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First total synthesis of caerulomycin K: a case study on selective, multiple C−H functionalizations of pyridines†

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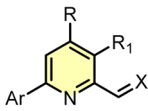
Caerulomycins, natural alkaloids with antimicrobial properties, have been previously synthesized starting with highly pre-functionalized building blocks or requiring many functional group manipulations. In this work, we report the first total synthesis of caerulomycin K, a diversely trifunctionalized pyridine readily assembled in three steps exploiting the recent advancements in the C−H activation of N-heterocycles.

Pyridines are ubiquitous in many natural products and drugs, often with a wide selection of functionalities decorating these aromatic rings.[1,2] While classical pyridine syntheses (*e.g.* Bohlmann–Rahtz reaction, Hantzsch condensation, *etc.*) allow the introduction of substituents in the final ring, the functionalization of existing pyridines using C−H activation is usually a better option to avoid the *de novo* synthesis of complex pyridines.[3] However, despite pyridines exhibiting a clear similarity to benzenes, they present distinct challenges when it comes to their C−H functionalization.[4,5] As a result, relatively simple pyridines may require several steps to be synthesized, especially if the substituents around the aromatic ring are different in nature. This is the case for caerulomycins (and related collismycins), a class of natural alkaloids produced by *Streptomyces caeruleus* and endowed with antimicrobial properties (Scheme 1A).[6–11] For instance, taking caerulomycin E as the prototype of this type of bioactive compounds, different routes have been designed to decorate the core pyridine ring with common substituents such as a carbonyl group (*ortho*-aldehyde), an alkoxide (*para*-MeO), and an aromatic ring (*ortho*-pyridine).[12–21] Yet, the installation of these functionalities *via* C−H activation is not straightforward since it requires several functional group interconversions (Scheme 1B).
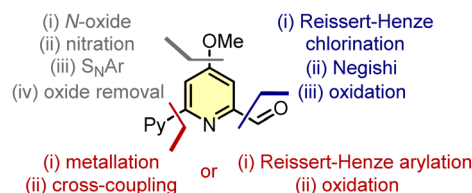
Specifically, the installation of the methoxy group can require four steps: formation of the N-oxide with an oxidant, nitration with concentrated H_2SO_4, nucleophilic aromatic

substitution (S_NAr) with MeONa, and removal of the oxide with Ac_2O.[18,19] The insertion of an *ortho*-pyridine group is usually more rapid but requires the use of Grignard reagents or pre-functionalized 2-bromopyridines.[15,16] Finally, the insertion of the carbonyl group is achieved by oxidation of a methyl group whose installation has been obtained only with a halogen (Cl or Br) already placed in *ortho*-position.[18,21] Given the recent advancements in selective C−H functionalizations of pyridines,[4,5] it would be expected that alternative strategies should now allow a faster synthesis of caerulomycins. Herein, we report our efforts to rapidly convert a cheap monosubstituted pyridine into caerulomycin K, a recently isolated alkaloid whose total synthesis has never been reported before.

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A) Caerulomycins' structures

Name	Ar	R	R₁	X
Caerulomycin A	Py	OMe	-	N-OH
Caerulomycin B	Py	OMe	OH	N-OH
Caerulomycin E	Py	OMe	-	O
Caerulomycin K	Ph	OMe	-	N-OH
Collismycin A	Py	OMe	SMe	N-OH
Collismycin D	Py	OH	SMe	N-OH

B) Previously reported approaches to caerulomycin E

(i) N-oxide
(ii) nitration
(iii) S_NAr
(iv) oxide removal

(i) Reissert-Henze chlorination
(ii) Negishi
(iii) oxidation

(i) metallation
(ii) cross-coupling

or

(i) Reissert-Henze arylation
(ii) oxidation

C) First total synthesis of caerulomycin K (this work)

Minisci → Minisci → FGI

Scheme 1 Structures and synthetic routes to caerulomycins.

