ORGANIC LETTERS

2010
Vol. 12, No. 19
4376−4379

A New Strategy for the Synthesis of Poly-Substituted 3-H, 3-Fluoro, or 3-Trifluoromethyl Pyridines via the Tandem C−F Bond Cleavage Protocol

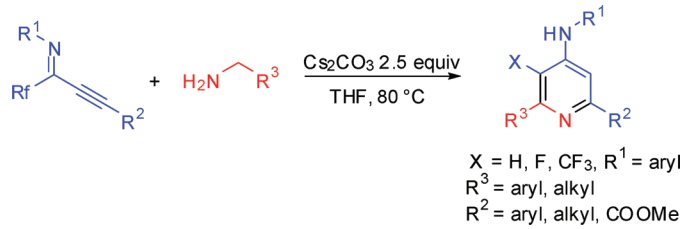
Zixian Chen,[†,‡] Jiangtao Zhu,[†] Haibo Xie,[†] Shan Li,[†] Yongming Wu,[*,†] and Yuefa Gong[*,‡]

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, 430074, China

ymwu@mail.sioc.ac.cn; gongyf@mail.hust.edu.cn

Received August 9, 2010

ABSTRACT



A new strategy for the synthesis of poly-substituted 3-H, 3-F, and 3-trifluoromethyl pyridines based on C−F bond breaking of the anionically activated fluoroalkyl group is described. A series of 2,6-disubstituted 4-amino pyridines were prepared through this domino process in high yields under noble metal-free conditions, making this method a supplement to pyridine synthesis.

The pyridine unit represents an important structural motif found in natural products and biologically relevant compounds,[1] which are the subject of considerable interest as potent antitumor,[2] antimicrobial,[3] and antiviral agents[4] and herbicides,[5] and it is also a significant component of many common ligands.[6] Therefore, efficient methods for the synthesis of these compounds are of great significance,[7] especially for their fluoro-containing counterparts, as the

[†] Chinese Academy of Sciences.
[‡] Huazhong University of Science and Technology.

(1) (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043–6061. (b) David, O. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (c) Balasubramanian, M.; Keay, J. G., In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 245.

(2) (a) Anchoori, R. K.; Kortenhorst, M. S. Q.; Hidalgo, M.; Sarkar, T.; Hallur, G.; Bai, R.; Van Diest, P. J.; Hamel, E.; Khan, S. R. *J. Med. Chem.* **2008**, *51*, 5953–5957. (b) Kuo, G.; Prouty, C.; Wang, A.; Emanuel, S.; DeAngelis, A.; Zhang, Y.; Song, F.; Beall, L.; Connolly, P. J.; Karnachi, P.; Chen, X.; Gruninger, R. H.; Sechler, J.; Fuentes-Pesquera, A.; Middleton, S. A.; Jolliffe, L.; Murray, W. V. *J. Med. Chem.* **2005**, *48*, 4892–4909.

(3) (a) Wang, Y.; Dong, X.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 3090–3098. (b) Wachter, G. A.; Davis, M. C.; Martin, A. R.; Franzblau, S. G. *J. Med. Chem.* **1998**, *41*, 2436–2438. (c) Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727–3735.

(4) (a) Kim, Y.; Hackett, J. C.; Brueggemeier, R. W. *J. Med. Chem.* **2004**, *47*, 4032–4040. (b) Skerlj, R. T.; Zhou, Y.; Wilson, T.; Bridger, G. J. *J. Org. Chem.* **2002**, *67*, 1407–1410.

(5) (a) Ren, Q.; Mo, W.; Gao, L.; He, H.; Gu, Y. *J. Heterocycl. Chem.* **2010**, *47*, 171–178. (b) Li, G.; Qian, X.; Cui, J.; Huang, Q.; Zhang, R.; Guan, H. *J. Agric. Food Chem.* **2006**, *54*, 125–129.

(6) (a) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100–8101. (b) Tsuboyama, A.; Iwawaki, H.; Furugori, M.; Mukaide, T.; Kamatani, J.; Igawa, S.; Moriyama, T.; Miura, S.; Takiguchi, T.; Okada, S.; Hoshino, M.; Ueno, K. *J. Am. Chem. Soc.* **2003**, *125*, 12971–12979.

(7) Eicher, T.; Hauptmann, S. *The chemistry of heterocycles: Structure, reactions, syntheses, and applications*; Wiley-VCH: Weinheim, 2003.

