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Thermally Controlled Decarboxylative [4 + 2] Cycloaddition between Alkoxyoxazoles and Acrylic Acid: Expedient Access to 3-Hydroxypyridines

Laurie-Anne Jouanno, Vincent Tognetti, Laurent Joubert, Cyrille Sabot,* and Pierre-Yves Renard*

Normandie Université, COBRA, UMR 6014 & FR 3038; Université Rouen; INSA Rouen; CNRS, 1 rue Tesnière 76821 Mont-Saint-Aignan, Cedex, France

cyrille.sabot@univ-rouen.fr; pierre-yves.renard@univ-rouen.fr

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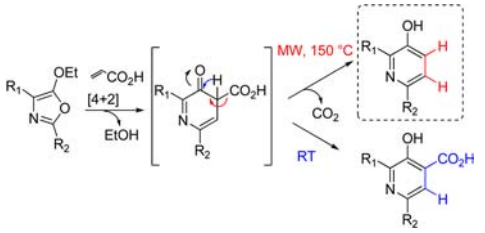
ABSTRACT



A modified Kondrat'eva cycloaddition involving an unprecedented thermally controlled metal-free decarboxylative aromatization affords an expedient access to natural 3-hydroxypyridine/piperidine systems.

The development of rapid, convergent, and economical approaches to heterocyclic ring systems from environmentally friendly and easily accessible reagents is a challenging problem of current interest. Among them, 3-hydroxypyridines have attracted particular attention due to their broad spectrum of biological activity such as bronchodilation (pirbuterol, trade name Maxair), human phosphorylated acetylcholinesterase (AChE) reactivation,[1] AChE inhibition,[2] and potent antioxidant activity (*N*-tocopherol).[3] Apart from these important biologically active chemicals, 3-hydroxypyridines also proved to be valuable key intermediates to access natural products as, for example, the tricyclic pyrido[4,3-*b*]indolizine pterocellin A[4] or abundant 3-hydroxypiperidine alkaloids such as (−)-deoxocassine or recently isolated microgrewiapine A.[5] In addition, pyridinyl hydroxyl groups afford further functionalization opportunity through, for instance, C−C bond formation via palladium or nickel chemistry.[6]

However, surprisingly few straightforward methods to access 3-hydroxypyridine scaffolds are reported in the literature.[7] Most of them suffer from different drawbacks such as the reaction conditions (expensive metal catalysts, long reaction times) and long synthetic approaches (stepwise

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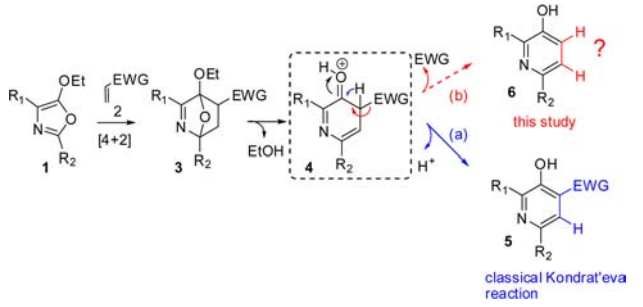
elaboration of the 3-hydroxypyridine ring system).[8] Among these methods, Kondrat'eva's hetero-Diels–Alder (HDA) reaction[9] between readily available 5-alkoxyoxazoles[10] and olefinic dienophiles affords a rapid access to a plethora of persubstituted 3-hydroxypyridine scaffolds. While this transformation is particularly valuable to generate highly functionalized synthetic pyridines, this strategy is paradoxically unsuitable for the preparation of naturally occurring 2,6-disubstituted-3-hydroxypyridine/piperidine derivatives.

As part of our research program, we were interested in a concise generation of diversely substituted 3-hydroxypyridines with a simple and cost-effective protocol. In this context, herein we report a rapid access to 3-hydroxypyridine moieties via HDA reactions of 5-alkoxyoxazoles with *acrylic acid, used as a dienophile equivalent of ethylene, under metal-free and microwave conditions*. This should considerably widen the scope of this reaction hampered by the requirement of an electron-withdrawing group (EWG) on the olefin partner to promote the cycloaddition step, as that group is often undesirable on the final pyridine ring system.

