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A Three-Component Reaction Forming Naphthyridones – Synthesis of Lophocladine Analogs

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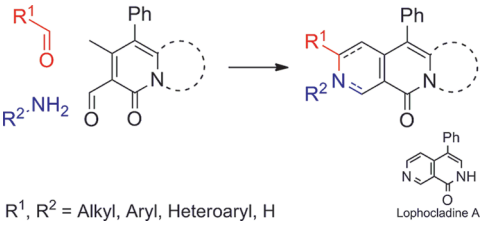
ABSTRACT



A three-component reaction forming dihydro 2,7-naphthyridine-1-ones has been developed. These unstable dihydro intermediates can be either oxidized or reduced to form naphthyridones or tetrahydro naphthyridones, respectively. The reaction tolerates a large variety of aldehydes and amines, and the produced compounds are analogs of the natural product lophocladine A.

Multicomponent reactions forming heterocyclic compounds are of great interest in the drug-discovery process as they can offer expedient synthesis of libraries of drug-like compounds.[1] In particular, multicomponent reactions generating natural product analogs are of special interest as natural products play an important role in the development of new therapeutics.[2] In the field of antibacterials, about two-thirds of all approved drugs in the past decades are natural products or natural product derivatives.[3]

Ring-fused 2-pyridones are frequently found in both biologically active synthetic compounds and natural products. The synthetic amino-substituted ring-fused 2-pyridone **1** and similar compounds are active as antibacterial agents targeting bacterial virulence.[4] A late step in the synthesis of **1** is a reductive amination of aldehyde **2** (Figure 1).[5]

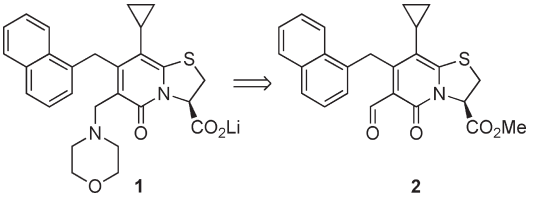


Figure 1. Compound **1** is a 2-pyridone-based compound with antibacterial properties.

In the work with related compounds it was noticed that the sterically less hindered aldehyde **3** (Figure 2), unlike **2**, does not simply give the imine when treated with a primary amine under mildly acidic conditions. Instead, based on LC-MS analysis, dimers hypothesized to be dihydro naphthyridones of general structure **4** appeared to form. By running the reaction in the presence of a second aldehyde, nondimeric compounds with different R^2-groups were obtained. It was also noted that the formation of **4** is reversible and preformed dimeric **4** could be equilibrated to nondimeric compounds by subsequent addition of a second aldehyde.

Although dihydro naphthyridones like **4** were difficult to isolate, when **3** was stirred at room temperature with

(1) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80.
(2) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266–276.
(3) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.
(4) (a) Pinkner, J. S.; Remaut, H.; Buelens, F.; Miller, E.; Åberg, V.; Pemberton, N.; Hedenström, M.; Larsson, A.; Seed, P.; Waksman, G.; Hultgren, S. J.; Almqvist, F. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 17897–17902. (b) Cegelski, L.; Pinkner, J. S.; Hammer, N. D.; Cusumano, C. K.; Hung, C. S.; Chorell, E.; Åberg, V.; Walker, J. N.; Seed, P. C.; Almqvist, F.; Chapman, M. R.; Hultgren, S. J. *Nat. Chem. Biol.* **2009**, *5*, 913–919. (c) Åberg, V.; Almqvist, F. *Org. Biomol. Chem.* **2007**, *5*, 1827–1834.
(5) Pemberton, N.; Pinkner, J. S.; Jones, J. M.; Jakobsson, L.; Hultgren, S. J.; Almqvist, F. *Tetrahedron Lett.* **2007**, *48*, 4543–4546.

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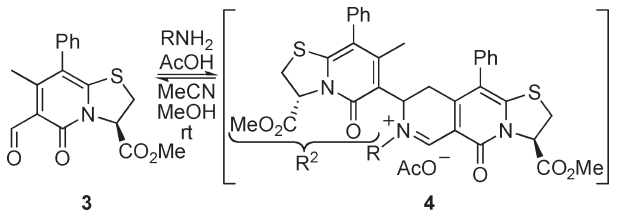
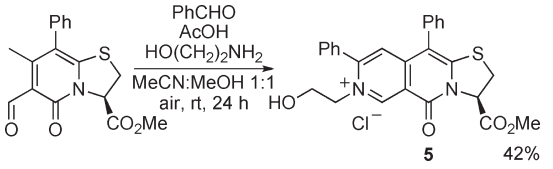


Figure 2. Reaction of compound **3** with primary amines.

