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Easy Access to Pyranoacridines, Pyranoxanthenes, and Arylchromenes Through a Domino Reaction

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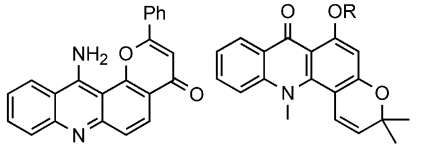
A series of pyrano[2,3,4-*kl*]acridines has been synthesized through an unprecedented domino reaction involving 1-hydroxy-3-methoxy-10-methylacridone and Grignard reagents. This method has been successfully applied to xanthone, anthracenone, and benzophenone derivatives, thus providing novel access to pyranoxanthenes, dihydronaphthochromenes, and arylchromenes.

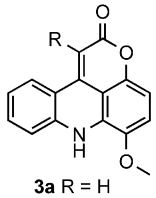
Introduction

Acridines exhibit a broad range of biological activities including antibacterial,[1] antiparasitic,[2] and antitumor activities.[3] Consequently, a large variety of synthetic methods for their preparation has been published over the years.[4]

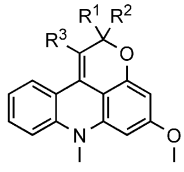


1

2a R = Me
2b R = H
2c R = $(CH_2)_2NMe_2$



3a R = H
3b R = CN



4a $R^1 = R^2 = R^3 = H$
4b $R^1 = R^2 = H$, $R^3 = Me$
4c $R^1 = R^2 = Me$, $R^3 = H$
4d $R^1 = H$, $R^2 = R^3 = Me$
4e $R^1 = R^3 = H$, $R^2 = Me$

Figure 1. Examples of pyranoacridines.

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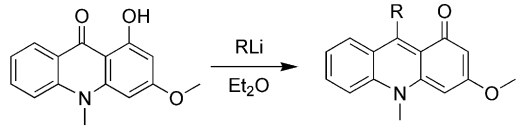
However, only a moderate number of examples of pyranoacridines has been described.[5] Among them, one can highlight pyrano[2,3,*a*]acridine **1**, a potent anticancer agent, and pyrano[2,3,*c*]acridines **2a** and **2b**, named acronycine and noracronycine, respectively (Figure 1).[6] This family of compounds is very interesting due to their broad-spectrum biological activity.[5,7] For example, water-soluble *O*-dimethylaminoethyl noracronycine **2c** exhibits significant cytotoxicity against several multidrug-resistant cells.[8]

We report herein the synthesis of pyrano[2,3,4-*kl*]acridines **4a**–**e** as novel compounds, related to 7*H*-pyrano[2,3,4-*kl*]acridin-2(3*H*)-ones **3a** and **3b** synthesized by Gorelik et al. in 2006 using periannulation of the pyran ring to 9-chloroacridine.[9] However, this approach requires several steps and strong acidic conditions (conc. HCl, 80 °C or 65% H_2SO_4, 140 °C) to achieve this cyclization process.

Results and Discussion

In the context of a medicinal program, we were interested in introducing various substituents at the 9-position of 1-hydroxy-3-methoxy-10-methylacridone (**5**) by using commercially available Grignard reagents. It is worthwhile noting that the condensation of **5** with alkyl- or aryllithium reagents led to acridin-1-ones **6**–**8** by dehydration (Scheme 1).[7]



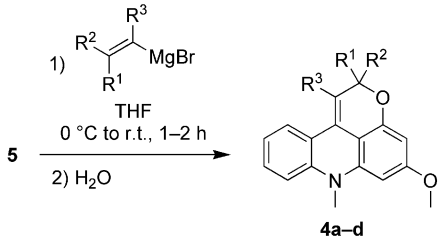
5

6 R = *n*Bu (66%)
7 R = $(CH_2)_3NMe_2$ (25%)
8 R = 4-$N(Me_2)C_6H_4$ (90%)

Scheme 1. Addition of alkyl- and aryllithium reagents to acridone **5**.

Thus, the reactivity of **5** was first examined by addition of vinylmagnesium bromide reagents. Unexpectedly, the 9-substituted products were not obtained, but instead novel pyranoacridines **4a**–**d** were isolated (Table 1).

Table 1. Reaction of acridone **5** with vinylic Grignard reagents.

