A Simple and Versatile Route to Novel Conjugated β-Enaminonitriles and Their Application for the Highly Regioselective Synthesis of Nicotinonitriles Using a Vilsmeier-Type Reagent

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A straightforward synthesis of conjugated β-enaminonitriles from ketones and β-aminocrotononitrile mediated by $TiCl_4$ is described. The reaction of these novel dienamines with a Vilsmeier-type reagent provides a mild and highly regioselective route for the preparation of nicotinonitriles.

Introduction

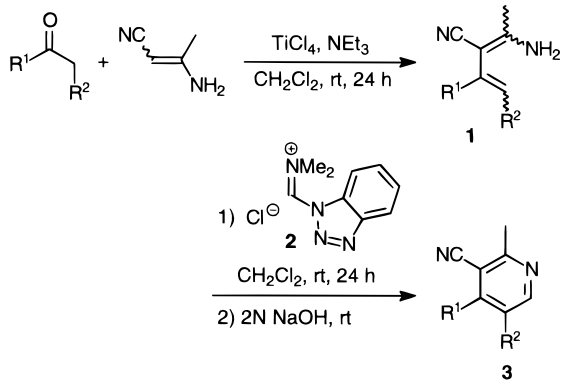
Dienamines are versatile building blocks in organic synthesis.[1] They are usually prepared from α,β-unsaturated aldehydes or ketones under conditions analogous to those used for the preparation of simple enamines.[2] We now report that $TiCl_4$-mediated reactions between ketones and β-aminocrotononitrile provide a series of novel conjugated β-enaminonitriles **1**. β-Enaminonitriles such as β-aminocrotononitrile are excellent building blocks for heterocyclic synthesis.[3] We demonstrate that this is also true for conjugated β-enaminonitriles **1** by their transformation into nicotinonitriles **3** using the Vilsmeier-type reagent **1** (Scheme 1, Table 1).

Pyridine derivatives occur in numerous natural products and are of fundamental importance to living systems (e.g., nicotinamide adenine dinucleotide (NAD)). They display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as general synthetic building blocks,[4] and many syntheses have been reported.[5] Nicotinonitrile-like pyridine derivatives are of special synthetic importance,[6] and the development of novel routes remains active.[7]

Results and Discussion

Recently, we disclosed that the Vilsmeier-type reagent **2** reacts with *N*-arylimines to give quinolines.[8] In an effort to extend the scope of this method toward the synthesis of nicotinonitriles, we attempted to prepare imines from ketones and β-aminocrotononitrile using a modification of the $TiCl_4$ procedure.[9] However, instead of the expected imines, we obtained the novel conjugated β-enaminonitriles **1** (Scheme 1) evidently by a tandem alkylation−elimination process, in which the β-aminocrotononitrile reacts as an enamine rather than as a primary amine (i.e., the enamine α-C atom is attacked by the carbonyl group[10]).

Scheme 1



Our methodology provides high yields and is of broad scope: we successfully transformed a variety of representative ketones including cyclic and acylic dialkyl or alkyl, aryl ketones, and sterically hindered ketones (see Table 1, entries 4, 5, 7, and 9) into the corresponding dienamines **1a**−**m**. Significantly, if unsymmetrical ketones are used the reaction is highly regioselective (Table

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(7) For recent examples, see: (a) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, 1321. (b) Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Tarrant, J. G.; Bruno, S. M.; Vargas, M.; Hosein, K. N.; Gupton, J. T.; Sikorski, J. A. *Tetrahedron* **1995**, *51*, 1575. (c) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776. (d) Matsui, M.; Oji, A.; Hiramatsu, K.; Shibata, K.; Muramatsu, H. *J. Chem. Soc., Perkin Trans. 2* **1992**, 201. (e) Gundersen, L.-L.; Rise, F.; Undheim, K. *Tetrahedron* **1992**, *48*, 5647. (f) Shing, T. L.; Chia, W.-L.; Shiao, M.-J.; Chau, T.-Y. *Synthesis* **1991**, 849.

