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Scope of a Novel Three-Component Synthesis of Highly Functionalized Pyridines†

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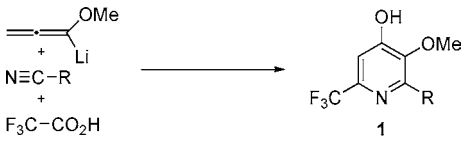
ABSTRACT

A mechanistically unique three-component synthesis provides a variety of functionalized pyridine derivatives in fair to excellent yields. The scope of this reaction was studied with respect to the alkoxyallene, the nitrile, and the carboxylic acid. Due to the 4-hydroxy group, these pyridine derivatives are suitable precursors for subsequent palladium-catalyzed reactions. Suzuki couplings of the corresponding pyridyl nonaflates lead to a variety of pyridine and bipyridine derivatives.

We serendipitously discovered a new synthesis of trifluoromethyl-substituted pyridine derivatives **1** which were formed by addition of lithiated methoxyallene to nitriles followed by treatment with trifluoroacetic acid. Four simple examples bearing CF_3 and methoxy groups have been reported (Scheme 1), but scope and limitations of this unique reaction are not known so far.[1,2] Since the two differentiated oxygen functionalities of compounds such as **1** are ideal tools for selective palladium-catalyzed coupling reactions[3] or other transformations, the generality of the pyridine synthesis was of much interest.

Scheme 1



R = *t*-Bu, Et, *i*-Prop, Ph

In this paper, we disclose that the new three-component reaction leading to highly substituted pyridine derivatives *is not restricted to methoxyallene and trifluoroacetic acid* as precursors. Most importantly, a variety of carboxylic acids or other alkoxyallene derivatives can be employed. Furthermore, the use of dinitriles establishes an extremely simple route to highly conjugated dipyridyl systems.

The intriguing mechanism of the reaction cascade leading to heterocycles **1** is illustrated in Scheme 2. Addition of the lithiated allene (generated by treatment of methoxyallene with *n*-butyllithium) to the nitrile furnishes the expected allenyl imine **2**,[4] which on treatment with trifluoroacetic acid gives iminium ion **3**. The central allene carbon reacts as electrophile with trifluoroacetate to provide diene **4**, and an acyl transfer gives amide **5**. Acid-catalyzed aldol-type condensation of the methyl ketone moiety to the amide carbonyl group finally delivers the pyridine ring. In most cases, mixtures of **5** and **1** were isolated, which were completely converted into 3-methoxy-4-hydroxypyridines **1** by subsequent treatment with trimethylsilyl triflate and triethylamine.

† Dedicated to Prof. Klaus Hafner on the occasion of his 80th birthday.

(1) Flögel, O.; Dash, J.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Chem. Eur. J.* **2004**, *10*, 4283−4290.

(2) Reissig, H.-U.; Flögel, O. German Patent Application DE 103 36 497 A1 (3.3.2005).

(3) For a few first examples, see ref 1.

(4) This intermediate could be isolated and characterized for R = *t*-Bu (see ref 1).

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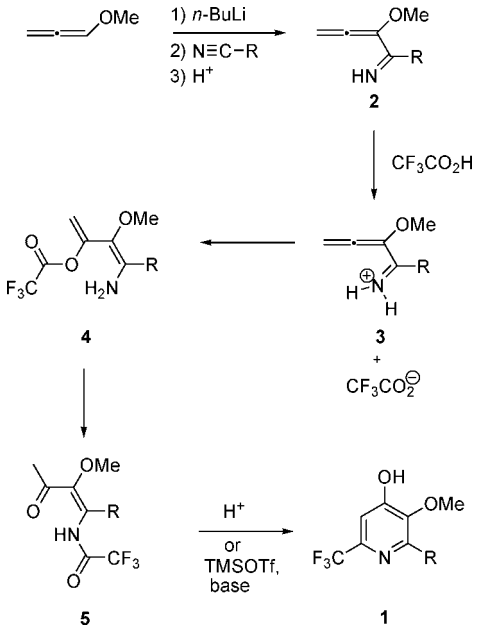
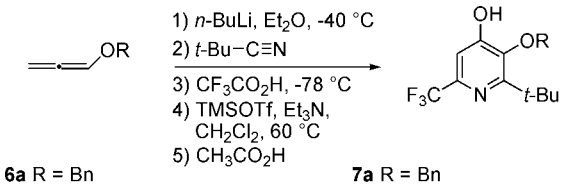
Scheme 2