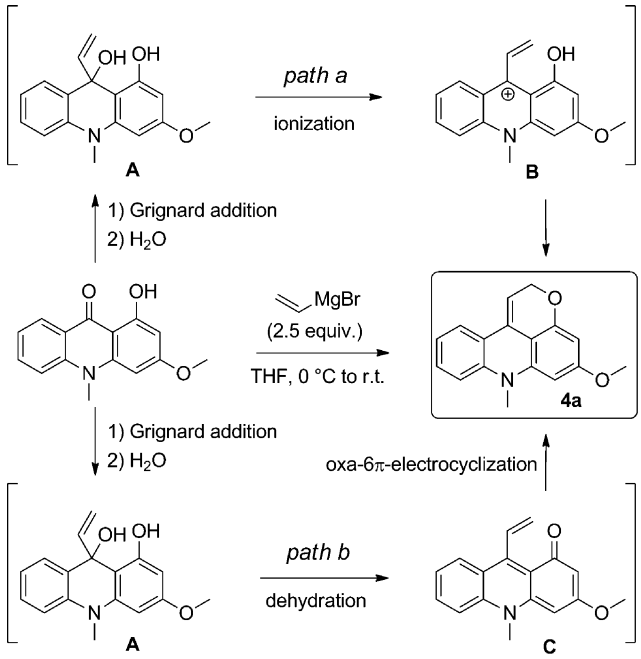


Entry	R^1, R^2, R^3	Product, Yield [%]
1	H, H, H	**4a**, 24 (23)[10]
2	H. H, Me	**4b**, 26 (55)[10]
3	Me, Me, H	**4c**, >95
4	H, Me, Me	**4d**, 91

Importantly, the pyran moiety is present in a large number of natural products, and synthetic methods to access the pyran ring system have been extensively studied, for example, involving hetero-Diels–Alder cycloaddition,[11] [3+3] cycloaddition,[12] electrophilic acid cyclization,[13] or electrocyclization.[14] However, to the best of our knowledge, this domino reaction process is unprecedented.

The postulated mechanism of this reaction is the following: The reaction is initiated by deprotonation of the phenol group of **5** by the first equivalent of the Grignard reagent. This is followed by nucleophilic attack at the carbonyl moiety by the second equivalent to give, after hydrolysis, hydroxyvinyl derivative **A**. At this stage, two mechanistic paths could be proposed to rationalize this domino process: either ionization/cyclization or dehydration/oxa-6π-electrocyclization. In the first one (Scheme 2, path a), the ionization of intermediate **A** could reasonably be conceived due to the resulting formation of highly stabilized carbocation **B** (double benzylic and vinylic). Subsequently, the carbocation could be intercepted by the phenol, leading to the isolated pyrano[2,3,4-*kl*]acridine compound. In the second mechanism (Scheme 2, path b), hydroxyvinyl derivative **A** could undergo dehydration to form intermediate **C**, which could give rise to the pyranoacridine through oxa-6π-electrocyclization.

It should be noted that the yields were dependent on the degree of substitution of the organometallic reagents. Indeed, whereas the use of either vinyl- or isopropenylmagnesium bromide led to cyclic products **4a** and **4b** in moderate yields (Table 1, Entries 1 and 2), the reaction of either 1- or 2-methyl-1-propenylmagnesium bromide gave quantitative access to the corresponding pyrano[2,3,4-*kl*]acridines **4c** and **4d** (Table 1, Entries 3 and 4). These latter results could be explained by the presence of electron-donating groups (alkyl groups) in the Grignard reagents that would stabilize either carbocation **B** (Scheme 2, path a) or favor the oxa-6π-electrocyclization step (Scheme 2, path b). Additionally,

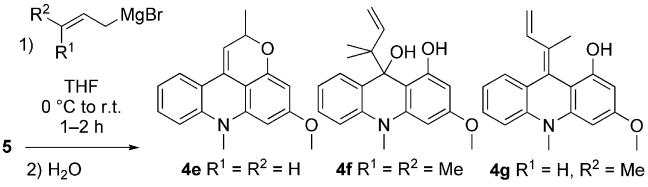


Scheme 2. Proposed mechanisms for the reaction of **5** with vinylmagnesium bromide.

compound **4b** showed weak stability towards silica gel chromatography.[10]

These results encouraged us to investigate the reactivity of acridone **5** towards allylmagnesium bromide. Thus, pyranoacridine **4e** was obtained, and its purification was also problematic (Table 2, Entry 1). The reaction of **5** with 3,3-dimethylallylmagnesium bromide corroborates our proposed mechanisms. Indeed, the presence of the *gem*-dimethyl moiety impedes the double bond isomerization, leading to the formation of **4f** (Table 2, Entry 2). Finally, the use of crotylmagnesium bromide yielded 1,3-diene-containing acridone **4g** upon dehydration of the lateral chain (Table 2, Entry 3).

