Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6235–6238

New and efficient RCM in pyridinic series: synthesis of 2*H*-dihydropyrano- or 2,3*H*-dihydrooxepino[3,2-*b*]pyridines

Estelle Banaszak, Corinne Comoy and Yves Fort*

Synthèse Organométallique et Réactivité, UMR CNRS-UHP 7565, Faculté des Sciences et Techniques, Université Henri Poincaré Nancy 1, BP 239, Bd des Aiguillettes, 54506 Vandoeuvre-les-Nancy, France

Received 19 May 2006; revised 23 June 2006; accepted 27 June 2006

Abstract—A new and very efficient route to polycyclic heterocycles with isosteric replacement of benzene by pyridine is reported. This strategy involving the RCM reaction in pyridinic series as a keystep allows us to prepare 2*H*-dihydropyrano- or 2,3*H*-dihydrooxepino[3,2-*b*]pyridines **1** and **2** in very good overall yields (47% and 44%, respectively).

Challenge posed by the development of a new series of derivatives, which present a potential biological activity, a great interest is displayed for the syntheses of polyheterocycles. In this context, we focus our attention to elaborate short and efficient access to polyheterocyclic pharmacophores with isosteric replacement of benzene by pyridine. For such a substitution of benzene by pyridine, one needs to develop novel synthetic strategies. As an example, we recently reported an original preparation of thieno[3,2-*b*]pyridines.[1] In our ongoing research, we gave our attention to pyrano- or oxepinopyridines. The outstanding interest of these frameworks is to allow further numerous functionalizations on nonaromatic rings (e.g., hydroxyamination, dihydroxylation, epoxidation) or/and on pyridinic moiety (e.g., metallation/halogenation, cross coupling, arylamination).

To our knowledge, whereas no reference reports the preparation of 2,3*H*-dihydrooxepino[3,2-*b*]pyridine **2** as benzoxepine isoster, only a few papers described the preparation of 2*H*-dihydropyrano[3,2-*b*]pyridine **1**, isostere of chromens (Fig. 1). Indeed only Sliwa and co-workers[2] proposed various multi-step accesses to heterocycle **1** but in very moderate overall yields (11–15%) and Schmidt and co-workers[3] obtained **1** after a thermolysis Claisen rearrangement of propynylpyridinyl ether but only in a mixture with furopyridines as side products. It is noteworthy that Evans and Stemp[4] developed a similar Claisen rearrangement of substituted propargylic ether as a route to 2,2-dimethyl analogues of **1**. On the other hand, numerous syntheses of substituted 2- or 4-azacoumarins are documented in the literature[5] and Briger and co-workers[6] recently patented the preparation of 4-azacoumarine, the carbonyl analogue of **1**.

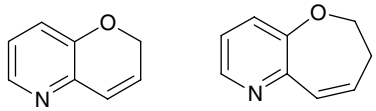


Figure 1. Structure of **1** and **2**.

Since the last decade, the ring-closing metathesis (RCM) strategy has been largely explored for carbocyclic- or heterocyclic ring construction with some direct applications to natural product syntheses.[7] Amongst the various examples described in the literature, very few are carried out using pyridine units.[8]

Herein we reported the first synthetic approach to heterocycles **1** and **2** involving an RCM reaction of *O*-alkenylpyridines. The key RCM sequence has been performed using ruthenium complexes **A** or **B** (Fig. 2).

The retrosynthetic analysis of compounds **1** and **2** is outlined in Scheme 1. The targeted molecules **1** and **2** could be disconnected to 3-alkenyloxy-2-vinylpyridines, which could be obtained starting from the commercially available 2-bromo-3-hydroxypyridine.

Keywords: 2*H*-dihydropyrano[3,2-*b*]pyridine; 2,3*H*-dihydrooxepino-[3,2-*b*]pyridine; Stille cross coupling; RCM reaction.
* Corresponding author. E-mail: yves.fort@sor.uhp-nancy.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.139

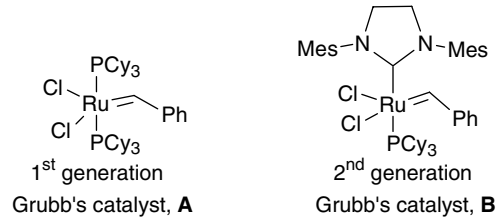
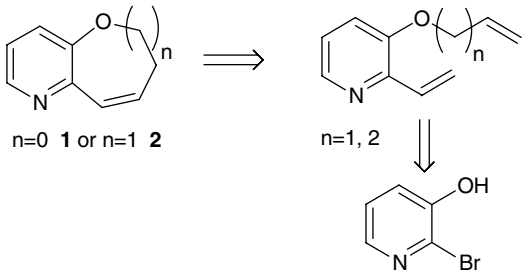