Scheme 1. Kondrat'eva's HDA Reaction



The Kondrat'eva reaction classically involves a first step of [4 + 2] cycloaddition between 5-alkoxyoxazoles **1** and electron-deficient olefinic dienophiles **2** to afford the corresponding cycloadduct **3**. The oxabicycle **3** thus generated undergoes ring-opening under acidic catalysis via loss of an alcohol to furnish the 3-hydroxypyridine **5** after final aromatization of the species **4** (Scheme 1, path a). Next, an additional step of removal of the EWG is required to furnish the 2,6-disubstituted-3-hydroxypyridine **6**, involving metal catalysts, high boiling point solvents (RP-HPLC), and high reaction temperatures weakly compatible with sensitive functional groups.[10] Alternatively, we reasoned that in the presence of a suitable labile EWG and under well-defined reaction conditions, the departure of the EWG from **4** may be greatly facilitated if it occurred along with its concomitant aromatization, instead of isomerization, to furnish the desired 2,6-disubstituted 3-hydroxypyridine **6** (path b). Consequently, this single-step HDA/alcohol elimination/removal of the EWG-aromatization strategy would shorten the whole process both in terms of number of steps and reaction time but would also drastically reduce the reaction temperature involved.

Three EWGs were first considered: SO_3H, CO_2H, and $CO_2{}^tBu$, releasing, respectively SO_3, CO_2, and CO_2 plus isobutylene. DFT calculations were carried out in order to select the best candidate. As shown in Figure 1, from a thermodynamical viewpoint, the formation of **6** was found to be electronically disfavored with respect to **5** in all cases but entropically favored. As temperature increases the entropy weight in the Gibbs energy, **6** becomes thermodynamically predominant when heating above room temperature in the carboxylic acid case.

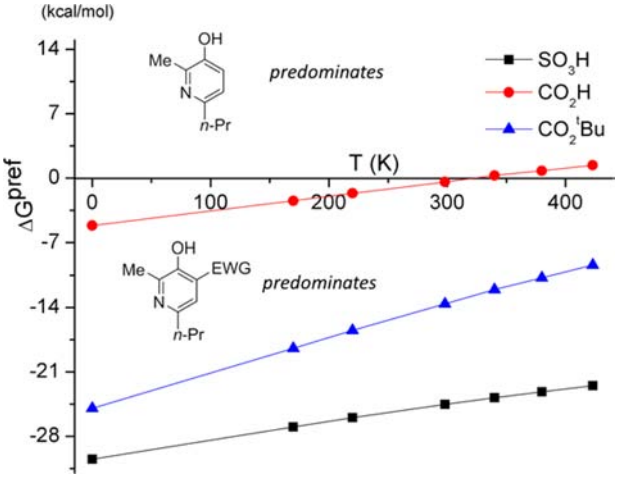
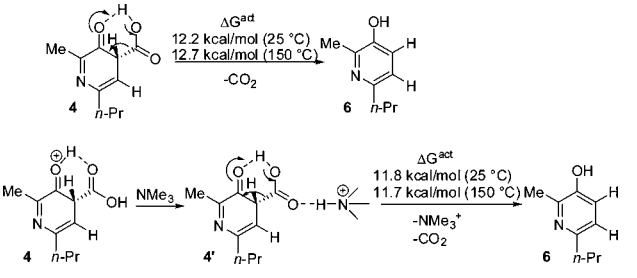


Figure 1. Relative thermodynamical stabilities of the possible products.

However, such a conclusion is useful for synthetic purposes only if the decarboxylative rearomatization is kinetically possible. We thus evaluated the activation barriers for this crucial step in two cases depending on the protonation state (which depends on the experimental conditions) of intermediate **4**, as depicted in Scheme 2.

Scheme 2. Decarboxylative Rearomatization



In the first case, the C=O group is already deprotonated, and an intramolecular hydrogen bond involving the OH group of the EWG promotes the decarboxylative rearomatization in one concerted step. In the second one, the COOH moiety is first deprotonated by a base, inducing the

(10) Jouanno, L.-A.; Sabot, C.; Renard, P.-Y. *J. Org. Chem.* **2012**, *77*, 8549–8555. Correction: Jouanno, L.-A.; Sabot, C.; Renard, P.-Y. *J. Org. Chem.* **2013**, *78*, 1706 and references cited therein.

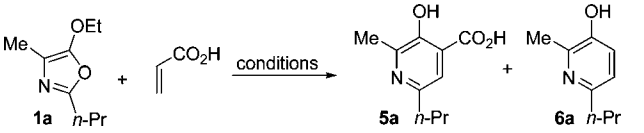
concomitant proton transfer from the oxonium to the carboxylic moiety (giving **4′**), which can similarly undergo the CO_2 release. In both cases, activation barriers are low (about 12 kcal/mol) and are almost insensitive to temperature effects.

For all these reasons, we turned toward the use of EWG=CO_2H (readily removed from β-keto acids under thermal conditions) to achieve our synthetic purposes.

