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Synthesis of a rhazinilam analogue acting as an inhibitor of tubulin assembly

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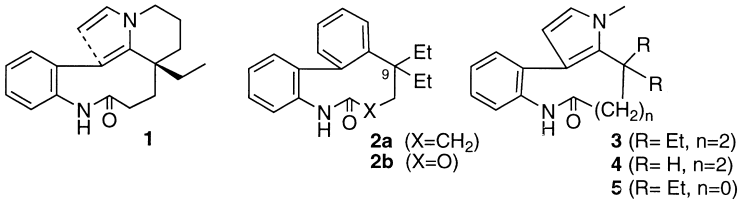
Abstract

The synthesis of a di-nor-secorhazinilam analogue is described. This phenylpyrrole compound has been prepared by a Susuki cross-coupling reaction between 1,2,5 trisubstituted pyrrole halides and 2-*N*-(*tert*-butoxycarbonyl)aminophenyl boronic acid. In contrast to rhazinilam, this new phenylpyrrole inhibits the assembly of tubulin into microtubules.

Keywords: rhazinilam; phenylpyrroles; coupling reactions; biological activity tubulin.

(–)-Rhazinilam **1** is a natural tetracyclic compound possessing a phenylpyrrole subunit and a nine-membered lactam ring.[1] It was found to act as an inhibitor of microtubules disassembly.[2] As part of a program[3] directed towards the synthesis of biaryls mimicking the structure of the anti-mitotic (–)-rhazinilam **1**, we previously reported the synthesis of various *ortho*-bridged biphenyls (compound **2**).[4,5] We showed that the replacement of the lactam (compound **2a**) by an urethane function (compound **2b**) increases the binding with tubulin and that the binding interaction is stereoselective.[5] Moreover, C-9-dialkylated lactam **3**[6] was found to be more active than compound **4**,[7] indicating that the presence of a quaternary carbon at position 9 greatly influences the biological activity.[8] In continuation of this study, we report herein the synthesis of a di-nor-secorhazinilam analogue **5** possessing a seven-membered lactam ring and an *ortho*-disubstituted phenyl–pyrrole subunit.[9]



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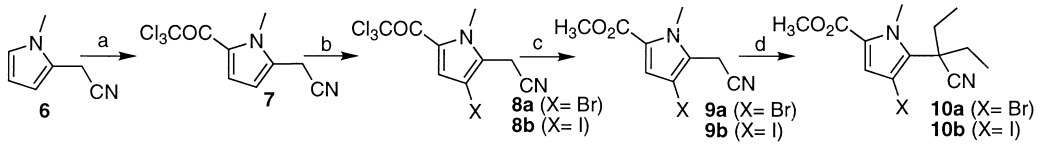
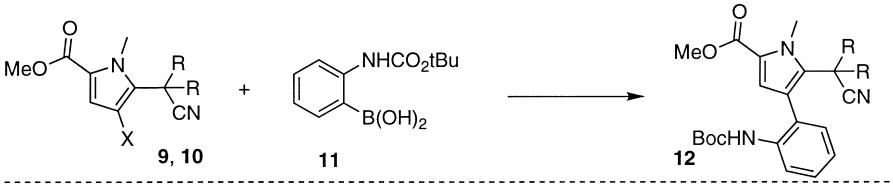
Following our synthesis of biphenyls **2**,[4,5] the approach to produce compound **5** was based on a Suzuki cross-coupling reaction[10] of *ortho*-substituted 3-halopyrroles **9** (X = Br or I) and **10** (X = Br or I) with a protected aniline derivative **11**.[11] 1,2,3,5-Tetrasubstituted pyrroles **9** and **10** were obtained from commercial 1-methyl-2-pyrroleacetonitrile **6** (Scheme 1). Due to the necessity of further transformations, pyrrole **6** was first protected at carbon 5 with a trichloroacetyl group. Pyrrole **7** was then converted into bromide **8a** or iodide **8b**. Treatment of the halide **8** with sodium methoxide led to compounds **9a** or **9b** which were dialkylated with lithium diisopropylamide and ethyl iodide to give pyrroles **10a** and **10b**.



Scheme 1. (a) $ClCOCCl_3$, Et_2O, 0°C (**7** 98%); (b) NBS or NIS, $(CH_3)_2CO$, rt (**8a** 98% or **8b** 99%); (c) MeONa, MeOH, 0°C (**9a** or **9b** 98%); (d) LDA, –78°C, EtI (–78– > 0°C) (**10a** or **10b** 54%)

The Suzuki cross-coupling reaction was attempted on compounds **9** (X = Br or I) and **10** (X = Br or I) with 2-*N*-(*tert*-butoxycarbonyl)aminophenyl boronic acid **11** (Table 1). The coupling reactions were performed with benzyl[bis(triphenylphosphine)]palladium(II) chloride (PdBnCl $(PPh_3)_2$). The coupling between arylboronic acid **11** and pyrrole bromide **9a** in a DME–water solution in the presence of sodium carbonate (entry 1) gave the corresponding 3-phenylpyrrole derivative **12a** in a modest yield (35%). The same reaction applied to the pyrrole iodide derivative **9b** was more efficient and led to **12a** in 80% yield (entry 2a). When the reaction was performed in

