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

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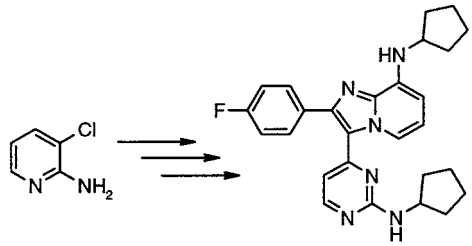
ABSTRACT



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.[1] Herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2) are highly prevalent[2] and cause cold sores and genital infections, respectively. While current drugs (acyclovir and valacyclovir) are efficacious,[3] there is considerable interest in identifying better treatments.[4] We recently identified a pyrazolo[1,5-*a*]pyridine scaffold **1** that showed promising antiherpes activity.[5] 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.[6] The general imidazopyridine scaffold has been popular in medicinal chemistry, and the marketed drug Ambien contains an imidazopyridine core.[7] 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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(3) (a) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716. (b) Elion, G. B. *J. Med. Virol. Suppl.* **1993**, *1*, 2. (c) Beutner, K. R. *Antiviral Res.* **1995**, *28*, 281.

(4) (a) Crute, J. J.; Grygon, C. A.; Hargrave, K. D.; Simoneau, B.; Faucher, A.-M.; Bolger, G.; Kibler, P.; Liuzzi, M.; Cordingley, M. G. *Nature Medicine* **2002**, *8*, 386. (b) Kleymann, G.; Fischer, R.; Betz, U. A. K.; Hendrix, M.; Bender, W.; Schneider, U.; Handke, G.; Eckenberg, P.; Hewlett, G.; Pevzner, V.; Baumeister, J.; Weber, O.; Henninger, K.; Keldenich, J.; Jensen, A.; Kolb, J.; Bach, U.; Popp, A.; Maben, J.; Frappa, I.; Haebich, D.; Lockhoff, O.; Rubsamen-Waigmann, H. *Nature Medicine* **2002**, 8, 392.

(5) (a) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. A.; Jung, D. K.; Sexton, C. J.; Boyd, F. L.; Peel, M. R. *Tetrahedron* **2003**, in press. (b) Boyd, F. L.; Chamberlain, S. D.; Cheung, M.; Gudmundsson, K. S.; Harris, P. A.; Johns, B. A.; Jung, D. K.; Peel, M. R.; Stanford, J. B.; Sexton, C. J. WO 0248148, **2002**.

(6) For publications describing different imidazopyridines with antiherpetic activity, see: (a) Chaouni-Bendallah, A.; Galtier, C.; Allouchi, H.; Kherbeche, A.; Chavignon, O.; Teulade, J.-C. et al. *Chem. Pharm. Bull.* **2001**, *49*, 1631. (b) Mavel, S.; Renou, J. L.; Galtier, C.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Arzneimittel-Forschung* **2001**, *51*, 304. (c) Lhassani, M.; Chavignon, O.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Snoeck, R.; Andrei, G.; Balazarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271.

(7) Langtry, H. D.; Benfield, P. *Drugs* **1990**, *40*, 291.

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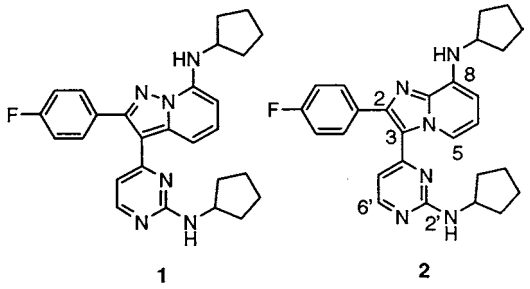


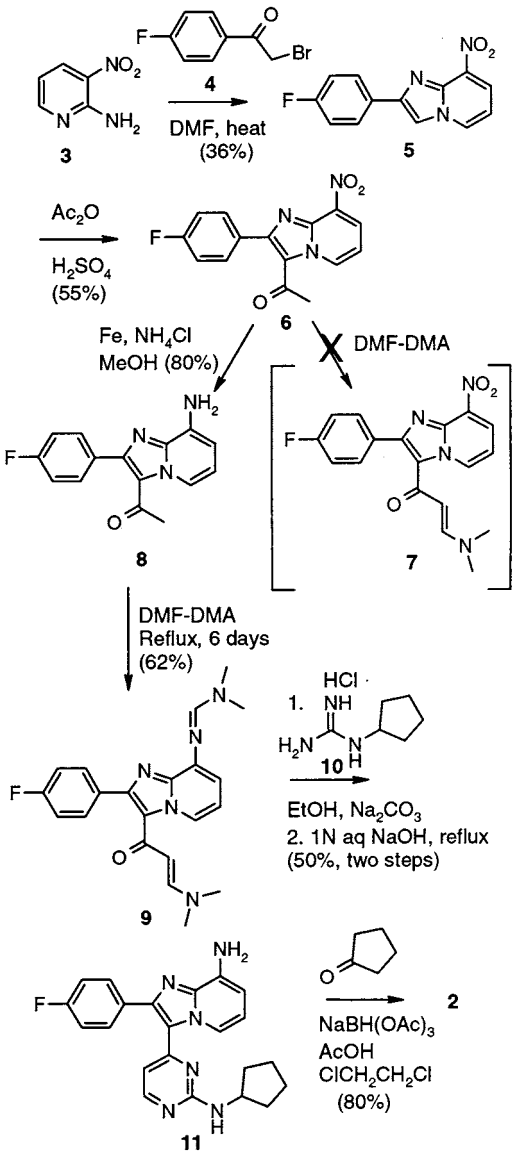
Figure 1. Pyrazolopyridine (**1**) with antiherpetic activity and identically substituted imidazopyridine (**2**).

