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Synthesis of Novel Fluoropicolinate Herbicides by Cascade Cyclization of Fluoroalkyl Alkynylimines

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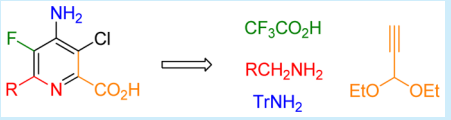
Supporting Information

ABSTRACT: The cascade cyclization of fluoroalkyl alkynylimines with primary amines has been modified to allow the synthesis of 4-amino-5-fluoropicolinates. Use of *N*-trityl and acetal protecting groups in the cyclization precursor led to 5-fluoropyridines that were easily deprotected to picolinaldehyde derivatives for further elaboration to structures of interest as potential herbicides. This method provided access to picolinic acids with alkyl or aryl substituents at the 6-position that were previously inaccessible via cross-coupling chemistry.



Picolinic acid herbicides have been an active area of commercial interest for decades. Broadleaf herbicides of this class function through an auxinic mode of action and are widely used in cereal and pasture applications. Examples of commercial picolinate herbicides include picloram[1] and aminopyralid[2] (Figure 1). More recently, new highly potent 6-arylpicolinate herbicides, including Arylex active[3] and DAS-534,[4] have been reported. These newer auxinic herbicides provide effective control of broadleaf weeds with extremely low use rates. The continued development of effective herbicidal products which maximize crop yields is necessary to support the growing world population and to counteract losses of arable land.[5]

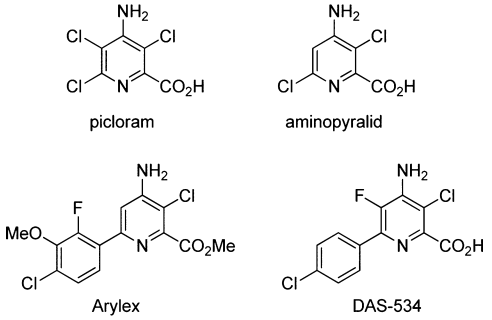
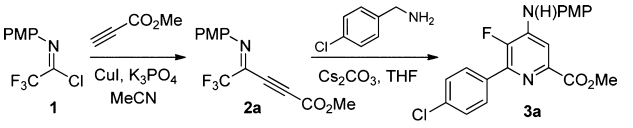


Figure 1. Picolinic acid auxinic herbicides.

Continued investigation of structure−activity relationships for the identification of new herbicides can be enabled by the development of new synthetic methods. In addition, route scoping for scale-up and synthesis of radiolabeled compounds often require the development of new synthetic methods. We were particularly interested in new strategies for the synthesis of 4-amino-3-chloro-5-fluoropicolinates with alkyl or aryl substituents at the 6-position because facile introduction of the 5-fluoro substituent is challenging. Previously, fluorination of aminopyralid[6] with F-TEDA, followed by cross-coupling reactions, has been employed to access synthetic targets.[7] This method has two major limitations. First, the electrophilic fluorination step suffers from marginal conversion and high reagent cost. Second, although many relatively simple aryl and heteroaryl boronates are commercially available, species with more complex substitution patterns are limited. As a result, far fewer pyridyl targets with aliphatic groups at the 6-position have been synthesized.

Attracted by a recent report of the synthesis of multiply substituted 5-fluoropyridines by the cascade cyclization of fluoroalkyl alkynylimines with primary amines,[8] we envisioned this method could provide access to new 5-fluoropicolinic acid herbicide targets if the resulting 4-NHAr substituent could be cleaved to an $-NH_2$ group (Scheme 1). Although most reported examples of this cascade cyclization employed *N*-phenyl imines, one example using a *N*-*p*-methoxyphenyl (PMP) imine was described. We proposed that oxidative deprotection of the resulting *N*-PMP group followed by pyridine ring chlorination could lead to new herbicidal analogs.