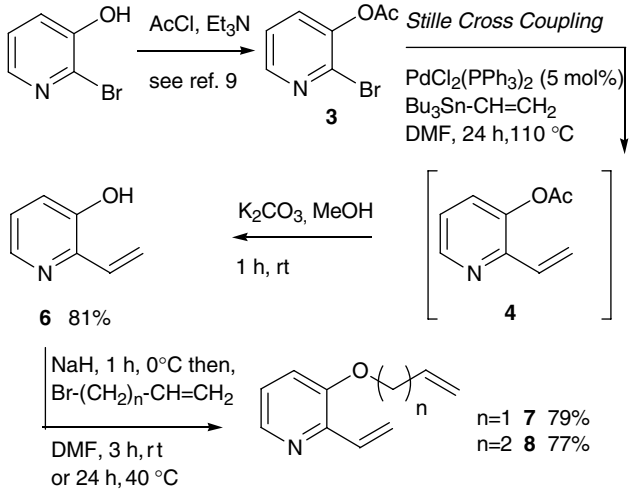
Figure 2.



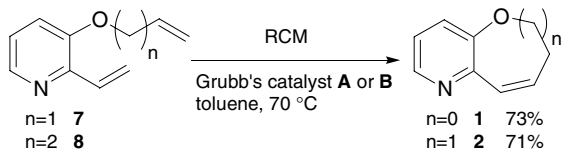
Scheme 1. Retrosynthetic route to **1** and **2**.

3-Hydroxy-2-vinylpyridine **6** was prepared by a Stille cross coupling using the acetate of 2-bromo-3-hydroxypyridine **3** and vinyltributyltin (1.1 equiv), bis(triphenylphosphine)palladium(II)dichloride ($Pd(PPh_3)_2Cl_2$, 5 mol %) as catalyst and in refluxing DMF as solvent (Scheme 2).[9] Deprotection of the crude vinyl product **4** was then performed using K_2CO_3 (1 equiv) in MeOH at rt for 1 h to afford the expected derivative **6**[10] in an excellent yield (81% starting from 2-bromo-3-hydroxypyridine). O-allylation or O-butenylation of 3-hydroxy derivative **6** was finally carried out using sodium hydride (1.2 equiv or 2 equiv, respectively) and allylbromide (1.2 equiv) or 4-bromo-1-butene (2 equiv) in DMF to yield 3-allyloxy-2-vinylpyridine **7** and 3-butenyloxy-2-vinylpyridine **8** in 79% and 77%, respectively.[11]

As mentioned above, the key step of our synthetic route to **1** and **2** was the ring closing metathesis (RCM) to



Scheme 2. Synthesis of 3-alkenyloxy-2-vinylpyridines **7**–**8**.



Scheme 3. RCM reaction of **7**–**8** to **1**–**2**.

afford 2*H*-dihydropyrano[3,2-*b*]pyridine **1** and 2,3*H*-dihydrooxepino [3,2-*b*]pyridine **2** (Scheme 3).

To optimize the ring construction, we planed to compare the two generations of Grubb's catalyst **A** (first generation) and **B** (second generation) (Table 1). The ring closure reaction was performed using **7** or **8** (1.0 mmol) and Grubb's catalyst (**A** or **B**) (4–10 mol %) in toluene at 70 °C. Employing **A** for the RCM reaction on 3-allyloxy-2-vinylpyridine **7** yielded 23% after stirring for 5 h at 70 °C, and an increase in yield of **1** to 68% was noted when the reaction time was extended to 24 h (Table 1, entries 1–3). Using the later version of Grubb's catalyst **B** led to an efficient RCM to afford the targeted compound with good to excellent yields (Table 1, entries 4–6). The best result was obtained using 10 mol % of the second generation of Grubb's catalyst **B**, in toluene at 70 °C for 24 h.[12]

In spite of the longer reaction time or increase of catalyst quantity, total conversion of **7** was not observed and the substrate was recovered in mixture with pyranopyridine **1**. Moreover, no degradation of the reaction solution was deplored. On the other hand, when the RCM reaction was performed with a reaction time up to 24 h no modification was observed (no variation in yield or degradation). Increase in the yield of **1** was closely bound to the catalyst quantity. It can be assumed that the pyridine moiety might block a coordination site of ruthenium catalyst and, consequently, inhibit the RCM (entries 4–6).

