JOC*Note*

Me_3SiCl-Promoted Three-Component Coupling Reaction of a Functionalized Enamine, an Acetal, and an Alkyne: An Unprecedented Approach to the Synthesis of Tetrasubstituted Pyridines via a [3 + 2 + 1] Intermolecular Cyclization

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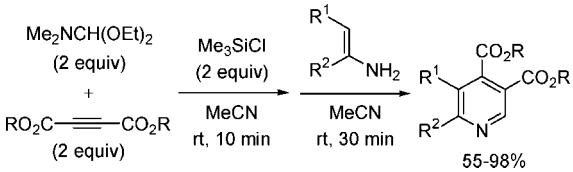

We have identified a Me_3SiCl-mediated three-component coupling reaction of a functionalized enamine, *N*,*N*-dimethylformamide diethyl acetal, and an internal alkyne having an electron-withdrawing group that produces 2,3,4,5-tetrasubstituted pyridine derivatives in good to excellent yields via a single-step reaction.

The pyridine ring system is one of the most important core structures and is widely found in naturally occurring compounds, biologically active substances, and clinical drugs.[1] A number of synthetic approaches have therefore been developed for the facile synthesis of these central skeletons.[1–3] Generally, previous synthetic routes to the pyridine framework have involved the dehydrated condensation of aldehydes, ketones, and α,β-unsaturated carbonyl compounds with ammonia and its amine derivatives[4] or aza-Diels−Alder reactions of a 1- or 2-azadiene derivative with a dienophile, such as an alkene and an alkyne.[5] In addition, [2 + 2 + 2] cycloaddition reactions of two types of alkynes with a nitrile have been identified.[6] However, most of these procedures have had restricted use due to complicated protocols. Moreover, these methods often require a high temperature, a prolonged reaction time, and expensive additives, such as transition metal complexes, resulting in a decline in the product yield. Hence, the development of a novel procedure for a simple, practical, single-step synthesis of a pyridine framework is highly desirable. We previously found that intermolecular cyclization of a multifunctionalized 1-azaallylic anion[7] with several Michael acceptors successfully led to the synthesis of nitrogen-containing heterocycles, such as polysubstituted pyridines,[8] pyrroles,[9] and pyrimidines.[10] We also showed that a Lewis acid catalyzed cyclization of a functionalized enamine,[11] which is formally equivalent to a 1-azaallyl anion with cyclic Michael acceptors, produced fused heterocycles.[12]

During ongoing exploration of a novel synthetic process of nitrogen-containing heterocyclic compounds, we found a new, practical Me_3SiCl-promoted three-component coupling reaction of a polyfunctionalized enamine, *N*,*N*-dimethylformamide diethyl acetal (DMF-DEA), and an internal alkyne having an electron-withdrawing group, leading to the production of

(1) For selected reviews, see: (a) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685. (b) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (c) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637. (d) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581.

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(4) For selected reviews, see: (a) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(5) For selected reviews, see: (a) van der Plas, H. C. *ARKIVOC* **2008**, 127. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379. (c) Buonora, P.; Olsen, J. C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (d) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (e) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(6) For selected reviews, see: (a) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (d) Maryanoff, B. E.; Zhang, H.-C. *ARKIVOC* **2007**, 7. (e) Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248. (f) Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 505.

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(10) Sakai, N.; Aoki, Y.; Sasada, T.; Konakahara, T. *Org. Lett.* **2005**, *7*, 4705.

(11) Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991.

(12) (a) Sakai, N.; Aoki, D.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 1261. (b) Sakai, N.; Hattori, N.; Tomizawa, N.; Abe, N.; Konakahara, T. *Heterocycles* **2005**, *65*, 2799.

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SCHEME 1. New Approach for a Single-Step Synthesis of Pyridine

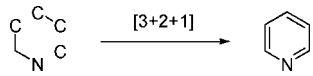
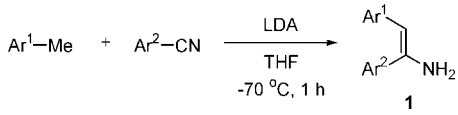
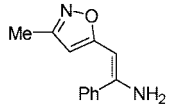
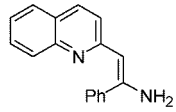
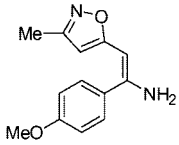
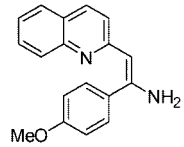
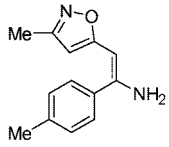
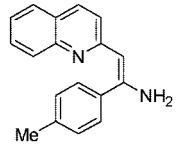
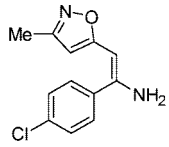
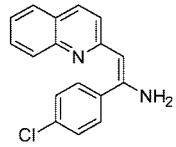
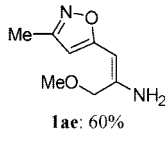
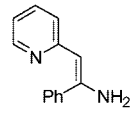
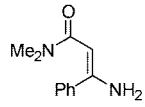


