ORGANIC LETTERS

2012
Vol. 14, No. 22
5664–5667

Electrocyclization of Oxatrienes in the Construction of Structurally Complex Pyranopyridones

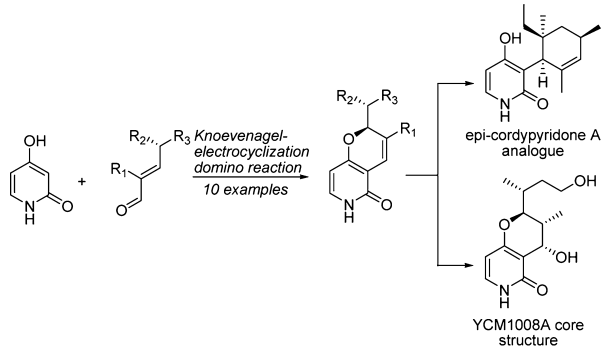
Anna D. Fotiadou and Alexandros L. Zografos*

Department of Chemistry, Laboratory of Organic Chemistry, Aristotle University of Thessaloniki, University Campus, 54124, Thessaloniki, Greece

alzograf@chem.auth.gr

Received September 25, 2012

ABSTRACT



Application of a tandem Knoevenagel/6π-electrocyclization sequence is able to produce highly substituted pyranopyridones from moderate to high yields in a one-step reaction. High diasteroselectivity is observed in some cases and was rationalized on the basis of the thermodynamic control of the evidenced reversibility of a 6π-electrocyclization reaction. Numerous examples are provided establishing a novel entry in natural product-like structures of pyranopyridone alkaloids.

Improvements on the understanding of biosynthetic pathways during the last two decades provided the opportunity to scientists to recognize and utilize common synthetic intermediates in order to access structurally unrelated natural compounds.[1] In this endeavor, recently, the authors reported a unique synthetic access to the structural diversity presented by pyridone alkaloids.[2] In the course of their study toward the total synthesis of citridone A,[3] the authors have witnessed the formation of a small amount of pyranopyridone **5**, representing the core structure of calcium channel inhibitor YCM1008A[4] (**2**) (Figure 1). Aimed at developing a unified synthetic strategy to construct pyridone natural products enclosing compounds such as YCM1008A or leporins (**1a**,**b**), a research project toward pyranopyridone heterocycles was initiated. Our previous experiments showed that when hydroxypyridone **3** was allowed to react under microwave irradiation with aldehyde **4** at 150 °C a 10% yield of pyranopyridone **5** was isolated along with compound **6** (Figure 1). On the other hand, when the same reactants reacted at lower microwave temperature (60 °C) and were directly treated with bismuth triflate a 3:1 mixture of citridone derivative **8** and pyranopyridone **5** was observed, evidencing for a cycloisomerization versus electrocyclization dual mechanistic pathway. On the basis of these observations, the use of unsaturated aldehydes was considered as the potential optimal way to access pyranopyridones constructs. Wishing to explore the synthetic feasibility of the described idea, citral was used as the model unsaturated aldehyde. To our delight, when

(1) Anagnostaki, E. E.; Zografos, A. L. *Chem. Soc. Rev.* **2012**, *41*, 5613–5625.

(2) Fotiadou, A. D.; Zografos, A. L. *Org. Lett.* **2011**, *13*, 4592–4595.

(3) Fukuda, T.; Tomoda, H.; Omura, S. J. *Antibiot.* **2005**, *58* 315–321.

(4) Koizumi, F; Fukumitsu, N.; Zhao, J.; Chanklan, R.; Miyakawa, T.; Kawahara, S.; Iwamoto, S.; Suzuki, M.; Kakita, S.; Rahayu, E. S.; Hosokawa, S.; Tatsuta, K.; Ichimura, M. *J. Antibiot.* **2007**, *60*, 455–458.

(5) (a) Thompson, S.; Coyne, A. G.; Knipe, P. C.; Smith, M. D. *Chem. Soc.Rev.* **2011**, *40*, 4217–4231. For excellent reviews on oxa-[3 + 3] annulations, see: (b) Buchanan, G. S.; Feltenberger, J. B.; Hsung, R. P. *Curr. Org. Synth.* **2010**, *7*, 363–401. (c) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23–44.