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 subtituent 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_2CO_3). Acetylation of **5** with Ac_2O and catalytic H_2SO_4 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.[8] 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[9] gave **8**. Subsequent treatment of **8** with DMF−DMA gave the amidine-protected vinylogous amide **9** in 62% yield.[10] Compound **9** was treated with

Scheme 1



cyclopentylguanidine **10**[11] in ethanol, followed by deprotection of the C-8 amine under basic conditions, to give intermediate **11**. Reductive amination with $NaBH(OAc)_3$ 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**.[12] Condensation

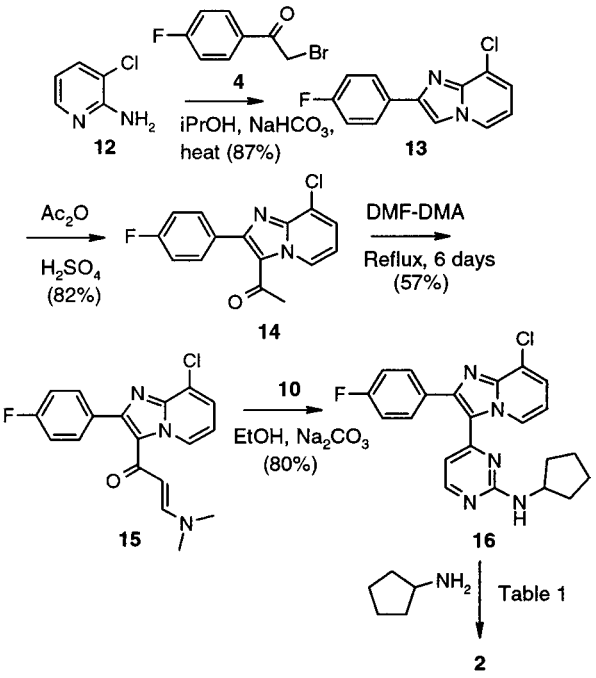
(8) Jacquier, R.; Lopez, H.; Maury, G. *J. Heterocycl. Chem.* **1973**, *10*, 755.

(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 2



of 2-amino-3-chloropyridine with 2-bromoacetophenone **4** gave **13**, which was subjected to acetylation conditions as described above to give **14** in excellent yield. Treatment of **14** with DMF−DMA gave the desired vinylogous amide **15**, but in only a moderate 57% yield (similar to the yield previously observed for the conversion of **8** to **9**). Condensation of **15** with **10** gave the 8-chloroimidazopyridine **16**. Initial attempts at thermally displacing the 8-chloro substituent with cyclopentylamine failed, but the 8-position could be coupled with cyclopentylamine using standard Buchwald amination conditions ($Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3).[13] These conditions gave a modest 55% yield of the desired substituted imidazopyridine **2** along with a significant quantity of undesired dechlorinated imidazopyridine byproduct. The amination conditions were optimized as outlined in Table 1.

Attempts to increase the yield of **2** by varying the palladium catalyst (entry 2), base (entry 3) or by running the reaction in neat cyclopentylamine (entry 4) failed. By replacing the BINAP ligand with P(*t*-Bu)$_3$ or more conveniently the air-stable (*o*-biphenyl)P(*t*-Bu)$_2$ ligand,[14] we were, however, able to improve the yields to >70% (entry 5 and 6). Under these conditions we still observed formation of small quantities of the dechlorinated imidazopyridine. Finally, by using neat cyclopentylamine instead of toluene, we were able to obtain >90% of the desired product and did not observe formation of the dechlorinated byproduct.

(12) We prepared 2-amino-3-chloropyridine by treating 2,3-dichloropyridine with aqueous ammonia at 190 °C for 48 h in a steel bomb. Also see: Trapani, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934.