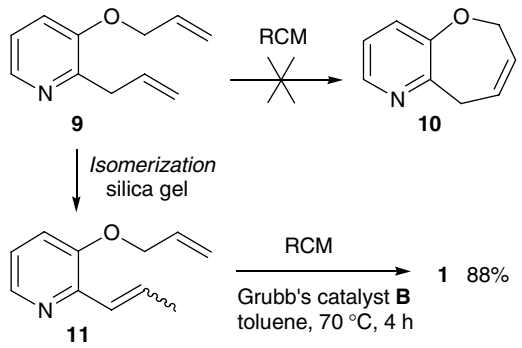
Applied to **8**, this methodology allowed the synthesis of 2,3*H*-dihydrooxepino[3,2-*b*]pyridine **2** in a 71% isolated yield (Scheme 3).[13]

It is interesting to note that we firstly envisioned the synthesis of dihydrooxepino[3,2-*b*]pyridine by RCM using 3-allyloxy-2-allylpyridine **9** (Scheme 4). Allylic derivative **9** was prepared according to the procedure described for **7** and **8**, using allyltributyltin for Stille

Table 1. RCM on 3-allyloxy-2-vinylpyridine **7**

Entry	Catalyst (mol %)		Reaction time (h)	Yields[a] of **1** (%)
1	**A**	4	5	23
2	**A**	6	24	60
3	**A**	10	24	68
4	**B**	4	5	44
5	**B**	6	24	65
6	**B**	10	24	73

[a] After chromatography on silica gel.



Scheme 4. Isomerization-RCM tandem.

cross coupling, in 43% yield starting from 2-bromo-3-hydroxypyridine. Treatment of **9** under various RCM conditions (temperature, catalyst loading) did not afford the expected heterocycle **10**, in these experiments only isomerization of **9** to **11** was observed in moderate yield. Taking into account this result, we performed the total isomerization of **9** to **11** by a successful treatment on silica gel. After which, we realized the RCM of **11** (catalyst **B**, 10 mol%) to yield **1** in 88%, after 4 h at 70 °C in toluene. Despite this excellent result for RCM, this synthetic sequence via **9** seemed less efficient than the procedure described in Scheme 3 because it afforded pyranopyridine **1** only in 38% overall yield starting from 2-bromo-3-hydroxypyridine.

In summary, we have succeeded in preparing expected 2*H*-dihydropyrano[3,2-*b*]pyridine **1** and 2,3*H*-dihydrooxepino[3,2-*b*]pyridine **2** in good yields starting from commercial 2-bromo-3-pyridinol (47% and 44%, respectively) and we have developed new, versatile and efficient syntheses using an RCM reaction with pyridine units as substrates. The extension of this work to the preparation of other potential biological scaffolds including fused heterocyclic moieties is currently under investigation.

Acknowledgements

We gratefully acknowledge the financial support from CNRS and UHP. We thank Sandrine Adach for recording low resolution mass spectra.

