

# Synthesis of Novel Imidazo[1,2-*a*]pyridines with Potent Activity against Herpesviruses

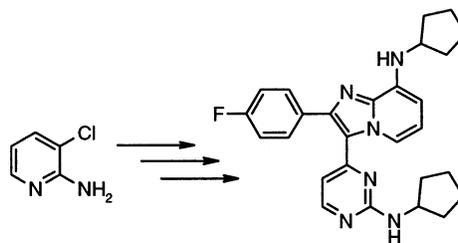
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## ABSTRACT



Synthesis of a novel imidazopyridine with potent activity against herpes simplex viruses is presented. Several synthetic approaches that describe the introduction of a C-3 pyrimidine substituent on the imidazopyridine core via construction of the pyrimidine or Stille coupling are outlined. Methodology for efficient installation of C-8 amine substituents was developed. The outlined strategies provide a high-yielding, scalable route that is amenable to rapid analogue synthesis.

Herpesviruses are a large family of viruses that infect humans.<sup>1</sup> Herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2) are highly prevalent<sup>2</sup> and cause cold sores and genital infections, respectively. While current drugs (acyclovir and valacyclovir) are efficacious,<sup>3</sup> there is considerable interest in identifying better treatments.<sup>4</sup> We recently identified a pyrazolo[1,5-*a*]pyridine scaffold **1** that showed promising antiherpes activity.<sup>5</sup> This discovery

prompted us to investigate the synthesis of related heterocyclic scaffolds such as the imidazo[1,2-*a*]pyridine **2** shown in Figure 1.<sup>6</sup> The general imidazopyridine scaffold has been popular in medicinal chemistry, and the marketed drug Ambien contains an imidazopyridine core.<sup>7</sup> However, imidazopyridines such as **2** have not been described. To conduct a detailed structure–activity relationship (SAR) study, we wanted an efficient route that could also be used to access a variety of analogues with different substituents at the C-8 position and allow for alterations of the pyrimidine moiety.

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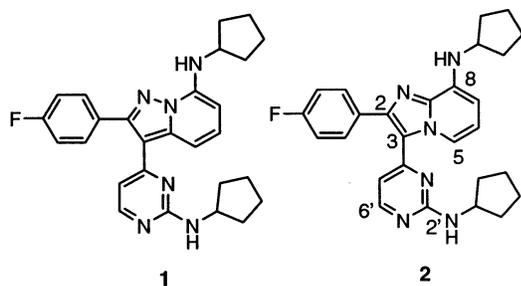
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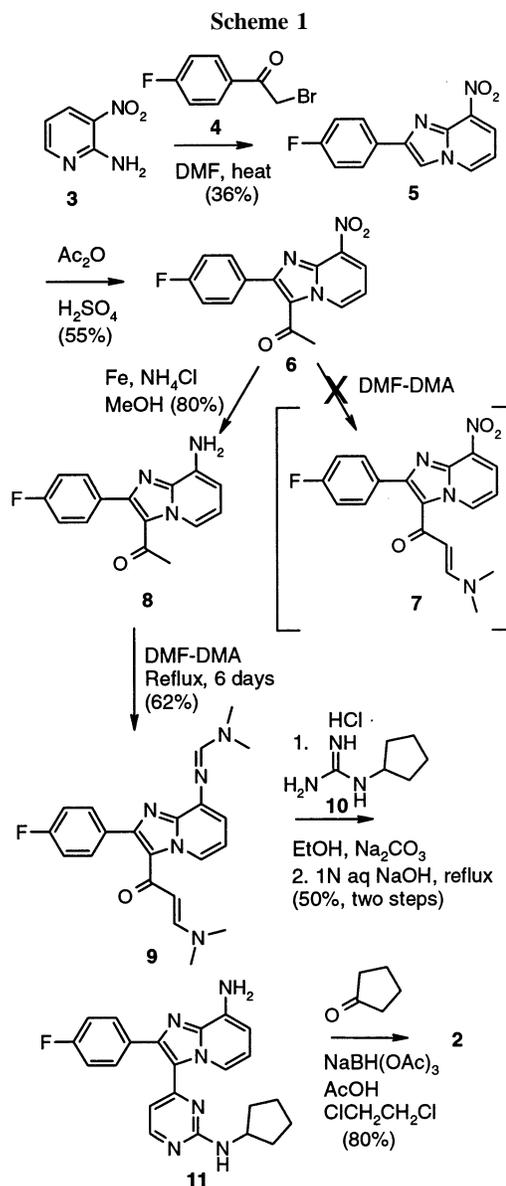


**Figure 1.** Pyrazolopyridine (**1**) with antihypertensive activity and identically substituted imidazopyridine (**2**).

We envisioned several approaches for the synthesis of **2** starting from either 2-(4-fluorophenyl)-8-nitroimidazopyridine **5** or 2-(4-fluorophenyl)-8-chloroimidazopyridine **13**. In each case, the 3-pyrimidinyl moiety could be built up onto the existing imidazopyridine core or installed via palladium coupling methodology.