For the exploration of the scope of this three-component reaction, we first studied benzyloxyallene **6a**, [2-(trimethylsilyl)ethoxy]allene **6b**, and (3-methoxybenzyloxy)allene **6c** (Scheme 3). Their lithiation followed by addition to pivalonitrile, treatment with trifluoroacetic acid, and finally condensation led to the expected pyridinols **7a**, **7b**, and **7c** in moderate to good yields.[5] These results demonstrate that other alkoxy groups can easily be installed at C-3 of the pyridine derivatives, which will allow milder dealkylation of this group.

Scheme 3

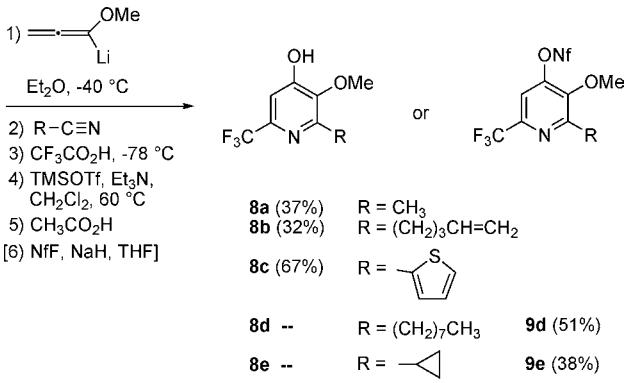


6a R = Bn
6b R = $(CH_2)_2TMS$
6c R = $CH_2C_6H_4$(3-OMe)

7a R = Bn (50%)
7b R = $(CH_2)_2TMS$ (42%)
7c R = $CH_2C_6H_4$(3-OMe) (37%)

We also prepared new methoxy-substituted compounds **8a**−**c**, **9d**, and **9e** as illustrated in Scheme 4. Whereas the use of acetonitrile and 5-hexenenitrile afforded the desired pyridine derivatives **8a** and **8b** only in moderate yields,[6] 2-cyanothiophene as electrophile gave the 2-thienyl-substituted pyridinol **8c** in good yield.[7] With nonanonitrile and cyanocyclopropane as components, we did not purify the corresponding intermediates **8d** and **8e** but directly converted the crude products into the pyridyl nonaflates.[8] By this simple protocol, compounds **9d** and **9e**, which are ready for palladium-catalyzed reactions, were obtained in 51% and 38% overall yields, respectively.

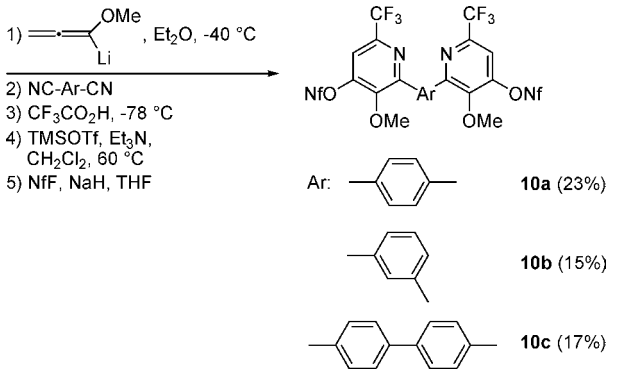
Scheme 4



8a (37%) R = CH_3
8b (32%) R = $(CH_2)_3CH{=}CH_2$
8c (67%) R =
8d -- R = $(CH_2)_7CH_3$ **9d** (51%)
8e -- R = **9e** (38%)

Three examples depicted in Scheme 5 demonstrate that fairly complex dipyridyl derivatives can be constructed from the corresponding aryl dinitriles in an astonishing simple manner. Although the yields of bisnonaflates **10a**−**c** are only in the range of 20%, it has to be considered that the formation of a single pyridine ring requires generation of four new bonds. Together with the nonaflation step not less than ten new bonds are generated during synthesis of each of these dipyridine derivatives in a protocol involving only one purification step!

Scheme 5



10a (23%)
10b (15%)
10c (17%)

A crucial step during the formation of **1** according to the mechanism suggested (Scheme 2) involves the intramolecular aldol type condensation of trifluoroacetamide **5** to generate

(5) Whereas methoxyallene was generally used in large excess (3 equiv) only 1 equiv of allenes **6a**−**c** was employed. This may explain the moderate yields.