Table 2. Reaction of acridone **5** with allylic Grignard reagents.

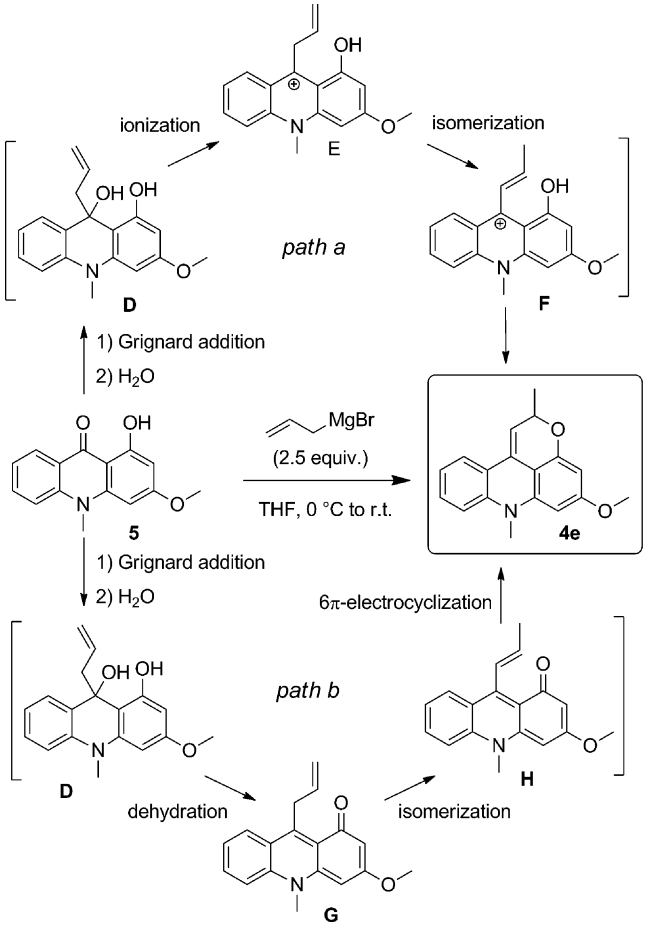


Entry	R^1, R^2	Product, Yield [%][b]
1	H, H	**4e**, 17(38)[10]
2	Me, Me	**4f**, 14
3[a]	H, Me	**4g**, 92 (*E*/*Z* = 1.5:1)

[a] *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy. [b] No starting material was recovered.

The formation of pyranoacridine **4e** with allylmagnesium bromide could be explained according to the mechanism shown in Scheme 3. Ionization of intermediate **D** would give carbocation **E**, followed by an isomerization of its terminal double bond. Resulting carbocation **F** would then be

intercepted by the phenol moiety, leading to **4e** (Scheme 3, path a). With respect to the mechanism involving the electrocyclic ring closure, dehydration of **D** could lead to acridin-1-one **G**, which would be transformed into intermediate **H** through isomerization of the terminal double bond. Hence, an oxo-6π-electrocyclization would form the desired pyranoacridine (Scheme 3, path b).

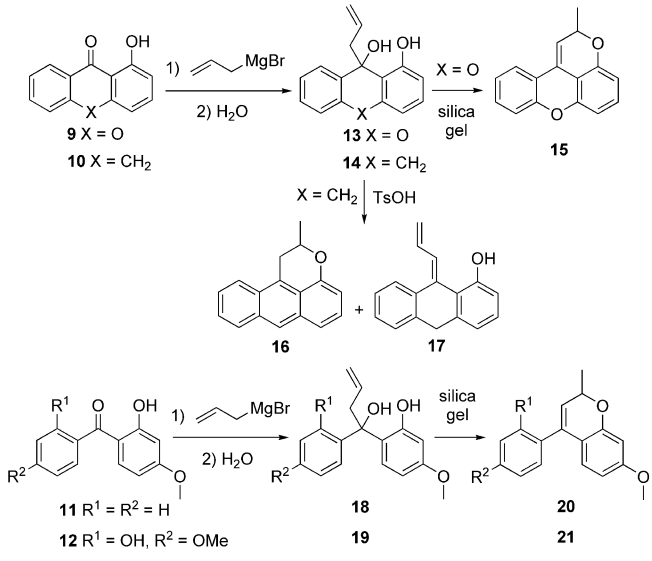


Scheme 3. Proposed mechanisms for the reaction of **5** with allylmagnesium bromide.