We initially chose to investigate the synthesis of **2** from 2-(4-fluorophenyl)-8-nitroimidazopyridine **5** by building up the 3-pyrimidine moiety followed by installation of the desired amine substituent at C-8. Our initial route was based on the belief that starting from the 8-nitroimidazopyridine would avoid potential problems with a halogen to amino substitution at C-8. For the synthesis of **5**, we condensed 2-amino-3-nitropyridine **3** with 2-bromoacetophenone **4** in DMF. The resulting modest yield of product **5** is likely attributed to the reduced nucleophilicity of the pyridine nitrogen due to electron-withdrawing effects of the 3-nitro group. Unsuccessful attempts were made to improve the yield of **5** by varying solvents (e.g., *i*-PrOH, DME, etc.) or addition of base to the reaction mixtures (e.g., Na<sub>2</sub>CO<sub>3</sub>). Acetylation of **5** with Ac<sub>2</sub>O and catalytic H<sub>2</sub>SO<sub>4</sub> at reflux for 30 min gave the 3-acetyl product **6**. The acetyl derivative **6** could not be converted to the corresponding vinylogous amide **7** upon treatment with dimethylformamide dimethylacetal (DMF–DMA) at reflux. Decomposition of **6** upon treatment with DMF–DMA at elevated temperature is presumably the result of a nucleophilic attack at the C-5 position and subsequent Dimroth-type ring opening of the imidazopyridine system.<sup>8</sup> Use of the more reactive dimethylformamide-di-*tert*-butylacetal also failed to give the desired product **7**. It was reasoned that this problem could be avoided by increasing the electron density of the imidazopyridine system.

Selective reduction of the 8-nitro compound **6** with iron and ammonium chloride<sup>9</sup> gave **8**. Subsequent treatment of **8** with DMF–DMA gave the amidine-protected vinylogous amide **9** in 62% yield.<sup>10</sup> Compound **9** was treated with



cyclopentylguanidine **10**<sup>11</sup> in ethanol, followed by deprotection of the C-8 amine under basic conditions, to give intermediate **11**. Reductive amination with NaBH(OAc)<sub>3</sub> and cyclopentanone in the presence of AcOH in dichloroethane gave the desired product **2**.

During this synthesis, it became clear that the 8-nitro group was not a satisfactory precursor for the desired 8-cyclopentylamine analogue. As such, we became interested in alternative approaches that did not carry a nitro/amino group through the synthesis.

A desirable alternative was to utilize either a 8-chloroimidazopyridine or a 8-bromoimidazopyridine as a starting point for our syntheses. We chose the 8-chloroimidazopyridine derivative **13** as our starting point since it could be easily prepared from 2-amino-3-chloropyridine **12**.<sup>12</sup> Condensation

(8) Jacquier, R.; Lopez, H.; Maury, G. *J. Heterocycl. Chem.* **1973**, *10*, 755.

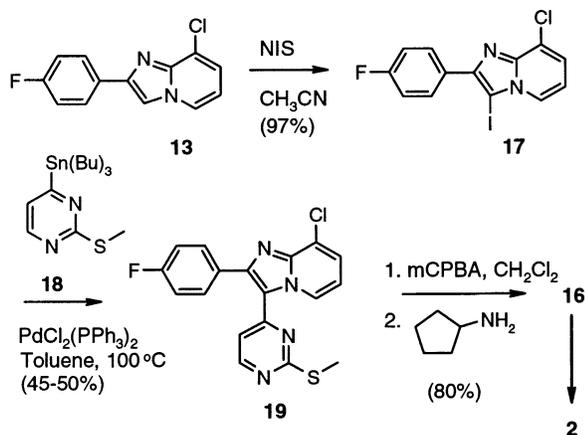
(9) Conditions similar to those described in: Ramadas, K.; Srinivasan, N. *Synth. Commun.* **1992**, *22*, 3189.

(10) Use of the more reactive dimethylformamide-di-*tert*-butylacetal in DMF shortened the reaction time to 36 h but gave a similar yield of the desired product (56%).

(11) Cyclopentylguanidine was made by a modification of a method described in: Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M. *Can. J. Chem.* **1958**, *36*, 1541.



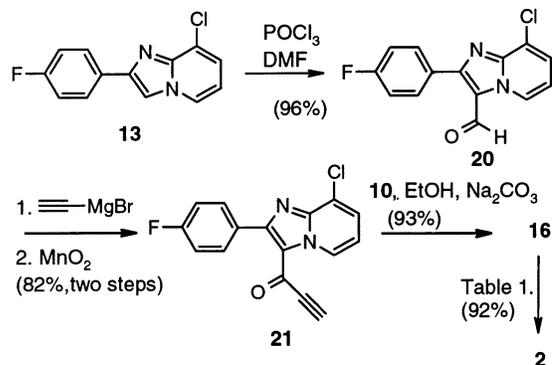
Scheme 3



$\text{MnO}_2$ . Other oxidation methods (e.g., Swern and Dess–Martin oxidations) gave lower yields. Treatment of the alkynyl ketone **21** with guanidine **10**, followed by amination (Table 1), gave an excellent yield of **2**.

In summary, by utilizing the synthetic route outlined in Scheme 4, we achieved our goal of designing a high-yielding (60% yield from **12**), scalable synthesis of **2**. In addition, the described synthesis allows for rapid preparation of diverse analogues at the C-8 and 2'-pyrimidine positions. Furthermore, the route in Scheme 4 allows for access to 6'-substituted pyrimidine analogues (via substituted acetylenes)

Scheme 4



not easily obtainable via the synthetic routes described in Schemes 1–3.

Compound **2** showed antiherpetic activity similar to that of acyclovir in our assays. Detailed SAR and antiviral activity will be published elsewhere.

**Supporting Information Available:** Experimental details and analytical data for all products described in Schemes 1 and 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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