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PAPER

2,3-Unsubstituted chromones and their enaminone precursors as versatile reagents for the synthesis of fused pyridines†

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A divergent and regioselective approach to fused pyridines was developed through formal [3 + 3] cyclocondensations from simple 2,3-unsubstituted chromones or their enaminone precursors.

In the recent decades, heteroannulated pyridines, which can be classified as purine isosteres, purinomimetics and psuedopurines, have attracted considerable attention of medicinal and synthetic organic chemists because of a wide range of biological activities,[1–4] like, antitumor, anti-inflammatory, antiallergic, and inhibitors of DNA-dependent protein kinase. Moreover, purines and purine isosteres as well as their nucleosides bearing aryl or heteroaryl group at the 2- and 6- positions are scaffolds widely known for their biological activity.[5,6]

Recently, laboratories of Iaroshenko,[7] Sosnovskikh,[7,8] and Volochnyuk[9] have published a number of methods related to the synthesis of various fused pyridine/pyrimidine derivatives. The syntheses were succeeded *via* the [3 + 3] heteroannulation reaction of pyridine/pyrimidine moiety on the core of electron-rich aminoheterocycles and anilines involving a set of 1,3-CCC- and 1,3-CNC-dielectrophiles. These elaborated strategies afford the possibility to generate a large number of pharmacologically important compounds.

Among the 1,3-CCC-dielectrophiles used are 3-substituted chromones[10] -moieties containing hidden 1,3-dielectrophilic fragments as a part of γ-pyrone framework. We and others have demonstrated that chromones bearing electron-withdrawing substituents in the 3-position react with 1,2- and 1,3-dinucleophiles delivering the corresponding five- and six-membered heterocycles. This domino-transformation usually involves initial nucleophilic addition on the 2-position of the chromone skeleton with the subsequent γ-pyrone ring opening. The transformations of this type are facilitated by the electron-withdrawing group at the 3-position.[8c,8d,9,10]

However, to the best of our knowledge, very scarce information is available about the reactions of 2,3-unsubstituted chromones with dinucleophiles leading to the pyrone ring opening with the subsequent formation of the new heterocyclic system. There have been only a handful of papers describing some reactions of chromone with dimethyl acetonedicarboxylate[11] and *N*-iminopyridinium ylide.[12] Recently, our laboratory have communicated a TMS-triflate mediated reaction of 2,3-unsubstituted chromones with 1,3-bis-silyl ethers, which resulted in the preparation of functionalized 6*H*-benzo[*c*]chromen-6-one derivatives.[13] All these reactions proceed by nucleophilic 1,4-addition followed by pyrone ring opening. A small number of such transformations can be explained taking into account the low electrophilicity of the 2-position of the chromone ring comparing with the derivatives having an EWG group in the 3-position.

Continuing our research program dedicated to the design and synthesis of novel fused pyridines[7] and in a view of the unique biological properties displayed by these compounds,[1–4] we have started our investigation in this area by the study of the reactions of 2,3-unsubstituted chromones **1** with a set of commercially available electron-rich heterocyclic amines **3–10** and aromatic amines **11–14** (Fig. 1).

It is known that 2,3-unsubstituted chromones **1** can be obtained in two steps from *o*-hydroxyacetophenones.[14] The first step is a synthesis of (*E*)-3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-ones **2** by reaction of *o*-hydroxyacetophenones with DMFDMA (*N*,*N*-dimethylformamide dimethyl acetal). Subsequent treatment of the product with perchloric acid leads to the chromone formation. In this work, the best reaction conditions for the synthesis of chromones **1** were found (DMF/TMSCl, under argon, 100 °C, 1–3 h) and of special interest is the formation of these compounds in nearly quantitative yield (90–97%) (Scheme 1). By this method we have prepared a set of chromones

