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# 3-Hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates—fast access to a heterocyclic scaffold for HIV-1 integrase inhibitors

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ABSTRACT

An efficient and reliable synthesis of the heterocyclic scaffold methyl-3-hydroxy-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine-2-carboxylate is described. The scope of the synthesis regarding the introduction of substituents on the pyrido-fused ring is explored.



In the context of our studies on tetrahydro-pyridopyrimidinones of type **A** as HIV-1 integrase inhibitors,[1] we became interested in the related unsaturated heterocyclic compounds of type **B** (Fig. 1). The corresponding core scaffold methyl-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate **C** (R = H, R′ = OMe, Fig. 2) has been reported in the literature.[2] The synthesis is described as a low yielding (17%) condensation reaction between 2-aminopyridine and dimethyl diacetoxyfumarate used in large excess. Unfortunately, we were unable to obtain the desired product following the described procedure. Thus, a new and reliable synthetic route was needed in order to conduct medicinal chemistry studies.

Our retrosynthetic analysis of methyl-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate or the corresponding carboxamides **C** is summarized in Figure 2. Our first attempt to obtain the pyridopyrimidinones by a dehydrogenation of the related tetrahydropyridopyrimidinones gave unsatisfactory results (option I, Fig. 2). When heated in high boiling solvents over palladium on carbon the dehydrogenated products were observed along with extensive degradation, and the yields were variable and very low. The best results were obtained when a methylamino-substituent was present on the tetrahydropyrido-ring (scheme 1).

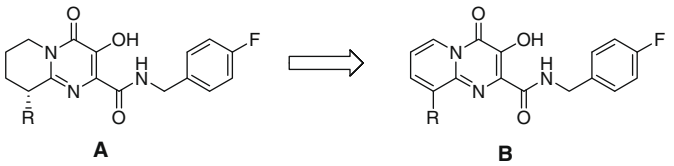


**Figure 1.** Tetrahydropyridopyrimidinone HIV-1 integrase inhibitors (**A**) and the targeted pyridopyrimidinone structure (**B**).

In the light of these results, our attention turned to options II and III, that is, the formation of **C** via a condensation reaction between dimethylacetylene dicarboxylate (DMAD) and 2-aminopyridine-*N*-oxides. We reasoned that this transformation could be possible because 2-aminopyridine-*N*-oxide can be regarded as a tautomeric form of cyclic amidoxime **D** (Fig. 2). Amidoximes, either acyclic or cyclic ones, are known to react with DMAD to give the desired hydroxypyrimidinone derivatives.[1,3] The introduction of the substituent in the 9-position on the pyrido-fused ring would be ideally achieved after formation of the core heterocycle in order to have a flexible late stage derivatization (option II, Fig. 2). Alternatively, already functionalized 2-aminopyridine-*N*-oxides could be used in the cyclization reaction (option III, Fig. 2).

2-Aminopyridine-*N*-oxide reacted smoothly with one equivalent DMAD in chloroform at 0 °C, forming an adduct as a mixture of *E*/*Z*-isomers (ca. 1:10, Scheme 2). NMR-analysis (via $^{1}H$–$^{13}C$-HMBC experiment) established this adduct to be the enamine **1** instead of the desired O-adduct **1a**. The diagnostic proton-carbon correlations detected for the NH-proton of **1** are reported in Scheme 2.[4] Upon heating to 150–165 °C in *o*-xylene, a rearrangement/cyclization to the desired methyl-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate **2** occurred. Mechanistic studies of this reaction have not been performed, but one possible mechanism is the rearrangement of **1** to the O-adduct (**1a**) which then undergoes a similar rearrangement/cyclization reaction as described for the saturated alkyl amidoximes,[1,3] involving the cleavage of the N–O-bond. For alkyl-amidoximes, a detailed mechanistic study of this rearrangement has been published recently.[5] After O-protection of **2** as a pivalate in order to facilitate its purification **2a** was isolated in 33% yield.[6,7]

With protected bicycle **2a** in hand, we then proceeded to seek a way to introduce a substituent R, ideally an amino group which then could be further modified for SAR studies. Selective nitration under mild conditions was unsuccessful, and our attention turned to the introduction of a bromine atom which then could