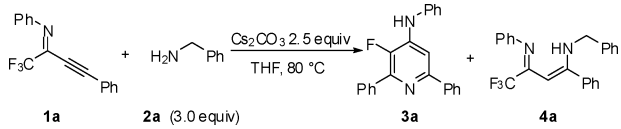
10.1021/ol101859p
Published on Web 09/02/2010

incorporation of fluorine or fluorine-containing groups into an organic molecule may lead to improvements in pharmacological properties.[8] Although synthesis of various substituted pyridines has been widely covered in the literature and inspired significantly different strategies,[1c,9] methods for the fluorine-containing substrates are rare,[10] and novel methods for poly-substituted pyridines are still desired. Herein we report a mild and efficient cascade procedure for chemoselective conversion of alkynylimines into the corresponding substituted pyridines.

The C−F bond is generally regarded as the strongest bond in organic molecules, so its cleavage has become a current subject of active investigation, as it provides us an opportunity to synthesize nonfluorinated products and partially fluorinated compounds, which are otherwise inaccessible.[11] It has been shown that the anionically activated trifluoromethyl group has great utility in the synthesis fluorine-containing compounds,[12] as it is easier to introduce a CF_3 group into a molecule then other fluorinated groups. The C−F bond breaking does rather easily occur when a CF_3 group is attached to a π-electron system because of electron pair acceptance into the π-system, and subsequent extrusion of a fluoride ion provides the driving force.[13] The formed intermediary *gem*-difluorovinyl can react with various nucleophiles[14] or react with electrophiles when it is attached to an anion,[15] leading to various difluoromethylene building blocks. Our strategy for the construction of diversely substituted pyridine derivatives is based on this cascade C−F cleavage/nucleophilic addition protocol.

As listed in Table 1, *N*-(1,1,1-trifluoro-4-phenylbut-3-yn-2-ylidene)aniline **1a** and benzylamine **2a** were chosen as model substrates to screen the optimal reaction conditions.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** (3.0 equiv) **3a** **4a**

				yield (%)[b]	
entry	solvent	base	time (h)	**3a**	**4a**
1	CH_3CN	Cs_2CO_3	2	45	-
2	toluene	″	6	30	4
3	DMF	″	2	47	2
4	DME	″	2	90	-
5	dioxane	″	3	59	-
6	THF	″	2	98 (97)	-
7	MeOH	″	2	5	-
8	THF	-	2	-	99 (98)
9	THF	KOH	2	80	20
10	THF	K_3PO_4	12	72	0
11	THF	K_2CO_3	12	12	88
12	THF	DBU	1	-	46

[a] Reactions were carried out on a 0.3 mmol scale with benzylamine (3.0 equiv), base (2.5 equiv), and solvent (2 mL) at 80 °C unless otherwise stated. [b] Reported yields were based on **1a** determined by ^{19}F NMR. Values in parentheses are of isolated yields.

Initial experiments were carried out using 3 equiv of benzylamine **2a** with 2.5 equiv of Cs_2CO_3 in CH_3CN at 80 °C. The desired 3-fluoropyridine product **3a** was obtained in 45% yield (Table 1, entry 1), which was confirmed by crystal diffraction (Figure 1).[16] Then other solvents were

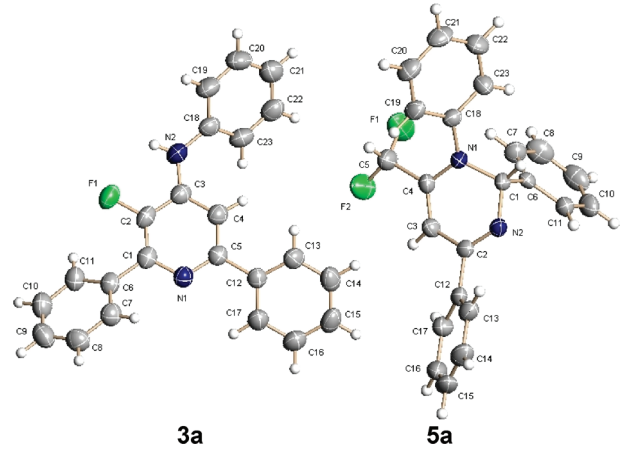


Figure 1. X-ray structure of **3a** and **5a**.

evaluated. Comparing with toluene, DMF, dioxane, and MeOH, the yield improved considerably when DME (1,2-

