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Pyrimidine to guanine PDE inhibitors: determination of chemical course via structure elucidation

Dinesh Gala,* Donald J. DiBenedetto, Max Kugelman and Mohindar S. Puar

Schering-Plough Research Institute, 1011 Morris Avenue, Union, NJ 07083, USA

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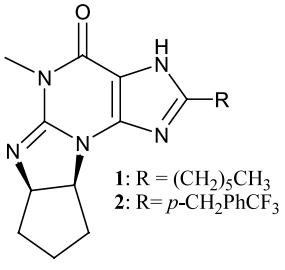
Abstract—Structure elucidation of several new pyrimidines containing a varying extent of hydrogen bonding allowed for determination of the course of chemical reactions towards the preparation of novel substituted pyrimidines.

Guanines, such as Sch 59498 (**1**) and 51866 (**2**) are potent Phosphodiesterase (PDE) Inhibitors.[1,2] In order to accommodate various substituents (R) in the imidazole portion of guanines efficiently a synthesis of common advanced tricyclic pyrimidines intermediate **8** was desirable. A stockpiling of such intermediate can allow for an expedited large scale deliveries of PDE inhibitors of clinical interest. This approach can significantly reduce the development period of a drug candidate leading to quick availability of a new drug at a reasonable cost. Although medicinal chemists use such approach routinely to synthesize various target compounds, a similar approach for development purposes is not well documented. We report here the challenges encountered during the preparation and structure elucidation of novel intermediates towards the attempted preparation of the tricyclic pyrimidines, and a resolution of these challenges.



1: R = $(CH_2)_5CH_3$
2: R= *p*-CH_2PhCF_3

Readily prepared[3] pyrimidine **3** was an attractive starting material for the preparation of the advanced tricyclic common intermediate **8** via the synthesis of unknown 2-chloro pyrimidine **4** as proposed in Scheme 1. Chlorination of **3** with $POCl_3$ resulted in a new compound in high (80%) yield with a mp of >275°C. Analytical data (NMR, elemental composition) of this product appeared to be in agreement with the structure **4**. Coupling of the resultant chloropyrimidine with (1*R*,2*R*)-2-aminocyclopentanol **5**[4,5] in *N*-methylpyrrolidinone (NMP) progressed in unoptimized 75% isolated yield to a new optically active compound, the mass spectrum and NMR of which appeared in agreement with structure **6**. Treatment of this compound with thionylchloride was quantitative to an optically active compound whose analytical data again appeared in agreement with the HCl salt of **7**, although the proton splitting pattern for the *cis* five-membered ring junction protons was unusual. In view of a lack of precedent for similar tricyclic ring system coupled with the fact that HCl could not be removed from this compound with treatment with aq. $NaHCO_3$, it was hypothesized, with some reservations, that the splitting pattern may be due to some peculiarities associated with the tricyclic system present in **7**. In view of the known base instability of the guanidine moiety of some PDE inhibitors,[9] a treatment with stronger base to remove HCl was deemed risky. Nitration of this compound was again high yielding (90%) and it resulted in a compound with proton NMR signals and elemental analysis in apparent agreement with **8**·HCl, with the unique ring junction splitting pattern intact.

As shown in Scheme 1, the nitro group was reduced to amine and this compound was coupled without isolation with *p*-trifluoromethyl phenylacetylchloride resulting in a good isolated yield (85%) of a new compound tentatively assigned structure **10**. Again all data except the ring junction proton coupling appeared in agree-

* Corresponding author.

