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'*Wake-Up Call of A Sleeping Beauty*': Straightforward Synthesis of Functionalized β-(2-Pyridyl) Ketones from 2,6-Lutidine

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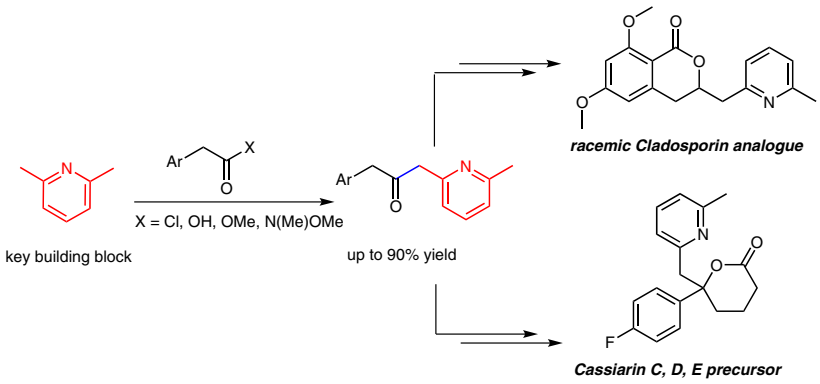

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Abstract β-(2-Pyridyl) ketones are a unique class of heterocycles with valuable physicochemical properties and emerging relevance as pharmacophores. Herein we report a one-step process for the preparation of various substituted β-(2-pyridyl) ketones from the common starting material, 2,6-lutidine. Furthermore, we demonstrate the utility of this building block by synthesizing of a small set of antimalarial natural products.

Key words β-(2-pyridyl) propanone, acylation, malaria, small-molecule natural-product analogues

Heterocyclic compounds play an important role in medicinal chemistry and drug synthesis.[1] Like any important functional class of compounds, developments that facilitate their preparation or elucidate their reaction mechanisms are significant for process chemists in the pharmaceutical industry. Over the last decades, β-(2-pyridyl) ketones have emerged as attractive precursors not only for heterocyclic bioactive molecules[2] but also for advanced materials such as organic semiconductors.[3]

Indeed, in a continuing search for bioactive molecules which display curative possibilities for many human ailments such as cancer, Alzheimer's disease, malaria, and pain, among others, we focused our attention on plants of medicinal importance. The vast diversity of plants on the planet gives a promising journey ahead in the quest for knowledge and represents a valuable source of new drug leads and novel scaffolds.

With renewed calls for malaria eradication, next-generation antimalarials will need to be active against drug-resistant parasites and efficacious against both liver- and blood-stage infections.[4] We screened a natural product library to identify inhibitors of *Plasmodium falciparum* blood- and liver-stage proliferation. Cladosporin (**1**)[5] and cassiarin D (**2**) were both identified as being potent antiparasitic compounds (Figure 1).

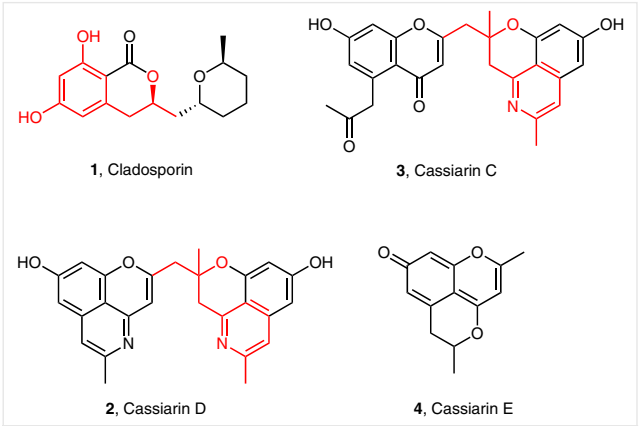
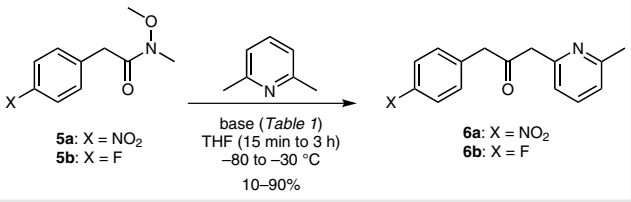