We investigated the generalization of the reaction to other related heterocycles, 1-hydroxyxanthone (**9**) and 1-hydroxyanthracenone (**10**) – and to benzophenone derivatives **11** and **12**. First, the addition of allylmagnesium bromide to **9** was performed to give crude 1,2 adduct **13** (determined by ^{1}H and ^{13}C NMR spectroscopy), which cyclized into **15** during flash chromatography on silica (Table 3, Entry 1). Seemingly, such a structure has not been reported so far in the literature.[15] This preliminary result could be extended to heterocycles with potential biological applications from other 1-hydroxyxanthones.

Then, in the case of **10**, only 1,2-carbonyl adduct **14** was obtained, as the cyclization did not proceed during the course of chromatography. However, subsequent treatment with TsOH (10 mol-%) in dichloromethane led to a mixture of unprecedented dihydronaphthochromene **16**[16] and hydroxydihydroanthracene **17** in 21 and 34% yield, respectively (Table 3, Entry 2). Finally, similar behavior was also observed from the acyclic benzophenone derivatives. Indeed, 1-hydroxybenzophenones **11** and **12** reacted with allylmagnesium bromide to furnish crude hydroxyalkyl benzophenones **18** and **19**, respectively (Table 3, Entries 3 and 4). The latter spontaneously cyclized into arylchromene **21** when purified through flash chromatography on silica gel. On the contrary, pure isolated compound **18** required more acidic conditions to cyclize into arylchromene **20** (10 mol-% TsOH). This domino reaction applied to 1-hydroxybenzophenones offers an alternative to the classical syntheses of arylchromenes,[17] which usually require the use of either high temperatures[18] or metal catalysts.[19]

Table 3. Reactivity of other substrates with allylmagnesium bromide.



Entry	Substrate	R^1, R^2	Product, Yield [%][c,d]
1[a]	**9**	–	**15**, 26
2[b]	**10**	–	**16**, 21; **17**, 34
3[b]	**11**	H, H	**20**, 62
4[a]	**12**	OH, OMe	**21**, 71

[a] The cyclization occurred during chromatography on silica gel. [b] Treatment with TsOH (10 mol-%) was required to obtain the cyclized product. [c] Each crude product obtained from the Grignard addition and aqueous workup was characterized by ^{1}H and ^{13}C NMR spectroscopy. [d] No starting material was recovered.

Conclusions

In summary, a new family of pyranoacridines was synthesized through a one-pot domino reaction from 1-hydroxy-3-methoxy-10-methylacridone and Grignard reagents. This reaction was successfully applied to 1-hydroxyxanthone and 1-hydroxybenzophenones by using modified reaction conditions to generate the corresponding pyranoxanthene and arylchromenes, respectively, whose skeletons are found in natural products. The scope and limitations of this process will be investigated by using other 1-hydroxyacridones and 1-hydroxyxanthones. Additionally, 1,3-diene-

containing compounds, such as **4g** and **17**, will be subjected to the intermolecular Diels–Alder reaction to create spiro compounds.

Experimental Section

General Procedure for the Synthesis of Pyranoacridines: To a solution of 1-hydroxy-3-methoxy-10-methylacridone (**5**; 300 mg, 1.18 mmol) in anhydrous THF (15 mL, 0.08 M) at 0 °C and under an argon atmosphere was added dropwise the Grignard reagent in dry Et_2O or THF (2.9 mL, 2.9 mmol, 2.5 equiv.). During the addition of the Grignard reagent, a color change from yellow to orange-red was observed. The reaction mixture was stirred at room temperature for 2–4 h. Then, water was added at 0 °C, and the reaction mixture was stirred for 5 min. The purple reaction mixture was then diluted with ethyl acetate and icy brine. Rapid extraction with ethyl acetate, drying over $MgSO_4$, filtration, and concentration gave the crude product as a dark red-purple oil. Certain pyranoacridines appeared to have low stability on silica, and in such cases, the yields were determined by ^{1}H NMR spectroscopy by using pentachloroethane (PCE, 20 μL) as internal standard.[20]