2.5 equiv of benzaldehyde and 1.5 equiv of ethanol amine under an atmosphere of air, an acetate salt was formed. After treatment with hydrochloric acid, naphthyridonium salt **5** could be isolated in 42% yield (Scheme 1).

Scheme 1. Synthesis of Naphthyridonium Salt **6**



Naphthyridonium salt **5** contains a new central fragment with similarities to the natural product lophocladine A. Lophocladines are a group of compounds with diverse biological activity. Lophocladine A (**6**) has δ-opioid receptor antagonist activity and lophocladine B (**7**) has cytotoxic properties (Figure 3).[6]

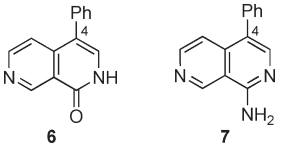
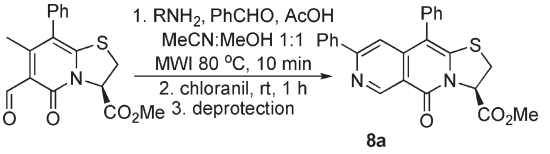


Figure 3. Structure of lophocladine A (**6**) and B (**7**).

2,7-Naphthyridine-1-ones are typically synthesized from nicotinamides or nitriles,[7] and both lophocladine A and B[8] and 4-substituted analogs[9] have previously been synthesized. However, these syntheses do not offer any expedient access to libraries of analogs varied in the pyridine part. Compound **5** can be regarded as a charged analog of lophocladine A formed in a three-component reaction. To examine if this three-component reaction also could generate uncharged analogs, ammonium acetate was used as the amine component. It was found that a larger excess (3.5 equiv) of ammonium acetate was necessary to efficiently give the dihydro naphthyridone. In addition, air was not sufficient to oxidize this intermediate. Instead, chloranil was added after generation of the dihydro naphthyridone to ensure reliable oxidation. It was also found that heating the three-component reaction could significantly shorten the reaction time, and microwave irradiation was used for convenience. This method yielded the uncharged analog **8a** in 42% yield (Table 1). The reaction proceeded smoother with primary amines, and a strategy using a primary amine followed by deprotection was evaluated. The use of *p*-methoxybenzylamine followed by acidic deprotection or β-alanine followed by thermal deprotection, presumably by fragmentation to **8a** and acrylic acid,[10] increased the yield of **8a** compared to the use of ammonium acetate.

Table 1. Evaluation of Different Ammonia Sources



entry	amine	deprotection	yield (%)
1	NH_4OAc	–	42
2	$PMBNH_2$	TFA/DCM/H_2O 10:20:1 MWI 100 °C, 40 min	68
3	β-alanine	MeCN/AcOH 2:1 MWI 140 °C, 10 min	78

The most promising nitrogen source was β-alanine. Although the deprotection step could be performed in the acetonitrile/methanol solvent mixture from the previous steps in the one-pot procedure, changing the solvent to an acetonitrile/acetic acid mixture increased the efficiency of the deprotection. These conditions were then used to examine the scope of aldehydes tolerated by this transformation of 2-pyridones to naphthyridones (Table 2). Both electron-rich and electron-poor benzaldehydes as well as both branched and unbranched alkyl aldehydes were well tolerated. Different heteroaryls could also be incorporated in good yields.

To make closer analogs of lophocladine A and to examine the reaction's tolerance for different 2-pyridones, compound **13** was prepared from 2-methoxypicoline **9** (Scheme 2). Compound **9** was dibrominated and then selectively lithiated using conditions similar to those

(6) Gross, H.; Goeger, D. E.; Hills, P.; Mooberry, S. L.; Ballantine, D. L.; Murray, T. F.; Valeriote, F. A.; Gerwick, W. H. *J. Nat. Prod.* **2006**, *69*, 640–644.

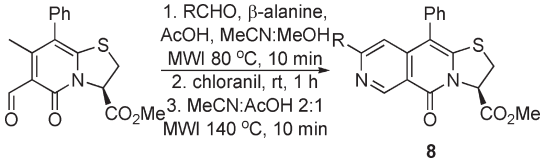
(7) (a) Wenkert, E.; Dave, K. G.; Lewis, R. G.; Sprague, P. W. *J. Am. Chem. Soc.* **1967**, *89*, 6741–6745. (b) Baldwin, J. J.; Mensler, K.; Ponticello, G. S. *J. Org. Chem.* **1978**, *43*, 4878–4880. (c) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 626–633.

