

An efficient route to a 5,6-dihydropyrano[3,4-*b*]pyridin-8-one core in two steps from enamminolactones

Cheikh Sall^a, Nicolas Desbois^a, Sandrine Paquelet^a, José R. Camacho^a,
Jean Michel Chezal^b, Jean-Claude Teulade^b, Yves Blache^{c,*}

^a *Laboratoire de Chimie Organique et Thérapeutique, EA 3660 Unité de Molécules d'Intérêt Biologique, Faculté de Pharmacie, 7 boulevard Jeanne d'Arc, BP 89700, 21079 Dijon, France*

^b *Laboratoire de Chimie Organique, Faculté de Pharmacie, UMR INSERM 484, 28 Place Henry Dunant, BP 38, 63001 Clermont-Ferrand, France*

^c *Laboratoire Matériaux à Finalité Spécifique, UFR Sciences et Techniques, Université du Sud Toulon-Var, BP 20132, 83957 La Garde Cedex, France*

Received 13 November 2007; revised 17 December 2007; accepted 19 December 2007

Available online 25 December 2007

Abstract

A convenient two step conversion of heterocyclic enamminolactones to heterocyclic fused 2-pyran-1-ones is reported. The use of this method can be applied to a wide variety of aromatic and heteroaromatic amines to give potentially biologically active compounds in good yields.

© 2007 Elsevier Ltd. All rights reserved.

Keywords: Pyrano[3,4-*b*]pyridine; Enaminolactone; Selenium dioxide

1. Introduction

Heterocycles possessing an aromatic or a heterocyclic fused 2-pyran-1-one system **1** represent interesting classes of natural or synthetic compounds displaying a wide range of biological properties. For example, mellein **2**, an 8-hydroxydihydroisocoumarin extracted from *Aspergillus ochraceus* W. exhibited toxic and cytotoxic effects on rats¹ and dihydroisocoumarin glucosides **3** extracted from the

fungus *Cephalosporium* sp. AL031 exhibited antibacterial and fungicidal properties.² In the field of discovery new classes of analogs of natural compounds, the synthetic aza-analogs pyrano[3,4-*b*]pyridine-8-one class of compound **4** represent an interesting target but has been poorly studied (Fig. 1).

Syntheses of the 3,4-dihydro-1*H*-2-benzopyran-1-one framework have been extensively studied and is often performed by means of coupling homophthalic acid

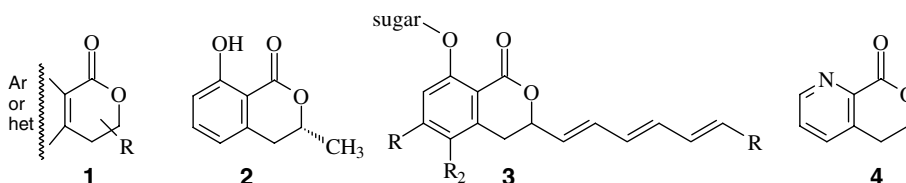


Fig. 1.

* Corresponding author. Tel.: +33 04 94 14 23 05.

E-mail address: blache@univ-tln.fr (Y. Blache).

derivatives with acyl chlorides.³ However, this methodology is difficult to apply to pyridines and related heterocycles since such diacids are not easy to obtain from heterocycles.

As a part of our program concerning the design of analogs of natural compounds as new classes of antimalarial compounds, we were previously interested in the chemistry of diaza-analogs of phenanthrene.⁴ In this context, derivatives of the 1,10-phenanthroline skeleton exhibited the best antiplasmodial activities in vitro against the Nigerian chloroquino-sensitive strain and the chloroquino-resistant FcBi-Colombia and FcM29 strains. To get more information on structure–activity relationships of such compounds, we now wish to associate this framework with a fused pyran-1-one ring. For this purpose, we needed an efficient route to access functionalized pyrano-fused heterocycles. In this context, we report here a simple and efficient two step-methodology for the preparation of dihydropyrano[3,4-*b*]pyridin-8-one (**7**) core from enaminolactones **5** (Fig. 2).