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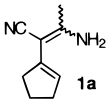
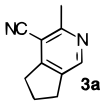
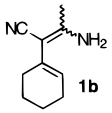
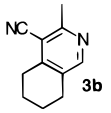
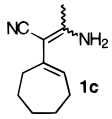
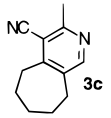
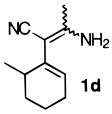
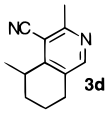
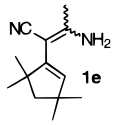
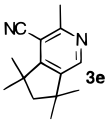
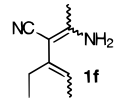
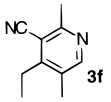
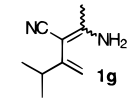
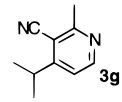
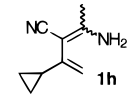
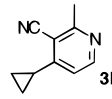
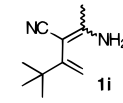
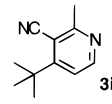
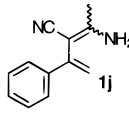
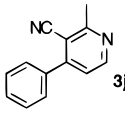
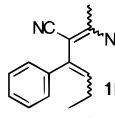
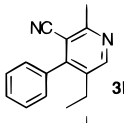
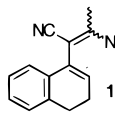
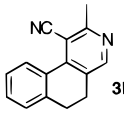
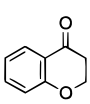
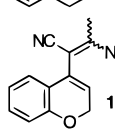
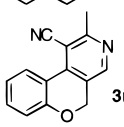
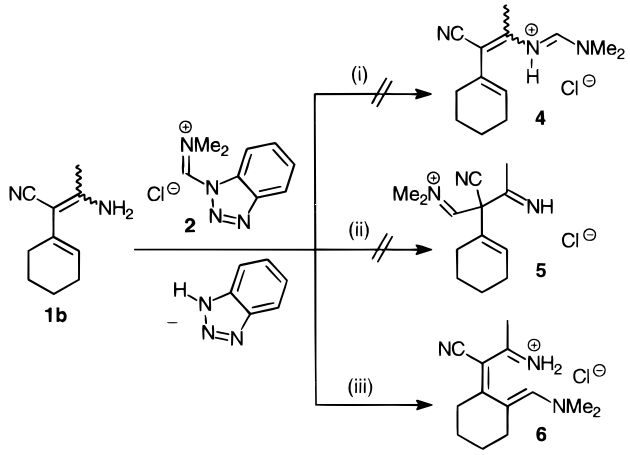
Table 1. Synthesis of Conjugated β-Enaminonitriles 1 from Ketones and β-Aminocrotononitrile Mediated by $TiCl_4$ and Conversion of 1 into Nicotinonitriles 3 by the Reaction with Iminium Salt 2

entry	ketone	enaminonitrile **1**	yield (%)[a]	nicotinonitrile **3**	yield (%)[b]
1		 **1a**	69	 **3a**	68
2		 **1b**	65	 **3b**	74
3		 **1c**	84	 **3c**	68
4		 **1d**	64	 **3d**	72
5		 **1e**	80[c]	 **3e**	60
6		 **1f**	65	 **3f**	75
7		 **1g**	72	 **3g**	57
8		 **1h**	72	 **3h**	50
9		 **1i**	73	 **3i**	56
10		 **1j**	66	 **3j**	60
11		 **1k**	78	 **3k**	70
12		 **1l**	77	 **3l**	55
13		 **1m**	59	 **3m**	50

[a] Yield of crude enaminonitrile **1**. [b] Isolated yield of nicotinonitrile **3** after Kugelrohr distillation. [c] The reaction time was 72 h.