Our investigation began with the design of a synthetic route that would furnish caerulomycin K in a few steps using two C–H activations, thus avoiding highly pre-functionalized starting materials. In an initial retrosynthetic approach, we imagined that the aldoxime group could be derived from a methyl group, as reported by Quéguiner and co-workers, thus leading to tri-functionalized pyridine **I** (Scheme 2A).[18] At this point, we envisaged that **I** could be accessed by a selective difunctionali-zation of pyridyl bis-phosphonium salt **III** *via* two sequential ligand-coupling (LC) reactions, that is formal S_NAr reactions where a phosphonium group is replaced by opportune nucleophiles.[22–24] Salt **III** could then be obtained from 2-phe-nylpyridine **1** *via* two consecutive C–P bond formation reac-tions, in analogy with a rare example of a pyridyl bis-phosphonium salt (Scheme 2B).[25,26]
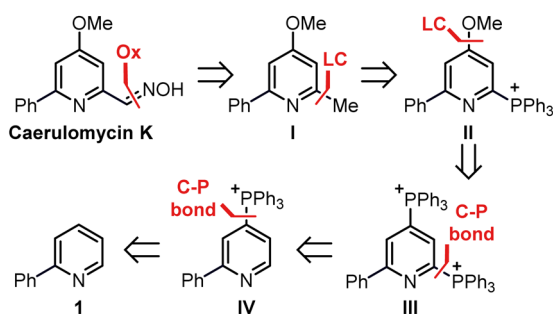
This strategy would provide the desired product in 5 steps, whereas the ionic nature of most intermediates would reduce the need for column chromatography. Moreover, considering the wide versatility of ligand-coupling reactions,[25,26] **III** would be a strategic intermediate for the synthesis of libraries of tri-functionalized pyridines by simply changing the order and the nature of the added nucleophiles. In the laboratory, **1** was dis-solved in dichloromethane and cooled down to −78 °C, before sequentially adding Tf_2O, Ph_3P, and DBU (Scheme 3). In agreement with McNally's work,[27] upon workup, **2** was easily precipitated out as a white powder from cold ether (88% iso-lated yield). Notably, the Ph_3P addition occurs almost exclu-sively at the *para*-position (due to stereoelectronic reasons), thus no regioselectivity problems are encountered during this reaction.[28] This was also confirmed by ^{31}P NMR, with only a sharp singlet observed at 23.01 ppm. Repeating the procedure using now **2** as the starting material, the reaction crude revealed two new signals of similar intensity at 23.55 ppm and 15.37 ppm.
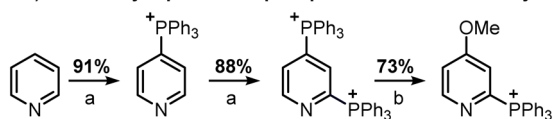

Scheme 2 Reactivity of bis-phosphonium salts and application in the planned retrosynthesis of caerulomycin K. The triflate anion is not reported for clarity.
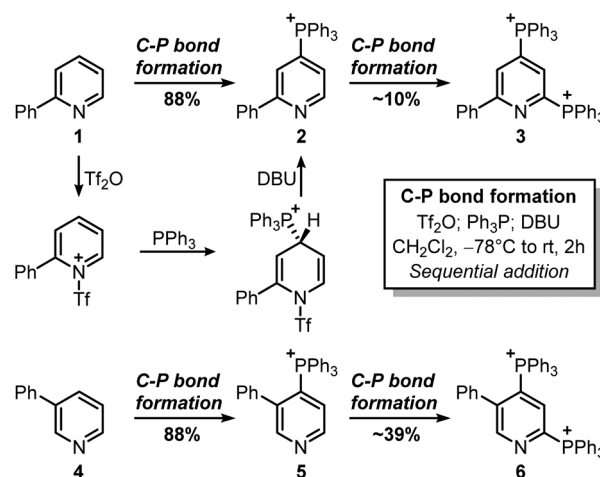
Scheme 3 Attempted bis-phosphonium salts synthesis. The triflate anion is not reported for clarity.

These signals were respectively assigned to the *para*- and *ortho*-phosphine of bis-phosphonium bis-triflate **3**. However, the conversion was only modest by ^{31}P NMR, with significant unreacted **2** and Ph_3PO observed in the reaction mixture. The failure of the second C–P bond formation was attributed to a problematic N-activation since **2** should be less nucleophilic than **1** due to its cationic nature. This was confirmed using phosphonium **5**, obtained in good yield from 3-phenylpyridine **4**: moving away the phenyl ring from the *ortho*- to the *meta*-position improved the second C–P bond formation (**5** less sterically encumbered than **2**), yet not to a significant extent due to electronic reasons. Indeed, bis-phosphonium **6** was found as a minor component in ^{31}P NMR spectrum of the reaction crude (signals at 21.93 ppm and 17.08 ppm, with a $^3J_{P–P} = 6.0$ Hz). Deuterodephosphination[29] of this reaction mixture further confirmed the poor conversion, with the isolated pyridine showing almost quantitative *d*-incorporation in *para*-position but a limited deuteration on the C6-site (Scheme 4).