(8) Lotter, M.; Schilling, J.; Reimann, E.; Bracher, F. *Arch. Pharm.* **2006**, *339*, 677–679.

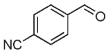
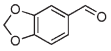
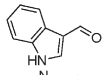
(9) Zhang, A.; Ding, C. Y.; Cheng, C.; Yao, Q. Z. *J. Comb. Chem.* **2007**, *9*, 916–919.

(10) Bargar, T. M.; Dulworth, J. K.; Kenny, M. T.; Massad, R.; Daniel, J. K.; Wilson, T.; Sargent, R. N. *J. Med. Chem.* **1986**, *29*, 1590–1595.

Table 2. Variation of Aldehydes

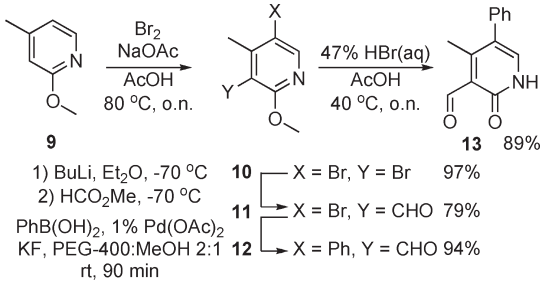


8

entry	RCHO	product	yield (%)
1		**8a**	78
2		**8b**	73
3		**8c**	77
4		**8d**	67
5		**8e**	65
6		**8f**	56
7		**8g**	55
8		**8h**	71

previously reported for 2-methoxypyridine.[11] Quenching with methyl formate afforded the formylated pyridine **11**. Ligand-free Suzuki coupling in polyethylene glycol[12] followed by deprotection of the methyl ether finally gave **13** in a total yield of 64% from **9**.

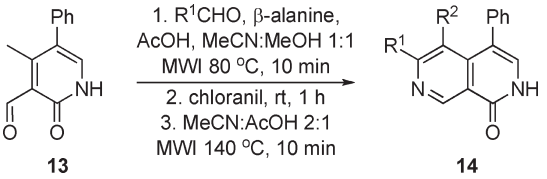
Scheme 2. Preparation of Pyridone **13**



By applying the same conditions as those described in Table 2, 6-phenyl lophocladine **14a** was successfully prepared from pyridone **13** using benzaldehyde as the second aldehyde component (Table 3).

Although benzaldehyde gave the expected product, the use of formaldehyde did not result in the anticipated formation of lophocladine A; instead the methyl-substituted analog **14b** was formed (Table 3). The product was formed without the need of any oxidation, presumably by reaction of the intermediate dihydro naphthyridone with a second equivalent of formaldehyde followed by dehydration. Decreasing the amount of formaldehyde to 1 equiv did not give any lophocladine A; instead **14b** and dimerized product were formed. Lophocladine A could though be synthesized by using ethyl glyoxylate as a protected formaldehyde source, which after hydrolysis was decarboxylated simultaneously with deprotection of the pyridine nitrogen (see Supporting Information). The oxidation step was however much slower with this aldehyde, which resulted in a more complex product mixture. Although the total yield of the transformation was low (16%), this route can potentially also provide unsubstituted compounds to complete libraries of other naphthyridones.

Table 3. Synthesis of Lophocladine A Analogs



13 **14**

entry	R^1	R^2	product	yield (%)
1	Ph	H	**14a**	54
2	H	Me	**14b**	54[a]

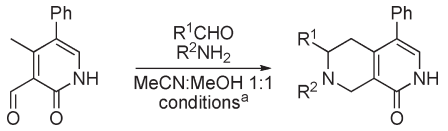
[a] The chloranil step was excluded.

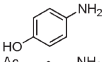
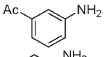
The initial three-component reaction in the one-pot sequence described above forms dihydro naphthyridones. Instead of oxidizing these reactive intermediates, it was also possible to reduce them to their tetrahydro counterparts. By adding $NaBH_4$ instead of chloranil as a second step, compounds of general structure **15** were obtained (Table 4). Although $NaBH_4$ could be used as a reducing agent (Method A), by using formic acid instead of acetic acid, **15** was in most cases generated without the need of a second step (Method B). These conditions also offer selectivity in reducing the intermediate iminium salts in the presence of other carbonyls usually reduced by $NaBH_4$ as exemplified by the synthesis of the ketone containing compound **15j**. When ammonia was used as the amine, formic acid was an inefficient reducing agent. Also with alkyl aldehydes the milder conditions with acetic acid had to be used, in this case to minimize self-condensation of the aldehyde.

