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A Concise and Selective Synthesis of Novel 5-Aryloxyimidazole NNRTIs

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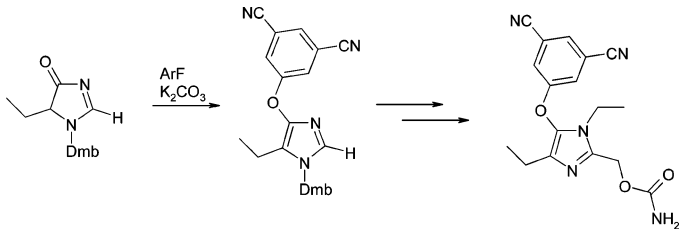
ABSTRACT



A concise and efficient route to the construction of a 5-aryloxyimidazole has been developed. The key step was the selective *O*-arylation of a 2,4-dimethoxybenzyl-protected imidazolone. The final compound is a potent inhibitor of HIV reverse transcriptase.

Reverse transcriptase (RT) is an essential enzyme in the infectious lifecycle of HIV and noncompetitive inhibition of this enzyme by nonnucleoside reverse transcriptase inhibitors (NNRTIs) has shown utility in the treatment of HIV. However, the established NNRTIs are particularly vulnerable to the development of viral resistance caused by amino acid mutations in RT that can retain viable enzymatic function. As a result, there is considerable interest in developing new, potent NNRTIs that exhibit less susceptibility to the clinically relevant RT mutations.[1]

Following our work in this area,[2] we have decided to report our successful exploits in the preparation of 5-aryloxy-substituted imidazole derivatives **1** (Figure 1). Interestingly, the *S*-linked imidazole analogues have themselves generated great interest in the anti-HIV arena, exemplified by capravirine, which exhibits a balanced potency profile against various clinically relevant RT mutations.[1] We reasoned that the corresponding *O*-linked imidazole derivatives **1** would retain the desirable mutant potency profile of compounds such as capravirine.

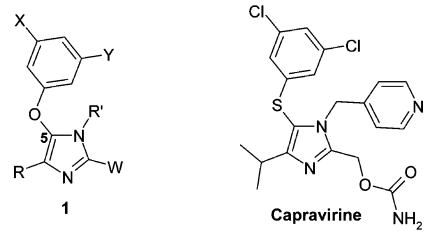


Figure 1. Imidazole NNRTIs.

At the outset we desired a facile and reliable method for the preparation of 5-aryloxyimidazoles, which would allow us to prepare a variety of related derivatives in this series.[3] Our strategy for their preparation involves the arylation of

(1) De Clercq, E. *Chem. Biodivers.* **2004**, *1*, 44.

(2) Edwards, P. J.; Jones, L. H.; Mowbray, C. E.; Stupple, P. A.; Tran, I. WO2004031156. Jones, L. H.; Mowbray, C. E.; Price, D. A.; Selby, M. D.; Stupple, P. A. WO2004029051. Barba, O.; Jones, L. H. WO2004029042. Jones, L. H.; Mowbray, C. E.; Price, D. A.; Selby, M. D.; Stupple, P. A. WO2002085860.

(3) Cu(I)-mediated phenol displacements of a 5-iodoimidazole (conditions which are successful when thiophenols are used in the preparation of *S*-linked imidazoles) were unsuccessful in our hands.

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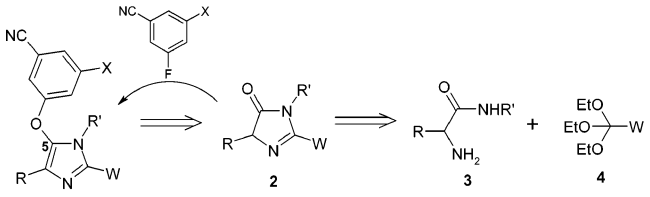
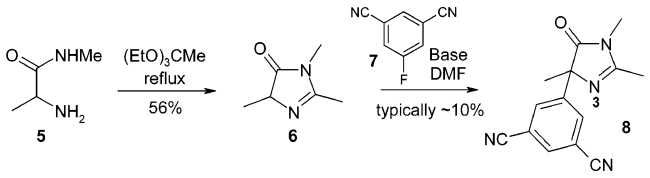
imidazolones such as **2** using electron-deficient aryl fluorides (Scheme 1). Imidazolones **2** can themselves be prepared via cyclization of amino amides **3** with a suitable ortho ester **4**.[4]

Scheme 1. Retrosynthesis



Our first attempt using this strategy on a model system gave an unexpected result (Scheme 2). Treatment of amino

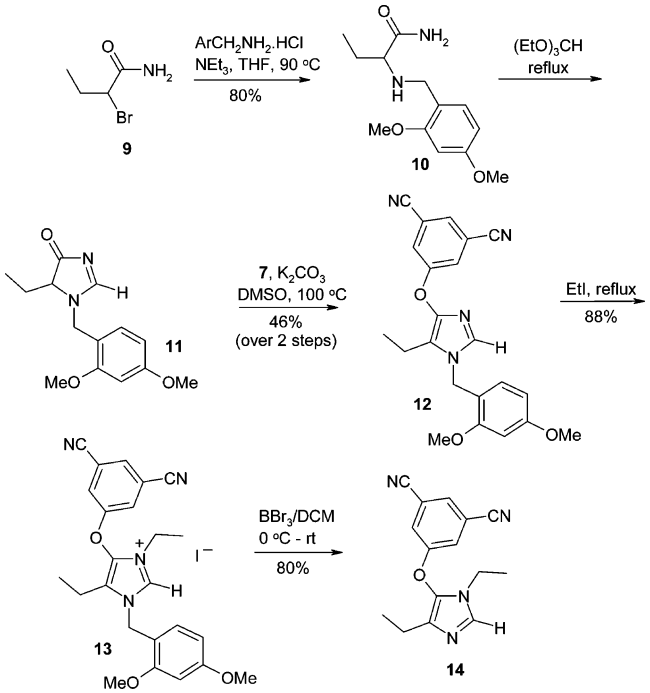
Scheme 2. Undesired *C*-Arylation of **6**



