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Development of an Alkaloid-Pyrone Annulation: Synthesis of Pleiomaltinine**

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Abstract

Odd Couple—Methodology for the synthesis of alkaloid-pyrones using a novel pyrone annulation of β -carboline and indoles with 3-siloxy-4-pyrones is reported. The approach has enabled semisynthesis of the unprecedented alkaloid-pyrone pleiomaltinine from the plant-derived indole-alkaloid pleiocarpamine.

Keywords

pyrone; natural products; annulation; quinone methide; alkaloid

γ -Pyrone natural products are an important class of compounds exhibiting a wide range of biological activity.^[1] Similarly, indole-containing compounds are found throughout nature as well as pharmaceuticals and agrochemicals.^[2] Recently, Kam and coworkers isolated pleiomaltinine^[3] **1** (Figure 1), an unusual alkaloid-pyrone natural product that is able to reverse multidrug-resistance in vincristine-resistant KB (VJ300) cells (IC₅₀=12 μ g/mL in the presence of 0.1 μ g/mL of vincristine). They proposed that pleiomaltinine may be derived biosynthetically from the indole-alkaloid pleiocarpamine^[4] **2**, co-isolated from the same plant species (*Alstonia angustifolia*), and the 2-methylene-3,4-diketone^[5] **3** derived from dehydrogenation of naturally occurring maltol **4**. We were intrigued by intermediate **3** and its potential reactivity in cycloaddition chemistry analogous to the known properties of *o*-quinone methides.^[6] Herein, we report the development of a methodology for the synthesis

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of alkaloid-pyrones using a novel pyrone annulation and the application of this methodology to synthesize pleiomaltinine **1** from pleiocarpamine **2**.

After initial unsuccessful attempts to generate reactive intermediate **3** by DDQ oxidation of **4**,^[7] we considered that **3** could alternatively be derived from a precursor such as 3-siloxy-4-pyrone **5**^[8] *via* fluoride-induced desilylation.^[9] In the event, treatment of **5** and *N*-methyl carbazole **6** with TBAF led to the formation of cycloadduct **7**^[10] in low yield (Scheme 1). Further optimization through a solvent screen revealed that benzene afforded **7** in 43% yield (Table 1, entry 1), a compound also produced in protic solvents such as methanol without the inclusion of additives (entry 2). With these results in hand, we hypothesized that HBr could be produced as a byproduct and that Brønsted acids may catalyze the reaction. This assertion was supported by the addition of Et₃N in methanol which greatly reduced the reaction rate and yield for the pyrone annulations. After evaluation of a number of Brønsted and Lewis acids, we found that a stoichiometric amount of anhydrous HCl in CH₃CN provided **7** in 81% yield (Entry 7). Lowering the amount of HCl to substoichiometric levels resulted in dramatically slower reaction conversion (32 h, entry 6). During the course of our optimization studies, we observed a minor side product in varying amounts. Treatment of **5** with HCl/CH₃CN in the absence of carbazole **6** produced dimer^[11] **8** in 32% yield, lending support to the formation of 2-methylene-3,4-diketone intermediate **3** (Scheme 2).

Our proposed mechanism for the formation of the 2-methylene-3,4-diketone intermediate is shown in Scheme 3. Protonation of siloxypyrone **5** at the carbonyl oxygen^[12] to give **9** should weaken the O-Si bond by hydrogen bonding. Desilylation of the aromatic oxidopyrylium^[13] tautomer form **10** may be followed by bromide expulsion, thereby forming the reactive, protonated 2-methylene-3,4-diketone derivative **11**. The latter intermediate may then react with indoles and related substrates either in a concerted inverse demand hetero-Diels-Alder cycloaddition^[14] or in a stepwise Michael-Mannich sequence.^[15]

We next examined the substrate scope for the pyrone annulation (Table 2). Free indoles were well tolerated, while electron withdrawing groups on the indole nitrogen inhibited the reaction. This limitation was presumably due to the decreased nucleophilicity at the C-3 position leading to the major formation of dimer **8**. β -Carbolines were also found to be viable substrates using an excess of siloxypyrone **5** to furnish cycloadducts in good yield (entries 3–6). Furthermore, the cycloadducts derived from phenyl β -carboline substrates were obtained as single diastereomers with the phenyl group *trans* to the *cis*-fused pyrone moiety (*cf.* entries 3 and 4).^[16]

In addition, the annulation was found to be applicable to other siloxypyrone reaction partners (Scheme 4). The known bromo maltol^[17] was silyl protected and brominated to afford bromosiloxypyrone **24** which was then further reacted with *N*-methyl carbazole **6** to afford cycloadduct **25** in good yield. We also wished to evaluate a diastereoselective variant of the pyrone annulation. Accordingly, siloxypyrone **26** was prepared from commercially available ethyl maltol. Adduct **27** was obtained as a single diastereomer from reaction of **26** with tetrahydrocarbazole **12** under our standard conditions in good yield. Product **27** may result from formal *endo* cycloaddition^[18] of **12** and the lower energy (DFT) (*Z*)-2-methylene-3,4-diketone reaction partner **28** (Figure 2).^[16]