1, entries 4 and 7) and forms almost exclusively the less substituted double bond, suggesting that the elimination step is kinetically controlled. The conjugated β-enaminonitriles **1a**−**m** were purified by distillation or column chromatography and characterized by elemental analysis, GC/MS, and NMR spectroscopy. According to their NMR spectra, they exist as *E*/*Z*- or as *E*,*E*/*E*,*Z*/*Z*,*E*/*Z*,*Z* diastereomeric mixtures. They can be stored at 0 °C for several weeks without any sign of decomposition. Dienamines corresponding to **1** but derived from aldehydes are unstable: attempts to prepare them (e.g., from propanal) by a method analogous to that used for the ketone derivatives **1a**−**m** led only to the formation of complex mixtures. To the best of our knowledge, conjugated β-enaminonitriles **1** have not been described before (e.g., no compounds of substructure $R^1CH{=}C(R^2)C(CN){=}C(R^3)$-$NH_2$ were found in the Beilstein Crossfire database).

Scheme 2



Reactions between the dienamines **1a**−**m** and the iminium salt **2** provided the nicotinonitriles **3a**−**m** in good yields (Scheme 1, Table 1). Structures **3a**−**m** were supported by comparison of the ^{1}H NMR data with those published for nicotinonitriles **3a**−**c**[11] and **3j**[12] (compare also ref 7b). Many literature methods are known for the preparation of specific classes of nicotinonitriles, e.g.: 4-trifluoromethyl,[7a] 6-aryl,[7b] 4-aryl,[7e] 4-benzyl,[7f] and 4,6-diaryl (or heteroaryl)[7d] derivatives. However, literature methods for the preparation of nicotinonitriles of type **3**[11,12] are of limited scope and generally give regioisomeric mixtures and poor yields. The reaction between dienamines **1** and iminium salt **2** provides for the first time a straightforward and versatile route to regioisomerically pure nicotinonitriles **3** (Table 1), including 4-alkyl and 4-phenyl derivatives (**3g**−**i**,**j**), simple 4,5-disubstituted derivatives (**3f**,**k**), and the corresponding fused bicyclic (**3a**−**e**) or tricyclic ring systems (**3l**,**m**). Our method can also be applied for the synthesis of nicotinonitriles **3** with bulky 4- and 5-substituents (**3d**−**e**,**g**,**i**).

To elucidate the mechanism of the transformation **1** into **3**, we monitored the reaction between the conjugated β-enaminonitrile **1b** and the Vilsmeier-type reagent **2** by ^{1}H and ^{13}C NMR spectroscopy. We observed the formation of a single iminium salt and of benzotriazole in virtually quantitative yield. A priori, reagent **2** could attack (i) at the amino group or (ii) at the α- or (iii) γ-C-atom of dienamine **1b**. Such modes of attack would produce intermediates **4**, **5**, or **6**, respectively (Scheme 2). However, an APT ^{13}C NMR experiment on the reaction

(11) Jutz, C.; Löbering, H.-G.; Trinkl, K.-H. *Synthesis* **1977**, 326.
(12) Shibata, K.; Urano, K.; Matsui, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2199.

mixture showed that the product possessed two CH_3 peaks at 21.7 and 34.6 ppm, four CH_2 peaks at 21.0, 21.1, 25.4, and 27.7 ppm, one CH peak at 149.5 ppm, and five quaternary C peaks at 109.7, 114.6, 131.7, 152.3, and 156.9 ppm. This spectrum is incompatible with structures **4** and **5** (inter alia, both molecules have two CH groups and four quaternary C atoms); therefore, the formation of **4** and **5** as intermediates can be excluded. By contrast, the NMR data for the transient intermediate are in good accord with structure **6** (only the most likely configuration is depicted). Hence, conjugated β-enaminonitriles such as **1b** react with iminium salt **2** in the manner of vinylogous enamines. Although a solution of intermediate **6** can be stored at ambient temperature for several days without decomposition, attempts to isolate **6** failed. The conversion of hydrochlorides such as **6** into their conjugated bases by the addition of aqueous NaOH solution evidently induces a spontaneous cyclization−elimination process furnishing the corresponding nicotinonitriles **3**.