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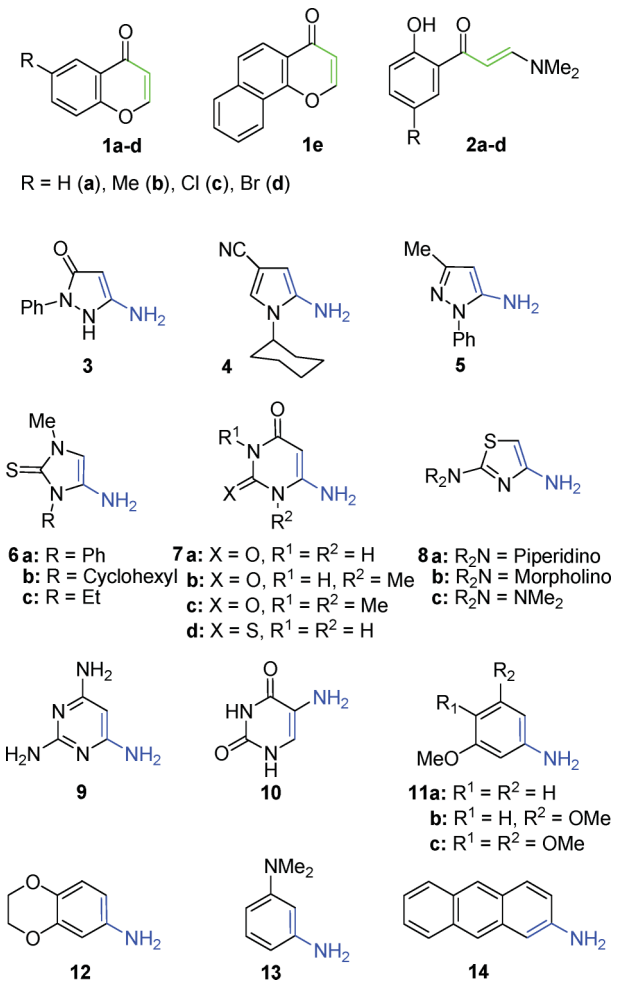
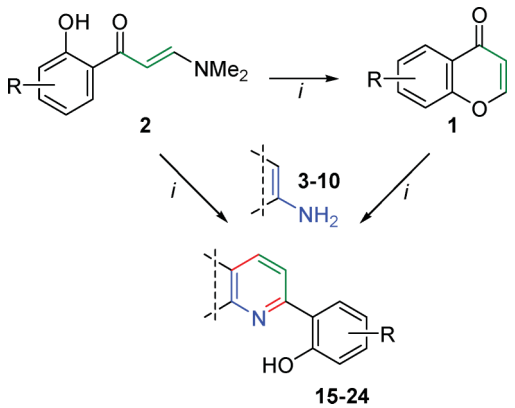


Fig. 1 Structures of the chromones and aminoheterocycles used in this study.



Scheme 1 *Reagents and conditions*: (*i*) DMF/TMSCl, under argon, 90–120 °C, 1–4 h.

1a–h (Table 1), however for the current study only chromones **1a–e** were used.

First, we have concentrated our efforts mainly on the setting optimal conditions for the reaction of **1** with heterocyclic amines **3–10**. We were aware that this transformation demands harsh reaction conditions. As a starting point acetic acid under reflux as well as DMF at 150 °C were tried, however, all these attempts were

Table 1 Synthesis of chromones **1**

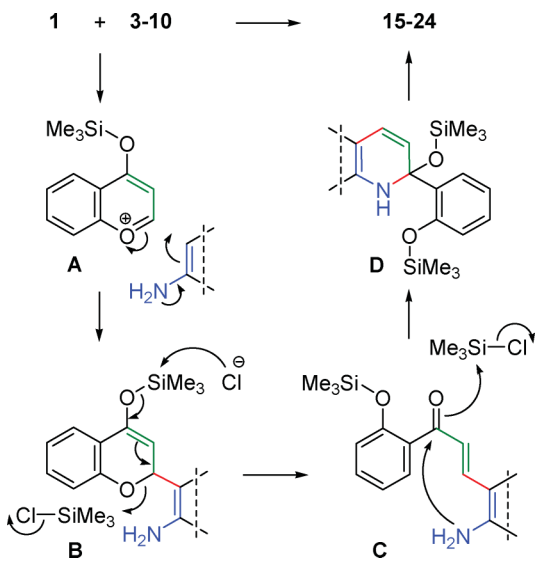
1	*R*	Yield (%)[a]
a	H	93
b	6-Methyl	97
c	6-Bromo	94
d	6-Chloro	97
e	7,8-Benzo	90
f	6-Methoxy	95
g	6-Chloro-7-methyl	95
h	7-Methoxy	94

[a] Yields of isolated products.

unsuccessful, leading mainly to the decomposition of the amine component. Next, it was decided to melt both reagents under inert atmosphere. Indeed, this delivered the desired products, however the reaction proceeded with low overall yields laying in the range of less then 20%. Recently,[9] water scavenging system DMF/TMSCl has gained the wide application as a media for the cyclocondensation reactions. Logically, this reaction media was taken as a reaction condition of choice.