Table 1
Coupling of pyrroles **9** or **10** with phenyl boronic acid **11**



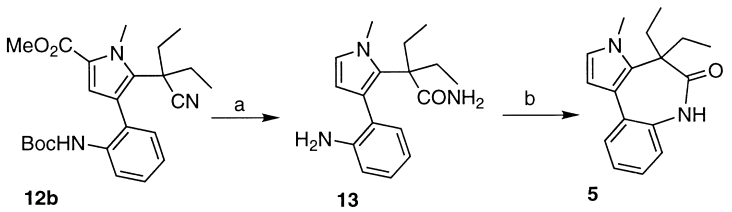
	Halide	Conditions[a]	yield (%)	Products[b]
1	**9a** R= H, X= Br	Na_2CO_3, DME-H_2O	35	
2	**9b** R= H, X= I	a) Na_2CO_3, DME-H_2O	80	**12a** (R= H)
		b) Na_2CO_3, Toluene-H_2O	50	
3	**10a** R= Et, X= Br	a) Na_2CO_3, DME-H_2O	30	
		b) K_3PO_4, DME-H_2O	48	
		c) $Ba(OH)_2$, DME-H_2O	0	**12b** (R=Et)
4	**10b** R= Et, X= I	K_3PO_4, DME-H_2O	47	

a) The reactions were carried out in refluxing solvent (2ml) for 3h. with pyrrole (0.16 mmol), halide **11**(0,176 mmol), PdBnCl$(PPh_3)_2$ (3% mol) and base (0.24 mmol). b) Compounds **12a** and **12b** were characterized by elemental analysis, ^1H and ^{13}C NMR and MS.

toluene (entry 2b), the yield of the coupling reaction decreased to 50%. Dialkylation of phenylpyrrole **12a** with LDA and ethyl iodide led to diethyl phenylpyrrole **12b** in 44% yield.

We then turned our attention to the cross-coupling reactions between phenyl boronic acid **11** and the more hindered pyrrole halides **10a** and **10b**. The coupling of bromide **10a** with phenylboronic acid **11** in the presence of sodium carbonate in DME–H_2O led to the expected product **12b** (entry 3a, 30%). When potassium phosphate was used as the base, the coupling product was isolated with 48% yield (entry 3b). A stronger base such as barium hydroxide proved inefficient to perform the coupling reaction. In the case of the dialkylated pyrroles, no improvement was obtained when the pyrrole iodide was used instead of the bromide (entry 4). In all performed experiments, the biphenylic homocoupling product as well as the dehalogenated pyrrole derivative were isolated as secondary products. It should be noted that the synthesis of 2-formyl-3-arylpyrroles has been recently described.[12] In particular, the coupling of 2-nitrophenylboronic acid with 2-formyl-3-iodo-1-tosylpyrrole is mentioned giving excellent yield of the coupling product when $Pd(dppf)_2Cl_2$ was used as the catalyst. In our case, the use of $Pd(dppf)_2Cl_2$ as catalyst did not improve the yield of the coupling product.

Basic hydrolysis of compound **12b** followed by treatment of the mixture with a 10% aqueous solution of hydrochloric acid gave directly the primary amide **13**. Finally, compound **13** was converted to the desired di-nor-secorhazinilam analogue **5**[13] after lactamization (Scheme 2).



Scheme 2. (a) 50% aq NaOH, MeOH, rfx, 3 h then 10% aq. HCl, rt 15 min (**13** 100%); (b) conc H_2SO_4, rfx, 10 min (**5** 100%)

The effect of phenylpyrrole **5** was first evaluated on the disassembly of microtubules;[14] **5** was found inactive. In contrast, compound (–)-**3**[6] which possesses a nine-membered ring, inhibits the cold disassembly of microtubules.[7] This confirms that the size of the lactam ring, and consequently the dihedral angle of the biaryl moiety, are playing an essential role in the inhibition of cold microtubules disassembly. Because many biaryl-type molecules are inhibitors of tubulin assembly,[15] the activity of compound **5** was also evaluated on the assembly of tubulin into microtubules. Interestingly, we found that phenylpyrrole **5** acts as an inhibitor of tubulin assembly with an IC_{50} value of 2.7×10^{-5} M. This compound was also found to be cytotoxic towards tumor KB cell lines with an IC_{50} value of 7×10^{-6} M. Although compound **5** is less active than colchicinoids, this result opens the door to new chemical and biological investigations on this type of molecule.

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13. Compound **5** was obtained as a white amorphous solid**.** ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (6H, 2t, $J=7.3$ Hz), 2.00 (2H, m), 3.83 (3H, s), 6.35 (1H, d, $J=2.5$ Hz), 6.56 (1H, d, $J=2.5$ Hz), 6.92 (1H, dd, $J=7.5$ and 1.5 Hz), 7.16 (2H, m), 7.55 (1H, dd, $J=7.5$ and 1.5 Hz), 7.77 (1H, bs). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 9.4, 23.0, 39.5, 53.1, 106.8, 119.3, 121.7, 123.9, 126.2, 126.7, 127.3, 127.9, 129.0, 134.3, 171.3. IR ($CHCl_3$) ν 3334, 3004, 1649, 1513, 1352 cm^{-1}. MS (CI+) m/z 269 ([M+H]$^+$). HRMS (CI+) m/z calcd (found) for $C_{17}H_{21}N_2O$ (MH^+): 269.1654 (269.1412).
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