amide **5**[5] with triethyl orthoacetate provided the known imidazolone **6**.[6] However, subsequent treatment with commercially available 3,5-dicyanofluorobenzene **7** surprisingly gave a poor yield of *C*-arylated material **8** (proved by HMBC and IR; see the Supporting Information) and none of the desired adduct, despite trying various solvents and bases. Poor yields for this reaction may be a reflection of the instability of imidazolone **6** which slowly dimerizes when stored at room temperature.[6] We reasoned that introduction of a protecting group to N3 would not only force the arylation to the relatively less encumbered oxygen of the imidazolone, but it may also improve the stability of this reactive intermediate.

Following extensive examination of benzyl and 4-methoxybenzyl protecting groups,[7] we discovered that the 2,4-dimethoxybenzyl group was ideal for our purposes as it was resilient to the somewhat harsh conditions used for imidazolone formation, but which could be removed later in the synthesis. The synthesis of **14** (Scheme 3), a representative of this series, commenced with the known bromide **9**,[8] which was reacted with 2,4-dimethoxybenzylamine to provide amino amide **10**. Cyclization with triethyl orthoformate provided imidazolone **11**, which was used immediately in

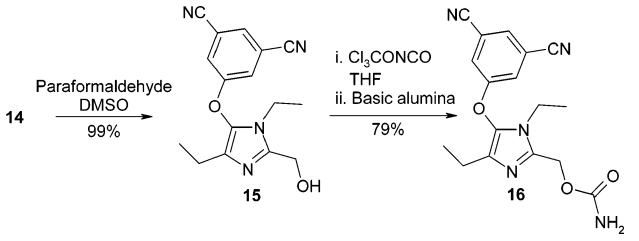
Scheme 3. Synthesis of 5-Aryloxyimidazole **14**



the next step. However, unlike **6**, **11** was actually stable when stored crude at room temperature for long periods (at least 2 months). Arylation of **11** using 3,5-dicyanofluorobenzene **7** proceeded regioselectively as we predicted to provide **12**, and none of the *C*-arylated material was detected. To aid deprotection and to provide the desired N1-Et isomer regioselectively, we performed the *N*-alkylation first. Indeed, we have shown that if imidazole **12** is deprotected first there is a preference for alkylation of the 5-aryloxy-NH-imidazole to proceed via the "undesired" nitrogen regioselectively (~3:1). Thus, treatment of **12** with EtI provided imidazolonium salt **13** and although the deprotection proved troublesome, it could be effected using BBr_3[9] to yield compound **14** in a respectable overall yield.

With **14** in hand, we next turned our attention to functionalization of the C1-position, which would allow us to prepare various derivatives from a late-stage intermediate. Reaction of **14** with paraformaldehyde proceeded smoothly to give the hydroxymethyl derivative **15** (Scheme 4). The hydroxy group now gives us a handle to prepare various analogues, which is ongoing work within our group and will

Scheme 4. Preparation of Carboxamide **16**



(4) For example: Maurer, F.; Hammann, I. DE 3136328.
(5) Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567.
(6) Maquestiau, A.; Van Haverbeke, Y.; Flammang-Barbieux, M.; Beaufays-Bar, F. *Bull. Soc. Chim. Belg.* **1976**, *85*, 573.
(7) These protecting groups could not be removed later in the synthesis despite using various deprotection conditions, including BBr_3, Pd−C/H_2, DDQ, CAN, and $AlCl_3$. We believed the more electron-rich 2,4-dimethoxybenzyl group could be deprotected more readily later in the synthesis.
(8) Yamazaki, H.; Harada, H.; Matsuzaki, K.; Yoshioka, K.; Takase, M.; Ohki, E *Chem. Pharm. Bull.* **1987**, *35*, 2243.

Table 1. Potencies against Wild-Type HIV Reverse Transcriptase[a]

compd	IC_{50}/nM
14	2100
15	476
16	103
capravirine	93

[a] Inhibition of wild-type RT with a poly(rA) ~300 template, (dT) 16 primer, and dTTP as substrate.

be reported elsewhere. Noteworthy from this work has been the facile preparation of **16** which posseses the carboxamide similar to capravirine and exhibits pleasing potency against the wild-type reverse transcriptase enzyme (Table 1).

Additionally, compounds **14**, **15**, and **16** possess IC_{50} values against the most clinically relevant mutation K103N that are within 10-fold of their wild-type potencies.

In conclusion, a concise and selective route to a novel and potent 5-aryloxy imidazole NNRTI was developed using new imidazolone chemistry. A detailed analysis of the biological activity of these derivatives will appear elsewhere.

Acknowledgment. We thank Chris Carr for preliminary investigations into 5-aryloxyimidazole preparation and Torren Peakman for HMBC experiments. We also thank Romu Corbau, Ian Burr, Alex Martin, and Amy Thomas for determining the potencies of these compounds.

Supporting Information Available: Representative procedures; spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Workup with 1 N NaOH aq significantly improves the yield of isolated product (compared to saturated $NaHCO_3$ solution), suggesting this reaction proceeds through a phenol intermediate. Indeed, we have on occasions been able to isolate intermediate phenols following anisole deprotection of similar substrates. The deprotection of **13** (and other similar substrates) could not be effected using TFA, concd HCl, $BuLi/O_2$, DDQ, potassium persulfate, $Pd-C/H_2$, $FeCl_3$, $AlCl_3$, or CAN.