2. Results

The key step of the synthesis resides in the oxidation of the methyl group of **6**⁴ to give a carboxylic acid which can be further implicated in a nucleophilic substitution with the chlorine atom of the chloroethyl chain. Such oxidation of an alkyl group attached to a pyrido system was a

frequently used method for the preparation of the corresponding carboxylic acid. KMnO₄ in water⁵ or SeO₂ in pyridine^{6a,b} were two classical methods used. In the case of phenanthroline **6a**, oxidation was firstly carried out by direct reaction of compound **6a** with SeO₂ in pyridine (Scheme 1). Under these conditions, the acid derivative **8** was not obtained, but lactone **7a** was isolated in 75% yield. Such lactone formation was previously observed in a single case by Coffen and McEntee^{6c} but no further applications were found. Structure of the lactone ring was established by ¹H, ¹³C NMR and mass spectroscopy.⁷

This lactonization reaction can be simply explained by the formation of the carboxylate salt in the presence of pyridine, followed by intramolecular cyclization (Scheme 2). To support this hypothesis, the reaction was investigated with KMnO₄ in acidic media to circumvent the formation of the carboxylate salt, but under these conditions, the reaction led only to a complex degradation mixture. Finally, SeO₂ oxydation was conducted in dioxane, and under these conditions, only the corresponding aldehyde was found⁸ as classically described for 1,10-phenanthroline ring.⁹

To explore the potential applications of this method, we set out to generalize the protocol. A wide variety of commercially aromatic compounds (except for 1-naphthylamine achieved using 1-nitronaphthalene¹⁰) containing amino groups were chosen as starting materials. The reactions and results are summarized in Table 1. Treatment of the different aminoaromatics **9a–h** by a 1.2 equiv of

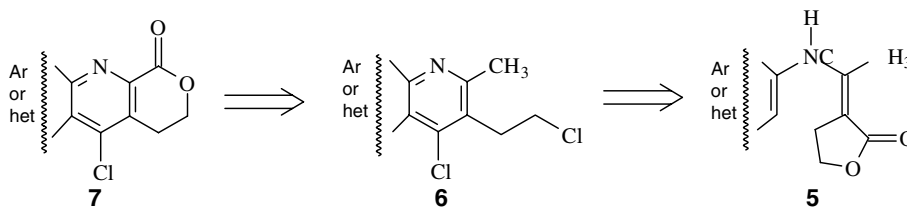
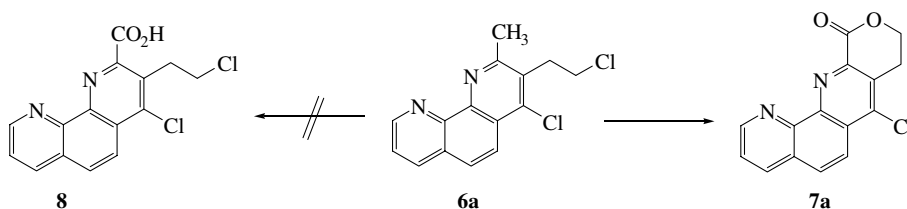
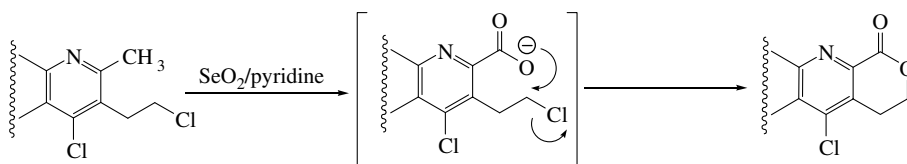


Fig. 2.

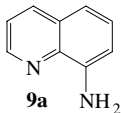
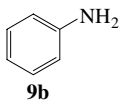
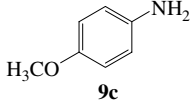
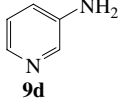
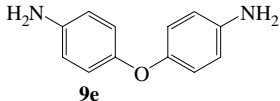
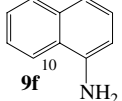
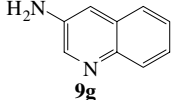
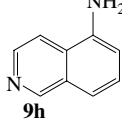


Scheme 1. Reagent and condition: SeO₂, pyridine, Δ.



Scheme 2. Mechanism of the lactonization process.