10.1021/ol3026457
Published on Web 11/01/2012

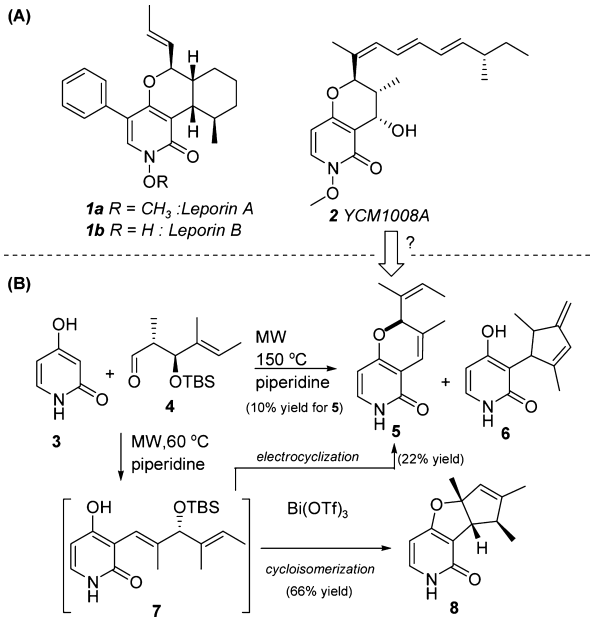


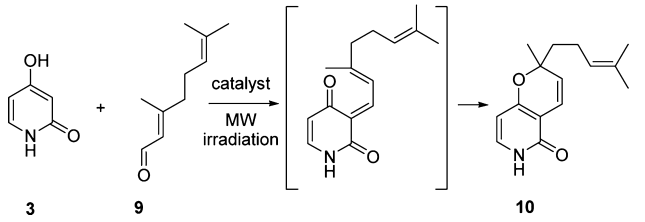
Figure 1. (A) Selected natural pyranopyridones and (B) lead experiments to pyranopyridones.

4-hydroxypyrid-2-one (**3**) was heated with citral (**9**) in the presence of an equivalent amount of piperidine in ethanol the [3 + 3] adduct **10** was isolated in 53% yield (entry 1, Table 1).

Regardless of the several examples that have been amassed in the literature demonstrating the capacity of pericyclic reactions in biosynthetic routes of natural products, only lately have pericyclic reactions been considered as convenient, selective, and powerful bond-forming processes with application in the construction of complex molecules.[5] In an elegant array of publications, Hsung's and Hua's groups demonstrated the ability of unsaturated aldehydes to react with dicarbonyl compounds to prepare pyranoheterocycles.[6] Despite their extensive research on the topic to the best of our knowledge, there are no reports on the synthesis of pyranopyridones based on a formal [3 + 3] reaction.[7]

Following our early success utilizing citral as the unsaturated aldehyde component, the quest for optimal reaction conditions revealed that even in the absence of piperidine the reaction proceeds in lower yields (23−27%) but without the formation of 1,4-adduct (entries 2 and 3, Table 1). This result, which comes in contrast to the reported studies by Hsung,[6] can be rationalized by an internal pyridone−iminium aldehyde activation.

Table 1. Optimization of Formal [3 + 3] Reaction[a]



entry	base (*x* equiv)	temp[b] (°C)	solvent	time (min)	yield[d] (%)
1	piperidine (1)	150	EtOH	10	53
2	none	150	EtOH	10	23
3	none	150	EtOH	20	27
4	piperidine (1)	60	EtOH	10	13
5	piperidine (0.3)	100	EtOH	10	68
6	piperidine (1)	100	EtOH	10	67
7	**piperidine (0.3)**	**100**	**EtOH**	**15**	**87**
8	piperidine (0.3)	100	H_2O	15	5
9	piperidine (0.3)	100	THF	15	72
10	piperidine (0.3)	100	CH_3CN	15	60
11	piperidine (0.3)	100	EtOH/H_2O[c]	15	45
12	DMAP (1)	150	EtOH	10	37
13	proline (0.3)	100	EtOH	15	70 (0% ee)

[a] Conditions: substrate **3** (0.16 mmol), citral (**9**, 0.16 mmol, 1.0 equiv), base (*x* equiv), solvent (0.4 mL, 0.4 M). [b] Heating under MW irradiation. [c] Ratio 1:1. [d] Isolated yields.