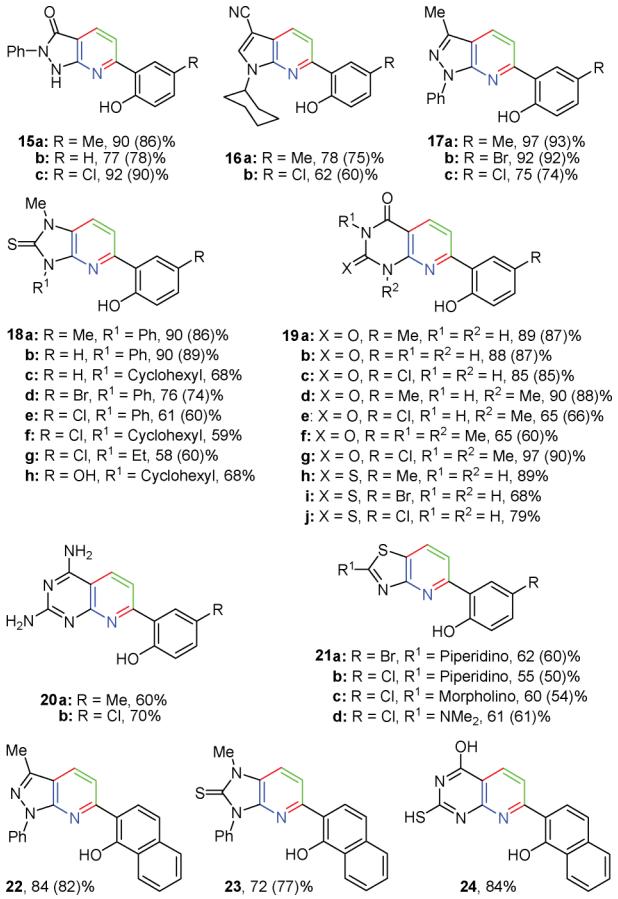
Chromones **1a–d** and benzo[*h*]chromone **1e** were reacted with aminoheterocycles **3–10** in DMF solution at 90–120 °C in the presence of Me_3SiCl. Under these conditions formation of the expected fused pyridines **15–24** as a result of pyridine ring annulation by 2,3-unsubstituted chromones onto the amine moiety was observed. Majority of the tested electron-excessive aminoheterocycles reacted with chromones **1** delivering the corresponding pyridines in 55–97% yields (Scheme 1, Table 2).

Giving insight into the reaction mechanism, it was necessary to admit that the pyridine ring annulation most probably proceeds as a consecutive domino-transformation involving formation of the intermediates **A–D** (Scheme 2). We suppose that the reaction starts with the formation of the benzopyrylium salt **A** by initial silylation which facilitates the nucleophilic attack. Subsequent electrophilic attack of **A** by the most electrophilic C-2 atom occurs on the enamine position of electron-excessive amine giving the first in this cascade intermediate **B**. Subsequently, γ-pyrone ring opens



Scheme 2 Putative reaction mechanism.

Table 2 Synthesis of fused pyridines **15–24** from chromones **1** (yields in brackets are from aminoenones **2**)



by cleavage of the C–O bond to form an intermediate **C**. Note that in our previous study we have described some similar structures, for instance (*E*)-3-(4-amino-2-(pyrrolidin-1-yl)thiazol-5-yl)-1-arylprop-2-en-1-ones, that were stable and have been isolated and characterized; in strong acidic media these compounds were converted to the thiazolo[4,5-*d*]pyridines.[15] Then, intermediate **C** undergoes the intramolecular attack of the free amine group onto carbonyl moiety forming the silylated pyridine hydrate **D**, which loses Me_3SiOH molecule giving rise to the fused pyridines **15–24**.