As part of our optimization efforts (*cf.* Table 1), we evaluated mild thermolysis of pyrone annulations but did not observe formation of the expected cycloadduct **7**. Instead, an interesting transformation where a [1, 3]-shift of the hydroxypyrone moiety to the 1 position of the carbazole occurred to afford 3-hydroxypyrone **29** (Scheme 5). The reaction could also be conducted cleanly by refluxing cycloadduct **7** in DCE. A proposed mechanism for this

transformation involves initial ring opening of the hemiaminal ether to form zwitterion **30**. Subsequent proton transfer affords the enamine **31**^[19] which can restore aromaticity of the indole by elimination of the pyrone, thereby creating ion pair **32**. The vinylogous addition of the pyrone^[20] to the stabilized carbocation yields the observed product **29**. Similar carbazole/carboline allylic carbocations to **32** have been proposed in the literature.^[21] In contrast, thermolysis of the *N*-H cycloadduct **13** provided the indolenine **33** (84%). Efforts to further rearrange **33** under basic conditions (*e.g.* NaH, Cs₂CO₃, and DBU) resulted either in retrocycloaddition or decomposition. Rearrangements were also attempted with cycloadducts **17** and **19** in order to produce carbazole-hydroxypyrene structures bearing a fully substituted carbon. Unfortunately, thermal and Lewis acid (*e.g.* Zn(OTf)₂, Yb(OTf)₃, Sc(OTf)₃) conditions with these substrates have thus far proved unsuccessful. The major product observed in these cases was retrocycloaddition to afford the starting indole or β -carboline.

Finally, application of the pyrone annulation to plant-derived pleiocarpamine^[22] **2** using siloxypyrene **5** with HCl in CH₃CN provided pleiomaltinine **1** in 51% yield as a single diastereomer after purification by preparative HPLC (Scheme 6). The diastereoselectivity of the reaction arises from pyrone annulation on the convex face of the pentacyclic alkaloid framework (Figure 3). Both synthetic and natural pleiomaltinine gave matching ¹H and ¹³C NMR spectra as well as TLC and HPLC retention values.^[16]

In summary, we have developed a novel pyrone annulation of carbazoles and related heterocycles with 3-siloxy-4-pyrones which provides access to unusual alkaloid-pyrone structures. Further rearrangements of the alkaloidal-pyrone structures were observed, including a formal [1,3] shift to access a 1-substituted carbazole. Application of the pyrone annulation to the plant-derived alkaloid pleiocarpamine resulted in the synthesis of the unusual alkaloid-pyrone pleiomaltinine. Further studies concerning the development of asymmetric pyrone annulations as well as additional reactivity studies of the alkaloid-pyrone structures are currently in progress and will be reported in due course.

Supplementary Material

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Figure 1.
Pleiomaltinine **1** and its proposed biosynthesis.

Figure 2.
(a) Molecular model (Spartan '10) of **27**. (b) Proposed [4+2] transition state.

Figure 3.
Molecular model (Spartan AM1 '10) of pleiocarpamine 2.

Scheme 1.
Initial pyrone annulation result.

Scheme 2.
Dimerization of pyrone.

Scheme 4.
Further applications of the pyrone annulation.

Scheme 5.

Thermolysis of carbazole-pyrone cycloadducts. DCE= 1,2-dichloroethane.

Scheme 6.
Synthesis of pleiomaltinine.

Table 1

Optimization of the pyrone annulation.

Entry	Conditions (25 °C)	Time (h)	Yield (%) ^a
1	2.0 equiv 6 , 1.5 equiv TBAF, 0.1 M PhH	0.5	43%
2	1.5 equiv 6 , 0.1 M MeOH	0.25	50%
3	1.5 equiv 6 , 1.0 equiv CSA, 0.1 M CH ₂ Cl ₂	30	82%
4	1.5 equiv 6 , 50 equiv aq. HCl, 0.1 M CH ₂ Cl ₂	5	61%
5	1.5 equiv 6 , 11 mol% SnCl ₄ ·5H ₂ O, 0.1 M CH ₂ Cl ₂	31	76%
6	1.5 equiv 6 , 10 mol% HCl in 0.1 M dioxane	32	67%
7	1.5 equiv 6 , 1.3 equiv HCl in dioxane, 0.2 M CH ₃ CN	0.5	81%

^a Isolated yield of product after silica gel chromatography.

TBAF=tetra-*n*-butyl ammonium fluoride, CSA=camphorsulfonic acid, HCl=hydrochloric acid

Table 2

Substrate scope.

Entry	Precursor (equiv)	Cycloadduct	Method ^a	Time (min)	Yield ^b (%)
1			A	10	80
2			A	15	84
3			B	60	71
4			B	45	77
5^c			B	60	62

Entry	Precursor (equiv)	Cycloadduct	Method ^a	Time (min)	Yield ^b (%)
6^c			B	60	51

^aMethod A: 1.5 equiv indole, 1 equiv pyrone, 3.0 equiv HCl, 0.2 M CH₃CN; method B: 1 equiv indole, 2 equiv pyrone, 1.5 equiv HCl, 0.2 M CH₃CN.

^bIsolated yield of product after silica gel chromatography.

^cDMSO as solvent.