Conclusion

In summary, we have developed a straightforward method for the preparation of previously unknown conjugated β-enaminonitriles **1** from ketones and β-aminocrotononitrile. We have demonstrated the great potential of dienamines **1** as synthetic building blocks. Their reaction with the Vilsmeier-type reagent **2** provides for the first time a broadly applicable and highly regioselective synthesis of nicotinonitriles of type **3**. Furthermore, our mild procedure should be suitable for sensitive substrates.

Experimental Section

General Methods. Melting points were determined on a Koefler hot-stage apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ referenced to TMS for the proton spectra and to the solvent for the carbon spectra. The benzotriazole iminium salt **2** was prepared by refluxing a THF solution of equimolar amounts of *N*-trimethylsilylbenzotriazole, DMF, and $SOCl_2$.[13] CH_2Cl_2 used for the reaction between dienamine **1** and iminium salt **2** was distilled under argon from CaH_2 prior to use. Column chromatography was conducted with silica gel (230−400 mesh).

General Procedure for the Synthesis of Conjugated β-Enaminonitriles 1. To a solution of β-aminocrotononitrile (4.9 g, 60 mmol) and NEt_3 (15.3 mL, 110 mmol) in CH_2Cl_2 (60 mL) cooled with an ice bath was added slowly with stirring a solution of $TiCl_4$ (3.3 mL, 30 mmol) in CH_2Cl_2 (40 mL). Subsequently, the ketone (50 mmol) was added in one portion. After the mixture was stirred for 24 h at ambient temperature, the solvent was removed in vacuo and the residue was crushed with a spatula. Then Et_2O (200 mL) was added, and the resulting mixture was stirred vigorously until the residue was ground to a fine powder. Subsequently, the powder was sucked off and washed with Et_2O (200 mL). Evaporation of the solvent provided the crude conjugated β-enaminonitriles **1**, which were used for the preparation of the nicotinonitriles **3** without prior purification. Analytical samples were purified by Kugelrohr distillation or flash column chromatography. In many cases, *E*/*Z* (the NMR data of the minor diasteromer are bracketed) or *E*,*E*/*Z*,*Z*/*E*,*Z*/*Z*,*E* mixtures were obtained. The diastereomeric ratios (dr) were determined by ^{1}H NMR spectroscopy after purification.

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3-Amino-2-(1-cyclopenten-1-yl)-2-butenenitrile (1a): yellow low-melting solid; dr = 3:1; ^{1}H NMR δ 5.56 (s, 1H), [5.42 (s, 1H)], 4.99 (br s, 2H), [4.80 (br s, 2H)], 2.60−2.20 (m, 2H, major and minor diastereomer), 2.11 (s, 3H), [2.01 (s, 3H)], 1.87−1.73 (m, 4H), [1.70−1.59 (m, 4H)]; ^{13}C NMR δ 155.0, [160.1], 135.9, [135.3], 125.6, [126.0], 121.6, [120.1], 78.5, [82.0], 35.8, [35.9], 33.2, [32.7], 22.5, [23.2], 20.9, [19.3]. Anal. Calcd for $C_9H_{12}N_2$: C, 72.93; H, 8.18; N, 18.91. Found: C, 73.11; H, 8.51; N, 18.46.

3-Amino-2-(1-cyclohexen-1-yl)-2-butenenitrile (1b): yellow solid; mp 76−77 °C; ^{1}H NMR δ 5.73 (br s, 1H), 4.69 (br s, 2H), 2.19−2.02 (m, 7H), 1.75−1.52 (m, 4H); ^{13}C NMR δ 153.7, 130.8, 127.8, 121.7, 83.2, 28.0, 25.4, 22.6, 21.9, 20.5. Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.72; N, 17.27. Found: C, 73.96; H, 9.08; N, 17.12.