First, the reaction between the model substrate 2-propyl-4-methyl-5-ethoxyoxazole **1a** and acrylic acid was carried out at room temperature under neat conditions. As expected, the 4-pyridinecarboxylic acid **5a** was obtained as the major product along with a small amount of the decarboxylated pyridine derivative **6a** in a 84:16 ratio, determined on the basis of HPLC analysis of the crude mixture (Table 1, entry 1). Next, the reaction was carried out under neat conditions at 130 °C. As expected from the theoretical studies, these conditions afforded **6a** in a promising 41:59 ratio of **5a**/**6a** (entry 2). To further improve this encouraging selectivity, microwave conditions in various solvent systems were tested. Gratifyingly, the reaction run in NMP or DMSO showed almost complete reversal of selectivity as compared with room temperature conditions **5a**/**6a** 22:78 (entry 3 and 4). Pleasingly, the same range of selectivities was obtained in lower boiling point solvents such as EtOH or acetonitrile (entries 5 and 6). Apolar aprotic solvents such as dioxane or toluene displayed less favorable ratios (33:67 and 40:60, respectively, entries 8 and 9). Finally, acid and base effects on the selectivity were investigated in acetonitrile. Surprisingly, the cycloaddition reaction carried out in the presence of acetic acid (entry 10) did not furnish any pyridine ring system. The starting material was recovered unchanged. In sharp contrast, the transformation performed in the presence of triethylamine (3 equiv, entry 12) in acetonitrile provided the desired product **6a** in a satisfying ratio of 12:88. It should be stressed the reaction conducted with *tert*-butyl acrylate instead of acrylic acid, under optimized conditions (3 equiv Et_3N, CH_3CN, MW, 150 °C), did not allow the transformation of **1a** into **6a**. Only the starting material was recovered. Besides, optimized reaction conditions did not enable the transformation of **5a** into **6a**, which is consistent with the plausible concomitant decarboxylation–aromatization mechanism described in Scheme 2, requiring the species **4**.

Then, with optimized reaction conditions in hand (i.e., 3 equiv of Et_3N, CH_3CN, MW, 150 °C, 60 min), the scope of the decarboxylative cycloaddition methodology was investigated with various 5-alkoxyoxazole derivatives (Scheme 3). Mono- and dialkyl-substituted oxazoles led to the corresponding 3-hydroxypyridines in good yields (from 40% to 70% yield for **6a**–**e**). The methodology was successfully extended to aryl-substituted 5-alkoxyoxazoles. These encouraging results prompted us to investigate the reaction with functionalized 5-ethoxyoxazoles such as the ester **1i**, the synthetically useful Weinreb amide **1j**, and nitrile **1k**. In these cases, the corresponding 3-hydroxypyridines **6i**–**k** were formed in good 59–79% yield. Satisfyingly, our conditions proved to be compatible with unprotected alcohol derivatives albeit with a lower yield of 36%. More remarkably, the sensitive ketone functional group was compatible under our optimized conditions and oxazole **1m** delivered the corresponding keto pyridine **6m** in a useful 60% yield.

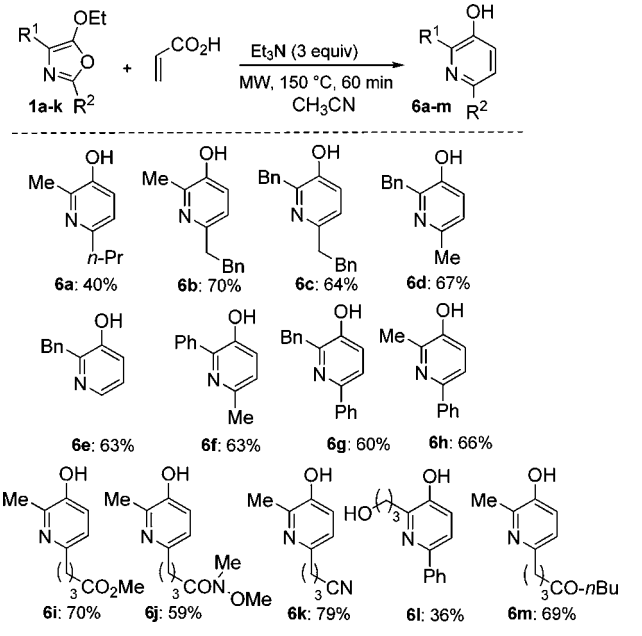
Table 1. Optimization of Decarboxylative HDA Reaction



entry	conditions[a]	ratio[b] 5a	6a
1	neat, rt, 3 d	84	16
2	neat, 130 °C, 20 min	41	59
3	MW, NMP, 150 °C, 40 min	22	78
4	MW, DMSO, 150 °C, 40 min	22	78
5	MW, EtOH, 150 °C, 40 min	18	82
6	MW, CH_3CN, 150 °C, 40 min	18	82
7	MW, CH_3CN, 130 °C, 40 min	25	75
8	MW, 1,4-dioxane, 150 °C, 40 min	33	67
9	MW, toluene, 150 °C, 40 min	40	60
10	MW, CH_3CN, AcOH (1 equiv) 150 °C, 40 min	–	–
11	MW, CH_3CN, Et_3N (1 equiv) 150 °C, 40 min	17	83
12	MW, CH_3CN, Et_3N (3 equiv) 150 °C, 40 min	12	88
13	MW, CH_3CN, Et_3N (5 equiv) 150 °C, 40 min	13	87