References and notes

1. Comoy, C.; Banaszak, E.; Fort, Y. *Tetrahedron* **2006**, *62*, 6036–6041.
2. (a) Sliwa, H.; Krings, K. P. *Heterocycles* **1979**, *12*, 493–495; (b) Billeret, D.; Blondeau, D.; Sliwa, H. *Tetrahedron Lett.* **1991**, *32*, 627–628; (c) Billeret, D.; Blondeau, D.; Sliwa, H. *Synthesis* **1993**, 881–884.
3. Bruhn, J.; Zsindely, J.; Schmidt, H. *Helv. Chim. Acta* **1978**, *61*, 2542–2559.
4. Evans, J. M.; Stemp, G. *Synth. Commun.* **1988**, *18*, 1111–1118.
5. For examples, see: (a) Moffet, R. B. *J. Org. Chem.* **1970**, *35*, 3596–3600; (b) Von Strandtmann, M.; Connor, D.; Shavel, J. *J. Heterocycl. Chem.* **1972**, *9*, 175–176; (c) Dejardin, J.-V.; Lapiere, C.-L. *Bull. Soc. Chim. Fr.* **1978**, *1–2*, 75–82; (d) Bohn, B.; Heinrich, N.; Vorbrueggen, H. *Heterocycles* **1994**, *37*, 1731–1746; (e) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **2001**, *42*, 5613–5615; (f) Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308–312; (g) Villani, F. J.; Mann, T. A.; Wefer, E. A.; Hannon, J.; Larca, L. L.; Landon, M. J.; Spivak, W.; Vashi, D. *J. Med. Chem.* **1975**, *18*, 1–8; (h) Passarotti, C.; Bandi, G. L.; Citerio, L.; Valenti, M. *Boll. Chim. Farmaceutico* **1991**, *130*, 312–314.
6. Bridger, G.; Skerlj, R.; Kaller, A.; Hartwig, C.; Bogucki, D.; Wilson, T. R.; Crawford, J.; McEachern, E. J.; Astma, B.; Nan, S.; Zhou, Y.; Schols, D.; Smith, C. D.; DiFluri, R. M. PCT Int. Appl. WO 0222600, **2002**.
7. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; (c) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452; (d) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113; (e) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808–2809; (f) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (g) Van Otterlo, W. A. L.; Ngidi, E. L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S. S.; De Koning, C. B. *Tetrahedron* **2005**, *61*, 9996–10006; (h) Van Otterlo, W. A. L.; Ngidi, E. L.; De Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 6483–6486; (i) Hong Nguyen, V. T.; Bellur, E.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 113–116; (j) Fürstner, A.; Ackermann, L. *Chem. Commun.* **1999**, 95–96; (k) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864–866.
8. (a) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305–6312; (b) Van Otterlo, W. A. L.; Morgans, G. L.; Khanye, S. D.; Aderibigbe, B. A. A.; Michael, J. P.; Billing, D. G. *Tetrahedron Lett.* **2004**, *45*, 9171–9175; (c) Branowska, D.; Rykowski, A. *Tetrahedron* **2005**, *61*, 10713–10718.
9. Colandrea, V. J.; Naylor, E. M. *Tetrahedron Lett.* **2000**, *41*, 8053–8057.
10. An other way to prepare **6** is described by Knochel: Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288–2289.
11. Preparation of 3-allyloxy-2-vinylpyridine **7**.
3-Hydroxy-2-vinylpyridine **6**[9,10] (1.763 g, 14.6 mmol) in solution in distilled DMF (20 mL) was added to sodium hydride (0.461 g, 19.2 mmol), at 0 °C, under a nitrogen atmosphere. After stirring at 0 °C for 1 h, a solution of allyl bromide (1.7 mL, 19.2 mmol) in DMF (10 mL) was added dropwise. Then the reaction medium was allowed to stir at room temperature for 3 h. The resulting solution was rapidly washed with a saturated aqueous NH_4Cl solution and extracted with dichloromethane (2×10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm, eluent: hexane/AcOEt 70:30), which yielded 3-allyloxy-2-vinylpyridine **7** (1.736 g, 79%) as an orange wax. ^{1}H NMR: δ_H 4.56 (dd, $J = 3.6$, 1.4 Hz, 2H), 5.30 (dd, $J = 10.5$, 1.3 Hz, 1H), 5.42 (dd, $J = 17.2$, 2.1 Hz, 1H), 5.47 (dd, $J = 10.9$, 2.1 Hz, 1H), 6.05 (m, 1H), 6.38 (dd, $J = 17.4$, 2.1, 1H), 7.15 (m, 3H), 8.18 (dd, $J = 4.10$, 1.52, 1H); ^{13}C NMR: δ_C 69.16, 118.07, 118.74, 119.46, 123.16, 130.84, 132.68, 141.40, 145.54, 152.05; MS (EI) m/z 162 ($[M+H]^+$, 8), 161 (M^+, 52), 160 ($[M-H]^+$, 63), 146 (45), 120 (100), 92 (86), 79 (28), 65 (60); IR (NaCl) ν 3020, 1578, 1442, 784.
12. Preparation of 2*H*-dihydropyrano[3,2-*b*]pyridine **1**.
Grubb's second generation catalyst (10 mol %) was added to a degassed solution of 3-allyloxy-2-vinylpyridine **7**

(0.161 g, 1 mmol) dissolved in degassed and anhydrous toluene (20 mL). The reaction mixture was then heated at 70 °C for 24 h under a nitrogen atmosphere. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on a silica gel (0.063–0.200 mm, eluent: hexane/AcOEt 70:30) which yielded 2*H*-pyrano[3,2-*b*]pyridine **1** (97 mg, 73%) as an orange oil. The spectroscopic data are in conformity with literature data (Ref. 2).

13. Preparation of 2,3*H*-dihydrooxepino[3,2-*b*]pyridine **2**. The RCM reaction of 3-butenyloxy-2-vinylpyridine **8** (130 mg, 0.74 mmol) was performed according to the method described for **1**, using second generation Grubb's catalyst (10 mol %) for 16 h at 70 °C and yielded **2** in 71% yield (77 mg) as a brown oil. ^{1}H NMR: δ_H 2.74 (m, 2H), 4.26 (m, 2H), 6.25 (m, 2H), 6.72 (d, $J = 12.1$ Hz, 1H), 7.08 (dd, $J = 9.2$, 4.5 Hz, 1H), 7.27 (d, $J = 9.2$ Hz, 1H), 8.30 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR: δ_C 34.12, 69.69, 122.07, 127.16, 130.87, 133.47, 143.15, 145.94, 155.50; MS (EI) m/z 148 ($[M+H]^+$, 8), 147 (M^+, 85), 146 ($[M-H]^+$, 100), 132 (38), 118 (21), 91 (15), 78 (9), 65 (15); IR (NaCl) ν. 3053, 2913, 1651, 1436, 1221, 994, 790. HRMS (ES^+) calcd for $C_9H_9NO = 147.0685$, found $[M+H^+]$: 148.0776.