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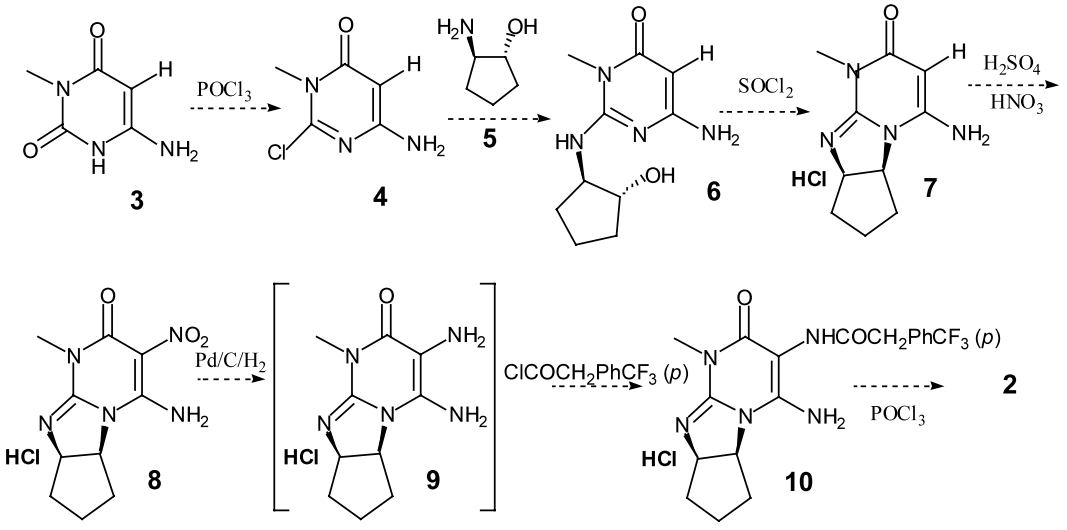
ment with HCl salt of **10**, however chromatographically (TLC) this compound was different from **10** prepared via alternate procedures,[6] the first known compound in this series. Finally it failed to cyclize to the PDE inhibitor **2**. This finding coupled with the unique proton NMR pattern, and inability to remove HCl from proposed compounds **7**, **8** and **10** prompted us to scrutinize the real outcome of this route.

For structure elucidation via NMR techniques, it was clear that compounds **3**, **4**, **6** or **7** would be of limited utility due to a lack of sufficient differentiating protons and carbons in them. Hence it was decided to use the advanced intermediates from the nitration reaction, and the coupled product of *p*-trifluoromethyl phenylacetylchloride reaction for this purpose. Proton NMR spectrum of the product obtained from the nitration reaction indicated the presence of resonances (δ, ppm) at 1.6–2.4 (CH_2), 3.47 (s, CH_3), 4.40 (br, CH) and 4.70 (br, CH). In the down field region NH and NH_2 protons were broad at δ 7.80, 8.65, 9.35 and 10.0. ^{13}C NMR (δ, ppm) showed resonances at 19.4 (CH_2), 32.6, 32.7, (2×CH_2), 27.6 (CH_3), 61.3 (CHNH), 65.9 (CHCl), and quaternary carbons at 108.5, 147.6, 153.6, and 153.7. Based on this data it was assigned structure **14**. Hydrogen bonding as shown in Figure 1 explains the multiplicity for the amine protons.



Scheme 1. Proposed synthesis of pyrimidine **3** to tricyclic intermediate **8**.

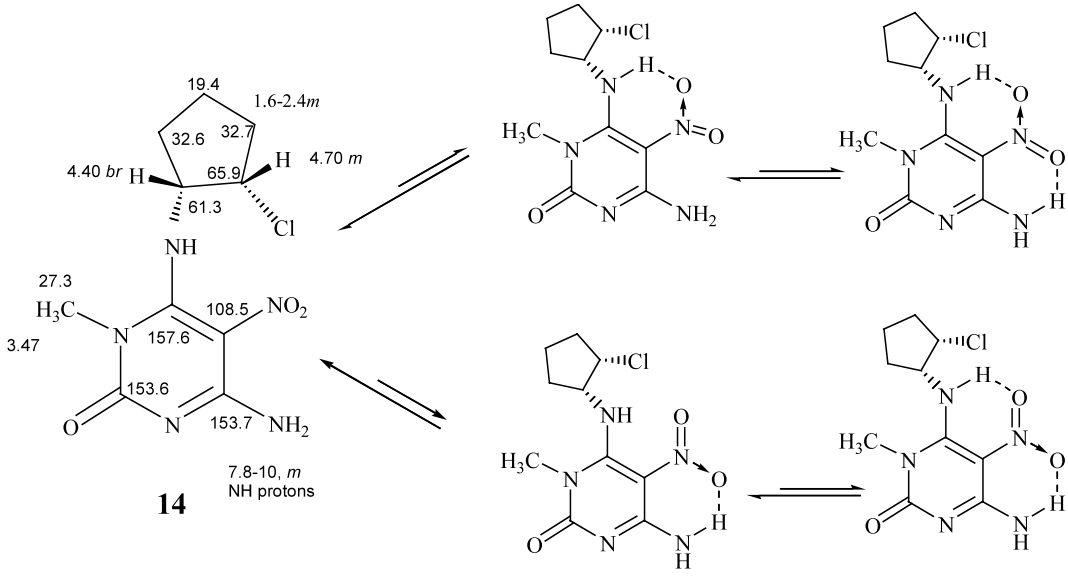


Figure 1. NMR data and structure for the nitration product.