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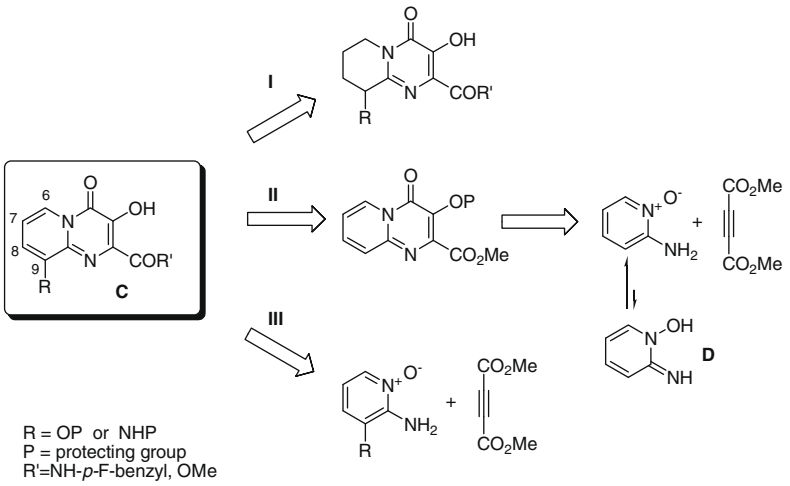
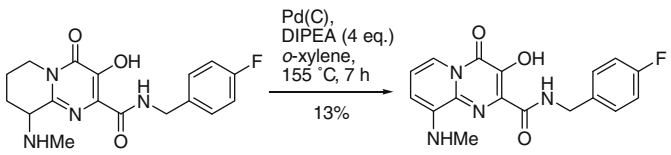



**Figure 2.** Retrosynthetic analysis of pyridopyrimidinone core scaffold **C**.




**Scheme 1.** Dehydrogenation of tetrahydropyridopyrimidinones.

conceivably be transformed by Pd-catalyzed amination. After a thorough screening of bromination conditions, compound **2a** was successfully brominated with NBS in a mixture of acetonitrile and acetic acid at 5 °C, leading to addition product **3**. The formation of an addition product indicates the partially olefin-like character of the pyrido-fused ring of **2a**. On the other hand, **2a** did not react with elementary bromine as one would expect for simple alkenes. Treatment of **3** with triethylamine in dichloromethane at room temperature afforded brominated elimination product **4** in moderate yield. The position of the bromine atom in **4** was confirmed by X-ray crystallography (Fig. 3).[8]

Although bromo-intermediate **4** proved to be a suitable substrate for further derivatization (e.g., Pd-catalyzed cross coupling reactions)[9] the 9-position was our preferred site of modification. Therefore, we decided to start the synthesis with aminopyridine-*N*-oxides already bearing a suitable functionality at the desired position (option III, Fig. 2).

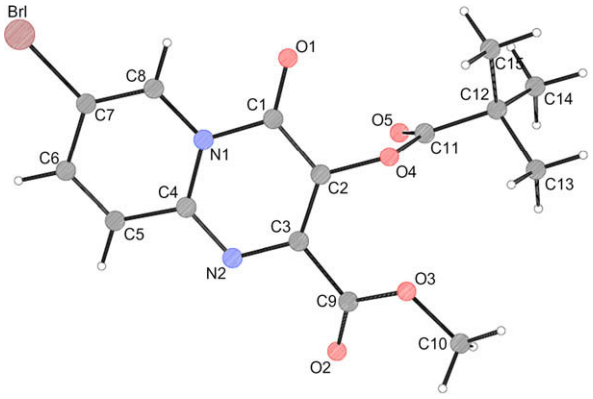
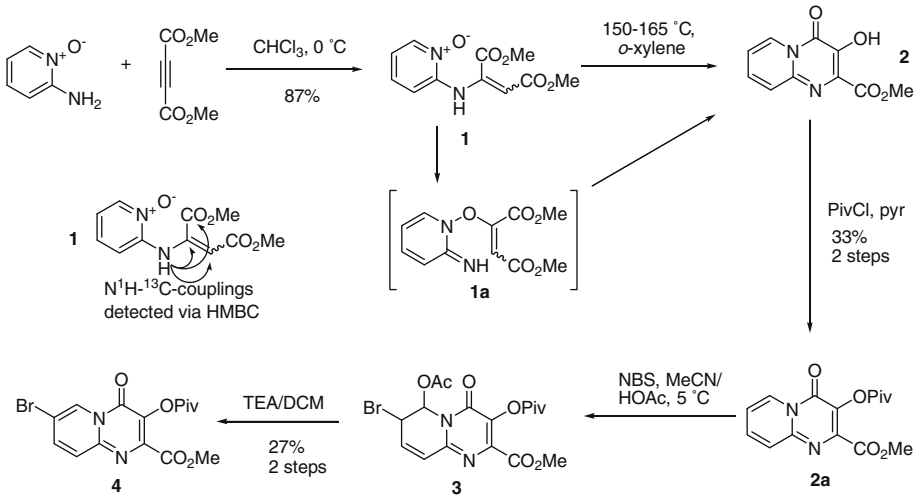
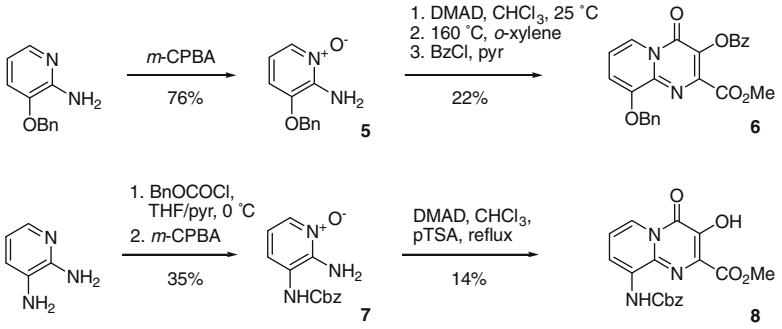