Figure 1 Structure of cladosporin and cassiarin C–E

Unlike cladosporin, which can be isolated from different fungal sources[6] (for instance: *Aspergillus flavus*, and several *Eurotium genus*), cassiarin D was extracted from a plant; *Cassia siamea Lam.* (*Leguminosae*) that has been used widely in traditional medicine, particularly for treatment of periodic fever and malaria in Indonesia. Notably, in 2009, three novel alkaloids, cassiarin C (**3**), D (**2**), and E (**4**), exhibiting a moderate antiplasmodial activity against *Plasmodium falciparum* 3D7 (24.2 μM, 3.6 μM, and 7.3 μM, respectively), were isolated and characterized by the group of Morita.[7] Cassiarin C–E display an unprecedented tricyclic skeleton where an elaborated pyridyl-propanone could serve as a starting point for their total synthesis. Similarly, observing the structure of cladosporin and evaluating possible medicinal chemistry development of the molecule, we envisioned the synthesis of a series of analogues with pyr-

idyl-propanone being our key building block. Notably, the synthesis of β-(2-pyridyl) propanones and their picolylderivative homologues, as it stands today, largely relies on the use of rather dangerous and toxic starting materials and are often accessible only via a multistep synthesis.[8]

With this in mind, we embarked on the development of an acylation reaction that should be robust, productive, scalable, and flexible. We started by developing the acylation conditions with Weinreb amides[9] bearing two specific types of electron-withdrawing groups (EWG), for which we had a synthetic preference, as they offer potential late-stage functionalization of drug-like molecules[10] (Scheme 1; EWG = F and NO_2).



Scheme 1 Synthesis of fluoro- and nitro-β-ketopyridyl

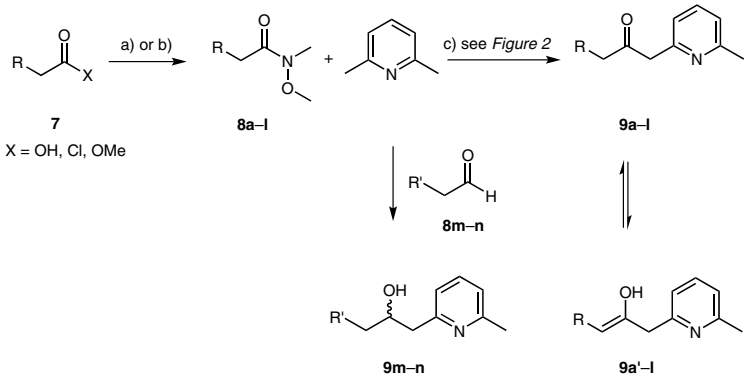
A literature search for additional acylation conditions in the presence of Weinreb amides returned only very limited references, indicating that this beautiful reaction,[11] asleep for many years, was due to for a revival. Indeed, to awake this 'sleeping beauty' we took a look at the 1977 paper published by H. Anderson et al.,[13] which investigated the acylation of the pyrrolyl ambident anion and rationalized most of their results using the principle of Pearson around hard and soft acids and bases. Based on this work, we postulated that direct acylation should proceed via deprotonation of the 2,6-lutidine, with a range of organolithium reagents (e.g., LDA, *n*-BuLi, *s*-BuLi, LiHMDS, and eventually KHMDS), according to the same principle. Pleasingly, we here demonstrated that in contrast to previous reports,[5] unreactive acylating agents such as **5a** and to a greater extent **5b**, in the presence of *s*-BuLi could give rise to the corresponding β-(2-pyridyl) ketone in 20% and 90% yield, respectively (Table 1).

Table 1 Exploration of the Conditions for the Synthesis of Fluoro- and Nitro-β-ketopyridyl

Entry[a]	X	Conditions	Yield (%)[b]
1	NO_2	*n*-BuLi (2 equiv), –80 °C for 1 h	–
2	NO_2	*s*-BuLi (2 equiv), –80 °C for 1 h	–
3	NO_2	*s*-BuLi (2 equiv), –80 °C to –30 °C for 2 h	**6a** 8
4	NO_2	*s*-BuLi (2 equiv), –30 °C for 1 h	**6a** 20
5	NO_2	KHMDS (2.1 equiv), –80 °C for 30 min	–
6	F	LDA (2.1 equiv), –80 °C for 30 min	**6b** 60
7	F	LiHMDS (2.1 equiv), –80 °C for 15 min	–
8	F	*n*-BuLi (2.1 equiv), –80 °C for 10 min	**6b** 77
9	F	*s*-BuLi (2 equiv), –80 °C for 1 h	**6b** 90

[a] Reactions were performed in THF on a 0.5–1 mmol scale.
[b] Yield of isolated products.