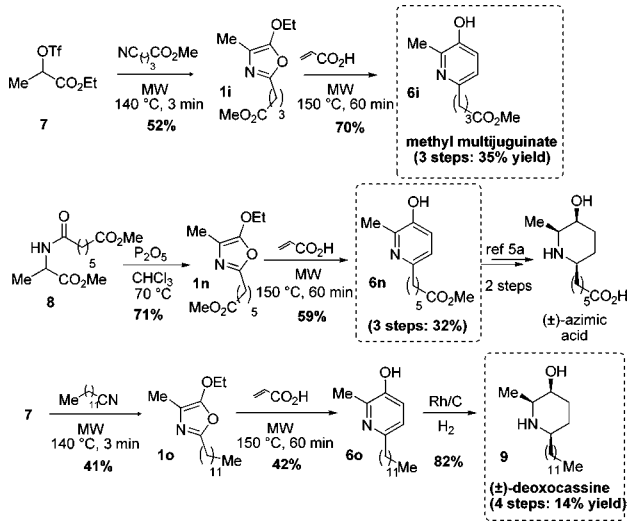
[a] All reactions were performed on 0.2 mmol of **1a** and 1 mL of the solvent considered. [b] Determined on the basis of HPLC analysis of the crude mixture.

Scheme 3. Scope of the Decarboxylative HDA Reaction[a]



[a] All reactions were carried out using alkoxyoxazole **1** (1.2 mmol) and acrylic acid (2.4 mmol, 2 equiv), Et_3N (3.6 mmol, 3 equiv) in CH_3CN (3 mL) at 150 °C for 60 min, under microwave conditions. All yields refer to isolated yields.

Scheme 4. Synthesis of Natural 3-Hydroxypyridines/Piperidines



Finally, to illustrate the high potency of this methodology, the flash synthesis of various natural nitrogen-containing heterocycles, such as 3-hydroxypyridines or 3-hydroxypiperidines, was investigated (Scheme 4). First, the synthesis of the methyl multijuguinate **6i** was successfully achieved within three steps in 35% overall yield, starting from ethyl lactate. Moreover, the two successive microwave-assisted heterocycle syntheses have enabled substantial gain of time, from couple of days to a few hours. More importantly, the decarboxylative aromatization proceeds without metal (such as AgOAc) and at much lower temperature (150 °C versus 250 °C) compared with classical protodecarboxylative conditions.[10] In addition, 3-hydroxypyridine derivatives also offer a nice avenue to natural and biologically active 3-piperidinol derivatives. Indeed, the formal synthesis of (±)-azimic acid, as a representative of this class of abundant compounds, was envisioned starting from commercially available alanine ethyl ester hydrochloride. The thermal cyclodehydration of α-amido ester **8** afforded **1n** in 71% yield. Next, the decarboxylative HDA reaction conducted to the formal synthesis of (±)-azimic acid in a total of three steps and 32% overall yield (previously shortest reported formal synthesis: five steps; 9% yield).[5a,11] Furthermore, to the best of our knowledge, this approach would also constitute the shortest currently reported synthesis described in the literature. As a further example, the total synthesis of (±)-deoxocassine was also undertaken. The α-triflyloxy ester **7** afforded the corresponding 5-ethoxyoxazole **1n** in 41% yield after 3 min reaction, in the presence of tridecanenitrile under recently developed microwave-assisted Ritter reaction. The cycloaddition step furnished the 3-hydroxypyridine **6o** in 42% yield. Final catalytic diastereoselective heterogeneous hydrogenation of the pyridine ring system delivered the racemic deoxocassine in unprecedented 4 steps and 14% overall yield (previously racemic synthesis reported: 13 steps, 5% yield).[12]

In summary, both a convenient choice of the olefin partner and a fine-tuning of the reaction conditions allowed a remarkably mild and selective access to 3-hydroxypyridines through a simple protocol and readily available 5-alkoxyoxazoles. Experimental results supported by a computational study demonstrated that this modified Kondrat'eva reaction involved a smooth and metal-free decarboxylative aromatization process mainly driven by thermodynamic considerations. The synthetic relevance of this strategy was clearly demonstrated through the shortest syntheses of naturally occurring hydropyridine/piperidine derivatives. Further mechanistic studies and applications particularly focused on the synthesis of polycyclic natural products are underway and will be published in due course.

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

(11) For a recent example, see: Bates, R. W.; Kasinathan, S. *Tetrahedron* **2013**, *69*, 3088–3092.

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The authors declare no competing financial interest.