Scheme 4 Deuterodephosphination of the **5/6** mixture (top) and ^{1}H NMR and ^{2}H NMR spectra (CDCl$_3$, 400 MHz) of the isolated mixture of **4-d$_1$**/**4-d$_2$** (bottom). Deuterium incorporation was determined by the relative integration of the signals of hydrogens on the pyridine ring.

Finally, attempts to use a more nucleophilic phosphine (*i.e.* (4-anisyl)₃P) did not improve the C–P bond formation, and neither did the use of it as the first installed phosphine (see ESI†). Indeed, the use of (4-anisyl)₃P mainly resulted in the formation of the corresponding phosphine oxide, as expected for electron-rich phosphines. Given the problematic separation of salts **2** and **3** and the modest conversion observed in the second step, we decided to perform one C–P bond formation at a time. Treatment of **2** with MeONa in dichloromethane gave disubstituted pyridine **7** in 53% ¹H NMR yield (Scheme 5), although its isolation was complicated by co-eluting Ph₃PO (the product, together with **1**, of competitive proto-dephosphination). Before performing the second C–P bond formation on **7**, the installation of a methyl group using **2** as a model compound was attempted.

Indeed, while the replacement of Ph₃P with chalcogens/pnictogen nucleophiles (–OR, –SR, –NR₂) is relatively straightforward,[27,30,31] the installation of alkyl or aryl groups *via* ligand-coupling requires additional manipulations.[32–34] However, the direct use of organolithium has been shown successful in a couple of cases (*e.g.* ArLi), hence we hoped the use of MeLi or MeMgBr wou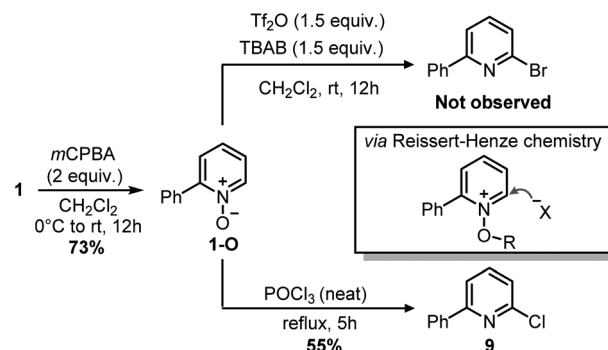ld avoid extra steps.[27] Unfortunately, treatment of **2** with these organometallics provided equimolar amounts of 2,4-diphenylpyridine **8** and Ph₂P(O)Me (Scheme 5), the latter observable in the ¹H NMR spectrum (2.01 ppm, d, ²J_{P-H} = 13.2 Hz, 3H, Me). This result highlights how, in contrast to alkoxides, the phenyl ring has a higher migration aptitude than a methyl group during the ligand-coupling of the phosphorane intermediate,[35,36] thus leading to **8** and Ph₂PMe (then oxidized during the workup). An alternative approach to the use of phosphonium salts would be an *ortho*-halogenation followed by Negishi coupling with MeZnCl, in analogy with the reported synthesis of caerulomycin E.[18] These halogenations (Reissert–Henze reactions) require the use of N-oxides, easily made upon treatment of pyridines with an oxidant such as H₂O₂ or *m*-chloroperbenzoic acid (*m*CPBA).[37] Initially, using **1-O** as a model substrate, activation with Tf₂O and bromination with tetra-*n*-butylammonium bromide (TBAB) was attempted, in analogy
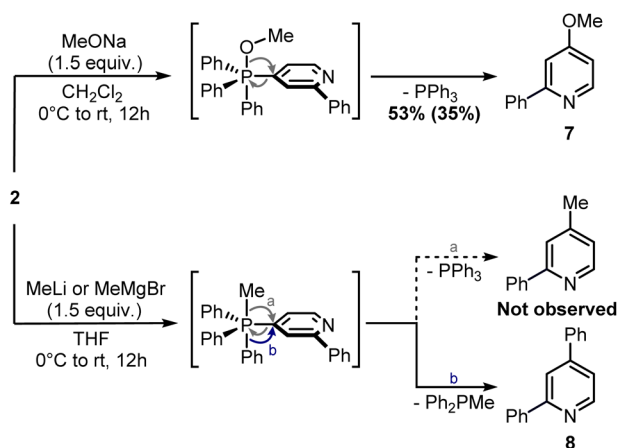
with the *ortho*-bromination of quinolines reported by Baran and co-workers (Scheme 6).[38] However, no desired product was observed, but only a mixture of brominated pyridines, probably due to some Br₂ formed from the residual oxidant (*m*CPBA) still present in **1-O**. In contrast to pyridines, the successful *ortho*-bromination observed by Baran for quinolines reflects the lower loss in resonance stabilization typical of bicyclic aromatics (*i.e.* naphthalene *vs.* benzene). Chlorination of **1-O** with POCl₃ gave better results (**9** isolated in 55% yield), but the need for harsh conditions (neat POCl₃ refluxing at 106 °C) somehow defeated our original purpose for a short and mild synthesis, thus a completely different strategy was considered.

