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EFFICIENT ONE-POT SYNTHESIS OF JM3100

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Abstract: A facile synthesis of JM3100 was reported. This strategy could also be successfully applied in the cyclen series.

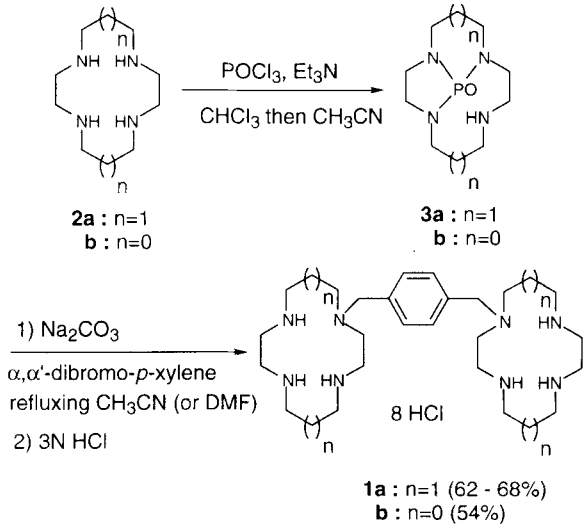
In addition to the interest generated by their numerous biomedical applications,[1] azamacrocycles have recently gained further attention due to the discovery of JM3100 (**1a**).[2] This compound, formed of two cyclam units bridged by a phenylenebis-methylene linker, displays highly potent anti-HIV properties together with an exceptionally low toxicity. Conversely to other drugs, **1a** does not easily generate resistant virus mutants,[3] so, whereas its mechanism of action is still unclear, it is one of the most promising lead candidates as novel anti-HIV drug.

The synthesis of **1a** from commercially available cyclam (**2a**) is very appealing. However, following this strategy, three of the four nitrogen atoms have primarly to be protected allowing a subsequent non-ambiguous mono *N*-substitution. For this purpose, the classical Boc chemistry has been proposed.[4] Nevertheless, this approach requires the use of an excess of the quite expensive **2a** whose recycling is generally not convenient. A second method of intramolecular tri *N*-protection that utilizes metaltricarbonyl complexes, trimethylsilyl, thiophosphoryl, boron, or phosphoryl entities has also been proposed.[5] In this latter case, a phosphoric triamide was obtained by oxidation, in the presence of large quantities of carbon tetrachloride, of the corresponding aminophosphorane. Considering that phosphoric triamides can easily be obtained by condensation of phosphorus oxychloride and the appropriate amines, we attempted to reinvestigate

the preparation of **3a** and were capable to prepare this latter compound simply by refluxing **2a** with one equivalent of $POCl_3$ in the presence of a slight excess (1.3 equiv.) of triethylamine in chloroform[6] then acetonitrile (Scheme 1). Condensation of **3a** with α,α'-dibromo-*p*-xylene (0.5 equiv.) in the presence of two equivalents of Na_2CO_3 was achieved in the same pot with no need to isolate **3a**. Removal of the protective group was accomplished by aqueous HCl using a previously reported procedure.[7] Extraction at alkaline pH of the solution mixture yielded an oil from which triethylamine was removed under high vacuum and that after dissolution in MeOH/ether and bubbling of an HCl stream yielded **1a**[8] in 62% as an hydrochloride salt that was filtered off. In order to evaluate the generality of our method, we decided to prepare, starting from also commercially available cyclen (**2b**), the corresponding known azamacrocyle **1b**[2] since *N*-substitution of phosphoric triamide **3b** by different halide compound has already been reported.[7] Using our conditions, **1b** was isolated in only 10 to 15% yield together with 65% of recovered **2b**. However, phosphoric triamide **3b** could be isolated in 65% yield by reacting **2b** in the conditions described to obtain **3a**. This suggested that the low yield step was the reaction between **3b** and α,α'-dibromo-*p*-xylene. Since *N*-substitution of **3b** has been reported to occur at 100°C in DMF,[7] we attributed the low reactivity of **3a** to the formation of a dimer complex[9] that is stable enough in refluxing acetonitrile to preclude the *N*-alkylation reaction, this complex being possibly broken at higher temperature. Consequently, we attributed the recovering of **2b** more likely to the hydrolysis of **3b** than to an absence of reaction between **2b** and $POCl_3$. To demonstrate this hypothesis, we repeated our procedure replacing acetonitrile by dry DMF. In these conditions, **1b**[8] was isolated in 54% yield. Synthesis of **1a** using DMF in place of acetonitrile could also been achieved in 68% yield.

Finally, we studied the possible complete substitution of the chloroform-acetonitrile solvent couple by DMF in the preparation of **1a**. When the reaction sequence was entirely conducted in refluxing DMF, **1a** could not be obtained. However this latter could be prepared when **2a**, $POCl_3$ and Et_3N were first stirred for 24 hours in DMF at 65°C then for 12 hours at 80°C. Nevertheless, in these conditions, **1a** was isolated in lower and less reproducable yields (30 to 50%).

In conclusion, our strategy allows an easy and efficient prepapration of JM3100 without using carbon tetrachloride. Despite the somehow necessary use of chloroform, as a solvent, and stoechiometric quantity of phosphorus oxychloride we believe that our method is more practical that the previously reported methods.



Scheme 1

Experimental Section

General procedure for the preparation of 1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane (1a).

In a dry 250-mL round bottomed flask, 1g (5 mmol) of **2a** was dissolved in 150 mL of chloroform. Triethylamine (2.2 mL) was added, then phosphorus oxychloride (478 µL). The solution was refluxed for 48 hrs then 60 mL of acetonitrile (or dry DMF) were added and the solution was allowed to boil then reflux for 10 hrs. Sodium carbonate (2 equiv., 530 mg) was added to the boiling solution then α,α'-dibromo-p-xylene (0.5 equiv., 660 mg) and the solution was refluxed overnight. The solvent was removed *in vacuo* and 450 mL of 3N HCl were slowly poured onto the residue. The solution was refluxed overnight. After cooling at 0°C, the solution was made alkaline by carefull addition of NaOH (pellets) and extracted twice with $CHCl_3$. The organic phases were combined, dried over $MgSO_4$, and concentrated. The obtained residue was placed under vacuum overnight then dissolved in a minimum amount of dry MeOH and ether. A stream of HCl was gently passed through the solution and the formed white precipitate was filtered off the solution yielding **1a** in pure form (yield 62 or 68%).

References and notes

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(8) Spectral data for **1** and **3** were in agreement with reported data.[2,9] **1a**: ^{13}C NMR (D_2O, 75 MHz) δ: 17.1, 17.9, 36.2, 40.2, 40.8, 42.6, 45.9, 57.1, 129.0, 131.6. **1b**: ^{13}C NMR (D_2O, 75 MHz) δ: 43.1, 43.2, 45.1, 48.6, 57.1, 132.2, 136,1. **3a**: ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.5, 27.7, 41.3, 41.8, 43.8, 44.4, 45.4, 45.8, 51.2. **3b**: ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 43.6, 43.5.

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