2,2-Dimethyl-5-methoxy-7-methylpyrano[2,3,4-*kl*]acridine (4c): This compound was prepared according to the general procedure starting from **5** (100 mg, 0.39 mmol) and was obtained as a light-brown residue (113 mg, 0.38 mmol, > 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, J = 8.0, 1.6 Hz, 1 H, 11-H), 7.12 (ddd, J = 8.0, 7.2, 1.6 Hz, 1 H, 9-H), 6.81 (m, 2 H, 8-H, 10-H), 5.98 (d, J = 2.4 Hz, 1 H, 4-H or 6-H), 5.94 (d, J = 2.4 Hz, 1 H, 6-H or 4-H), 5.40 (s, 1 H, 1-H), 3.67 (s, 3 H, 12-H), 3.23 (s, 3 H, 13-H), 1.37 (s, 6 H, 14-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3 (C-5), 153.6 (C-3a), 140.1 and 140.0 (C-6a, C-7a), 128.9 (C-9), 124.1 (C-11a), 122.6 (C-11), 120.3 (C-10), 119.7 (C-11b), 113.5 (C-8), 109.1 (C-1), 102.5 (C-11c), 93.8 and 92.3 (C-4, C-6), 77.1 (C-2), 55.2 (C-12), 33.4 (C-13), 27.7 (C-14) ppm. IR (ATR): $\tilde{\nu}$ = 2935, 1744, 1606, 1561, 1468, 1327, 1310, 1190, 1151, 1091, 1053, 818, 757 cm^{-1}. MS (ESI+): m/z = 294.1 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{19}H_{20}NO_2$ $[M + H]^+$ 294.1494;, found 294.1504.

9-(But-3-en-2-ylidene)-9,10-dihydro-3-methoxy-10-methylacridin-1-ol (4g): This compound was prepared according to the general procedure starting from **5** (149 mg, 0.58 mmol) and commercially available crotylmagnesium bromide. Purification by flash chromatography on silica gel (pentane/ethyl acetate, 1:1) led to **4g** as an inseparable mixture of regioisomers with E/Z = 1.5:1, as determined by ^{1}H NMR spectroscopy (157.9 mg, 0.54 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (2*dd, J = 7.6, 1.5 Hz, 1 H, 8-H, 8′-H), 7.31–7.25 (m, 1 H, 6-H, 6′-H), 7.14 (dd, J = 17.8, 10.9 Hz, 0.4 H, 12′-H), 7.06 (2*dd, J = 7.5, 1.0 Hz, 1 H, 7-H, 7′-H), 6.98 (dd, J = 8.2, 0.9 Hz, 1 H, 5-H, 5′-H), 6.62 (dd, J = 17.3, 10.8 Hz, 0.6 H, 12-H), 6.31 (d, J = 2.3 Hz, 0.6 H, 2-H), 6.21 (d, J = 2.3 Hz, 0.6 H, 4-H), 6.19 (d, J = 2.3 Hz, 0.4 H, 2′-H), 6.06 (d, J = 2.3 Hz, 0.4 H, 4′-H), 5.51 (dd, J = 17.3, 1.3 Hz, 0.6 H, 13-H$_E$), 5.41 (dd, J = 17.3, 1.4 Hz, 0.4 H, 13-H′$_E$), 5.32 (dd, J = 10.8, 1.3 Hz, 0.6 H, 13-H$_Z$), 5.19 (dd, J = 10.9, 1.4 Hz, 0.4 H, 13-H′$_Z$), 3.83 (s, 1.8 H, 15-H), 3.82 (s, 1.2 H, 15′-H), 3.39 (s, 1.8 H, 16-H), 3.38 (s, 1.2 H, 16′-H), 2.16 (s, 1.8 H, 14-H), 2.00 (s, 1.2 H, 14′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (C-3), 160.3 (C-3′), 152.5 (C-1, C-1′), 145.9 (C-4a′), 145.7 (C-4a), 143.3 (C-10a), 143.2 (C-10a′), 137.4 (C-12), 136.8 (C-12′), 128.6 (C-11′), 128.5 (C-8′), 128.0 (C-8), 127.3 (C-11), 127.2 (C-6), 127.1 (C-6′), 126.32 (C-9), 126.27 (C-9′), 125.8 (C-8a), 125.4 (C-8a′), 119.9 (C-7′), 119.8 (C-7), 116.0 (C-13), 114.5 (C-13′), 112.1 (C-5′), 112.0 (C-5), 106.1 (C-9a′), 105.5 (C-9a), 93.6 (C-2), 93.5 (C-2′), 92.1 (C-4), 91.7 (C-4′), 55.3 (C-15), 55.1 (C-15′), 33.7 (C-16), 33.6 (C-16′), 16.5 (C-14′), 15.3 (C-14) ppm. IR (film): $\tilde{\nu}$ = 2924, 2853, 1720, 1611, 1467, 1233, 1208, 1165, 761 cm^{-1}. MS (ESI–): m/z = 292.1 $[M – H]^-$, 293.1 $[M]^-$. HRMS (ESI+): calcd. for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1338; found 292.1337.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full spectroscopic data for all new compounds. Copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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