3-Amino-2-(1-cyclohepten-1-yl)-2-butenenitrile (1c): yellow oil; dr = 8:1; ^{1}H NMR δ 5.91 (t, J = 6.6 Hz, 1H), [5.69 (t, J = 6.6 Hz, 1H)], 4.87 (br s, 2H), [4.77 (br s, 2H)], 2.34−2.30 (m, 2H), [2.55−2.48 (m, 2H)], 2.25−2.19 (m, 2H, major and minor diastereomer), 2.12 (s, 3H), [1.98 (s, 3H)], 1.85−1.70 (m, 2H, major and minor diastereomer), 1.61−1.48 (m, 4H, major and minor diastereomer); ^{13}C NMR δ 153.2, [153.1], 137.1, [137.0], 132.8, [133.1], 122.0, [120.2], 83.7, [83.6], 32.8, [43.6], 32.0, [33.7], 28.2, [30.1], 26.7, [26.2], 26.5, [24.0], 20.1, [19.1]; HRMS calcd for $C_{11}H_{16}N_2$ 176.1313, found 176.1316.

3-Amino-2-(6-methyl-1-cyclohexen-1-yl)-2-butenenitrile (1d): light yellow low-melting solid (consists of a major diastereomer, traces of the minor diastereomer and a regioisomer); major diastereomer, ^{1}H NMR δ 5.69 (t, J = 3.8 Hz, 1H), 4.73 (br s, 2H), 2.42−1.40 (m, 7H), 2.14 (s, 3H), 1.00 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 154.8, 135.5, 128.7, 121.8, 81.5, 31.2, 30.3, 25.7, 19.9, 19.5, 18.7. Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.17; N, 15.90. Found: C, 74.81; H, 9.24; N, 15.82.

3-Amino-2-(3,3,5,5-tetramethyl-1-cyclopenten-1-yl)-2-butenenitrile (1e): white solid; mp 41−43 °C; dr = 4:1; ^{1}H NMR δ 5.33 (s, 1H), [5.12 (s, 1H)], 4.75 (br s, 2H, major and minor diastereomer), 2.10 (s, 3H), [1.88 (s, 3H)], 1.62 (s, 2H, major and minor diastereomer), 1.13 (s, 6H), [1.08 (s, 6H)], 1.05 (s, 6H), [1.03 (s, 6H)]; ^{13}C NMR δ 157.1, [158.2], 140.5, [140.0], 140.4, [141.0], 122.1, [120.5], 74.7, [73.5], 54.9, [54.9], 48.4, [48.0], 42.9, [42.4], 30.4, [30.2], 29.4, [29.4], 20.1, [18.5]. Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.41; H, 9.89; N, 13.71. Found: C, 76.54; H, 10.24; N, 14.05.

2-(1-Aminoethylidene)-3-ethyl-3-pentenenitrile (1f): yellow oil (mixture of four diastereomers); major diastereomer, ^{1}H NMR δ 5.57−5.44 (m, 1H), 4.74 (br s, 2H), 2.24−2.12 (m, 6H, together with minor diastereomers), 1.74−1.66 (m, 2H), 1.02−0.92 (m, 3H, together with minor diastereomers); ^{13}C NMR δ 154.9, 134.9, 125.4, 122.0, 82.0, 22.9, 20.0, 13.2, 12.6. Anal. Calcd for $C_9H_{14}N_2$: N, 18.65. Found: N, 18.66.

2-Aminomethylidene-3-isopropyl-3-pentenenitrile (1g): yellow low-melting solid (consists of a major diastereomer, traces of the minor diastereomer and the regioisomer); major diastereomer, ^{1}H NMR δ 4.72 (s, 2H), 4.20 (s, 2H), 2.50−2.35 (m, 1H), 2.04 (s, 3H), 1.67 (s, 3H), 1.00 (t, J = 6.3 Hz, 3H); ^{13}C NMR δ 152.8, 132.9, 121.9, 120.2, 82.2, 32.2, 21.2, 20.0, 17.4. Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.41; N, 18.65. Found: C, 72.21; H, 9.48; N, 19.17.

3-Amino-2-(1-cyclopropylvinyl)-2-butenenitrile (1h): yellow oil; ^{1}H NMR δ 5.12 (s, 1H), 5.10−5.00 (m, 2H), 4.96 (s, 1H), 2.18 (s, 3H), 1.57−1.45 (m, 1H), 0.76 (d, J = 6.6 Hz, 2H), 0.61 (d, J = 5.2 Hz, 2H); ^{13}C NMR δ 155.6, 143.1, 121.8, 111.7, 80.5, 20.5, 16.2, 6.7. Anal. Calcd for $C_9H_{12}N_2$: C, 72.93; H, 8.18; N, 18.91. Found: C, 72.86; H, 8.31; N, 19.11.