(6) The lower yield may be due to side reactions of the 2-alkyl side chain during the relatively harsh conditions of the condensation step.

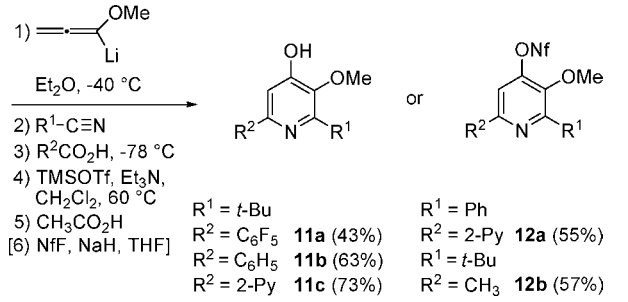
(7) Unfortunately, cyanopyridines were not suitable substrates for the addition of lithiated alkoxyallenes. So far, only complex mixtures of compounds were isolated.

(8) The unpolar pyridyl nonaflates are much easier to separate from byproducts. Furthermore, they are excellent precursors for the anticipated palladium-catalyzed coupling reactions. For examples of the reactions of alkenyl nonaflates, see: Högermeier, J.; Reissig, H.-U. *Chem. Eur. J.* **2007**, *13*, 2410−2420 and references cited in this publication.

the pyridine ring. We were therefore very curious to learn whether less electrophilic amides derived from other carboxylic acids would also be suitable substrates of the reaction cascade leading to pyridinols. A successful extension would dramatically increase the scope of our novel pyridine synthesis.

Gratifyingly, most of the carboxylic acids examined turned out to be excellent components for the pyridine synthesis, thus allowing installation of a variety of substituents in position 6 of the pyridine ring. In Scheme 6 we assembled

Scheme 6

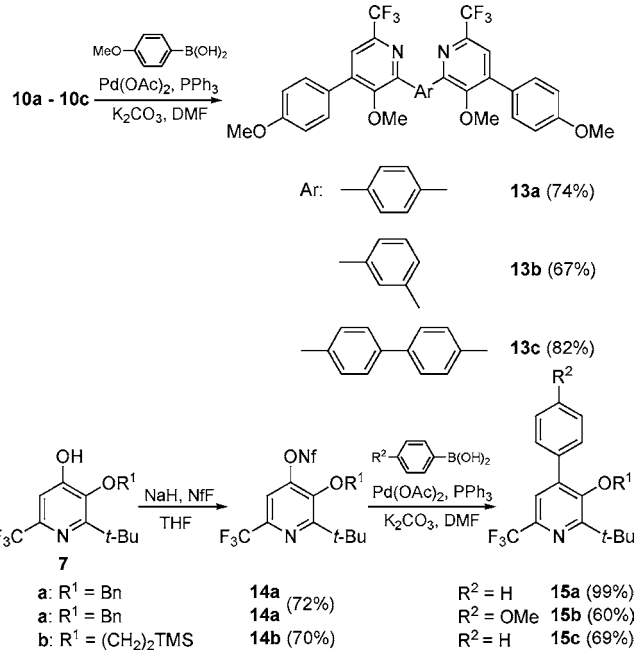


typical examples demonstrating that pentafluorobenzoic acid, benzoic acid, 2-pyridinecarboxylic acid, and also simple aliphatic carboxylic acids such as acetic acid furnish the expected pyridine derivatives **11** or **12**. In most cases, the enamide intermediates with structures analogous to **5** (Scheme 2) were isolated as primary products after step 3 of our sequence, thus clearly emphasizing the expected lower tendency to undergo the intramolecular aldol condensation. However, these enamides smoothly undergo the expected cyclizations to pyridinols **11a**−**c** by treatment with trimethylsilyl triflate and triethylamine. We also include two examples where the unpurified pyridinols were directly converted into the nonaflates **12a** and **12b** in good overall yield. Of particular importance is the short synthesis of specifically functionalized 2,2-bipyridyl derivatives such as **11c** and **12a**.