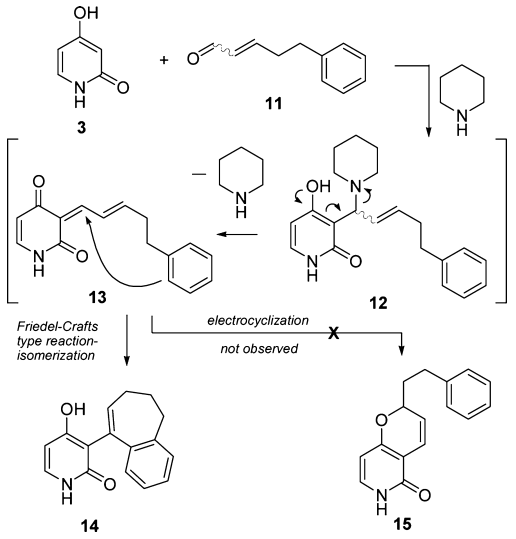
Lowering the microwave temperature to 100 °C led to cleaner reactions even when longer reaction times were applied avoiding the formation of dipyridone byproduct (entries 6 and 7, Table 1). Substoichiometric quantities of piperidine at 0.3 equiv did not affect the yield (entry 5), while ethanol was established as the optimal solvent (entries 8−11). Other bases, including chiral proline, had inferior results. In the case of proline, no enantioselectivity was observed, indicating a mechanism through the formation of an achiral oxatriene intermediate.

To further support our mechanistic assumption, an internal trap of the hypothetical oxatriene intermediate was envisioned. Thus, when electron-rich aromatic aldehyde **11** was applied on our optimal reaction conditions no electrocyclization reaction was observed, but instead compound **14** was isolated in 22% yield through an intramolecular Friedel−Crafts-type reaction on the oxatriene intermediate (Scheme 1).

(6) (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690–691. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729–1735. (c) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888–6896. (d) McLaughlin, M. J.; Shen, H. C.; Hsung, R. P. *Tetrahedron Lett.* **2001**, *42*, 609–613. (e) Buchanan, G. S.; Dai, H.; Hsung, R. P.; Gerasyuto, A. I.; Scheinebeck, C. M. *Org. Lett.* **2011**, *13*, 4402–4405.

(7) The closest literature precedent concerning the preparation of hydroxy quinolones: (a) McLaughlin, M. J.; Hsung, R. P. *J. Org. Chem.* **2001**, *66*, 1049–1053. For selected publications on the preparation of pyranopyridones, see: (b) Fan, X.; Feng, D.; Qu, Y.; Zhang, X.; Wang, J.; Loiseau, P. M.; Andrei, G.; Snoeck, R.; De Clercq, E. *Biorg. Med. Chem. Lett.* **2010**, *20*, 809–813. (c) Magedov, I. V.; Manpadi, M.; Ogasawara, M. A.; Dhawan, A. S.; Rogelj, S.; Van slambrouck, S.; Steelant, W. F. A.; Evdokimov, N. M.; Uglinskii, P. Y.; Elias, E. M.; Knee, E. J.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. *J. Med. Chem.* **2008**, *51*, 2561–2570. (d) Magedov, I. V.; Manpadi, M.; Evdokimov, N. M.; Elias, E. M.; Rozhkova, E.; Ogasawara, M. A.; Bettale, J. D.; Przheval'skii, N. M.; Rojelj, S.; Kornienko, A *Biorg. Med. Chem. Lett.* **2007**, *17*, 3872–3876.