Encouraged by this finding, next optimization of the method discovered was conducted. We have considered the corresponding precursors **2** to be suitable for the pyridine ring annulation reaction. In this context, we have scanned the amines depicted in Fig. 1 and have compared the yields of the reaction with the one conducted by the recruiting of the chromones **1**. In fact, cyclocondensations proceeded smoothly giving rise to the corresponding pyridines. As shown in Table 2, the reaction with **2** appeared to be a versatile synthetic method for the preparation of the fused pyridines **15–24**, their yields are in brackets.

The constitution of the synthesized fused pyridines **15–24** was mainly established by 1D and 2D NMR methods. Moreover, the structures of compounds **15a–c**, **17a**, and **21b** were independently established by X-ray single crystal analysis (Fig. 2, 3 and Fig. 1–3 in the ESI†).[16] In all structures the intramolecular hydrogen bonding is present.

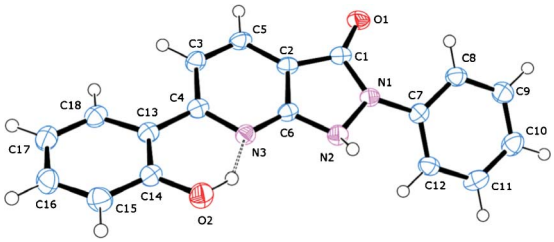


Fig. 2 Molecular structure of compound **15b**.

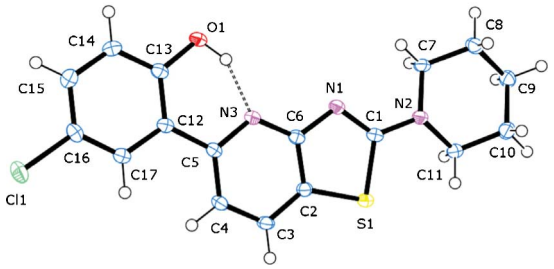
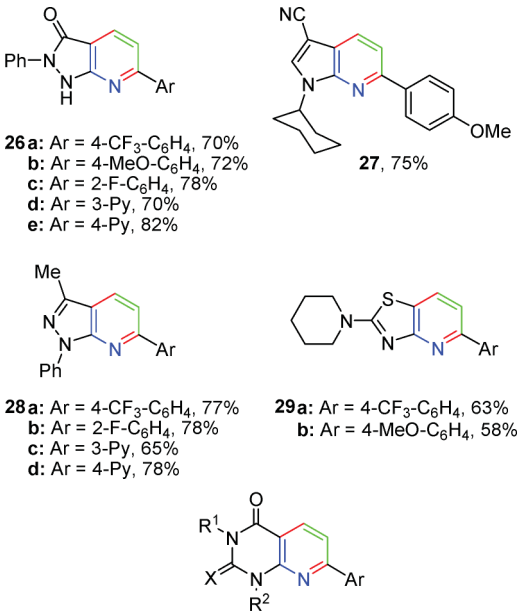
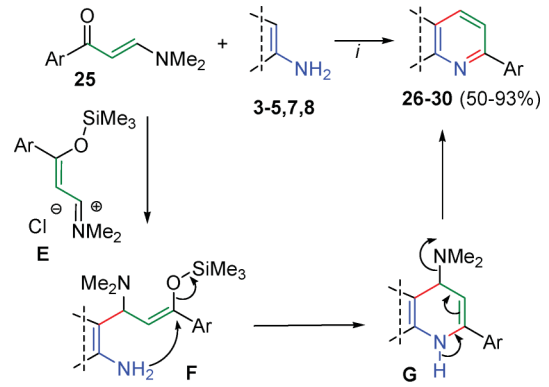


Fig. 3 Molecular structure of compound **21b**.

