New *N*-Halosuccinimide-Mediated Reactions for the Synthesis of Pyridines

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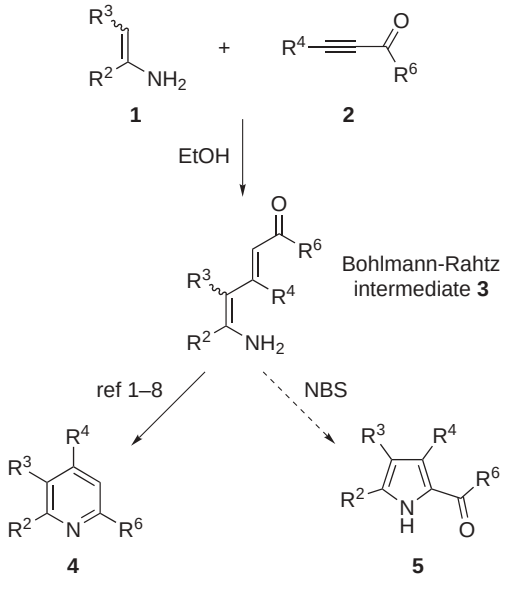
Abstract: 5-Bromo-2,6-dialkylpyridine-4-carboxylates are generated in excellent yield by the Michael addition of enaminoesters and ethynyl ketones followed by bromocyclization using *N*-bromosuccinimide within 1 hour at 0 °C. Treatment of the same aminopentadienone intermediates with *N*-iodosuccinimide facilitates a low temperature cyclodehydration under very mild conditions to give 2,3,6-trisubstituted pyridines with total regiocontrol.

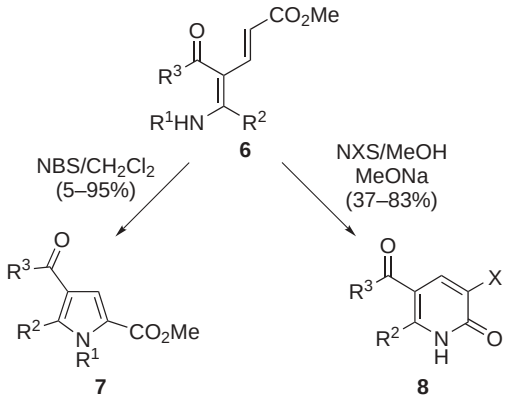
Key words: pyridines, β-enaminoesters, bromocyclization, Bohlmann–Rahtz

The development of new routes to polysubstituted pyridines, with diversity in the nature of substituents, continues to attract considerable attention for application in heterocyclic chemistry, natural product synthesis and medicinal chemistry. We have developed new heteroannulation methods for the synthesis of 2,3,6-trisubstituted and 2,3,4,6-tetrasubstuted pyridines **4** using either the acid catalyzed Bohlmann–Rahtz reaction[1–3] or microwave irradiation[4] of enaminoesters **1** and alkynones **2** (Scheme 1) and applied these reactions in the synthesis of fused heterocycles[5,6] and multiple-component reactions.[7] In order to expand the versatility of these processes, and introduce diversity in the target heterocycle accessible from these precursors, we set out to investigate the bromocyclization of aminodienone intermediates **3** generated in the traditional Bohlmann–Rahtz reaction.[8]



Scheme 1 Proposed route for pyrrole **5** synthesis.

Dechoux reported recently that when δ-dienaminoesters **6** were treated with *N*-bromosuccinimide (NBS) under neutral conditions, 1,2,3,5-tetrasubstituted pyrroles **7** were formed,[9] whereas under basic conditions treatment with *N*-halosuccinimides generated the corresponding 3-halo-2-1*H*-pyridones **8** in reasonable yield (Scheme 2).[10] Based upon this precedent, the NBS-mediated bromocyclization of Bohlmann–Rahtz intermediates, generated by a Michael addition, under neutral conditions was expected to provide a two-step route to pyrrole heterocycles **5** (Scheme 1).