The reaction displayed a broad substrate scope. Anilines gave the highest yields, while lower yields were observed for branched alkyl amines. By using a chiral amine (Table 4, entry 6) a separable mixture of diastereomers was obtained, which potentially can be used to afford enantiomerically enriched compounds. The aminopyridine substituted compound **15k** was obtained in low yield using Method B. This was attributed to slow equilibration between the dimer and the phenyl-substituted intermediate, and by first allowing the species to equilibrate before

(11) DeBernardis, J. F.; Gifford, P.; Rizk, M.; Ertel, R.; Abraham, D. J.; Siuda, J. F. *J. Med. Chem.* **1988**, *31*, 117–121.
(12) Han, W.; Liu, C.; Jin, Z. L. *Org. Lett.* **2007**, *9*, 4005–4007.

Table 4. Synthesis of Tetrahydro Naphthyridones



entry	R^1	R^2NH_2	method	product	yield (%)
1	*i*Pr	$MeNH_2$	A	**15a**	50
2	Ph	NH_3	A	**15b**	20
3	Ph	$MeNH_2$	B	**15c**	67
4	Ph		B	**15d**	69
5	Ph		B	**15e**	43
6	Ph		B	**15f**	23 + 26[b]
7	Ph		B	**15g**	81
8	Ph		B	**15h**	84
9	Ph		B	**15i**	86
10	Ph		B	**15j**	68
11	Ph		B	**15k**	30
12	Ph		C	**15k**	54

[a] Method A: 2 equiv of R^1CHO, 3 equiv of R^2NH_2, 2% AcOH, MWI 80 °C 10 min, then $NaBH_4$. Method B: 2 equiv of R^1CHO, 3 equiv of R^2NH_2, 5% HCO_2H, MWI 100 °C 15 min. Method C: 2 equiv of R^1CHO, 3 equiv of R^2NH_2, 2% AcOH, MWI 100 °C 2.5 h, then 5% HCO_2H, MWI 100 °C 30 min. [b] Isolated as separate diastereomers.

the addition of formic acid (Method C) the yield of **15k** was increased from 30 to 54%.

The methyl group of the 2-pyridones used in the reaction shows an unusual reactivity, and two possible mechanistic pathways have been considered (Figure 4). One of the suggested mechanisms (B) involves a Mannich-type of reaction. However, any attempts to trap intermediates similar to **III** by using a secondary amine have been unsuccessful. Further, when compound **13** was reacted with a preformed imine and 0.5 equiv of aniline, a dimer, in this particular case the hemiaminal ether **16**, proved to be the kinetic product (Figure 5). This is not consistent with the proposed mechanism B as the suggested intermediate **I** reacts faster with excess **13** than the benzylideneaniline. Neither were any detectable (LC-MS) aldol adducts with **13** formed. Although not proven, based on these findings, path A, which involves

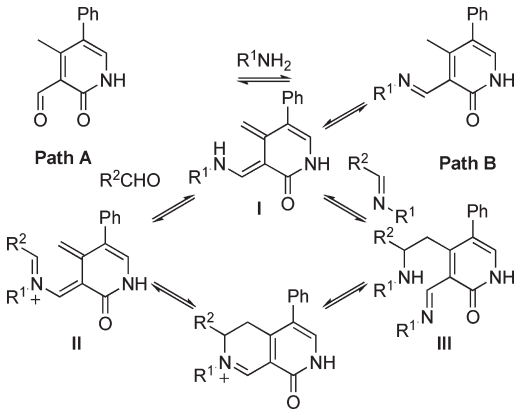


Figure 4. Outline of two tentative mechanisms.

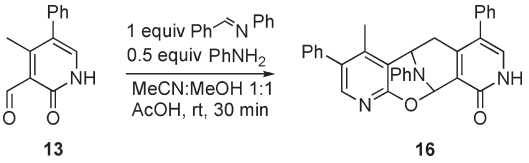


Figure 5. Determination of the kinetic product in an imine/aldehyde competitive reaction.

an electrocyclic reaction of intermediate **II**, is proposed as a more plausible mechanism.

In conclusion, a three-component reaction generating dihydro naphthyridones has been developed. The reaction tolerates a large variety of amines and aldehydes, and postreaction transformations (or change of reaction conditions) can provide naphthyridonium salts, naphthyridones, or tetrahydro naphthyridones. The products can be regarded as analogs of lophocladine A. As this three-component reaction allows facile synthesis of diverse libraries of natural product-like compounds with new central fragments, we envisage it will be useful in the development of a variety of biologically active compounds.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.