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THE SYNTHESIS OF A DIPYRIDO[3,2-b:3',4'-e][1,4]DIAZEPINONE: CONVENIENT ACCESS TO A C-RING ISOMER OF THE HIV-1 REVERSE TRANSCRIPTASE INHIBITOR NEVIRAPINE

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Abstract: The synthesis of 11-ethyl-5-methyldipyrido[3,2-b:3',4'-e][1,4]diazepin-6-one **6**, the first representative of a C-ring dipyridodiazepinone isomer of the HIV-1 reverse transcriptase inhibitor nevirapine **1** is described. The key step involves the regiospecific lithiation of 3-(^{t}butoxycarbonylamino)pyridine **7** followed by trapping with N-(2-chloropyridyl)-N-methylcarbamoyl chloride **10**.

Introduction. Nevirapine **1**[1,2] is a potent and selective non nucleoside inhibitor of HIV-1 reverse transcriptase (RT) and is currently in clinical trials undergoing evaluation for the treatment of AIDS. In parallel with our studies on the structure activity relationship with respect to substituents on the dipyridodiazepinone system, we have pursued the synthesis of the A- and C-ring pyridine isomers in order to determine whether the dipyrido[3,2-b:2',3'-e][1,4]diazepinone ring system represented by nevirapine confers the highest potency against RT. We have chosen the N(5)-methyl-N(11)-ethyl substitution pattern exemplified in **2** as the standard for comparison of enzyme inhibition across different tricyclic ring systems. Compound **2** is a marginally less potent inhibitor of RT than nevirapine, but in general compounds with this substitution pattern are synthetically more accessible. We recently reported the synthesis of the three A-ring isomers, **3** - **5**,[3] and in this letter we demonstrate a convenient access to one of the C-ring isomers, the dipyrido[3,2-b:3',4'-e][1,4] diazepinone **6**.

Figure I

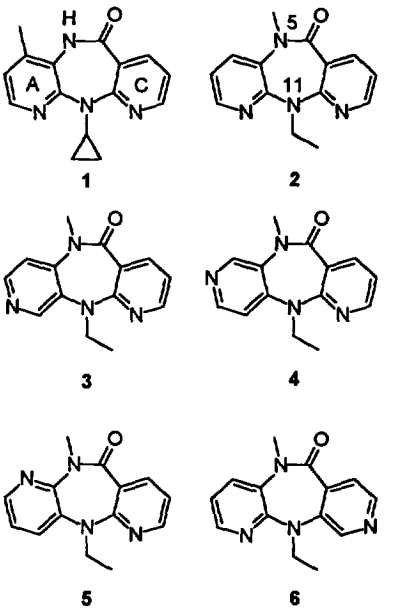
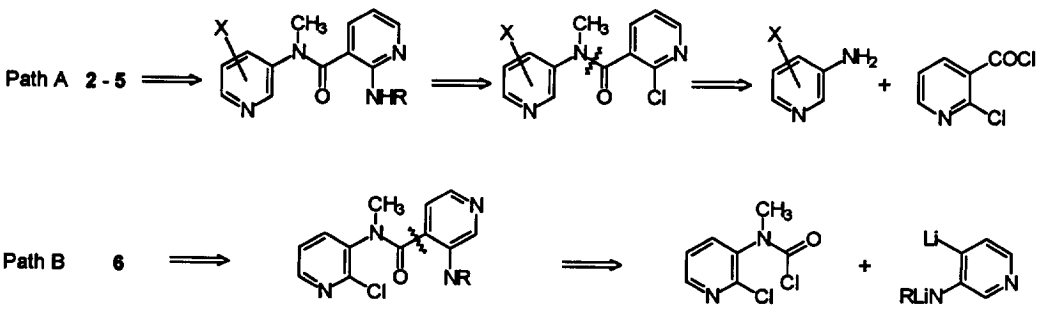
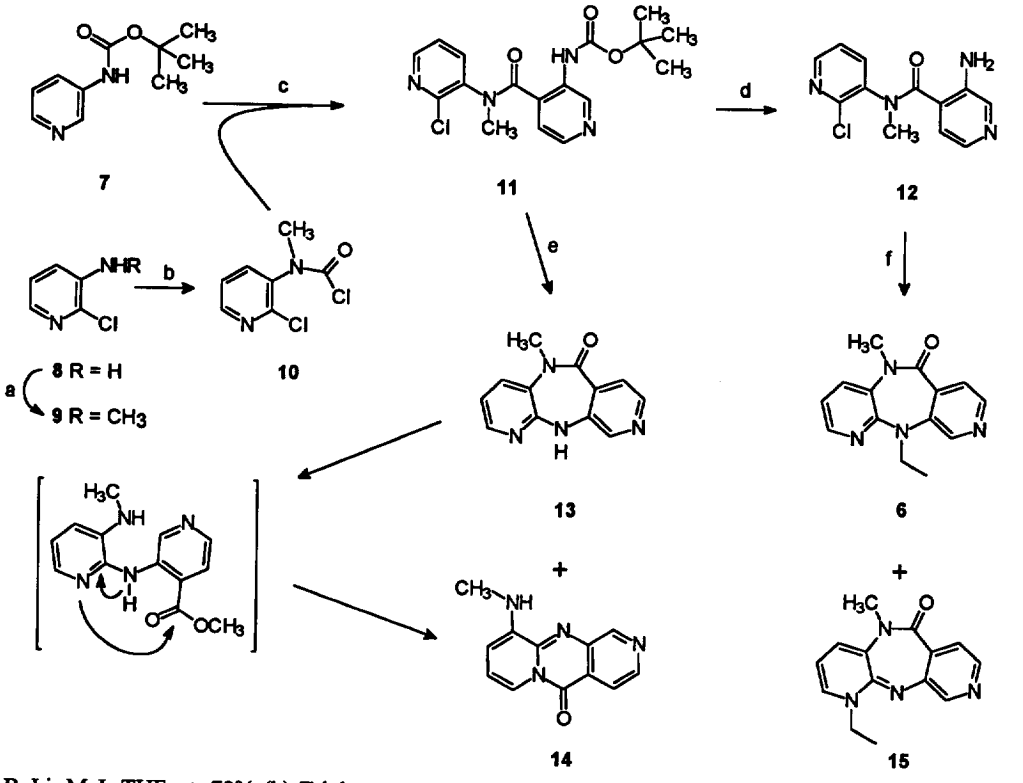