(13) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019. (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

Table 1. Optimization of Buchwald Amination of **16**

entry	catalyst/ligand[a]	base	solvent (*T*, °C)	% yield[b]
1	$Pd(OAc)_2$/BINAP	Cs_2CO_3	toluene (100)	55
2	$Pd(dba)_2$/BINAP	Cs_2CO_3	toluene (100)	57
3	$Pd(OAc)_2$/BINAP	tBuOK	toluene (100)	49
4	$Pd(OAc)_2$/BINAP	Cs_2CO_3	amine[c] (100)	53
5	$Pd(dba)_2$/P(*t*-Bu)$_3$	Cs_2CO_3	toluene (80)	70
6	$Pd(OAc)_2$/BP(*t*-Bu)$_2$	tBuOK	toluene (80)	75
7	$Pd(OAc)_2$/BP(*t*-Bu)$_2$	tBuOK	amine (80)	92
8	$Pd(dba)_2$/ BP(*t*-Bu)$_2$	tBuOK	amine (80)	90

[a] Pd catalyst (0.1 equiv) was used for all entries. Ratio of Pd to ligand was 1:1.5−2 except for entry 5, where the ratio was 1:1. Reactions were run overnight at the indicated temperature. BP(*t*-Bu)$_2$ is (*o*-biphenyl)P(*t*-Bu)$_2$. [b] Yields are isolated yields after silica column purification. [c] Reactions were run in neat amine at the indicated temperature. For all entries in Table 1, the amine is cyclopentylamine. A variety of other primary and secondary amines also couple under the conditions outlined.

While Scheme 2 gives **2** in 30% overall yield from **12**, we felt that we could improve the efficiency of the synthesis by avoiding the low-yielding formation of the vinylogous amide **15**.

As such, we examined Stille methodology to couple the pyrimidine directly to the 3-iodoimidazopyridine **17**, thereby avoiding construction of the pyrimidine.[15] Compound **17** was formed in nearly quantitative yield by treating **13** with *N*-iodosuccinimide. The required stannane **18** was synthesized in two steps as described in the literature.[16] Coupling of **17** and **18** afforded only a modest 50% yield of **19**.[17] Oxidation of **19** with *m*-CPBA, followed by treatment with cyclopentylamine at elevated temperatures, gave **16**. The poor yield for the Stille coupling, the tedious synthesis of the coupling partner **18**, and the undesirable aspects of tin use made this route less appealing.

We then decided to investigate an alternative route for building the pyrimidine, avoiding the vinylogous amide. Looking at the mechanism by which vinylogous amides condense with guanidines to form pyrimidines, we reasoned that an alkynyl ketone could serve as a surrogate for the vinylogous amide.[18] Thus, formylation of **13** under Vilsmeier−Haack conditions gave an excellent yield of the remarkably stable aldehyde **20**. This aldehyde was treated with the commercially available ethynyl Grignard reagent at low temperatures to give the propargyl alcohol in excellent yield. This alcohol was easily oxidized to the ketone **21** using

(14) (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughenessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

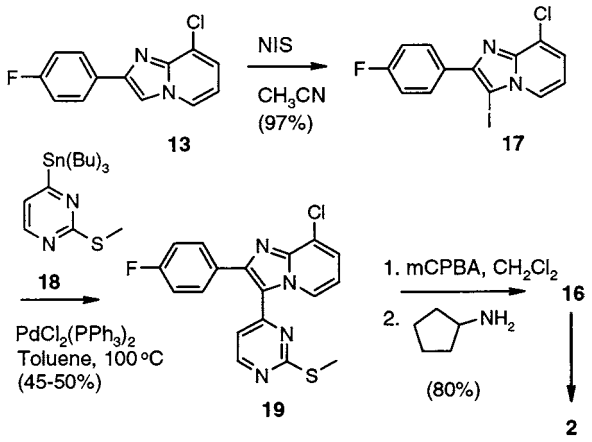
(15) For Suzuki-type cross-coupling of 3-iodoimidazopyridines, see: Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572.

(16) (a) Sandosham, J.; Undheim, K. *Tetrahedron* **1994**, *50*, 275. (b) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993.

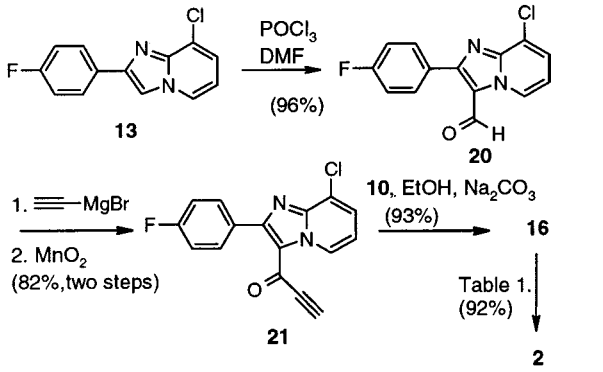
(17) Suzuki couplings of **17** with pyridylboronic acids gave 50−60% yield of the desired coupled product.

(18) A similar cyclization protocol appeared in the literature during the course of our work: (a) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 855. (b) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *Chem. Commun.* **1997**, 1757.

Scheme 3



Scheme 4



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) 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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