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Synthesis of a Conformationally Constrained Analogue of BW A78U, an Anticonvulsant Adenine Derivative

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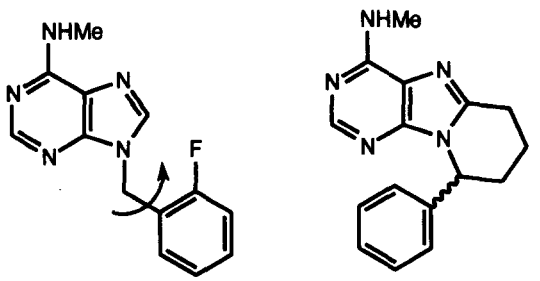
Abstract : The synthesis of a conformationally constrained analogue of the anticonvulsant BW A78U, a 9-benzyl-adenine derivative, has been devised, using silicon tetrachloride in a new cyclodehydration.

As a part of our program dealing with structural modification of BW A78U, a potent anticonvulsant and anxiolytic drug[1-3], we were interested in synthesizing a constrained analogue of this drug. Previous work has shown that conformationally restricted analogues are valuable probes in drug design[4,5]. We report here the synthesis of the bridged compound **1**, that is considered a semi-rigid analogue of BW A78U.

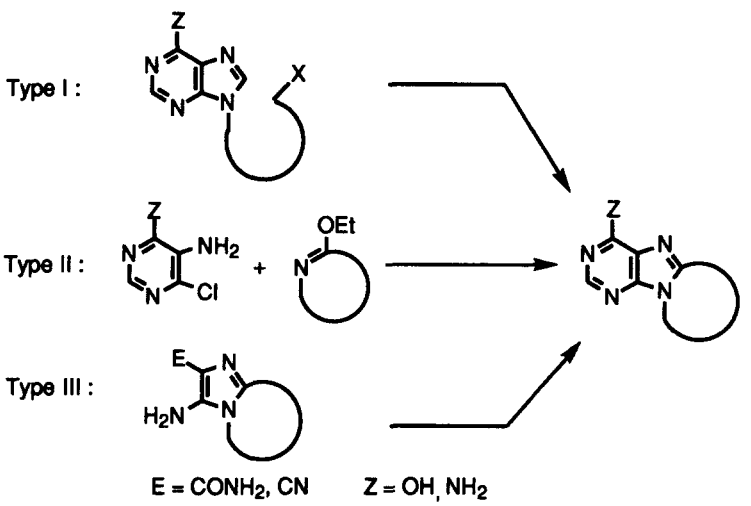


BW A78U 1

Three different strategies can be formally applied for the preparation of cycloadenine derivatives (scheme 1). The most convenient approach (type I) involves an adenine ring bearing a functionalized residue at the N(9) nitrogen. This method was applied in radical[7-11] or ionic[12] cyclization of adenosine derivatives leading to C(5') -C(8) bridged cycloadenosines. The second method (type II) starts from a functionalized pyrimidine, which is cyclocondensed with a cyclic iminoether, whereas the type III involves a C(2)-N(1) bridged imidazole carboxamide [13] or carbonitrile[14]. The only attempt to synthesize a C(8)-N(9) bridged adenine derivative according to a type II, which has been described, failed[13]. Preparation of compound **1** was carried out following a modified type II strategy.

The catalytic hydrogenation of the oxime prepared from 4-benzoylbutyric acid **2** afforded the corresponding δ-aminoacid **3** (scheme 2). This compound did not react with 4,6-dichloro-5-aminopyrimidine **4** to yield **5**, but easily cyclized into lactam **6**. However, the treatment of **3** with the more electrophilic 4-methylamino-5-nitro-6-chloropyrimidine **7**[15] afforded the amidine **8**, which was catalytically hydrogenated to

give the triaminoacid **9**. Different attempts to cyclize **9** with classical dehydration agents failed (phosphorus oxychloride, triphenyl or tributylphosphine in CCl_4, anhydrous phosphoric acid, hydrochloric acid in ethanol). In each case either no reaction was observed, or degradation occurred.