TABLE 1. Synthesis of Enamine 1[a]



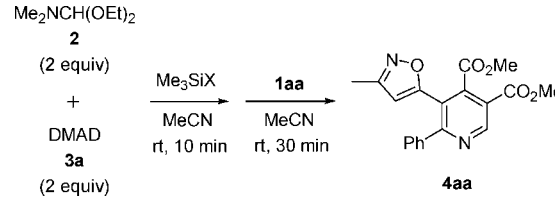
run	enamine **1**	run	enamine **1**
1	 **1aa**: 90%	7	 **1ca**: 92%
2	 **1ab**: 75%	8	 **1cb**: 90%
3	 **1ac**: 51%	9	 **1cc**: 78%
4	 **1ad**: 84%	10	 **1cd**: 99%
5	 **1ae**: 60%	11	 **1da**: 51%
6	 **1ba**: 67%		

[a] Isolated yield.

tetrasubstituted pyridines. To our knowledge, this type of preparation of a pyridine core through a one-pot [3 + 2 + 1] coupling process, shown in Scheme 1, has not previously been reported. This paper details the results of this coupling reaction.

On the basis of previous work,[13] we first prepared a variety of functionalized enamines as starting materials, and the results are summarized in Table 1. For example, the mixture of 3,5-dimethylisoxazole with benzonitrile was initially treated with lithium diisopropylamide (LDA) in THF at −70 °C for 1 h, followed by addition of water to the reaction mixture at room temperature, to produce the desired enamine **1aa** in a 90% yield (run 1). The coupling reaction of prepared enamine **1aa**, DMF-DEA, and dimethyl acetylene dicarboxylate (DMAD) was then systematically investigated, and the results are outlined in Table 2. When a CH_3CN solution of enamine **1aa**, 2 equiv of DMF-DEA **2**, and DMAD **3a** was stirred at room temperature for 30 min, the tetrasubstituted pyridine **4aa** was obtained in only 7% yield (run 1). The structure of pyridine **4aa** was determined by spectral data and elemental analysis and was unambiguously confirmed by the X-ray structure analysis of compound **4ab** (see Supporting Information).[14] To enhance the yield, the reaction conditions were optimized with several different solvents and a Lewis acidic silicon compound as an additive.[15] As a result, it was found that the desired product **4aa** was dramatically improved to a nearly quantitative yield when the reaction mixture, including 2 equiv of trimethylchlorosilane (Me_3SiCl), was vigorously stirred for 10 min before the addition of enamine **1aa** (run 2). In contrast, reducing the amount of Me_3SiCl to 1 equiv drastically decreased the yield to 13% (run 3). Moreover, the use of trimethyliodosilane (Me_3SiI) and trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) instead of Me_3SiCl, even with an increased amount of these silicon catalysts, was ineffective for the improvement of the yield of pyridine **4aa** (runs 4−7). Consequently, we decided that the experimental operation using 2 equiv of Me_3SiCl in CH_3CN was the best procedure for the ring-forming reaction (run 2).

TABLE 2. Optimization of Reaction Conditions



run	Me_3SiX (equiv)	yield (%)[a]
1	none	7
2	Me_3SiCl (2)	98[b]
3	Me_3SiCl (1)	13
4	Me_3SiI (1)	trace
5	Me_3SiI (2)	17
6	Me_3SiOTf (1)	trace
7	Me_3SiOTf (2)	8

[a] NMR yield. [b] Isolated yield.