To further explore the scope of the reaction, a series of potential acylating agents of varying softness and reactivity were studied: acyl chloride, esters, Weinreb amides, and aldehydes.[14] As predicted, Weinreb amides were less problematic over its acyl chloride and the esters counterparts in terms of potential for overalkylation and were further carried on for the preparation of a small collection of pyridyl derivatives in moderate to good yields (**9a–l**). Interestingly, it should be noted that all the β-(2-pyridyl) ketones exist as a mixture of keto–enol tautomers, whose ratio depends on the carbonyl substitution[15] (**9′**, Scheme 2). Particularly noteworthy, are the examples shown in entry **9m** and **9n**, in which Weinreb amides were replaced by their corresponding aldehydes **8m** (2-cyclohexylacetaldehyde) and **8n** [(*R*)-citronellal], to afford the desired alcohols in high yield and without any further decomposition (Figure 2).



Scheme 2 Synthesis a small collection of β-ketopyridyls and racemic 1-(6-methylpyrdin-2-yl) alcohols. *Reagents and conditions*: a) $SOCl_2$, reflux followed by Weinreb amine in pyridine–CH_2Cl_2 at r.t., or b) DIPEA, EDCI, Me(MeO)NH·HCl in CH_2Cl_2 at r.t.; for c) see Figure 2; **8m** corresponds to 2-cyclohexylacetaldehyde and **8n** to (*R*)-citronellal.

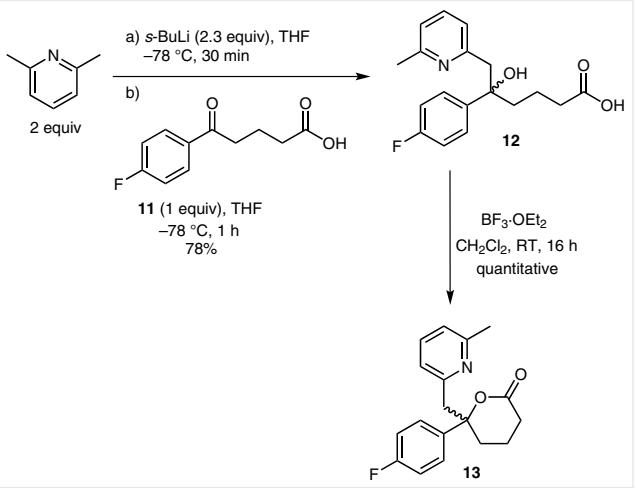
This methodology also enables the synthesis of asymmetric β-(2-pyridyl) alcohol (**9m**,**n**, dr = 2:1), reacting the enantiopure (*R*)-citronellal and cyclohexanal with the 2,6-lutidine under standard conditions, as exemplified in Figure 2.[16]

Finally, more elaborated arylketones were also investigated. Substrates bearing multiple functionalities (**11** and **14**) were successfully prepared.

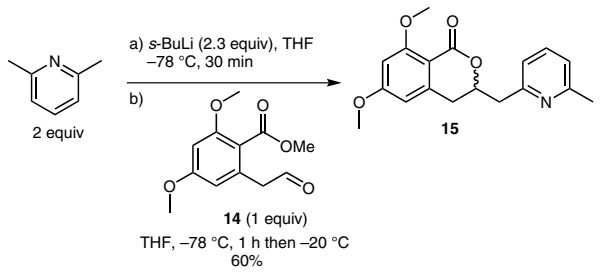
Addition of 2-pyridylmethyl lithium to the 5-(4-fluorophenyl)-5-oxopentanoic acid (**11**) commercially available under optimized conditions (Scheme 3) followed by Lewis acid catalyzed cyclization in the presence of $BF_3{\cdot}OEt_2$ opened a convenient entry into the fluorophenyl-pyridinyl-substituted lactone **13** [78% for **12** (ref. 16), quantitative for **13** (see supporting information)].

With this methodology established, compound **14**[17] was swiftly elaborated into the pyridinyl-isocoumarin **15** (60%), mimicking the signature tetrahydropyran-isocoumarin motif as a first racemic cladosporin natural product analogue (Scheme 4). This compound is currently being evaluated for its antimalarial properties.

