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A novel synthesis of guanine PDE inhibitors via tricyclic imidazopyrimidines

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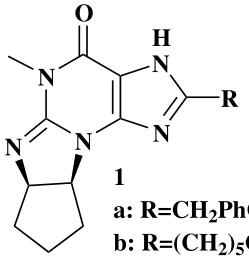
Abstract—A new method for the preparation of developmental tetracyclic guanine PDE inhibitors via a common tricyclic pyrimidine intermediate is described.

Guanines, such as 51866 (**1a**) and Sch 59498 (**1b**) are potent phosphodiesterase (PDE) inhibitors.[1,2] In order to accommodate various substituents (R) in the imidazole portion of guanines efficiently, a large scale synthesis of common advanced intermediates such as tricyclic pyrimidines **8** or **9** was desirable.[3] In our last publication[3] we reported the challenges encountered during the preparation and structure elucidation of novel intermediates towards the attempted preparation of the tricyclic pyrimidines such as **9**, and a resolution of these challenges via the use of NMR. Here we report an alternative chemistry for the preparation of the tricyclic pyrimidine intermediate **9** and its conversion to the above PDE inhibitors.



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a: R=CH_2PhCF_3 (*p*)

b: R=$(CH_2)_5CH_3$

As reported, initially readily prepared[4] pyrimidine **3** was an attractive starting material for the preparation of the advanced tricyclic common intermediate via the synthesis of previously unknown 2-chloro pyrimidine **2c** (Scheme 1). However, as it was eventually proven, the chlorination of **3** with $POCl_3$ resulted in the formation of 4-chloropyrimidine **4**. Alternately, the preparations of methoxy pyrimidine **2a**, and thiomethyl pyrimidine **2b** are known from the corresponding ureas **5a**, and **5b**, respectively.[1,2,5] It was conceivable that either of these 2-substituents of pyrimidines **2a** or **2b** was potentially a leaving group and hence they could provide an alternate to the 2-cholorpyrimidine **2c** for coupling with amino alcohol **6**[6] towards the preparation of **9**. Thus, both pyrimidines **2a**, and **2b** were prepared and were investigated for this coupling. The preparation of **2b** was higher yielding compared to the preparation of **2a**. Numerous attempts to directly displace either the methoxy group or the thiomethyl group by heating it with **6** in a number of solvents led to poor conversion to **7**. Compound **2a** appeared unstable to the reaction conditions whereas **2b** was stable. Attempts were made to oxidize the sulfide **2b** to its sulfoxide as the latter is an activated leaving group, and the byproduct of this upon coupling with **6** would be less objectionable compared to its sulfide precursor. This oxidation (H_2O_2 w/wo CH_3COOH, Oxone, CAN, $NaBrO_3/Al_2O_3$, etc.) led to a limited success. During the course of this work it was recognized that alternate means of activating the leaving group may allow for a better reaction of **6** with the activated pyrimidine allowing for an improved preparation of **9** (Scheme 2).

To this end two approaches that were eventually successful[7] are depicted in Scheme 2. Nitrososation and nitration of **2b** allowed for the formation of the corresponding nitroso ($n=1$), **10a** and nitro ($n=2$) compound **10b** in 35 and 80%, unoptimized isolated yields, respectively. Not only the formation of **10a** was low yielding, but its reaction with **6** was also poor. For example, when heated to 110°C with **6** and $EtN(i\text{-}Pr)_2$ in NMP, **10a** decomposed, whereas in refluxing CH_3CN it reacted with **6** to produce the corresponding coupled compound in only 35% crude yield. On the other hand, **10b** was stable to the high temperature needed for its