(8) (a) Yamazaki, T.; Taguchi, T.; Ojima; I., In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Eds.; Wiley-Blackwell: Weinheim, 2009; pp 3−46. (b) Ioannidis, S.; Lamb, M. L.; Davies, A. M.; Almeida, L.; Su, M.; Bebernitz, G.; Ye, M.; Bell, K.; Alimzhanov, M.; Zinda, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6524–6528. (c) Balko, T. W.; Buysse, A. M.; Epp, J. B.; Fields, S. C.; Lowe, C. T.; Keese, R. J.; Richburg, J. S., III; Ruiz, J. M.; Weimer, M. R.; Green, R. A.; Gast, R. E.; Bryan, K.; Irvine, N. M.; Lo, W. C.-L.; Brewster, W. K.; Webster, J. D. US6784137, 2004. (d) Phillips, G.; Davey, D. D.; Eagen, K. A.; Koovakkat, S. K.; Liang, A.; Ng, H. P.; Pinkerton, M.; Trinh, L.; Whitlow, M.; Beatty, A. M.; Morrissey, M. M. *J. Med. Chem.* **1999**, *42*, 1749–1756. (e) Saari, W. S.; Halczenko, W.; King, S. W.; Huff, J. R.; Guare, J. P.; Hunt, C. A.; Randall, W. C.; Anderson, P. S.; Lotti, V. J. *J. Med. Chem.* **1983**, *26*, 1696–1701. (f) Rauckman, B. S.; Roth, B. *J. Med. Chem.* **1980**, *23*, 384–391.

(9) (a) Parthasarathy, K.; Jeganmohan, M.; Cheng, C. *Org. Lett.* **2008**, *10*, 325–328. (b) Hu, J.; Zhang, Q.; Yuan, H.; Liu, Q. *J. Org. Chem.* **2008**, *73*, 2442–2445. (c) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096–10097. (d) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592–4593. (e) Barluenga, J.; Pozo, C.; Olano, B. *Synthesis* **1996**, *1996*, 133–140. (f) Oliver Kappe, C. *Tetrahedron* **1993**, *49*, 6937–6963. (g) Barluenga, J.; Tomás, M.; Jardón, J.; Rubio, E.; Gotor, V. *Synthesis* **1989**, *1989*, 230–232.

(10) (a) Fields, S. C.; Lo, W. C.; Brewster, W. K.; Lowe, C. T. *Tetrahedron Lett.* **2010**, *51*, 79–81. (b) von Kieseritzky, F.; Lindström, J. *Synthesis* **2010**, *63*, 66. (c) Dolbier, W. R.; Xu, Y. *J. Fluorine Chem.* **2003**, *123*, 71–73. (d) Fukuhara, T.; Yoneda, N.; Suzuki, A. *J. Fluorine Chem.* **1988**, *38*, 435–438. (e) Pews, R. G.; Lysenko, Z. *J. Org. Chem.* **1985**, *50*, 5115–5119. (f) Boudakian, M. M. *J. Fluorine Chem.* **1981**, *18*, 497–506.

(11) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119–2183.

(12) Kiselyov, A. S.; Piatnitski, E. L.; Doody, J. *Org. Lett.* **2004**, *6*, 4061–4063, and references therein.

(13) (a) Uneyama, K. In *Organofluorine Chemistry*; Blackwell Publishing Ltd.: Oxford, 2006; p 107. (b) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, *1323*, 1324.

(14) (a) Kiselyov, A. S.; Piatnitski, E. L.; Doody, J. *Org. Lett.* **2004**, *6*, 4061–4063. (b) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.* **2003**, *5*, 1455–1458.

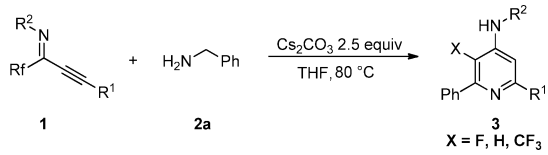
(15) (a) Kobayashi, T.; Nakagawa, T.; Amii, H.; Uneyama, K. *Org. Lett.* **2003**, *5*, 4297–4300. (b) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103–3105.

