A New Convenient Synthesis of 2-Amino-N,N,N-trimethyl-1H-purine-6-ammonium chloride for Preparation of 6-Substituted Guanines

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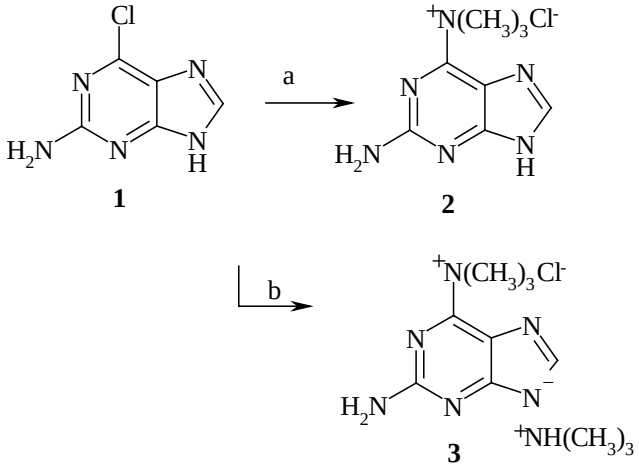
Abstract:
A new convenient synthesis is reported for 2-amino-N,N,N-trimethyl-1H-purine-6-ammonium chloride **2**, starting from commercially available 2-amino-6-chloro purine **1** and trimethylamine (TMA) in ethanolic solution, avoiding highly volatile and low temperature condensed trimethylamine.

6-Substituted guanines were proved to be important targets as effective inactivators of O^6-alkylguanine-DNA alkyltransferase (MGMT), a human DNA repair protein that leads to a significant reduction in the cytotoxic response of human tumor cells and tumor xenografts to chemotherapeutic drugs whose mechanism of action involves modification of DNA guanine residues at the O^6-position[1]. O^6-benzylguanine and its analogues inhibit MGMT by reacting with a specific cysteine residue. Therefore, O^6-substituted guanines containing a benzyl or hetarylmethyl moiety are of great medical interest. There are some synthetic methods described in the literature of which the reaction of 2-amino-N,N,N-trimethyl-1H-purine-6-ammonium chloride **1** with respective benzyl- and hetarylmethyl alcohols was proved to be the most suitable[2].
The original synthetic route of **2** includes the low temperature condensation of gaseous TMA which is problematic owing to its high volatility and subsequent reaction with 2-amino-6-chloro purine **1**[3]. To avoid that critical step and to make the preparation more convenient, we established a synthesis starting from commercially available ethanolic TMA solution (4.2 N) and 2-amino-6-chloro purine **1** under well defined reaction conditions (scheme 1).

Results

Under the optimized conditions shown in scheme 1, the desired compound **2** was obtained in 76 % chemical yield using 2 equivalents of TMA. No further recrystallisation of **2** was necessary. This reaction depends highly on the amount of TMA used in the synthesis.

Scheme 1
Reagents and conditions:
(a) TMA (4.2 N) in ethanol (2 eq), DMSO, rt, 12 h, 76 %
(b) TMA (4.2 N) in ethanol (10 eq), DMSO, rt, 2 h, 74 %.



1 **2** **3**

More than 3.2 equivalents of TMA are unfavorable because the formation of a byproduct which proved to be the double salt **3** becomes the main reaction.
The structures of **2** and **3** were confirmed by FD-MS, ^{1}H-NMR and ^{13}C-NMR.

This reaction is also suitable for the synthesis of N,N,N-trimethyl-1H-purine-6-ammonium chloride to prepare 6-substituted adenine derivatives.

References

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