Table 1
Access to 5,6 dihydropyrano[3,4-*b*]pyridin-8-one compounds **7a–h**

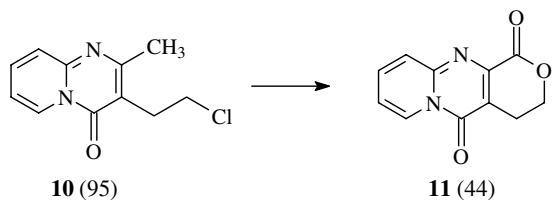
Entry	Starting material	Yield (%)		
		Enaminone	Pyridine	Lactone
1		5a ^{4a} (64)	6a ^{4a} (55)	7a (75)
2		5b ¹³ (65)	6b ¹⁴ (55)	7b (75)
3		5c (65)	6c ¹⁵ (55)	7c (76)
4		5d (95)	6d (69)	7d (51)
5		5e (98)	6e (42)	7e (54)
6		5f (40)	6f ¹⁶ (62)	7f (55)
7		5g ^{4a} (72)	6g ^{4a} (75)	7g (60)
8		5h ^{4a} (81)	6h ^{4a} (63)	7h (80)

Reagents and conditions: (i) 2-acetylbutyrolactone, toluene, APTS, Δ ; (ii) POCl_3 , Δ ; (iii) dry pyridine, 3 equiv SeO_2 , Δ .

2-acetylbutyrolactone in refluxing toluene with a catalytic amount of *p*-toluenesulfonic acid gave the corresponding enaminolactones **5a–h** in good yield.¹¹ By treatment with freshly distilled phosphorus oxychloride,¹² these synthetic intermediates underwent cyclizations and subsequent ring and side chlorination to give compounds (**6a–h**). In the case of 3-aminopyridine (entry 4) and 3-aminoquinoline (entry 7), the cyclizations were regioselective on the C-4 positions leading exclusively to **6d** and **6g**, respectively, while in the case of entry 5, a double condensation

occurred leading to the dimeric cyclic compound **6e**. Compounds **6a–h** reacted with selenium dioxide and dry pyridine under reflux conditions to afford cyclized compounds **7a–h**. Yields of lactonization are moderate to good (51–80%).

In the particular case of aza cyclization with 2-aminopyridine we obtained pyridopyrimidinone compound **10**¹⁷ (Scheme 3). Next, oxidation of the methyl group was performed using conditions designed before. The cyclized product **11** was isolated in moderate yield (44%).



Scheme 3. Lactonization with 2 aminopyridine. Reagent and condition: SeO_2 , pyridine, Δ .

In conclusion, we have described a simple and efficient route to polyfused 5,6-dihydropyran[3,4-*b*]pyridin-8-one in two steps from enaminone compounds. The wide variety of starting aromatic and heterocyclic amines used in this study indicates that this methodology can be useful in a large range of synthetic applications.