Scheme 2 Dechoux's synthesis of pyrroles **7**[9] and pyridinones **8**.[10]

In order to facilitate the initial Michael addition, enamines **1a**–**d** were reacted with alkynones **2a**–**f**[3] in ethanol at 50 °C to give the aminodienones **3a**–**g**[8] after purification on silica (Scheme 3). The course of reaction was followed by TLC analysis, in order to minimize cyclodehydration of dienones **3** to pyridines **4**. The optimum conditions[11] involved stirring the enamine **1** and alkynone **2** in EtOH at 50 °C for 1–18 hours to give the Michael addition product **3a**–**g**, for the most part, in good yield (Table 1).

Ethynyl ketones, such as **2a**–**d**, were usually successful in this reaction (Scheme 3, Table 1, entries 1–4), but transformations involving hexynone **2e**, phenylbutynone **2f** or aminocrotonitrile **1d** failed to give appreciable yields of the product, principally due to spontaneous cyclodehydration under the reaction conditions to give the corresponding pyridine **4**.

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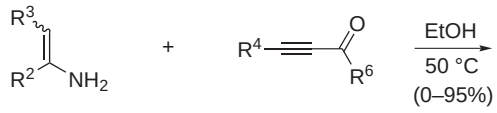
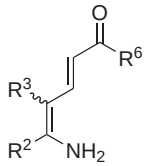


1 R^2, R^3
a Me, CO_2Et;
b Ph, CO_2Et;
c Me, $CO_2{}^tBu$;
d Me, CN.

2 R^4, R^6
a H, Ph; **b** H, 4-$MeOC_6H_4$;
c H, 4-ClC_6H_4; **d** $SiMe_3$, Me;
e Et, Me; **f** Ph, Me.



3 R^2, R^3, R^6
a Me, CO_2Et, Ph;
b Me, CO_2Et, 4-$MeOC_6H_4$;
c Me, CO_2Et, 4-ClC_6H_4;
d Me, CO_2Et, Me;
e Ph, CO_2Et, Ph;
f Ph, CO_2Et, Me;
g Me, $CO_2{}^tBu$, Me.

Scheme 3 Synthesis of Bohlmann–Rahtz intermediates **3a–g**.

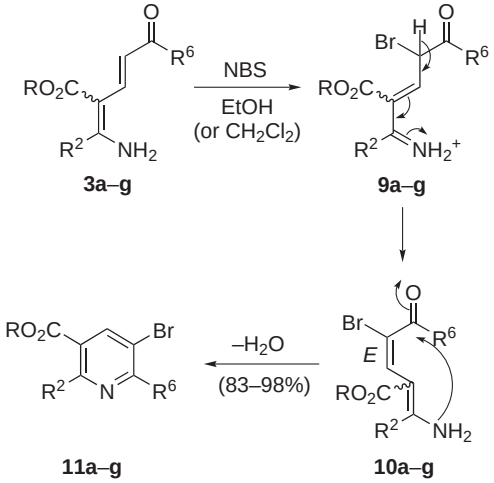
Table 1 Michael Addition of Enamines **1** and Alkynones **2**

Entry	Enamine	Alkynone	Product	Time (h)	Yield (%)
1	**1a**	**2a**	**3a**	1	85
2	**1a**	**2b**	**3b**	6	95
3	**1a**	**2c**	**3c**	6	86
4	**1a**	**2d**	**3d**	6	82
5	**1a**	**2e,f**	–	6	0[a]
6	**1b**	**2a**	**3e**	7	68
7	**1b**	**2d**	**3f**	3	23[a]
8	**1c**	**2d**	**3g**	18	68

[a] Significant cyclodehydration to pyridine **4** accompanied the reaction.

The bromocyclization of aminodienone **3a** (R^2 = Me, R^3 = CO_2Et, R^6 = Ph) with NBS was investigated in CH_2Cl_2 at 0 °C according to the reported conditions.[9] However, surprisingly, no pyrrole **5** could be isolated from the reaction mixture and instead facile bromination-cyclodehydration occurred to give the bromopyridine **11a** (Scheme 4) in 63% yield along with a trace of trisubstituted pyridine **4a** (R^4 = H) that could be separated easily from the main product by washing with dilute acid as a consequence of the reduced basicity of the 5-bromopyridine.