3-Amino-2-[1-(*tert*-butyl)vinyl]-2-butenenitrile (1i): white solid; mp 77−79 °C; ^{1}H NMR δ 5.30 (s, 1H), 4.96 (s, 1H), 4.54 (br s, 2H), 2.10 (s, 3H), 1.10 (s, 9H); ^{13}C NMR δ 155.8, 150.6, 122.5, 116.5, 80.0, 37.9, 29.4, 19.7. Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.84. Found: C, 72.91; H, 10.00.

3-Amino-2-(1-phenylvinyl)-2-butenenitrile (1j): yellow oil; dr = 4:1; ^{1}H NMR δ 7.43−7.30 (m, 5H, major and minor diastereomer), 5.57 (s, 1H), [5.55 (s, 1H)], 5.38 (s, 1H), [5.21 (s, 1H)], 4.52 (br s, 2H), [4.88 (br s, 2H)], 2.19 (s, 3H), [1.78 (s, 3H)]; ^{13}C NMR δ 156.0, [157.2], 141.4, [141.8], 138.3, [140.0], 128.6, [128.6], 128.4, [128.3], 126.8, [126.2], 122.0, [120.5],

116.9, [117.0], 79.9, [79.2], 20.9, [18.9]. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.22; H, 6.58. Found: C, 78.09; H, 6.88.

2-(1-Aminoethylidene)-3-phenyl-3-hexenenitrile (1k): yellow low-melting solid (mixture of two diastereomers); dr = 6:1; ^{1}H NMR δ 7.34−7.17 (m, 5H, major and minor diastereomer), 6.00 (t, J = 7.4 Hz, 1H), [5.79 (t, J = 7.4 Hz, 1H)], 4.30 (br s, 2H), [4.73 (br s, 2H)], 2.17−2.10 (m, 5H), [2.08−2.00 (m, 5H)], 1.02 (t, J = 7.4 Hz, 3H), [0.93 (t, J = 7.4 Hz, 3H)]; ^{13}C NMR δ 155.8, [158.8], 139.0, [138.1], 136.2, [135.7], 131.1, [132.9], 128.5, [128.8], 127.5, [128.3], 126.2, [127.1], 121.7, [122.3], 82.9, [82.9], 23.3, [23.4], 19.8, [21.2], 13.5, [14.2]. Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.61; N, 13.20. Found: C, 78.83; H, 7.92; N, 13.21.

3-Amino-2-(3,4-dihydro-1-naphthalenyl)-2-butenenitrile (1l): yellow solid; mp 57−60 °C; ^{1}H NMR δ 7.21−7.13 (m, 4H), 6.20 (t, J = 4.5 Hz, 1H), 4.33 (br s, 2H), 2.79 (t, J = 7.9 Hz, 2H), 2.41−2.33 (m, 2H), 2.25 (s, 3H); ^{13}C NMR δ 156.1, 136.2, 131.9, 131.6, 130.3, 127.7, 127.5, 126.5, 124.0, 122.3, 77.3, 27.4, 23.1, 19.9. Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.72. Found: C, 80.20; H, 6.77.

3-Amino-2-(2*H*-chromen-4-yl)-2-butenenitrile (1m): tan solid; mp 110−113 °C; ^{1}H NMR δ 7.13−7.11 (m, 2H), 6.87 (t, J = 7.2 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 5.84 (s, 1H), 5.02 (br s, 2H), 4.76 (d, J = 2.9 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR δ 157.5, 154.3, 129.4, 127.8, 124.5, 123.7, 121.7, 121.1, 120.7, 115.8, 73.5, 64.8, 19.7. Anal. Calcd for $C_{13}H_{12}N_2O$: N, 13.20. Found: N, 13.22.