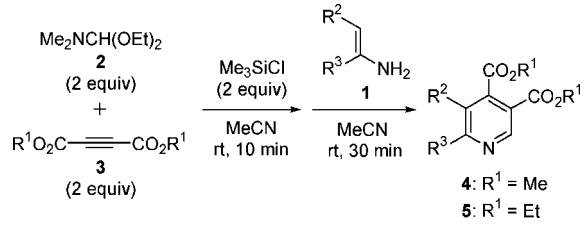
We then used this procedure to extend the preparation of polyfunctionalized pyridine derivatives, and the results are summarized in Table 3. The reaction of enamines **1ab**−**ad**, containing not only an electron-donating group but also an electron-withdrawing group on the benzene ring, with acetal **2** and DMAD was conducted in the presence of Me_3SiCl to produce the expected pyridine derivatives **4ab**−**ad** in good to excellent yields (runs 2−4). Similarly, the use of enamine **1ba** and **1ca**−**cd** tethered with other substituted groups, such as an amide group or a qunolin-2-yl group, gave the corresponding pyridines **4ba** and **4ca**−**cd** in excellent yields

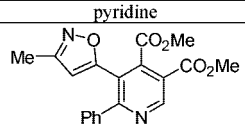
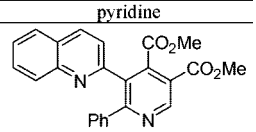
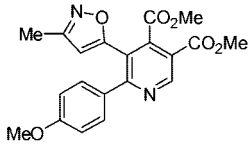
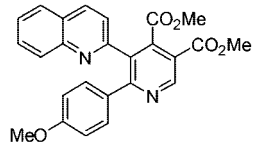
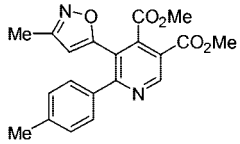
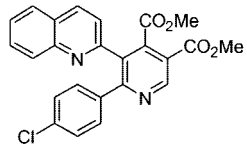
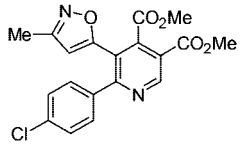
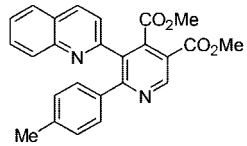
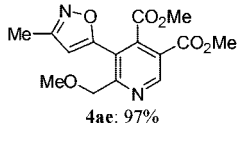
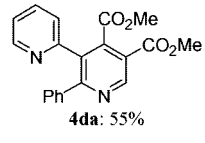
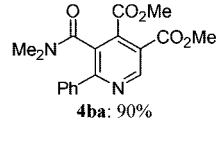
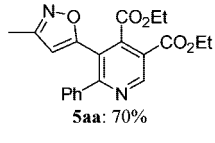
(13) (a) Akiba, K.; Kashiwagi, K.; Ohyama, Y.; Yamamoto, Y.; Ohkata, K. *J. Am. Chem. Soc.* **1985**, *107*, 2721. (b) Konakahara, T.; Takagi, Y. *Heterocycles* **1980**, *14*, 393.

(14) Crystal data for **4ab**: $C_{20}H_{18}N_2O_6$, MW = 382.36, monoclinic, a = 6.7232(10) Å, b = 24.783(4) Å, c = 10.9025(16) Å, β = 95.596(2)°, U = 1808.0(5) Å^3, space group $P2_1/c$, Z = 4, μ(Mo Kα) = 0.105 mm^{-1}, 10719 reflections measured, 4068 independent reflections (R_{int} = 0.0379), R_1 = 0.1298, wR_2 = 0.3149. Also see the details in Supporting Information.

(15) Typical solvents, such as THF, $CHCl_3$, and toluene, and typical Lewis acids, such as $InCl_3$, $ZnBr_2$, $Cu(OTf)_2$, $MgBr_2\cdot OEt_2$, $BF_3\cdot OEt_2$, and $AlCl_3$, were ineffective or only slightly effective for the reaction.

TABLE 3. Synthesis of Tetrasubstituted Pyridines 4 and 5[a]



run	pyridine	run	pyridine
1	 **4aa**: 98%	7	 **4ca**: 95%
2	 **4ab**: 81%	8	 **4cb**: 95%
3	 **4ac**: 80%	9	 **4cc**: 96%
4	 **4ad**: 90%	10	 **4cd**: 96%
5	 **4ae**: 97%	11	 **4da**: 55%
6	 **4ba**: 90%	12	 **5aa**: 70%

[a] Isolated yield.

(runs 6−10). Surprisingly, when enamine **1da** having a pyridin-2-yl group was employed, the yield of the product **4da** was moderate (run 11). Also, when diethyl acetylenedicarboxylate (**3b**) was used instead of DMAD, the desired pyridine **5aa** was obtained in a 70% yield (run 12). Unfortunately, an alternative activated alkyne, such as ethyl propiolate, and a less-activated alkyne, such as diphenylacetylene, yielded no product.[16]

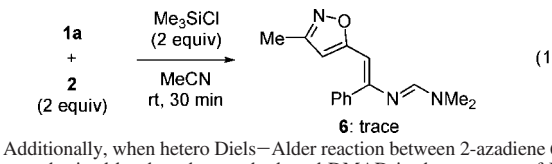
In conclusion, we have developed a novel Me_3SiCl-promoted three-component coupling reaction of a polyfunctionalized enamine, DMF-DEA, and an internal alkyne having a strong electron-withdrawing group, via a single step. This reaction proceeds cleanly in a short time to produce a variety of tetrasubstituted pyridines in good to excellent yields.