Considering the difficulty experienced in previous studies to facilitate the acid-catalyzed cyclodehydration of Bohlmann–Rahtz intermediates,[1–3] which proceeds under traditional uncatalyzed conditions often at temperatures in excess of 120 °C (and for certain substrates requires temperatures in the region of 200 °C),[5,8] this finding seemed startling since the reaction was complete after only 15 minutes at 0 °C. The course of the reaction was rationalized by considering initial regioselective addition to give *s-cis* bromide **9a**, in equilibrium with the *s-trans* conformer (Scheme 4).[9] Facile deprotonation, rather than intramolecular nucleophilic substitution, prevents the formation of pyrrole **4a** and gives instead the (4*E*)-hexadienone intermediate **10a**, thus avoiding the need for double bond isomerization. This will undergo spontaneous cyclodehydration under mild reaction conditions to give pyridine **11a**. We would expect that the cyclization of bromodienone **10a** to pyridine **11a** would be much more facile than the corresponding cyclization of δ-dienaminoesters **6** to give pyridinones **8** and so proceeds under milder reaction conditions in the absence of sodium methoxide base.[10] This method provides 5-substituted pyridines possessing latent functionality suitable for subsequent elaboration, a substitution pattern hitherto unavailable by traditional Bohlmann–Rahtz methodology.



Scheme 4 Proposed mechanistic course of the bromocyclization.

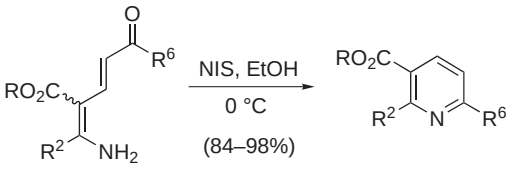
In order to explore the scope of this new bromination-heteroannulation procedure, a range of different aminodienones **3a–g** was treated with NBS at 0 °C for between 30 and 60 minutes. It was found that reactions conducted in EtOH,[12] as opposed to CH_2Cl_2, were much more efficient, reducing formation of the corresponding pyridine **4** as a reaction byproduct, to give the 5-bromopyridines **11a–g**[13–19] in excellent yield (Scheme 4, Table 2).

Table 2 Bromocyclization of Aminodienones **3a–g** with NBS

Entry	Diene	Product	R^2	R	R^6	Yield (%)
1	**3a**	**11a**[13]	Me	Et	Ph	92
2	**3b**	**11b**[14]	Me	Et	4-$MeOC_6H_4$	88
3	**3c**	**11c**[15]	Me	Et	4-ClC_6H_4	89
4	**3d**	**11d**[16]	Me	Et	Me	96
5	**3e**	**11e**[17]	Ph	Et	Ph	83[a]
6	**3f**	**11f**[18]	Ph	Et	Me	>98
7	**3g**	**11g**[19]	Me	*t*-Bu	Me	97

[a] Reaction was run at –10 °C to prevent formation of pyridine **4e**.

With the scope and versatility of the method established, it was decided to investigate other *N*-halosuccinimides in the halogenation/heteroannulation process. The use of *N*-chlorosuccinimide in EtOH at 0 °C led only to a complex mixture of products. However, when aminodienones **3a**–**d**, **3f** or **3g** were treated with *N*-iodosuccinimide (NIS) in EtOH at 0 °C none of the corresponding 5-iodopyridines were produced and instead an extremely facile cyclodehydration of the normally stable[20] dienes **3** occurred to give the 2,3,6-trisubstituted pyridines **4**[3] (Scheme 5, Table 3).[21] Furthermore, the use of a catalytic quantity of NIS (20 mol%) did not adversely affect the course or efficiency of reaction, generating pyridine **4a** in quantitative yield (entry 2).



3a–d,f,g **4a–d,f,g**

Scheme 5 NIS-mediated cyclodehydration of aminodienones **3**.