(16) The X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre under deposition number 769650 (**3a**) and 778755 (**5a**).

dimethoxyethane) or THF was used (Table 1, entries 4 and 6). Next, different bases were screened with THF as the solvent. The weaker bases prolonged the reaction time with lower yields (Table 1, entries 10 and 11), and no pyridine was detected when organic base such as DBU was used (Table 1, entry 12). **4a** was isolated without further conversion in the absence of a base (Table 1, entry 8), which can form the final product in quantitative yield if Cs_2CO_3 is added. After optimization, the best reaction conditions were ascertained as 3 equiv of **2a** and 2.5 equiv of Cs_2CO_3 in THF at 80 °C.

With the optimized conditions in hand, we examined the generality of this process. Other fluoroalkyl substrates were tested. When CF_2Br was in place of CF_3, the corresponding product was formed in good yield (Table 2, entry 1), and

Table 2. Reactions of Various Alkynylimines with Benzylamine[a]



1 2a 3 X = F, H, CF_3

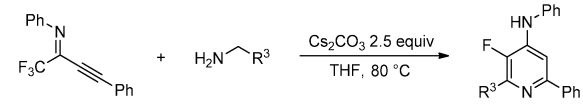
entry	R_f	R^1	R^2	product	yield (%)[b]
1	CF_2Br	Ph	Ph	**3a**	80
2	CF_2Cl	Ph	Ph	**3a**	64
3	CF_2H	Ph	Ph	**3b**	80[c]
4	CF_3CF_2	Ph	Ph	**3c**	74[d]
5	CF_3	*p*-MeC_6H_4	Ph	**3d**	99
6	CF_3	*n*-butyl	Ph	**3e**	59
7	CF_3	*p*-FC_6H_4	Ph	**3f**	84
8	CF_3	2-thienyl	Ph	**3g**	90
9	CF_3	COOMe	Ph	**3h**	60
10	CF_3	Ph	*p*-$MeOC_6H_4$	**3i**	97
11	CF_3	Ph	*p*-CNC_6H_4	**3j**	96
12	CF_3	Ph	*m*-MeC_6H_4	**3k**	95

[a] Reactions were carried out on a 0.4 mmol scale in THF (2 mL) with **2a** (3.0 equiv) and base (2.5 equiv) at 80 °C unless otherwise stated. [b] Isolated yields. [c] X = H. [d] X = CF_3.

the yield for the CF_2Cl group was acceptable as well (Table 2, entry 2). Surprisingly, when CF_2H and CF_3CF_2 substrates were used, the resultant 3-H pyridine and 3-trifluoromethyl pyridine were obtained, respectively, in favorable yields (Table 2, entries 3 and 4), rendering more versatility. All substrates with various alkynyl moieties could be the candidates. Electron-rich aryl substituents gave excellent yields (Table 2, entries 5 and 8), while electron-deficient yields were slightly lower (Table 2, entry 7). When an alkyl group is attached, a longer reaction time (24 h) was required with a poorer yield (Table 2, entry 6). An ester group also afforded the desired products in moderate yield (Table 2, entry 9). Further studies on the *N*-aryl group revealed that electronic effects of its substitution did not significantly affect the reactivity (Table 2, entries 10−12).

To expand the scope of the intermolecular tandem reaction of alkynylimine with benzylamine, a variety of substituted benzylamines and hetarylmethylamines were tested under the optimal reaction conditions. In general, the reaction tolerates various amines containing aryl groups. Amines with electron-rich aromatic rings showed greater reactivity compared with those with electron-deficient aryl rings. For example, the reaction of 4-methylbenzylamine and **1a** proceeded in 98% isolated yield (Table 3, entry 1), while the inactive amines

Table 3. Reactions of **1a** with Various Amines[a]



1a 2 3

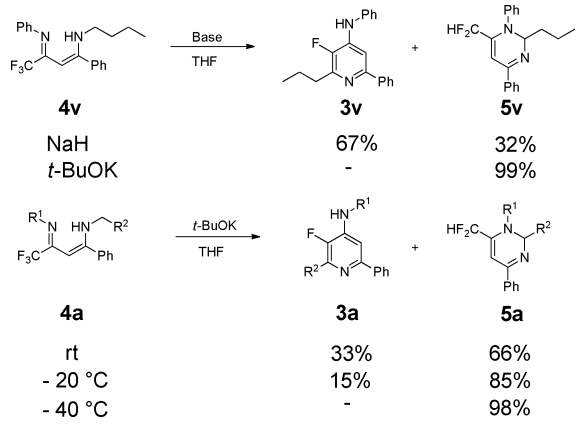
entry	R^3	product	yield (%)[b]
1	*p*-MeC_6H_4	**3l**	98
2	*o*-MeC_6H_4	**3m**	89
3	3,4-di$MeOC_6H_4$	**3n**	93
4	*p*-ClC_6H_4	**3o**	85
5	*p*-$CF_3C_6H_4$	**3p**	52
6	*o*-$CF_3C_6H_4$	**3q**	50
7	1-naphthyl	**3r**	93
8	2-thienyl	**3s**	96
9	2-pyridyl	**3t**	62
10	2-furyl	**3u**	80