**Figure 3.** X-ray crystal structure of **4**.

As precursors for further derivatives a benzyl ether as well as a benzyl carbamate was chosen. To this end, 3-(benzyloxy)pyridin-2-amine 1-oxide (**5**) was prepared by *N*-oxidation of the commercially available 3-(benzyloxy)pyridin-2-amine, while benzyl




**Scheme 2.** Synthesis of pyridopyrimidinones.




**Scheme 3.** Synthesis of substituted pyridopyrimidinones **6** and **8**.

(2-amino-1-oxidopyridin-3-yl)carbamate (**7**) was prepared by N-oxidation of benzyl (2-aminopyridin-3-yl)carbamate, derived from a 3-N-protection of 2,3-diaminopyridine (Scheme 3). With these starting materials in hand, we proceeded to investigate the formation of DMAD adducts and subsequent rearrangement/cyclization reactions. In the case of the benzyl ether **5**, the adduct formation with DMAD proceeded to completion at room temperature within 8 h. Without isolation the formed adduct was treated in the same way as for **1**, leading to the expected methyl 9-(benzyloxy)-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate which was benzoylated to give compound **6** in 22% overall yield. The adduct formation of pyridine-*N*-oxide **7** with DMAD was very slow at room temperature. At reflux in chloroform in the presence of catalytic *p*-TSA, the direct formation of the desired product **8** was observed which was isolated in low yield (14%).[10]

In summary, a new and reliable procedure for fast access to substituted methyl-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates, a new scaffold for HIV-1 integrase inhibitors, is described. The synthesis starts from commercially available or readily prepared starting materials and furnishes a complex heterocyclic scaffold in essentially one step. Attempts to introduce a substituent on the naked scaffold indicated position 7 of the pyrido-fused ring as the most reactive one toward electrophilic attack. The cyclization reaction was found to be sensitive to the presence of additional substituents on the aminopyridine-*N*-oxide. Additionally, the desired products with substitution at the 9 position could be synthesized from the appropriate amino pyridines, but in low yields. Biological results regarding the newly obtained class of inhibitors will be reported elsewhere.