Table 3 Cyclodehydration of Aminodienones **3** with NIS

Entry	Diene	Product	R^2	R	R^6	Yield%
1	**3a**	**4a**	Me	Et	Ph	>98
2[a]	**3a**	**4a**	Me	Et	Ph	>98
3	**3b**	**4b**	Me	Et	4-$MeOC_6H_4$	>98
4	**3c**	**4c**	Me	Et	4-ClC_6H_4	97
5	**3d**	**4d**	Me	Et	Me	66
6[b]	**3d**	**4d**	Me	Et	Me	71
7[c]	**3d**	**4d**	Me	Et	Me	84
8	**3f**	**4f**	Ph	Et	Me	>98
9[b]	**3g**	**4g**	Me	^{t}Bu	Me	>98

[a] A catalytic (20 mol%) quantity of NIS was used.
[b] Reactions were run in the presence of $NaHCO_3$.
[c] Reaction was run over the course of 4 h rather than 1 h.

It was proposed that the Lewis acidity of NIS was responsible for this remarkably facile cyclodehydration, that traditionally requires temperatures well in excess of 120 °C, and this was supported by further experimentation. Repeating the process in the absence of NIS returned unreacted starting material **3** only. When the NIS was purified by recrystallization prior to use, or employed in the presence of $NaHCO_3$ (to remove HI present or generated throughout the course of reaction), this did not adversely affect the yield of pyridine **4** and in some instances improved the reaction efficiency. The use of NIS in EtOH represents a new mild method for the low temperature cyclodehydration of Bohlmann–Rahtz intermediates for the synthesis of 2,3,6-trisubstituted pyridines **4** in excellent yield and with total regiocontrol.

In summary, *N*-halosuccinimide-mediated processes provide complementary and efficient routes to either 2,3,5,6-tetrasubstituted or 2,3,6-trisubstituted pyridines under mild conditions. The reaction of Bohlmann–Rahtz intermediates, generated by Michael addition of an enaminoester and ethynyl ketone, with *N*-bromosuccinimide provides facile access to 5-bromopyridines, whereas treatment of the same aminodienone intermediates with *N*-iodosuccinimide facilitates the rapid cyclodehydration of these substrates at a, comparatively, low temperature.

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References

(1) Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149.
(2) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523.
(3) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.
(4) Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331.
(5) Bagley, M. C.; Hughes, D. D.; Lloyd, R.; Powers, V. E. C. *Tetrahedron Lett.* **2001**, *42*, 6585.
(6) Bagley, M. C.; Hughes, D. D. *Synlett* **2002**, 1332.
(7) Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682.
(8) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
(9) (a) Agami, C.; Dechoux, L.; Hebbe, S. *Synlett* **2001**, 1440. (b) Agami, C.; Dechoux, L.; Hamon, L.; Hebbe, S. *Synthesis* **2003**, 859.
(10) Agami, C.; Dechoux, L.; Hebbe, S.; Moulinas, J. *Synlett* **2002**, 79.
(11) **General Procedure for Michael Addition of Enamines 1 and Alkynones 2.** A solution of enamine **1** (0.36 mmol, 1 equiv) and alkynone (0.56 mmol, 1.5 equiv) in EtOH (5 mL) was stirred at 50 °C for 1–7 h, cooled and evaporated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc–light petroleum gave dienone **3**.
(12) **General Procedure for the Bromocyclization of Aminodienones 3 using NBS.** A solution of aminodienone **3** (0.28 mmol, 1 equiv) and *N*-bromosuccinimide (0.34 mmol, 1.2 equiv) in EtOH (5 mL) was stirred at 0 °C for 1 h and evaporated in vacuo. Purification by column chromatography on silica gave bromopyridine **11a**–**g**.
(13) Ethyl 5-bromo-2-methyl-6-phenylpyridine-3-carboxylate (**11a**). Mp 88–89 °C (aq MeOH). HRMS: *m/z* [MH] calcd for $C_{15}H_{14}{}^{79}BrNO_2$: 320.0286; found [$MH^+$]: 320.0286. IR (KBr): 2974, 2925, 1730, 1571, 1432, 1286, 1259, 1090, 1016, 928, 835, 780, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, 4-H), 7.64 (m, 2 H, *o*-Ph*H*), 7.41 (m, 3 H, *m,p*-Ph*H*), 4.34 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.77 (s, 3 H, 2-Me), 1.36 (t, *J* = 7.1 Hz, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.6 (C), 160.2 (C), 158.8 (C), 143.8 (CH), 139.3 (C), 129.8 (CH), 129.7 (CH), 128.5 (CH), 125.4 (C),