[a] Reactions were carried out on a 0.4 mmol scale in THF (2 mL) with methylamines (3.0 equiv) and base (2.5 equiv) at 80 °C unless otherwise stated. [b] Isolated yields.

such as 4-(trifluoromethyl)benzylamine required longer time to afford the corresponding pyridine with a reduced yield (Table 3, entry 5). Because of steric hindrance, the ortho-substituted benzylamine resulted in a slight decrease in yield (Table 3, entry 2). Moreover, substrates with a heterocyclic ring could also provide the product in satisfactory yield (Table 2, entries 8−10), which may serve as a good ligand, such as 2,2′-bipyridine. The cyclization process did not occur when *n*-butylamine was used, providing **4v** as a sole product in quantitative yield, which could form the pyridine product if NaH was used as the base (Scheme 1). Surprisingly, a byproduct dihydropyrimidine **5v** was isolated in 32% yield in addition to the desired compound, while use of a soluble base *t*-BuOK yielded **5v** as the sole product. Amazingly, annulation of **4a** under this condition also gave a mixture of **3a** and **5a**, while lowering the temperature to −40 °C led to formation of **5a** only.[16]

A possible mechanism of this transformation is proposed in Scheme 2. The first step is the hydroamination of alkynylimine with amine to form the intermediate vinylogous amidine **4**, which undergoes deprotonation and dehydrofluorination to generate an anion and an imine coexisting in one molecule. When the reaction is carried out at a low temperature with a soluble base (path a), the in situ generated amide nucleophile attacks imine immediately without isomerization to form dihydropyrimidine through a kinetically controlled pathway. Raising the reaction temperature (path b), however, makes the carbon nucleophilic addition become

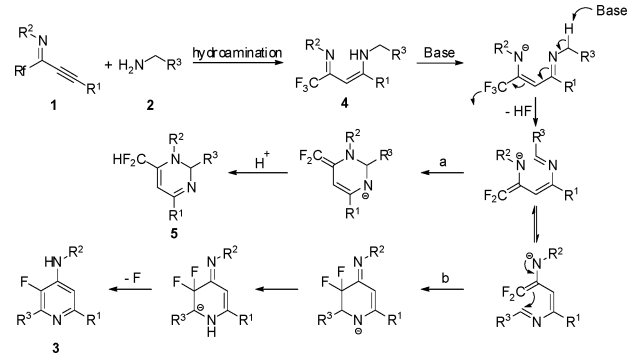
Scheme 1. Base-Controlled Cyclization Reaction



an option, rendering a 1,2-dihydropyridine ring under thermodynamic control, which finalizes the pyridine ring after proton migration, β-F elimination, and isomerization, and an insoluble base can effectively inhibit the kinetic pathway.

In conclusion, we have designed a new strategy for the chemoselective synthesis of poly-substituted pyridines using amines and alkynylimines, through a cascade process based on anionical C−F bond activation. The substituents of the pyridine ring can be introduced stepwise from initial fluoroalkyl acids in high yields.[17] A variety of functional groups can be employed, rendering this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules. Further investigations into the reaction

Scheme 2. Proposed Mechanism



mechanism, and the *gem*-difluoromethylation based on this strategy, are currently underway in our laboratory.

Acknowledgment. This work was supported by the National Science Foundation of China (Nos. 20772145).

Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all the products and typical procedure for the annulation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101859P

(17) (a) Chen, Z.; Zhu, J.; Xie, H.; Li, S.; Wu, Y.; Gong, Y. *Adv. Synth. Catal.* **2010**, *352*, 1296–1300. (b) Wu, Y.; Zhang, M.; Li, Y. *J. Fluorine Chem.* **2006**, *127*, 218–222. (c) Wu, Y.; Li, Y.; Deng, J. *J. Fluorine Chem.* **2005**, *126*, 791–795. (d) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32–35. (e) Uneyama, K.; Watanabe, H. *Tetrahedron Lett.* **1991**, *32*, 1459–1462.