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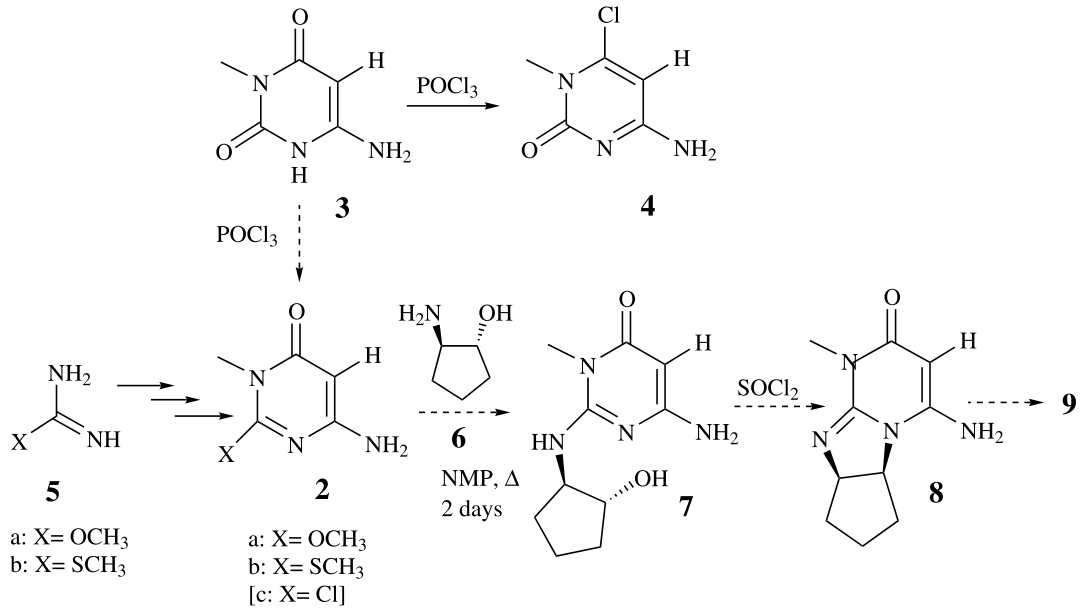
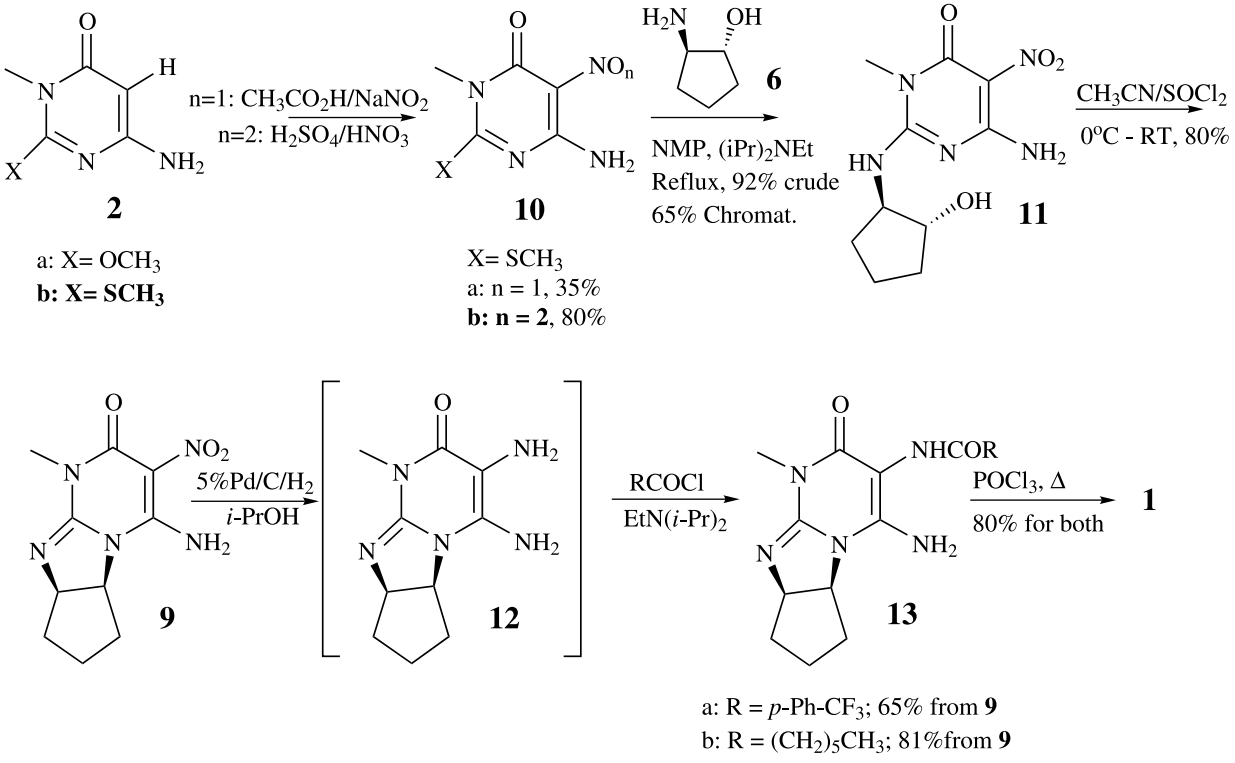