Scheme 1. Trapping Experiment of Oxatriene Intermediate

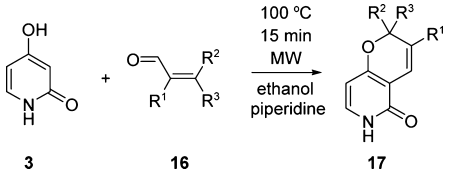


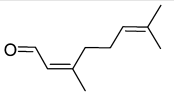
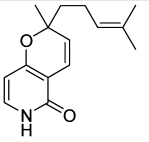
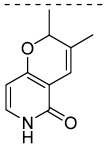
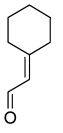
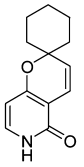
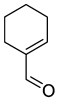
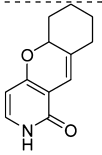
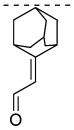
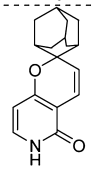
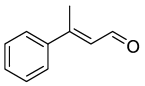
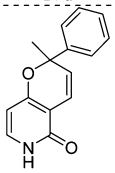
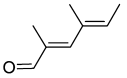
In order to explore the scope and limitations of the formal [3 + 3] reaction on the synthesis of complex pyranopyridones, a number of unsaturated aldehydes were allowed to react with 4-hydroxypyridone-2 under our optimal conditions. In this study, no concern is given in preparing pure *Z* or *E* isomers of the unsaturated aldehydes due to their known thermal equilibration of unsaturated imines under these conditions.[8] Following our results as summarized in Table 2, unsaturated aldehydes (**9**, **16a**−**c**) bearing substituents in both α and *β*-positions are well tolerated providing moderate to high yields of pyranopyridone compounds along with unreacted starting material (entries 1−4) regarding the bulkiness of the aldehyde (**16d**, entry 5). Unsaturated aldehydes conjugated with aromatics can also be applied to produce low yields of α-phenyl pyranopyridone compounds (**16e**, entry 6). On the other hand, nonaromatic conjugated aldehydes failed to couple with hydroxypyridone (**16f**, entry 7) but instead provided the self-cyclized product by thermal ene-type reaction. Finally, an attempt to couple pyridone with unsaturated ketones provided only the unreacted starting components.

While this annulation appears to be an attractive strategy for the construction of YCM1008A (**2**) and leporin natural products (**1a**,**b**), it was considered that it would probably lack the essential stereoselectivity on the newly formed C−O bond because of the pericyclic nature of the reaction. Surprisingly, when commercially available enantiopure unsaturated aldehydes **16g** and **16h** were used, high diastereoselectivities were observed (entries 1 and 2, Table 3). To this end, enantiopure aldehydes (**16i**−**k**) have been prepared and used in order to verify their ability to produce enantiopure pyranopyridones. Unfortunately, utilization of **16i**−**k** revealed only moderate diastereoselectivities (64−75% dr) as this was determined by ^{1}H NMR but comparable yields of products with those of

(8) Cossio, F. P.; Arrieta, A.; Sierra, M. *A Accounts Chem. Res.* **2008**, *41*, 925–936.

Table 2. Scope of the Carbonyl Partner[a]

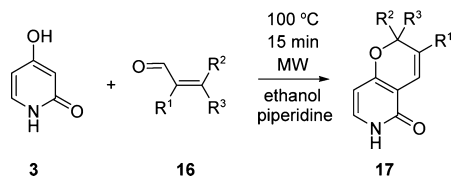


entry	carbonyl compound	pyranopyridone	% yield[b]
1	 **9**	 **10**	87
2	 **16a**	 **17a**	52[c]
3	 **16b**	 **17b**	61
4	 **16c**	 **17c**	52
5	 **16d**	 **17d**	68
6	 **16e**	 **17e**	42
7	 **16f**	None	0

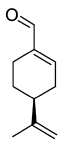
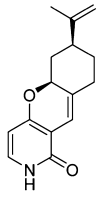
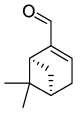
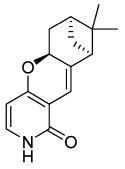
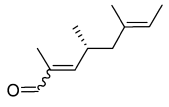
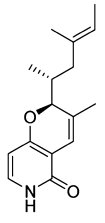
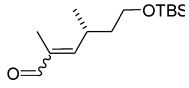
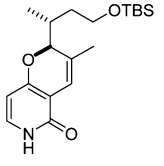
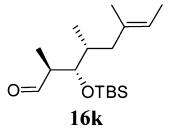
[a] Conditions: substrate **3** (0.16 mmol), substrate **16** (0.16 mmol, 1.0 equiv), piperidine (0.3 equiv), solvent (4 mL, 0.4 M), 100 °C, 15 min MW irradiation. [b] Isolated yields. [c] Solvent: EtOH/H_2O.

aldehydes **16a**−**e**. Chiral saturated aldehydes bearing a *β*-silyloxy or acetoxy group can also be used as precursors to the requisite unsaturated aldehydes. Thus, when aldehyde **16k** was used, comparable yield and diastereoselectivity with aldehyde **16i** were provided.