Scheme 1. Cascade Cyclization of Trifluoromethylalkynyl Imines



We first explored this strategy for the synthesis of DAS-534. Alkynylimine **2a** was prepared by Sonogashira coupling of **1** with methyl propiolate in 74% yield. Cyclization of **2a** with 4-chlorobenzylamine using Cs_2CO_3 in THF at 80 °C gave pyridine derivative **3a** in 40% isolated yield. Oxidative removal[9]

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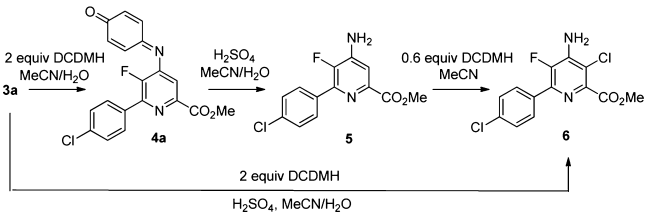
of the *N*-PMP group using $NaIO_4$ was unsuccessful. Fortunately, reaction of **3a** with 2 equiv of 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (DCDMH) in CH_3CN/H_2O gave the azaquinone, **4a**, in 79% isolated yield (Scheme 2).

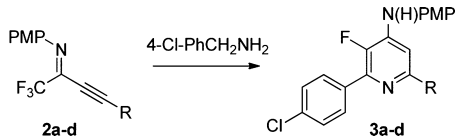
Scheme 2. Oxidative Deprotection−Chlorination Sequence



Hydrolysis of azaquinone **4a** with aqueous sulfuric acid gave the 4-aminopyridine **5** in 85% yield. Chlorination of the pyridine ring at the 3-position of **5** with 0.60 equiv of DCDMH gave **6** in 73% yield. Alternatively, **3a** can be directly converted to **6** in 38% yield by one-pot deprotection−chlorination using 2 equiv of DCDMH in CH_3CN/H_2O in the presence of H_2SO_4. Hydrolysis of **6** with NaOH in MeOH gave DAS-534 in 11% overall yield from **1**, thus demonstrating the successful application of the cascade cyclization sequence to the synthesis of picolinate herbicides.

Given the relatively low yield for cyclization of **2a** to **3a**, we explored the use of alkynylimine substituents that could be eventually converted to a carboxylic acid after cascade cyclization (Table 1). Cyclization of the *t*-Bu ester **2b** with 4-

Table 1. Effect of Alkynylimine Substituent on Cascade Cyclization Yield with 4-Chlorobenzylamine (Conditions: Cs_2CO_3, THF, 80 °C)

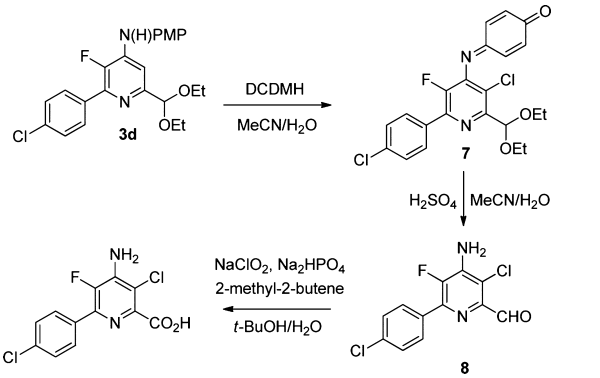


R	pyridine	yield (%)
CO_2Me	**3a**	40
CO_2tBu	**3b**	12
2-Furyl	**3c**	61
$CH(OEt)_2$	**3d**	81

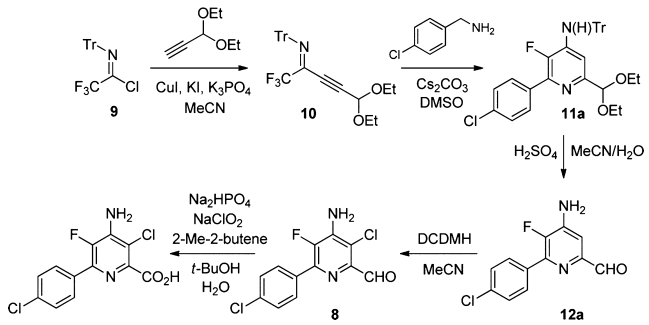
chlorobenzylamine occcurred in very low yield. The 2-furylalkynylimine **2c** underwent cyclization in higher yield, but attempts to convert the resulting 2-furyl substituent oxidatively to a carboxylic acid were unsuccessful. The acetal-protected alkynylimine **2d** cyclized efficiently in THF with 4-chlorobenzylamine to give **3d** in 81% yield (Scheme 3). Removal of the *N*-PMP group was performed by a two-step procedure. Reaction of **3d** with DCDMH gave the 3-chloroazaquinone derivative **7** in 30% yield. Subsequent hydrolysis of the azaquinone and acetal groups with 1 M H_2SO_4 gave the 4-amino picolinaldehyde **8** in 68% yield. Pinnick oxidation of **8** gave DAS-534 in 72% yield.