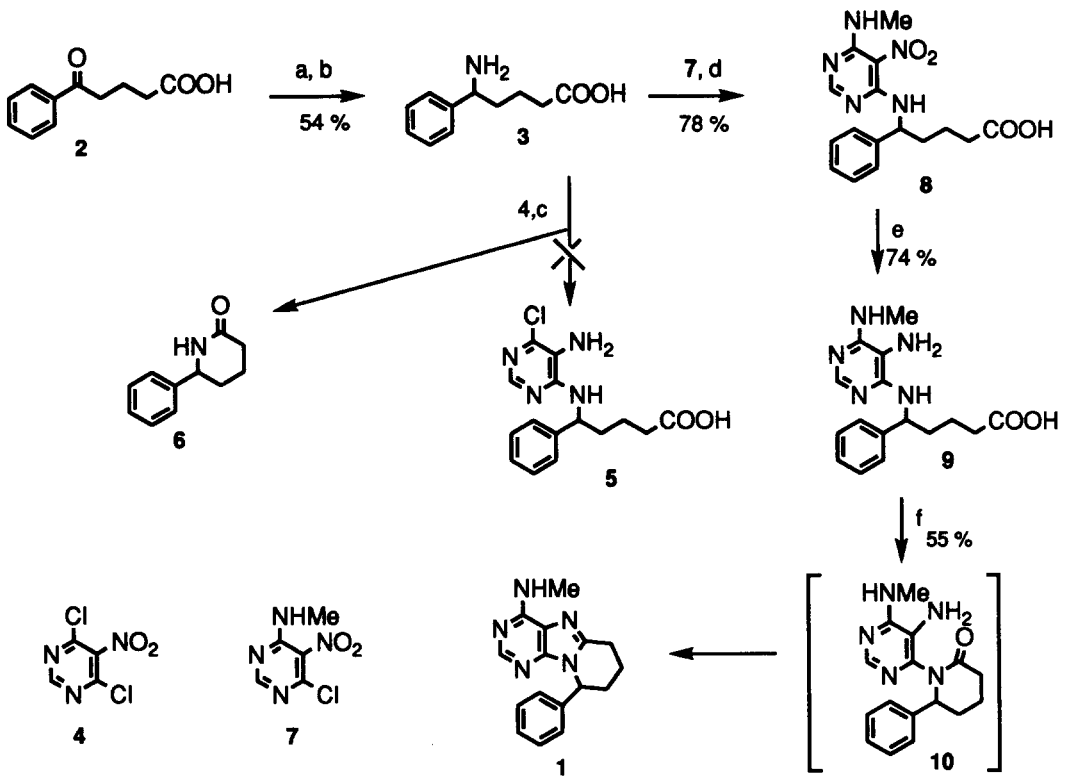
Scheme 1: Strategies for the synthesis of cycloadenine derivatives.

The general problem to overcome is efficient activation of the tertiary amide **10** (scheme2) without blocking the nucleophilic character of the vicinal 5-amino function. As far as we know, among the tertiary amides, only formamides **I** ($R \neq H$, $R' = H$) have been cyclized to provide fused imidazolic heterocycles **II**, because of their satisfactory electrophilic character[16]. DMF activation has been performed using silicium derivatives such as tertiobutyl dimethyl silyl chloride[17], or TMSCl[18]. The reaction has been extended by us to other tertiary amides ($R' \neq H$) by means of $SiCl_4$ as dehydrating agent.

Thus, treatment of orthophenylenediamine **11** with DMF and 2.5 equivalents of $SiCl_4$ in refluxing CH_2Cl_2 led to benzimidazole **12** (scheme 3). Moreover, the N-aryl lactame **13** considered as a model compound of our intermediate **10**, afforded the awaited bridged benzimidazole **14**.

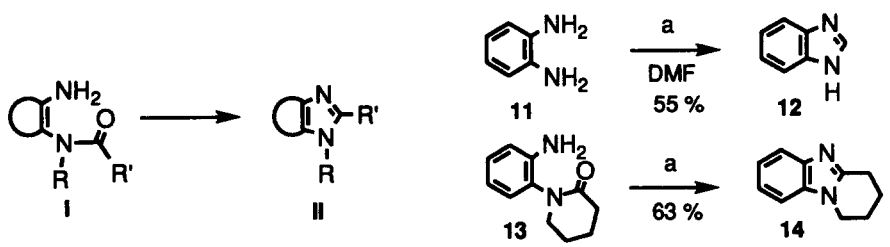
When considering the amino lactame **10**, the formation of N-Si bonds with the amino groups is reversible and the reaction is driven by the higher oxygen affinity for silicium leading to the cyclized compound **1** and silica. $SiCl_4$ is known as an efficient dehydrating agent[19-21]. However, only one example of activation of a tertiary amide using $SiCl_4$ is described in the literature. It concerns the dehydration of N-alkyl N-acyl alanines leading to mesoionic oxazolones [22]. The same experimental procedure let us to achieve in one step the cyclization of **9** into **1** (mp 170-171°C) with a satisfactory overall yield (55 %).

The application of activation of tertiary amides by $SiCl_4$ for the synthesis of the cycloadenine derivative **1** and benzimidazoles **12** et **14** demonstrates the potential of this methodology in the synthesis of imidazoheterocycles. The anticonvulsant properties of compound **1** are under investigation, and will be reported elsewhere.



a) $NH_2OH.HCl$, 65°C, 12 h; b) H_2, Pd/C, EtOH; c) **4**, Et_3N, nBuOH, reflux; d) **7**, $KHCO_3$, MeOH, 50°C, 2 days; e) H_2, Raney Ni, H_2O ; f) $SiCl_4$, Et_3N, CH_2Cl_2, reflux, 4 days

Scheme 2



a : $SiCl_4$, Et_3N, CH_2Cl_2, reflux

Scheme 3

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