Scheme 1. Proposed synthesis of tricyclic pyrimidine **9**.



Scheme 2. Preparation of tricyclic pyrimidine **9** via activation of pyrimidine.

coupling with **6**. This made compound **10b** the intermediate of choice for the rest of the synthesis. Reaction of amino alcohol **6** with **10b** showed that the displacement of SMe group was cleaner for the nitro compound **10b** compared to the nitroso compound **10a**. Although the crude compound (obtained in 92% yield) could have been suitable for the further use, for investigational purposes it was decided to purify this compound to ensure a complete removal of NMP and **6**. As anticipated, the five-membered intramolecular cyclization of **11** to form the *cis* bridged tricyclic **9** was very facile and afforded good yields (80%) of isolated **9**. Compound **9** is a solid stable intermediate that can be stored under ambient conditions for months, an extremely desirable quality for preparation on scale.

Recently we have reported[8] that under basic aqueous conditions the guanidine moiety in the strained gua-

nines can hydrolyze the pyrimidine portion of guanine to generate substituted imidazoles. With this in view, exposure of compound **9** and subsequent intermediates to the aqueous basic conditions was minimized. The reduction of **9** to diamine **12** progresses well under standard hydrogenation conditions (60 *psi* H_2, 50% water wet 5% Pd/C, rt, overnight). Compound **12** without isolation, was reacted with appropriate acid chlorides in the presence of Hunigh base as an acid scavenger to form stable, isolable, solids **13a** and **13b** in unoptimized 65 and 80% yields, respectively.[9] Cyclization of **13** to the corresponding PDE inhibitors proved difficult under a variety of conditions (toluene, pTSA, reflux, solvent/$SOCl_2$ or oxalyl chloride) especially in view of the fact that it is an intramolecular reaction and it forms a five membered ring. This may be due to conformational rigidity imparted by the preexisting three rings in **13**. However, when **13** was refluxed in neat $POCl_3$, it was transformed to the target compounds in good (80% for both **1a**, and **1b**) isolated yield.[10]

In summary, a new synthetic strategy for the preparation of the tetracyclic guanine PDE inhibitors from an advanced tricyclic pyrimidine intermediate has been developed. This strategy bypasses recently reported regio chemistry issues with the common intermediate approach.

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7. Nitrosation as well as nitration of **2a** were both poor yielding reactions leading to a mixture of products. After partial purification, when these compounds were reacted with **6**, they led to a complex mixture of products. For these reasons the methoxy group was deemed less desirable than the thiomethyl group, and hence it is not described in this manuscript.
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9. Preliminary work suggests that *p*-CF_3-Ph-CH_2COCl is more susceptible to hydrolysis leading to a lower yield compared to $CH_3(CH_2)_5COCl$. 50% Water Wet 5% Pd/C used for hydrogenation reaction was the source of water in reaction medium.
10. Here, prior to isolation of the products, a carefully temperature (0–20°C) and pH (0–10) controlled neutralization of residual $POCl_3$ was preformed to prevent hydrolysis of the products (Ref. 7).