The results of this venture and of a first round of chemical synthesis of elaborated scaffolds are summarized. A range of β-(2-pyridyl) ketones and their picolylderivative homologues were successfully synthesized in a single-step process. Our group is currently exploring the enantiomeric aspect of this fundamental reaction. This method may



Scheme 3 Synthesis of a novel functionalized lactone **13**



Scheme 4 Synthesis of a racemic non-natural cladosporin analogue **15**

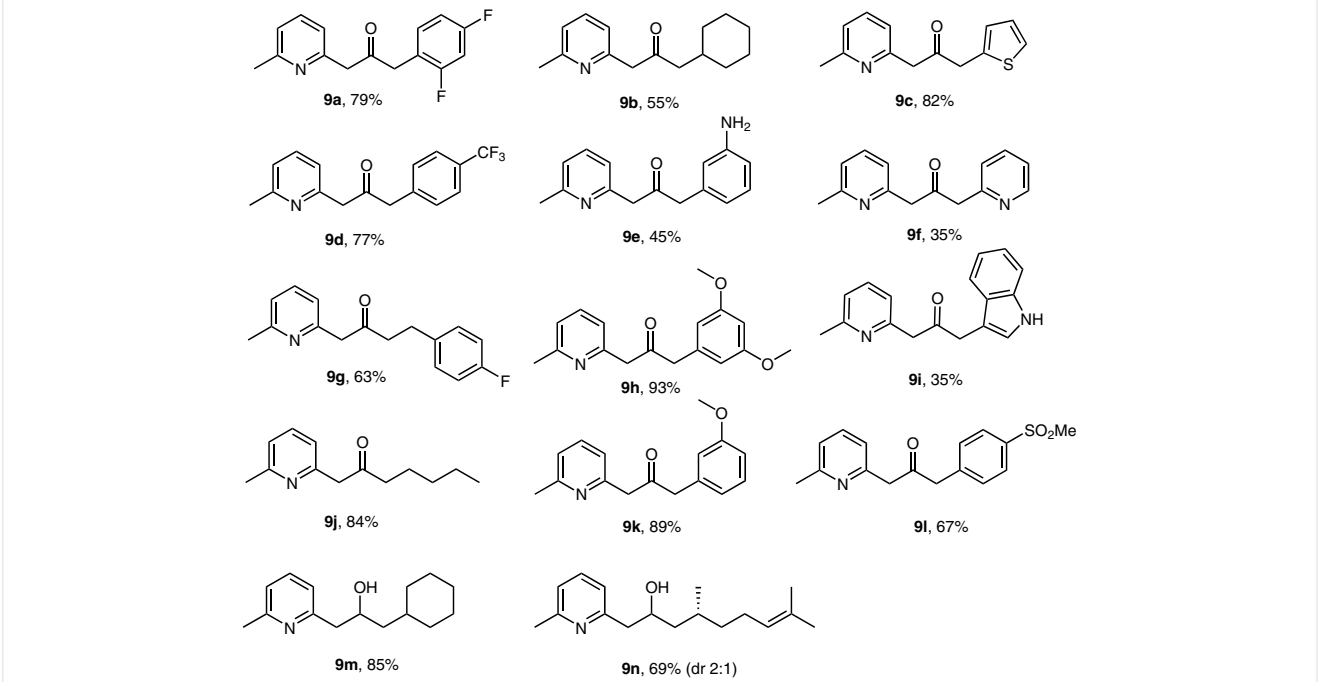


Figure 2 Scope of the acylation reaction. Yields of isolated compounds after column chromatography are given.

prove highly useful in the context of the synthesis of cladosporin analogues and other cassiarin natural products. Further results will be reported in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588154.

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(9) **General Procedure for the Preparation of Weinreb Amide**
Method A
In a dry round-bottom flask, the corresponding carboxylic acid (1 equiv, 0.5 mmol) was added to a solution of $SOCl_2$ (20 equiv), and stirred under reflux over a period of 5 h. The excess of $SOCl_2$ was then removed under reduced pressure. Under inert atmosphere, the crude residue was taken into CH_2Cl_2, added dropwise to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 equiv) and pyridine (2.2 equiv) at 0 °C (NB: final concentration must not exceed 0.1 mol/L) and slowly warmed to r.t. After completion of the reaction, the crude mixture was diluted with CH_2Cl_2, and rinsed three times with water. The organic phase was decanted and was washed with a sat. solution of $NaHCO_3$, and neutralized with a solution HCl (1 M) until pH 7. The organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient of eluent from 100% heptane to 100% EtOAc) to afford the corresponding Weinreb amide.
Method B
Diisopropylethylamine (4 equiv, 0.1 mmol), followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1 equiv were sequentially added to a dry solution of the corresponding carboxylic acid (1 equiv) in CH_2Cl_2 and stirred for 10 min at r.t. *N*,*O*-Dimethylhydroxylamine hydrochloride (2 equiv) was added, and the resulting mixture was stirred until all starting materials were consumed (TLC and LC–MS monitoring). The crude reaction was quenched with a sat. aq NH_4Cl solution and extracted with EtOAc. The organic layers were washed with a sat. solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient of eluent from 100% heptane to 100% EtOAc) affording the desired Weinreb amides.
See the Supporting Information for full characterization and spectra.