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4. *Dimethyl-2-[(1-oxidopyridin-2-yl)amino]but-2-enedioate* **1**: To a stirred solution of 2-aminopyridine-*N*-oxide (3.76 g, 34 mmol) in $CHCl_3$ (150 mL) at 0 °C was added dropwise a solution of DMAD (4.27 mL, 34 mmol) in $CHCl_3$ (20 mL). After addition the cooling bath was removed and stirring was continued for 1 h. Further, DMAD (1 mL) was added and stirring was continued for 2 h. The solution was filtered over a silica gel plug (20 g), and after washing with EtOAc/petrol ether (4:6, 1 L) the product was eluted with MeOH/EtOAc (1:4, 1 L). The combined organic phases were concentrated to dryness to afford the product as a light brown oil (7.5 g, 87%). The product was a mixture of *E*/*Z*-isomers (ca. 1:10) and was used without separation of the isomers. Main isomer: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 10.49 (s, 1H), 8,26 (m, 1H), 7.31 (m, 1H), 7.03 (m, 2H), 5.70 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 167.4, 162.7, 144.3, 142.5, 137.9, 126.9, 118.6, 113.9, 98.8. MS *m*/*z*: 253 $(M+H)^+$.
5. Pye, P. J.; Zhong, Y.-L.; Jones, G. O.; Reamer, R. A.; Houk, K. N.; Askin, D. *Angew Chem., Int. Ed.* **2008**, *4722*, 4134–4136.
6. *Methyl-3-[(pivaloyl)oxy]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate* **2a**: **1** (7.56 g, 29.7 mmol) was suspended in dry *o*-xylene (400 mL), and the suspension was stirred and heated to reflux for 3 h. The mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in pyridine (154 mL). Pivaloyl chloride (3.75 mL, 29.7 mmol) was added and the mixture was stirred for 2 h at rt. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (500 mL) and 0.6 M aq HCl (500 mL). The aq phase was extracted with EtOAc (3 × 500 mL). The combined org. phases were washed with water, brine, dried over $Na_2SO_4$, and concentrated to dryness. The product was purified by silica gel chromatography (petrol ether/EtOAc). The pooled product fractions were concentrated to dryness to afford the title compound as a light brown solid (2.99 g, 33%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.92 (d, $J$ = 7.8 Hz, 1H), 8.05 (m, 1H), 7.84 (d, $J$ = 7.5 Hz, 1H), 7.48 (m, 1H), 3.88 (s, 3H), 1.32 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 174.8, 163.4, 153.3, 148.1, 144.1, 137.5, 127.8, 127.2, 126.4, 117.5, 52.8, 26.7. MS *m*/*z*: 305 $(M+H)^+$. Mp (recrystallized from methanol): 149.2 °C.
7. For characterization of unprotected **2** a sample of the reaction crude was purified by reverse phase MPLC with subsequent crystallization from methanol. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 10.43 (s, 1H), 8.87 (d, $J$ = 7.2 Hz, 1H), 7.66 (d, $J$ = 9.2 Hz, 1H), 7.51 (m, 1H), 7.03 (m, 1H), 4.11 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 169.6, 154.2, 143.3, 143.1, 132.5, 127.7, 127.0, 126.2, 115.2, 53.7. MS *m*/*z*: 221 $(M+H)^+$.
8. Crystals were grown from 1:1 EtOAc:heptane. Compound $C_{15}H_{15}Br\ N_2O_5$, $M_r$ = 383.200, triclinic, *P*1, $a$ = 12.089(3), $b$ = 12.687(3), $c$ = 12.812(3) Å, $\alpha$ = 63.406(3)°, $\beta$ = 88.062(4)°, $\gamma$ = 64.406(3)°, $V$ = 1553.4(6) Å$^3$, $Z$ = 4, $D_x$ = 1.638 g cm$^{-3}$, monochromatized radiation $\lambda$(Mo) = 0.71073 Å, $\mu$ = 2.67 mm$^{-1}$, $F$(000) = 776, $T$ = 100 K. Data were collected on a Bruker CCD diffractometer to a $\theta$ limit of 26.32°, which yielded 18,499 reflections. There are 6303 unique reflections with 4626 observed at the 2$\sigma$ level. The structure was solved by direct methods (SHELXS-97, Sheldrick, G. M. *Acta Crystallogr., Sect. A*, 1990, 46, 467–473) and refined using full-matrix least-squares on $F^2$ (SHELXL-97, Sheldrick, G. M. *SHELXL-97. Program for the Refinement of Crystal Structures.* Univ. of Göttingen, Germany). The final model was refined using 423 parameters and all 6303 data. All non-hydrogen atoms were refined with anisotropic thermal displacements. The final agreement statistics are: $R$ = 0.040 (based on 4626 reflections with $I > 2\sigma(I)$), $wR$ = 0.097, $S$ = 1.00 with $(\Delta/\sigma)_{max} < 0.01$. The maximum peak height in a final difference Fourier map is 1.268 e Å$^{-3}$. CCDC 692685 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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10. *Methyl-9-{[(benzyloxy)carbonyl]amino}-3-hydroxy-4-oxo-4-H-pyrido-[1,2a]-pyrimidine-2-carboxylate* **8**: To a solution of benzyl (2-amino-1-oxidopyridin-3-y1) carbamate **7** (2.0 g, 7.69 mmol) in $CHCl_3$ (250 mL, filtered over alumina) was added DMAD (1.04 mL, 8.46 mmol) and pTSA (50 mg). The suspension was stirred at 70 °C for 12 h. The solvent was removed under reduced pressure, and to the residue was added MeOH. The formed solid was filtered off, washed with MeOH, and dried under vacuum to afford the title compound as a light brown solid (400 mg, 14%). $^1$H NMR (400 MHz, $CD_3CN$) $\delta$: 9.95 (s, br, 1H), 8.68 (s, br, 1H), 8.43 (d, $J$ = 7.3 Hz, 1H), 8.19 (d, $J$ = 7.3 Hz, 1H), 7.51–7.43 (m, 4H), 7.12 (m, 1H), 5.3 (s, 2H), 4.04 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 165.4, 154.6, 152.5, 138.3, 135.9, 135.6, 131.5, 130.9, 128.5, 128.2, 119.0, 115.6, 114.9, 66.8, 52.5.MS *m*/*z*: 370 $(M+H)^+$.