General Procedure for the Synthesis of Nicotinonitriles 3. The reactions were conducted in a water-free apparatus under argon. To a solution of the conjugated β-enaminonitriles **1** (4 mmol) in CH_2Cl_2 (20 mL) was added the iminium salt **2** (5 mmol) in one portion. The mixture was stirred for 24 h at ambient temperature. Subsequently, dilute NaOH (2 N, 40 mL) was added, and the resulting mixture was stirred vigorously for ca. 5 min. The organic phase was decanted off, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Kugelrohr distillation of the residue provided the nicotinonitriles **3**.

3-Methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile (3a): tan solid; mp 74−75 °C; ^{1}H NMR δ 8.41 (s, 1H), 3.03 (t, J = 7.5 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.66 (s, 3H), 2.10−2.03 (m, 2H); ^{13}C NMR δ 158.6, 158.4, 147.5, 137.7, 116.1, 105.8, 32.5, 30.1, 24.5, 23.1. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.38; N, 17.71. Found: C, 75.61; H, 6.56; N, 17.68.

3-Methyl-5,6,7,8-tetrahydro-4-isoquinolinecarbonitrile (3b): tan solid; mp 100−101 °C; ^{1}H NMR δ 8.34 (s, 1H), 2.96−2.88 (m, 2H), 2.80−2.73 (m, 2H), 2.70 (s, 3H), 1.92−1.81 (m, 4H); ^{13}C NMR δ 158.8, 152.2, 150.0, 130.5, 116.0, 109.1, 27.7, 25.7, 23.2, 21.8, 21.7. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.04; N, 16.27. Found: C, 76.65; H, 7.44; N, 16.30.

3-Methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carbonitrile (3c): light yellow solid; mp 35−37 °C; ^{1}H NMR δ 8.25 (s, 1H), 3.10−2.94 (m, 2H), 2.76−2.70 (m, 2H), 2.64 (s, 3H), 1.87−1.77 (m, 2H), 1.66−1.52 (m, 4H); ^{13}C NMR δ 159.4, 155.7, 150.8, 136.1, 116.5, 108.7, 33.6, 32.5, 32.0, 27.3, 26.4, 23.5; HRMS calcd for $C_{12}H_{14}N_2$ 187.1232, found 187.1235.

3,5-Dimethyl-5,6,7,8-tetrahydro-4-isoquinolinecarbonitrile (3d): yellow oil; ^{1}H NMR δ 8.35 (s, 1H), 3.30−3.20 (m, 1H), 2.83−2.78 (m, 1H), 2.74−2.60 (m, 1H), 2.71 (s, 3H), 1.90−1.78 (m, 4H), 1.36 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 158.8, 154.6, 152.4, 129.5, 116.1, 108.5, 30.7, 28.5, 25.5, 23.1, 21.3, 16.7. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.59; N, 15.04. Found: C, 76.93; H, 7.87; N, 15.13.

3,5,5,7,7-Pentamethyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile (3e): yellow solid; mp 63−65 °C; ^{1}H NMR δ 8.33 (s, 1H), 2.69 (s, 3H), 1.93 (s, 2H), 1.45 (s, 6H), 1.29 (s, 6H); ^{13}C NMR δ 163.0, 160.5, 147.2, 145.0, 116.1, 104.1, 57.0, 44.1, 41.0, 31.1, 28.7, 23.2. Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.48; N, 13.07. Found: C, 78.80; H, 8.87; N, 13.29.

4-Ethyl-2,5-dimethylnicotinonitrile (3f): yellow oil; ^{1}H NMR δ 8.30 (s, 1H), 2.83−2.73 (q, J = 7.4 Hz, J = 7.7 Hz, 2H), 2.64 (s, 3H), 2.25 (s, 3H), 1.16 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ 159.6, 155.1, 152.6, 128.7, 116.3, 109.0, 25.0, 23.4, 15.5, 13.3. Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.56; N, 17.49. Found: C, 74.64; H, 8.12; N, 17.56.