116.6 (C), 62.0 (CH_2), 25.0 (Me), 14.7 (Me). MS (APcI): *m*/*z* (%) = 322 (36) {M[^{81}Br]H$^+$}, 320 (37) {M[^{79}Br]H$^+$}, 242 (9), 93 (23), 79 (100).

(14) Ethyl 5-bromo-2-methyl-6-(4-methoxyphenyl)pyridine-3-carboxylate (**11b**). Mp 90–91 °C (MeOH). HRMS: *m*/*z* [MH] calcd for $C_{16}H_{16}BrNO_3$: 350.0392; found [MH$^+$]: 350.0393. IR (KBr): 2963, 1724, 1609, 1570, 1512, 1433, 1257, 1178, 1087, 1027, 803, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H, 4-H), 7.66 (d, *J* = 8.8Hz, 2 H, 2′-H, 6′-H), 6.91 (d, *J* = 8.8 Hz, 2 H, 3′-H, 5′-H), 4.34 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$Me), 3.79 (s, 3 H, OMe), 2.75 (s, 3 H, Me), 1.34 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7 (C), 160.8 (C), 159.6 (C), 158.7 (C), 143.8 (CH), 131.6 (C), 131.4 (CH), 124.8 (C), 116.2 (C), 113.8 (CH), 61.9 (CH_2), 55.8 (Me), 25.0 (Me), 14.7 (Me). MS (APcI): *m*/*z* (%) = 352 (32) {M[^{81}Br]H$^+$}, 350 (50) {M[^{79}Br]H$^+$}.

(15) Ethyl 5-bromo-2-methyl-6-(4-chlorophenyl)pyridine-3-carboxylate (**11c**). Mp 106–108 °C (aq EtOH). HRMS: *m*/*z* [MH] calcd for $C_{15}H_{13}BrClNO_2$: 353.9896; found [MH$^+$]: 353.9896. IR (KBr): 2973, 1730, 1595, 1570, 1534, 1492, 1432, 1259, 1089, 1016, 928, 835, 780 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H, 4-H), 7.61 (d, *J* = 8.6 Hz, 2 H, 2′-H, 6′-H), 7.37 (d, *J* = 8.6 Hz, 2 H, 3′,5′-H), 4.34 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$Me), 2.75 (s, 3 H, Me), 1.35 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.1 (C), 158.5 (C), 158.4 (C), 143.5 (CH), 137.2 (C), 135.4 (C), 130.8 (CH), 128.3 (CH), 125.3 (C), 116.0 (C), 61.7 (CH_2), 24.5 (Me), 14.3 (Me). MS (APcI): *m*/*z* (%) = 358 (16) {M[^{81}Br^{37}Cl]H$^+$}, 356 (100) [MH$^+$], 358 (71) {M[^{79}Br^{35}Cl]H$^+$}, 117 (38), 71 (30).

