64
8b	**12p**		55
8c	**12q**		60
8d	**12r**		44

[a] Yields of isolated products.

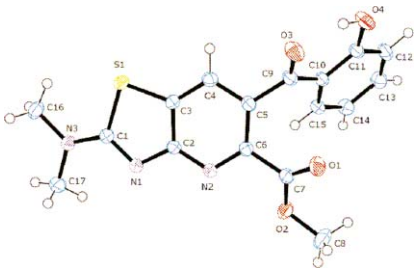
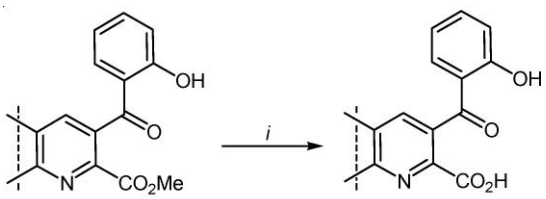


Fig. 4 Molecular structure of compound **12l**.

potassium hydroxide in methanol. Subsequent acidification of the reaction mixture with concentrated hydrochloric acid gave the corresponding acids **13** in excellent yields (Scheme 3, Table 2).

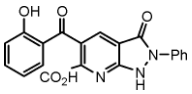
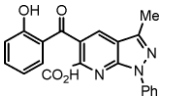
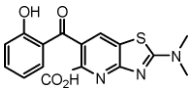
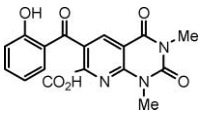


12d,k,l,p **13d,k,l,p**

Scheme 3 *Reagents and conditions*: (i): a) MeOH, KOH, reflux, 2 h; b) conc. HCl.

In summary, we have reported the synthesis of 3-methoxalylchromone and its cyclocondensation with various electron-rich aminoheterocycles. This simple one-pot procedure

Table 2 Synthesis of acids **13d, k, l, p**

	Product	% (*13*)[a]
13d		80
13k		82
13l		79
13p		81

[a] Yields of isolated products.

now opens new avenues to a wide range of fused pyridines. Studies addressing the biological activity and chemical properties of pyridines synthesised are currently under investigation.

Acknowledgements

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