Table 3 Synthesis of fused pyridines **26–30** from aminoenones **25**



As a part of an ongoing research, we desired the expedient access to α-aryl substituted fused pyridines by employing easily accessible enaminones **25** without *o*-hydroxyl group. The investigated reaction proceeded regioselectively to give pyridines **26–30** in good to excellent yields (50–93%) as a single product. The method illustrated here is also suitable for the introduction of heteroaryl substituent, namely β- and γ-pyridyl rests in α-position of annulated pyridine ring (Scheme 3, Table 3). Note that compounds **9–13** appeared to be inactive towards the pyridine ring annulation. The NMR spectral properties of pyridines **26–30** are in a good correspondence with the scaffolds **15–24** and previously



Scheme 3 *Reagents and conditions*: (*i*) DMF/TMSCl, under argon, 90–120 °C, 1–2 h.

synthesized purine isosters. The X-ray single crystal analysis has confirmed the structure of compound **29b** (Fig. 4).[16]

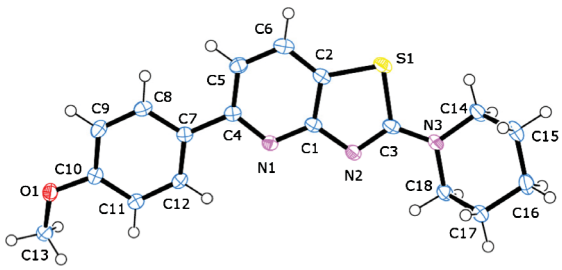


Fig. 4 Molecular structure of compound **29b**.

The putative reaction mechanism can be summarized in the four steps represented in the Scheme 3, namely, the first step which initiates this reaction is formation of the salt **E** by reaction of enaminones **25** with TMSCl. Electrophilic attack of the iminium fragment onto the enamine-position of electron-excessive aminoheterocycles gives rise to second intermediate **F**. The latter, through the intermolecular reaction of the free amino group with silyl-enol ether moiety forms dehydropyridines **G**. Elimination of the dimethyl amine molecule delivers final fused pyridines **26–30**.

It is important that very recently synthesis of substituted pyrido[2,3-*d*]pyrimidinediones by the reaction of 6-aminouracils with enaminones of type **25** has been described. The reaction was conducted in acetic acid, however, it was accomplished by formation of the 1,3,5-triaroylbenzene derivatives as products of enaminone trimerization; this significantly decreased the overall yields.[17] Under our reaction conditions the formation of the self-condensation products were not observed.

Concerning unsuccessful trials, it should be noted that all tested electron-rich anilines **11–13**, as well as electron neutral and deficient anilines have shown themselves to be not appropriate for pyridine ring annulation. Increasing temperature as well as using of dimethylacetamide (DMA) instead of DMF did not trigger the reaction. In contrary, anthracen-2-amine **14** reacted readily with chromones **1** as well as enaminones **2** giving rise to the corresponding naphtho[2,3-*f*]quinolones. Unfortunately, due to extremely low solubility of these products, NMR methods could not be used to confirm the structure. However, the mass-spectrometry as well as HRMS and element analysis have proven the formation of the naphtho[2,3-*f*]quinolone framework, but there are doubts with regards to the regioselectivity, since the formation of two regioisomers, namely 1- or 3-substituted naphtho[2,3-*f*]quinolones, is possible. In the case of 5-aminopyrimidine-2,4(1*H*,3*H*)-dione (**10**), in reactions with **1** and **2** the formation of the mixture of unidentified by-products was observed.

Finally, the synthesis of the fused pyridines was developed by the two-component heteroannulation reaction starting from non-activated 2,3-unsubstituted chromones, aminoenones, and electron-rich heterocyclic amines. The scope and limitations of this new methodology have been studied with a wide range of substrates. The majority of the products obtained are not readily available by other methods.

Experimental

General procedure for the synthesis of compounds 1, 15–24, 26–30

Corresponding chromone **1** or enaminone **2** or **25** (2 mmol) and heterocyclic amine (2.2 mmol) were placed in pressure tube under the flow of dry argon and dissolved in dry DMF (10 mL) containing 1 mL of TMSCl. The mixture was heated at 90–120 °C during 1–4 h (controlled by TLC, Table 1 and 2 in the ESI†). Then this solution was evaporated under reduced pressure, treated with water, filtrated, dried on the air, and recrystallized from an appropriate solvent, or was subjected to a column chromatography over silica gel.

Acknowledgements

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16 X-Ray Crystallographic data (excluding structure factors) for the structures **15a–c**, **17a**, **21b** and **29b** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 835825–835830 and can be accessed with the ESI†.

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