References and notes

- (a) Uchida, K.; Ishigami, K.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2007**, *63*, 1281–1287; (b) Moore, J. H.; Davis, N. D.; Diener, U. L. *Appl. Microbiol.* **1972**, 1067–1072.
- Bi, Y. B.; Bib, X. B.; Zhao, Q. R.; Chenc, Y. T.; Xie, J. L. *Helv. Chim. Acta* **2004**, *84*, 2890–2895.
- Shafiq, Z.; Arfan, M.; Rama, N. H.; Hameed, S.; Abbas, G.; Hussain, M. T. *Turk. J. Chem.* **2005**, *29*, 321–325.
- (a) Yapi, A. D.; Mustofa, M.; Valentin, A.; Chavignon, O.; Teulade, J. C.; Mallie, M.; Chapat, J. P.; Blache, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1886–1889; (b) Yapi, A. D.; Valentin, A.; Chezal, J. M.; Chavignon, O.; Chaillot, B.; Gerhardt, R.; Teulade, J. C.; Blache, Y. *Arch. Pharm.* **2006**, *339*, 201–206; (c) Tapia, R. A.; López, C.; Morello, A.; Maya, J. D.; Valderrama, J. A. *Synthesis* **2005**, 903–907; (d) Badaway, E.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327–332.
- Wu, W. S.; Liu, S. X. *Wuji Huaxue Xuebao* **2003**, *19*, 1065–1072.
- (a) Miao, R.; Zheng, Q. Y.; Chen, C. F.; Huang, Z. T. *J. Org. Chem.* **2005**, *70*, 7662–7671; (b) Zhichkin, P.; Cillo Beer, C. M.; Rennells, W. M.; Fairfax, D. J. *Synlett* **2006**, 3, 379–382; (c) Coffen, D. L.; McEntee, T. E., Jr. *Chem. Commun.* **1971**, 11, 539.
- Typical procedure for lactonization:** A solution of **6a** (0.69 mmol) and SeO_2 (0.23 g, 2.07 mmol) in dry pyridine (5 mL) was stirred at reflux for 3 h. The hot reaction mixture was filtered, and the solvent was evaporated to give the residue which was, after addition of a little amount of water, extracted with CHCl_3 . The CHCl_3 layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography through silica gel using dichloromethane/methanol (95:5; v/v) to give **7a**: mp 238–240 °C; ^1H (300 MHz, CDCl_3) δ 3.48 (t, 2H, $J = 6$ Hz), 4.72 (t, 2H, $J = 6$ Hz), 7.72 (dd, 1H, $J = 4.5$, 8 Hz), 8.02 (d, 1H, $J = 9$ Hz), 8.23 (d, 1H, $J = 9$ Hz), 8.29 (d, 1H, $J = 8$ Hz), 9.27 (d, 1H, $J = 4.5$ Hz); ^{13}C (75 MHz, CDCl_3) δ 26.2, 66.3, 121.7, 124.2, 128.3, 128.6, 130.8, 132.2, 136.1, 141.2, 142.6, 145.8, 146.5, 151.6, 161.2; MS m/z 286 ($\text{M}^+ + 2$, 34), 284 (M^+ , 100). Anal. Calcd for $\text{C}_{15}\text{H}_9\text{N}_2\text{O}_2\text{Cl}$: C, 63.28; H, 3.18; N, 9.84. Found: C, 63.31; H, 3.01; N, 9.79.
- Mp 182–184 °C; ^1H (300 MHz, CDCl_3) δ 3.83 (t, 2H, $J = 7$ Hz), 4.00 (t, 2H, $J = 7$ Hz), 7.74 (dd, 1H, $J = 4$, 8 Hz), 8.05 (d, 1H, $J = 9$ Hz), 8.33 (m, 2H), 9.29 (d, 1H, $J = 4$ Hz), 10.58 (s, 1H); ^{13}C (75 MHz, CDCl_3) δ 31.2, 42.5, 122.6, 124.2, 128.3, 128.8, 130.9, 131.3, 136.5, 145.2, 145.3, 145.6, 150.1, 151.6, 194.8. Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_2\text{Cl}_2$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.12; H, 3.21; N, 9.06.
- De Cian, A.; DeLemos, E.; Mergny, J. L.; Teulade-Fichou, M. P.; Monchaud, D. *J. Am. Chem. Soc.* **2007**, *129*, 1856–1857.
- Zeynizadeh, B.; Setamdideh, D. *Synth. Commun.* **2006**, *36*, 2699–2704.
- Typical procedure for obtaining aminoethylidene-4,5-dihydrofuran-2-ones 5:** A mixture of 2-acetyl-butylolactone (1.23 g, 9.60 mmol) and aminoaromatic (or heteroaromatic) compounds **9** (8.00 mmol), and a catalytic amount of *p*-toluene sulfonic acid in toluene (25 mL), was refluxed under nitrogen with a Dean Stark apparatus for 12 h. After evaporation of solvent, water was added and the mixture was basified (10%, Na_2CO_3) saturated with NaCl, and extracted with dichloromethane. Organic layers were washed with brine (50 mL), dried over sodium sulfate and evaporated in vacuo. The remaining oils were treated with ether, cooled, and the precipitate was filtered. Recrystallization from ethanol gave pure product **5**.
- Typical procedure for POCl_3 cyclization:** Compound **5** (4.00 mmol) was heated with phosphorus oxychloride (25 mL) until the end of exothermic reaction (80–90 °C). The mixture was then refluxed for 3 h. Excess phosphorus oxychloride was removed, water was added and the mixture was neutralized with a saturated solution of sodium carbonate. After extraction with dichloromethane, the organic layers were washed with brine (50 mL), then dried (Na_2SO_4). Solvent evaporation gave a black oily product which was purified on a neutral alumina and eluted with dichloromethane to afford compound **6**.
- Khosropour, A. R.; Khodaei, M. M.; Kookhazadeh, M. *Tetrahedron Lett.* **2004**, *45*, 1725–1728.
- Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem.* **1990**, *33*, 527–533.
- Beck, P. H.; Brown, M. B.; Clark, D. E.; Coates, A.; Dyke, H. J.; Hu, Y.; Londebrough, D. J.; Mills, K.; Pallin, T. D.; Reid, G. P.; Stoddart, G. WO 2007/054693, 2007.
- Ozawa, T.; Nagaoka, S.; Matsui, M.; Mitani, M. *Yakugaku Zasshi* **1957**, *77*, 90–93.
- Kim, N. D.; Lee, J. H.; Lee, M. S.; Chang, Y. K.; Lee, G. S. WO 2004/035573, 2004.