Selected examples demonstrate the potential of pyridyl nonaflates in palladium-catalyzed reactions. Suzuki couplings of dipyridyl derivatives **10a**−**c** with 4-methoxyphenylboronic acid provided the expected products **13a**−**c** in good yields. In compound **13c**, six (hetero)aromatic rings are in conjugation, which makes compounds of type **13** to interesting extended π-systems.[9] They exhibit some similarity to pyrimidine-phenylene oligomers which are known as blue-light-emitting compounds.[10]

In a similar fashion, pyridyl nonaflates **14a** and **14b** could be coupled with boronic acids affording 4-aryl-substituted pyridines **15a**−**c**. Dealkylation of R^1 under mild conditions, conversion into nonaflates, and a second palladium-catalyzed step allow introduction of a variety of substituents at C-3.

Scheme 7



Not only Suzuki couplings but also Sonogashira, Stille, and Heck reactions are easily possible employing our 4-pyridyl and 3-pyridyl nonaflates.[11]

The pyridine ring constitutes a privileged structural motif in compounds of importance for medicinal chemistry, supramolecular chemistry, and material science.[12] Our highly flexible and fairly efficient method makes available a large variety of new functionalized pyridine derivatives which should be of interest for these applications.[13] Not only can perfluorinated substituents such as CF_3 or C_6F_5 easily be introduced,[14] but most importantly, many other substituents can be incorporated to the pyridine core at C-2 and C-6.

(9) Several of the compounds prepared show interesting photophysical properties, which will have to be investigated in more detail.

(10) Wong, K.-T.; Hung, T. S.; Lin, Y.; Wu, C.-C.; Lee, G.-H.; Peng, S.-M.; Chou, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513−516.

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(13) For reviews on pyridine syntheses, see: McKillop, A; Boulton, A. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, p 67. Newkome, G. R., Ed. *Pyridine and its Derivatives* in *Heterocyclic Chemistry*; Wiley: New York, 1984; Vol. 15, Part 5. Jones, G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Ed. Pergamon Press: Oxford, 1996; Vol. 5, p 167. Spitzner, D. *Science of Synthesis*; Thieme: Stuttgart, 2004; Vol. 15, pp 11−284. Henry, G. D. *Tetrahedron* **2004**, *60*, 6043−6061. Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459−2482. For selected recent syntheses of pyridine derivatives, see: Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Guiseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959−6966. Vasilév, N. V.; Koshelev, V. M.; Romanov, D. V.; Lyssenko, K. A.; Antipin, M. Y.; Zatonskii, G. V. *Russ. Chem. Bull.* **2005**, *54*, 1680−1685. Dediu, O. G.; Yehia, N. A. M.; Oeser, T.; Polborn, K.; Müller, T. J. J. *Eur. J. Org. Chem.* **2005**, 1834−1848. Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899−902. Emmerich, T.; Reinke, H.; Langer, P. *Synthesis* **2006**, 2551−2555. Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152−3154. Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335−1337 and references cited in these publications.

The oxygen functions at C-3 and C-4 allow palladium-catalyzed substitutions which strongly enhance the versatility of this approach to pyridine derivatives. In this paper, we clearly demonstrate for the first time the wide scope of this new pyridine synthesis employing lithiated alkoxyallenes in a unique reaction cascade.[15]

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Supporting Information Available: Detailed description of typical experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For reviews on fluorinated heterocycles, see: Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: Chichester, 1995. Kirsch, P. *Modern Fluorine Chemistry*; Wiley-VCH: Weinheim, 2004. Schlosser, M. *Angew. Chem.* **2006**, *118*, 5558−5572; *Angew. Chem., Int. Ed.* **2006**, *45*, 5432−5446. Isanbor, C.; O'Hagon, D. *J. Fluorine Chem.* **2006**, *127*, 303−319. Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013−1029. Thayer, A. M. *Chem. Eng. News* **2006**, June 5, 27−32. For recent selected syntheses of fluorinated pyridine derivatives, see: Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 327−330. Sosnovskikh, V. Y.; Usachev, B. I.; Sizov, A. Y.; Vorontsov, I. I.; Shkiyaev, Y. V. *Org. Lett.* **2003**, *4*, 3123−3126. Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *Mendeleev Commun.* **2006**, 165−167. Loska, R.; Majcher, M.; Makosza, M. *J. Org. Chem.* **2007**, *72*, 5574−5580. Schirok, H.; Figuera-Pérez, S.; Thutewohl, M.; Paulsen, H.; Kroh, W.; Klewer, D. *Synthesis* **2007**, 251−258.

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