Figure II



Scheme I



(a) BuLi, MeI, THF, rt, 72% (b) Triphosgene, THF, Et_3N, rt 92% (c) BuLi, THF, -30°C, 1h, then **10** and allowed to come to rt, **11** 68%. (d) HCl, MeOH, 70 °C, 2h, **12** 89% (e) HCl, MeOH, 100 °C, 2h, **13** 39%, **14** 46% (f) NaHMDS (2.2 eq), DMSO, rt, EtI, **6** 76%, **15** 16%.

Retrosynthesis The synthesis of dipyridodiazepinones[2, 3] has previously followed the disconnection outlined in Figure II (path A) in which the precursor for the final cyclization to the tricyclic ring system derives from the coupling of a pyridylamine and a nicotinoyl chloride, followed by reaction of this product with an alkylamine. We were interested in exploring an alternative strategy, outlined in path B, for the synthesis of isomer **6**. The lithiation of a suitably protected 3-aminopyridine should occur at the 4-position of the pyridine ring,[4, 5] and trapping with a carbamoyl chloride should give the amide precursor of the tricyclic material **6**. The ^{t}butoxycarbonyl (BOC) group was chosen to protect the 3-aminopyridine because of its ability to promote ortho-lithiation and its easy removal.[5, 6] In this sequence the nitrogen atom destined to be N(11) and the methyl substituent on N(5) are already incorporated into the two monocyclic pyridine precursors leading to an efficient convergent synthesis.

Synthesis and biological data The synthesis of **6** proceeded as shown in Scheme I.[7] The carbamoyl chloride **10** is accessible in two steps from 2-chloro-3-aminopyridine **8**. The N-methylation to **9** is conveniently carried out by deprotonation of **8** with butyllithium and quenching with methyl iodide. Subsequent reaction of the methylaminopyridine **9** with triphosgene[8] gives the carbamoyl chloride **10**.