Similarly, based on ^{1}H, and ^{13}C NMR of the product obtained after the coupling with *p*-trifluoromethylphenyl acetylchloride the compound was assigned structure **16**. The chemical shits data for **16** obtained via SINEPT and 1D-NOE is depicted in Figure 2.

From these structure assignments, the synthetic scheme was been revised (Scheme 2) to explain the actual chemical course endured during the above synthesis.

The above work has resulted in the following interesting findings:[6] (i) A literature search[7] indicated an alternate multi-step synthesis of 4-chloropyrimidine **11** where the melting point is much different from the one reported via $POCl_3$ reaction of this paper. This may be due to the fact that the two preparations result in different polymorphic forms of this compound. In fact, a repeated crystallization of the $POCl_3$ chlorination product from boiling water did result in the isolation of a solid with a mp of 224–226°C (decomp.). (ii) During the thionyl chloride reaction, a complete inversion of chirality at the carbon bearing hydroxyl group was observed (Scheme 3), a result inconsistent with involvement of protonated aziridine **18** via the anticipated chlorosulfinate intermediate **17**. Involvement of the aziridinium intermediate would lead to **19**, the *trans* amine and chlorine orientation with an overall retention of chirality at the carbon center. It is likely that HCl generated during the reaction of **12** with $SOCl_2$

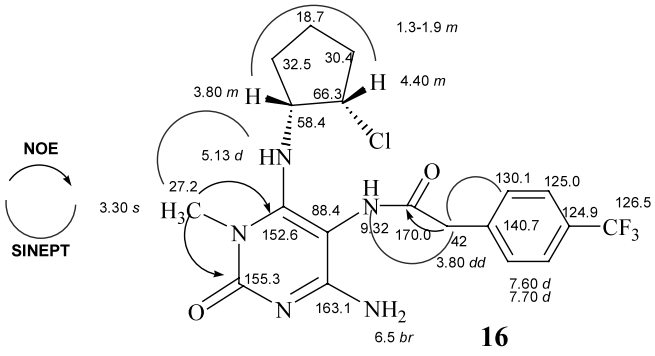
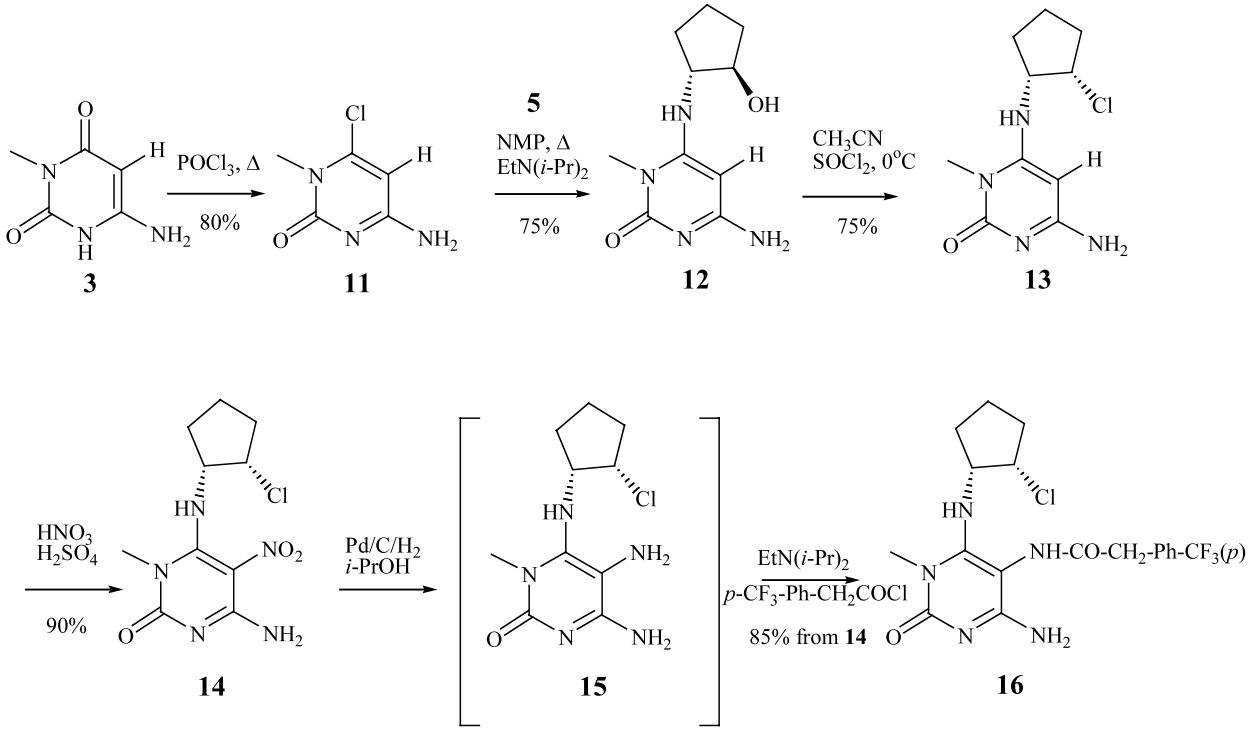
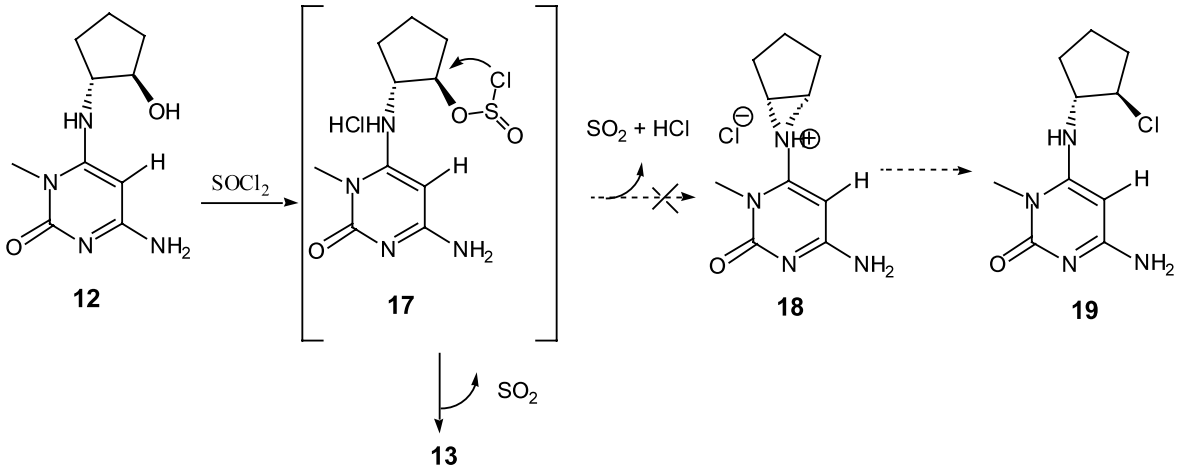