4-Isopropyl-2-methylnicotinonitrile (3g): yellow oil; ^{1}H NMR δ 8.51 (d, J = 5.2 Hz, 1H), 7.10 (d, J = 5.3 Hz; 1H), 3.33−3.20 (m, 1H), 2.71 (s, 3H), 1.26 (d, J = 6.8 Hz, 6H); ^{13}C NMR δ 161.8, 161.5, 151.8, 117.8, 116.0, 108.8, 32.4, 23.9, 22.4. Anal. Calcd for $C_{10}H_{12}N_2$: N, 17.49. Found: N, 17.58.

4-Cyclopropyl-2-methylnicotinonitrile (3h): tan crystals; mp 62−64 °C; ^{1}H NMR δ 8.37 (d, J = 5.5 Hz, 1H), 6.53 (d, J = 5.4 Hz, 1H), 2.68 (s, 3H), 2.26−2.15 (m, 1H), 1.22−1.18 (m, 2H), 0.84−0.81 (m, 2H); ^{13}C NMR δ 161.4, 158.0, 151.4, 116.3, 114.9, 109.7, 23.8, 14.0, 11.3. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.38; N, 17.71. Found: C, 75.96; H, 6.55; N, 17.58.

4-(*tert*-Butyl)-2-methylnicotinonitrile (3i): yellow crystals; mp 57−59 °C; ^{1}H NMR δ 8.47 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 5.5 Hz, 1H), 2.73 (s, 3H), 1.44 (s, 9H); ^{13}C NMR δ 163.3, 162.9, 151.7, 118.1, 117.9, 107.5, 35.7, 29.2, 24.1. Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.11; N, 16.08. Found: C, 75.89; H, 8.44; N, 16.24.

2-Methyl-4-phenylnicotinonitrile (3j): tan crystals; mp 103−104 °C; ^{1}H NMR δ 8.66 (d, J = 5.2 Hz, 1H), 7.59−7.49 (m, 5H), 7.27 (d, J = 5.2 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR δ 162.6, 153.1, 151.5, 135.9, 129.8, 128.9, 128.3, 121.2, 116.6, 107.7, 24.0. Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.20; N, 14.43. Found: C, 80.24; H, 5.15; N, 14.23.

5-Ethyl-2-methyl-4-phenylnicotinonitrile (3k): yellow oil; ^{1}H NMR δ 8.48 (s, 1H), 7.40−7.36 (m, 3H), 7.20−7.15 (m, 2H), 2.68 (s, 3H), 2.42 (q, J = 7.7 Hz, 2H), 0.94 (t, J = 7.7 Hz, 3H); ^{13}C NMR δ 159.0, 152.4, 152.1, 135.1, 134.7, 128.9, 128.5, 128.0, 116.2, 109.3, 23.4, 23.2, 15.0. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.04; H, 6.36; N, 12.61. Found: C, 80.79; H, 6.36; N, 12.94.

2-Methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carbonitrile (3l): tan crystals; mp 165−167 °C; ^{1}H NMR δ 8.51 (s, 1H), 8.43−8.39 (m, 1H), 7.44−7.38 (m, 2H), 7.35−7.31 (m, 1H), 2.83 (s, 3H), 2.85−2.79 (m, 4H); ^{13}C NMR δ 161.8, 150.4, 144.9, 139.6, 130.8, 130.6, 129.7, 128.3, 127.2, 126.9, 118.0, 103.8, 28.6, 25.4, 24.0. Anal. Calcd for $C_{15}H_{12}N_2$: N, 12.72. Found: N, 12.59.

2-Methyl-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitrile (3m): tan crystals; mp 163−165 °C; ^{1}H NMR δ 8.51 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 5.04 (s, 2H), 2.84 (s, 3H); ^{13}C NMR δ 163.3, 156.6, 147.3, 140.1, 133.2, 126.3, 124.7, 122.6, 119.0, 117.9, 117.4, 102.3, 65.4, 24.1. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.31; H, 4.69; N, 12.39.

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Supporting Information Available: ^{1}H and C^{13} NMR and HRMS spectra for compounds **1c** and **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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