Lithiation of 3-(^{t}butoxycarbonylamino)pyridine **7**[5, 9] followed by reaction with **10** yields the amide **11** in 68% yield. Due to the low solubility of **7** in diethyl ether, THF is a superior solvent for this reaction. Removal of the BOC protecting group is sluggish at room temperature but, on warming, the 3-aminopyridine-4-carboxamide derivative **12** is obtained in good yield. Indeed, deprotection and cyclization to the dipyridodiazepinone **13** can be effected in one pot, but the higher temperature required for the cyclization reaction under acidic conditions leads to the formation of substantial quantities of the side product **14**. This compound derives from cleavage of the amide bond of **10** followed by recyclization as shown.

The cyclization of **9** is more conveniently carried out under basic conditions. Using LHMDS in THF, the dipyridodiazepinone **13** is formed instantly at ambient temperature. With DMSO as the solvent and NaHMDS as the base, the cyclization and ethylation at N(11) are accomplished in one pot giving **6** directly. Some competing alkylation on the N(1) atom of the A ring, giving the isomer **15**, is also seen in this reaction.

A comparison of the *in vitro* RT inhibitory activity[10] of **6** with the tricyclic isomers **2 - 5** and with nevirapine **1** is given below in Table I. This first example of a C-ring dipyridodiazepinone isomer is a less potent inhibitor of RT than any of the A-ring isomeric analogs **2 - 5**.

Table I. Inhibition of HIV-1 RT by Dipyridodiazepinones 1 - 6.

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1	0.084	**3**	0.35	**5**	1.3
2	0.125	**4**	1.6	**6**	6.4

Acknowledgments: We thank Eva David, Janice Rose and Peter Grob for assaying compounds **1 - 6** against HIV-1 RT. Usha Patel and Dr. Terence A. Kelly provided the 3-^{t}butoxycarbonylaminopyridine used in these experiments.

References and Notes

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6. (a) For the *ortho*-lithiation of N-(^{t}butoxycarbonyl)aniline see: Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798-4801. (b) For α-lithiation in saturated systems promoted by the BOC group see: Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197-1200.
7. Characterization of compounds **6**, **11** - **15**.

   6. Mp 157-159 °C (^{i}Pr$_2$O); ^{1}H NMR ($CDCl_3$) δ 8.46 (1H, s), 8.34 (1H, d), 8.17 (1H, dd), 7.61 (1H, d), 7.48 (1H, dd), 7.10 (1H, dd), 4.2 (1H, br), 3.8 (1H, br), 3.53 (3H, s), 1.28 (3H, t). Anal: Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.33; H, 5.58 ; N, 22.05.

   11. Mp 192-193 °C (^{i}Pr$_2$O / EtOAc); ^{1}H NMR ($CDCl_3$) δ 9.34 (1H, s), 8.29 (1H, m), 8.00 (1H, m), 7.94 (1H, m), 7.42 (1H, m), 7.18 (1H, m), 6.72 (1H, m) 3.44 (3H, s), 1.54 (9H, s). Anal: Calcd for $C_{17}H_{19}N_4O_3Cl$: C, 56.28; H, 5.28; N, 15.44. Found: C, 56.08; H, 5.34 ; N, 15.21.

   12 Mp 174-176 °C (EtOAc). NMR signals are broadened due to the slow interconversion of the two N-methyl amide conformers. Anal: Calcd for $C_{12}H_{11}N_4OCl$: C, 54.87; H, 4.22; N, 21.33. Found: C, 55.04; H, 4.31; N, 21.02.

   13. Mp 245-247 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.29 (2H, m), 8.04 (1H, dd), 7.72 (1H, d), 7.48 (1H, dd), 7.10 (1H, dd), 6.62 (1H, br s), 3.50 (3H, s). Anal: Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.29; H, 4.21 ; N, 24.39.

   14. Mp 220-223 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 9.24 (1H, d), 8.59 (1H, d), 8.27 (1H, dd), 8.15 (1H, dd), 6.91 (1H, dd), 6.40 (1H, d), 6.20 (1H, br), 3.03 (3H, d). Anal: Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.64; H, 4.47 ; N, 24.52.

   15. Mp 152-153 °C (EtOAc / ^{i}Pr$_2$O); ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, s), 8.00 (1H, d), 7.63 (1H, d), 6.97 (1H, dd), 6.74 (1H, dd), 6.11 (1H, dd), 4.16 (2H, q), 3.30 (3H, s), 1.42 (3H, t). Anal: Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.41; H, 5.45; N, 21.80.
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10. For details of the enzyme assay see ref 2.

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