Minisci-type chemistry is an excellent method for *ortho*-functionalizations of pyridines, especially employing nucleophilic carbon-based radicals (ideal for the synthesis of caerulomycin K).[39,40] Moreover, starting with a 4-substituted pyridine would prevent regioselectivity issues (C2 *vs.* C6) typical of unsymmetrical starting materials. For the *ortho*-arylation of pyridines, Baran and others have shown how aryl boronic esters, in combination with AgNO₃, Na₂S₂O₈, and TFA, are excellent aryl radical precursors.[41,42] To install a carbonyl group, Angeles, Yeung, and colleagues have used 1,3,5-trioxanes as an aldehyde equivalent in Minisci-type carbonylation of pyridines.[43] Based on this precedent, a Minisci arylation of 4-chloropyridine **10** was performed (Scheme 7). In this case, an excess of phenylboronic acid (1.5 equiv.) was needed to compensate for competitive protodeboronation, whereas a higher loading of AgNO₃ allowed the isolation of product **11** in 56% yield. A second Minisci reaction was then performed on this pyridine using 1,3,5-trioxane in the presence of (*n*Bu₄N)₂-S₂O₈. A successful *ortho*-alkylation gave product **12** in 50% yield (a value in agreement with previous reports),[44–47] whereas a subsequent nucleophilic aromatic substitution allowed to access trifunctionalized pyridine **13** almost quantitatively. It has to be noted that starting from 4-methoxypyridine **14** would shorten the synthesis, but the electron-donating effect of the methoxy group will negatively affect both steps since Minisci reactions are based on the addition of nucleophilic radicals. The final conversion of **13** into caerulomycin K was achieved in a one-pot procedure by treatment with HCl (to reveal the aldehyde functionality), followed by condensation with NH₂OH. Importantly, **12** could be directly converted into caerulomycin K

Scheme 5 Ligand-coupling reactions with phosphonium salt **2**. ¹H NMR yield determined using CH₂Br₂ as internal standard (in brackets, isolated yield).
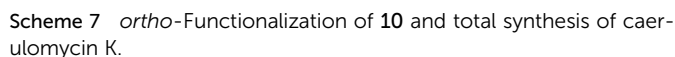

Scheme 6 *ortho*-Halogenations with **1-O**.

Scheme 7 *ortho*-Functionalization of **10** and total synthesis of caerulomycin K.

without the need for isolation of **13**, further simplifying the synthesis (route in green). Therefore, this three-step total synthesis (overall yield of 10%) represents the first synthesis of caerulomycin K as well as a potential alternative to the synthesis of caerulomycins.

In conclusion, the first total synthesis of caerulomycin K has been reported. Starting from monofunctionalized pyridines, the first strategy looked at a double C–H activation by means of phosphonium chemistry. However, a poor conversion of the second C–P bond formation and a problematic *ortho*-methylation, including *via* halogenation, prompted the search for a better alternative. This was achieved by sequential Minisci *ortho*-arylation and *ortho*-alkylation, with the latter converted in one pot into the desired oxime. Compared to previously reported caerulomycin syntheses, this novel approach does not require highly pre-functionalized starting materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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