Despite the improved cyclization yield obtained with the acetal-protected alkynylimine, the low yielding oxidative removal of the *N*-PMP group limited the utility of this method. Use of an *N*-trityl protecting group was found to allow deprotection in much higher yield than *N*-PMP (Scheme 4). *N*-Trityl alkynylimine **9** was prepared analogously to **2d** from

Scheme 3. Chlorination/Deprotection of *N*-PMP Acetal 3d



Scheme 4. Use of *N*-Trityl Protecting Group in Cascade Cyclization Synthesis of DAS-534



Ph_3CNH_2, CCl_4, and CF_3CO_2H in the presence of PPh_3 and Et_3N, followed by Sonogashira coupling. The initial report of cascade cyclization of CF_3-alkynylimines with primary amines included the results of a solvent screen which showed that ethers, such as THF and DME, gave higher selectivity to fluoropyridine products.[8a] During our investigation, we found that use of DMSO led to faster cyclization rates than THF with no decrease in yield. Cyclization of **10** with 4-chlorobenzylamine in DMSO proceeded in 81% yield to give *N*-trityl-protected pyridine **11a**. Both the *N*-trityl and acetal protecting groups were hydrolyzed in 90% yield to give the 4-amino picolinaldehyde **12a**. Chlorination of aldehyde **12a** with DCDMH gave 3-chloro-4-amino picolinaldehyde **8** in 70% yield.

By incorporating *N*-trityl and acetal protecting groups in **10**, the combined yield of the cascade cyclization and deprotection steps was significantly improved. A variety of primary amines were cyclized with **10** (Table 2) to yield 6-alkyl substituted picolinaldehyde derivatives after deprotection. Notably, this method allowed synthetic access to pyridine derivatives with alkyl and cycloalkyl substituents at the 6-position that were difficult to prepare by cross-coupling routes, due to the instability and/or lack of accessibility of the requisite organometallic reagent. Use of $MeNH_2$ allowed access to the 6-H derivative **11b**, whereas *neo*-pentylamine reacted with **10** to form 6-*tert*-butylpyridine **11d**. Cyclization of **10** with allylamine gave the 6-vinyl derivatives **11g**. Heterocyclic primary amines were also tolerated. Notably, ethanolamine reacted with high chemoselectivity at the amine functional group to give 6-hydroxymethyl derivative **11j**. Subsequent deprotection under acidic conditions proceeded smoothly.

In summary, the utility of the cascade cyclization of fluoroalkyl alkynylimines with primary amines has been

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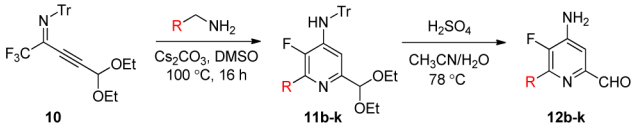
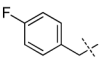
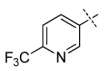
Table 2. Synthesis of Substituted 4-Amino-5-fluoro-6-alkylpicolinaldehydes by Cascade Cyclization



entry	R	yield (%)		entry	R	yield (%)	
		11b	**12b**			**11g**	**12g**
1	H	61	87	6	vinyl	52[a]	62
		11c	**12c**			**11h**	**12h**
2	*n*-Pr	83	84	7		84	95
		11d	**12d**			**11i**	**12i**
3	*t*-Bu	97	73	8		56	83
		**11e**	**12e**			**11j**	**12j**
4		87	88	9	CH_2OH	54[b]	84
		**11f**	**12f**			**11k**	**12k**
5		78	88	10		42	43

[a]100 °C, 2.5 h. [b]60 °C, 3 h.

optimized for the synthesis of 4-amino-5-fluoropicolinates by incorporating *N*-trityl and acetal protecting groups in the cyclization precursor. The resulting pyridines were easily deprotected to picolinaldehyde derivatives for further elaboration to structures of interest as potential herbicides. This method provides access to picolinic acids with alkyl or aryl substituents at the 6-position that were previously inaccessible by cross-coupling chemistry. In addition, radiolabeled compounds can also be prepared by use of isotopically labeled amines.[10]

■ ASSOCIATED CONTENT

Supporting Information

Experimental data, characterization data, and spectra of compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01176.

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Notes

The authors declare no competing financial interest.

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(10) Synthesis of ^{14}C-labeled pyridines using this method will be reported separately.

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