Table 3. Diastereoselective Electrocyclization[a]



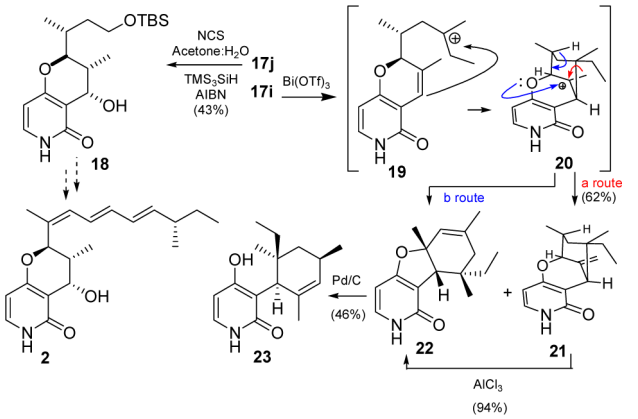
3 16 17

entry	carbonyl compound	pyranopyridone[b]	ratio[c]	yield[d] (%)
1	 **16g**	 **17g**	95:5	60
2	 **16h**	 **17h**	95:5 (68:32 after 1 day)	71
3	 **16i**	 **17i**	64:36	72
4	 **16j**	 **17j**	74:26	58
5	 **16k**	**17i**	64:36	72

[a] Conditions: substrate **3** (0.16 mmol), aldehyde (**16h**–**k**, 0.16 mmol, 1.0 equiv), piperidine (0.3 equiv), solvent (4 mL, 0.4 M) 100 °C, 15 min, MW irradiation. [b] The major product is represented. [c] Ratio determined by NMR. [d] Isolated yields.

Interestingly, the reactions, as was evidenced by 2D NMR experiments in isomeric mixtures, had always a preference in producing the thermodynamically more stable isomer in accordance with Spartan^{TM} AM1 calculations. While these ratios are modest, this result provides an opportunity to examine oxatriene pericyclic reaction more closely from mechanistic perspective. A [3 + 3] annulation under these conditions is not expected to provide any diastereomeric induction due to the high degree of conformational freedom on the chirality of the alkyl chain. Under this logic, a reversible nature in the formation of pyrane ring was considered. To support the reversibily of 6π-pericyclic process, the major isomer of **17i** was isolated and subjected to microwave irradiation at 100 °C with or without the aid of piperidine. In either case, the formation of a 64:36 mixture of isomers was obtained witnessing for the heating equilibration of the pyrane skeleton.

Scheme 2. Pyranopyridones as Tools for Accessing Natural Diversity



Adding in the synthetic utility of pyranopyridones compounds, **17i** and **17j** were further transformed to access two diverse core structures presented in pyridone alkaloids (Scheme 2). When compound **17i** was subjected in reaction with bismuth triflate a highly stereoselective cationic cyclization was realized to produce compounds **21** and **22** in 62% and 10% yields, respectively. A high-yielding aluminum chloride rearrangement of compound **21** to compound **22** allowed the palladium on carbon mediated ether opening of the latter compound to produce **23** in 46% yield, representing the core structure for *epi*-cordypyridone A and B natural products.[9] On the other hand, compound **17j** was chlorohydroxylated with NCS and radically reduced with $(TMS)_3SiH$ to afford compound **18**, a potential precursor to YCM1008A natural product.

In conclusion, the utilization of a tandem Knoevenagel/electrocyclization sequence is described for the first time as an efficient method to access structurally complex pyranopyridones. Selected pyranopyridones can serve as excellent precursors for the synthesis of structurally diverse natural product-like pyridones.

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

The authors declare no competing financial interest.

(9) Isaka, M.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2001**, *66*, 4803–4808.