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(15) A ratio in favor of the enol form compared to the ketone form was observed in the case of carbonyls bearing electron-withdrawing aromatic groups. When reacting in the presence of heteroaromatic rings, such as thiophene, pyridine, and indole rings, the equilibrium was in favor of the ketone form.

(16) **General Procedure for the Preparation of β-Keto-Pyridyls**
In a 50 mL dry three-neck round-bottom flask was introduced a solution of 2,6-lutidine (2 equiv, 0.09 mmol) in THF under argon. The solution was cooled to –78 °C and a solution of *s*-BuLi (1.4 M in cyclohexane, 2.3 equiv) was added dropwise to the reaction mixture, which was then stirred for 15–30 min at –78 °C. A solution of the electrophile of choice (1 equiv) in THF was then added dropwise and stirred for 15–60 min at –78 °C. The crude reaction was quenched with a sat. aq NH_4Cl solution

at –78 °C and allowed to warm up to r.t. The aqueous phase was then extracted three times with EtOAc. The combined organic layers were washed with a sat. solution of NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient of eluent from 100% heptane to 100% EtOAc) to afford the desired products (**6a**,**b**, **9** and **9′** series, and **12**; for **15** see the Supporting Information).

See the Supporting Information for full characterization and spectra.

(±)-(4*R*)-4,8-Dimethyl-1-(6-methylpyridin-2-yl)non-7-en-2-ol (9n)

Compound **9n** was obtained in 69% yield as a colorless oil. The compound was isolated as a mixture of two diastereoisomers (dr = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.4 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.97 (d, *J* = 7.3 Hz, 1 H), 5.18–5.06 (m, 1 H), 4.19–4.06 (m, 1 H), 2.96–2.76 (m, 2 H), 2.56 (s, 3 H), 2.13–1.91 (m, 2 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.55–1.39 (m, 2 H), 1.34–1.11 (m, 3 H), 0.96 (dd, *J* = 6.6, 4.7 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1, 156.7, 136.8, 130.6, 124.4, 120.6, 120.1, 68.6, 68.2, 44.3, 44.2, 43.1, 42.4, 37.5, 36.4, 28.8, 28.3, 25.2, 25.0, 24.9 ppm. LC–MS (t_R = 1.00 min for a 2 min run): *m/z* calcd for $[C_{17}H_{27}NO + H^+]$: 262.4 $[M + H]^+$.

(±)-5-(4-Fluorophenyl)-5-hydroxy-6-(6-methylpyridin-2-yl)hexanoic Acid (12)

Compound **12** was obtained in 78% yield as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 7.49 (t, *J* = 7.7 Hz, 1 H), 7.40 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.09–6.98 (m, 3 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 3.26–3.08 (m, 2 H), 2.39 (s, 3 H), 2.08 (td, *J* = 7.8, 2.5 Hz, 2 H), 1.89–1.74 (m, 1 H), 1.67 (td, *J* = 13.4, 12.5, 4.7 Hz, 1 H), 1.51 (qd, *J* = 12.3, 7.5 Hz, 1 H), 1.18 (dt, *J* = 12.0, 5.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ = 174.37, 161.65, 159.25, 157.89, 156.18, 142.80, 136.82, 127.41/127.34, 121.62, 120.78, 114.16, 113.95, 75.83, 47.93, 41.83, 33.93, 23.85, 18.94 ppm. LC-MS (t_R = 0.74 min for a 2 min run): *m/z* calcd for $[C_{18}H_{20}FNO_3+H^+]$: 318.3 $[M + H]^+$.

(±)-6,8-Dimethoxy-3-[(6-methyl-pyridin-2-yl)methyl]isochroman-1-one (15)

Compound **15** was obtained in 60% yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (t, *J* = 7.5 Hz, 1 H), 7.17 (d, *J* = 7.4 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.41 (d, *J* = 2.2 Hz, 1 H), 6.30 (d, *J* = 2.2 Hz, 1 H), 4.92–4.83 (m, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.36–3.30 (m, 1 H), 3.23–3.12 (m, 1 H), 3.02–2.86 (m, 2 H), 2.57 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 166.3, 162.8, 158.3, 157.7, 143.1, 137.0, 122.4, 119.5, 108.6, 104.1, 98.5, 79.9, 55.8, 55.2, 39.8, 33.3, 24.6 ppm. LC–MS (t_R = 0.73 min for a 2 min run): *m/z* calcd for $[C_{18}H_{19}NO_4+H^+]$: 314.3 $[M + H]^+$.

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