Figure 2. NMR data and structure for the product of coupling with *p*-trifluoromethylphenyl acetylchloride.



Scheme 2. Revised chemical course based on structure elucidation.



Scheme 3. Formation of *cis*-chloro amine.

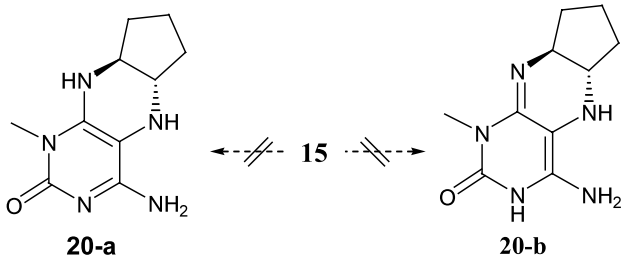


Figure 3. Intramolecular cyclization of diamine **15**: possible structures.

protonated the amine rendering it non-nucleophilic for the aziridine formation. (iii) Although the 5-amino groups of pyrimidines are known to be nucleophilic, in this instance the intramolecular displacement of chlorine to a *trans* six-membered tricyclic intermediate **20** (Fig. 3) did not take place.[6]

In summary, starting from the formation of 4-chloropyrimidine a series of chemical reactions resulted in novel pyrimidines. The structures of novel compounds, which involved different degrees of hydrogen bonding, were elucidated by NMR spectroscopy. Structure determination was instrumental in establishing the course of this unusual chemistry. These observations are being used for the development of alternate synthetic routes, involving activation of the 2 position of pyrimidines, for the preparation various guanine PDE inhibitors including **2**. These findings will be reported in future articles.[8]

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6. NMR work on **14** and **16** implies that the lack of reaction is not due to the existence of any ring strained in **15**. In addition, during the reduction of the nitro group to amine, no appreciable dehalogenation resulted.
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