(16) Ethyl 5-bromo-2,6-dimethylpyridine-3-carboxylate (**11d**). Mp 32.1–32.2 °C. Anal. Calcd for $C_{10}H_{12}BrNO_2$: C, 46.5; H, 4.7; N, 5.4. Found: C, 46.5; H, 5.0; N, 5.4. HRMS: *m*/*z* [MH] calcd for $C_{10}H_{12}{}^{79}BrNO_2$: 258.0129; found [MH$^+$]: 258.0124. IR (film): 2984, 1725, 1576, 1542, 1436, 1392, 1366, 1267, 1232, 1100, 1025, 970, 780, 680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H, 4-H), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.69 (s, 3 H, 6-Me), 2.60 (s, 3 H, 2-Me), 1.33 (t, *J* = 7.1 Hz, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6 (C), 160.3 (C), 158.4 (C), 142.0 (CH), 124.7 (C), 118.3 (C), 61.8 (CH_2), 25.4 (Me), 24.7 (Me), 14.6 (Me). MS (APcI): *m*/*z* (%) = 260 (100) {M[^{81}Br]H$^+$}, 258 (95) {M[^{79}Br]H$^+$}.

(17) Ethyl 5-bromo-2,6-diphenylpyridine-3-carboxylate (**11e**). HRMS: *m*/*z* [M] calcd for $C_{20}H_{16}NO_2Br$: 381.0364; found [M$^+$]: 381.0360. IR (KBr): 2976, 1732, 1558, 1426, 1372, 1244, 1114, 1088, 1017, 922, 772, 687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 1 H, 4-H), 7.71 (m, 2 H, 6-(*o*-Ph*H*)], 7.50 (m. 2 H, 2-(*o*-Ph*H*)], 7.43–7.33 (m, 6 H, *m*,*p*-Ph*H*), 4.12 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.02 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7 (C), 159.2 (C), 157.2 (C), 143.0 (CH), 139.2 (C), 138.8 (C), 129.6 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 126.5 (C), 117.3 (C), 61.8 (CH_2), 13.7 (Me). MS (APcI): *m*/*z* (%) = 384 (100) {MH$^+$}, 382 (80) [MH$^+$], 304 (15).

(18) Ethyl 5-bromo-6-methyl-2-phenylpyridine-3-carboxylate (**11f**). HRMS: *m*/*z* [MH$^+$] calcd for $C_{15}H_{14}NO_2Br$: 320.0281; found: 320.0281. IR (nujol): 2918, 2853, 1725, 1572, 1462, 1377, 1295, 1242, 1112, 1061, 1027, 771, 722, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H, 4-H), 7.50–7.34 (m, 5 H, Ph*H*), 4.05 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.68 (s, 3 H, Me), 1.00 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (C), 159.6 (C), 157.2 (C), 141.3 (CH), 139.5 (C), 128.7 (CH), 128.5 (CH), 128.2 (CH), 125.8 (C), 119.3 (C), 61.7 (CH_2), 25.3 (Me), 13.7 (Me). MS (APcI): *m*/*z* (%) = 322 (100) [MH$^+$], 320 (98).

(19) *tert*-Butyl 5-bromo-2,6-dimethylpyridine-3-carboxylate (**11g**). HRMS: *m*/*z* [M$^+$] calcd for $C_{12}H_{16}NO_2Br$: 285.0359; found: 285.0359. IR (nujol): 2922, 2852, 1726, 1579, 1462, 1377, 1277, 1167, 1095, 970, 848, 782, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, 4-H), 2.81 (s, 3 H, Me), 2.62 (s, 3 H, Me), 1.55 (s, 9 H, CMe_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3 (C), 165.1 (C), 159.9 (C), 157.9 (C), 142.0 (CH), 124.5 (C), 118.1 (C), 24.9 (Me), 24.1 (Me), 14.3 (Me). MS (APcI): *m*/*z* (%) = 288 (100) [MH$^+$], 286 (94).

(20) For example, stirring a solution of aminodienone **3d** in EtOH at 0 °C for 1 h results in the return of unreacted starting material and no cyclodehydration to pyridine **4d**.

(21) **General Procedure for the Cyclodehydration of Aminodienones 3 using NIS.** A solution of aminodienone **3** (0.2 mmol, 1 equiv) and *N*-iodosuccinimide (0.25 mmol, 1.2 equiv) in EtOH (4 mL) was stirred at 0 °C for 1 h and evaporated in vacuo. Purification by flash chromatography on silica, eluting with EtOAc–light petroleum, gave pyridine **4**.