Experimental Section

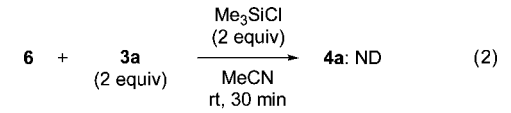
General Procedure for Synthesis of Enamine 1. To a THF solution (50 mL) of diisopropylamine (2.53 g, 25.0 mmol) was added *n*-BuLi (27.5 mmol, in hexane) at −70 °C, and the mixture was stirred at the same temperature. After 30 min, 2-methylquinoline (3.58 g, 25.0 mmol) was added dropwise, and the mixture was stirred for 1 h at −70 °C. *p*-Anisonitrile (3.33 g, 25.0 mmol) was gradually added to the solution, and the reaction mixture was further stirred for 1 h at the same temperature and then for 1 h at room temperature. To quench the reaction, water was added to the mixture. The mixture was extracted several times with AcOEt, and the combined organic extracts were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by recrystallization (AcOEt-hexane) to give enamine 2-(quinolin-2-yl)-1-(4-methoxyphenyl)-1-ethenamine **1cb** (6.22 g, 90%) as a yellow crystal: mp 156.7−158.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.84 (s, 3H), 5.56 (s, 1H), 6.94 (d, 2H, J = 8.5 Hz), 7.12 (d, 1H, J = 8.0 Hz), 7.33 (t, 1H, J = 8.0 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.88 (d, 1H, J = 8.0 Hz), 7.88 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3, 94.7, 114.0, 122.6, 124.0, 125.1, 127.3, 127.4, 127.5, 129.0, 132.0, 134.9, 147.4, 152.4, 159.9, 160.4; MS (FAB) *m*/*z* 276 (M^+, 100%). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14, Found: C, 78.40; H, 5.76; N, 10.06.

General Procedure for Synthesis of Tetrasubstituted Pyridine 4. To a MeCN solution (0.6 mL) of *N*,*N*-dimethylformamide diethyl acetal (**2**, 88 mg, 0.60 mmol) and dimethyl acetylenedicarboxylate (**3**, 85 mg, 0.60 mmol) was added freshly distilled trimethylchlorosilane (65 mg, 0.60 mmol) at room temperature under a N_2 atmosphere, and the mixture was stirred at the same temperature. After 10 min, enamine **1** (0.3 mmol) was added to the resulting solution, and the reaction mixture was further stirred for 30 min at room temperature. To quench the reaction, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added to the mixture. The mixture was extracted several times with $CHCl_3$; the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane) to produce pyridine **4** in the yields shown in Table 3. Dimethyl 3-(3′-Methylisoxazol-5′-yl)-2-phenylpyridin-4,5-dicarboxylate (**4aa**): a pale yellow crystal (AcOEt/hexane); mp 94.8−95.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 6.00 (s, 1H), 7.33−7.42 (m, 5H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 53.0, 53.1, 106.9, 119.8, 120.7, 128.3, 128.8, 129.6, 138.1, 144.2, 151.9, 159.7, 162.3, 164.0, 164.5, 166.2; MS (FAB) *m*/*z* 353 (M + H, 100%). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95, Found: C, 64.76; H, 4.53; N, 8.12.

(16) Reviewers suggested a reaction route via a hetero Diels−Alder reaction of a 2-aza-1,3-diene that was generated from an enamine and acetal, with DMAD. However, when the reaction of enamine **1a** with acetal **2a** was carried out in the presence of Me_3SiCl, the starting material **1a** was recovered in 99% NMR yield (eq 1).



Additionally, when hetero Diels−Alder reaction between 2-azadiene **6**, which was synthesized by the other method, and DMAD in the presence of Me_3SiCl was run, the desired reaction barely proceeded, resulting in recovery (83%) of 2-azadiene **6** (eq 2).



The above results implied the existence of another reaction route for the three-component coupling reaction of enamine, acetal, and alkyne.

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Supporting Information Available: Detailed experimental procedures and characterization data for novel compounds, ORTEP diagram of **4ab**, X-ray data for **4ab** in CIF format, and copies of ^{1}H and ^{13}C NMR spectra of novel products were prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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