An Efficient Synthesis of Fused 3-Formylpyridines and 5-Formylpyrimidines

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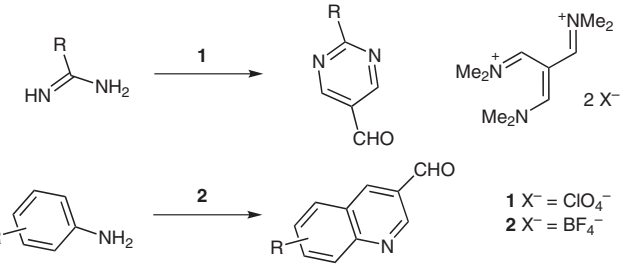
Abstract: Cyclization of 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate with various amino heterocycles led to the formation of a series of fused heterocyclic systems containing a 3-formylpyridine or 5-formylpyrimidine unit.

Key words: fused pyridines, fused pyrimidines, cyclization reactions, amino heterocycles, 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate

Derivatives of 3-formylpyridine and 5-formylpyrimidine are valuable building blocks commonly used in medicinal chemistry.[1] These compounds are usually obtained through multistep and low-yielding synthetic procedures that can not be applied to combinatorial synthesis of diverse compound libraries needed for systematic QSAR studies.[2] The reaction of 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate (**1**) with amidines gives the corresponding 2-substituted 5-formylpyrimidines (Scheme 1).[3] It is also known that an analogue of **1**, 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane bis(tetrafluoroborate) (**2**), reacts with electron-rich anilines to provide 3-formylquinolines (Scheme 1).[4] We expected that similar cyclization reactions of the readily available vinamidinium salt **1**[5] might occur with various five-membered amino heterocycles to give novel compounds containing a fused 3-formylpyridine or 5-formylpyrimidine unit.

Indeed, the reaction of salt **1** with derivatives of 2-aminopyrrole **3**, 2-aminofuran **4**, 2-aminothiophene **5** and **6**, 3-aminothiophene **7**, 5-aminoisoxazole **8**–**11** and 3-aminopyrazole **12** and **13** in the presence of 0.4 N sodium methoxide in methanol under reflux led to the formation



Scheme 1 Synthesis of 5-formylpyrimidines and 3-formylquinolines[3,4]

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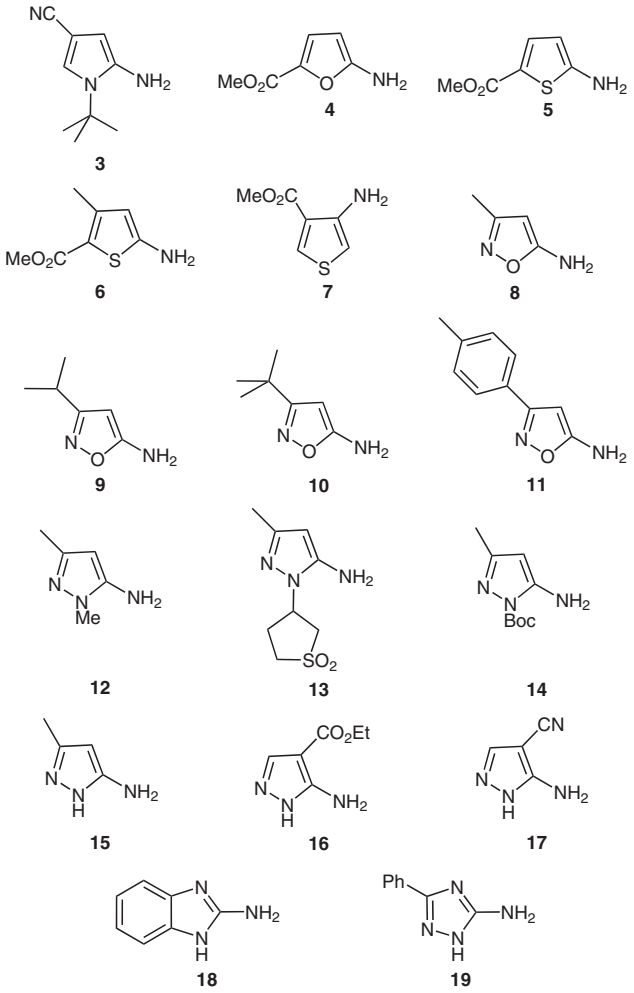


Figure 1 Structures of the five-membered amino heterocycles **3**–**19**

of the corresponding fused 3-formylpyridines **3a**–**13a** in 34–99% yield (Figure 1 and Table 1).

Unexpectedly, the *N*-Boc-protected aminopyrazole **14** under the same reaction conditions afforded two isomeric products **14a** (32%) and **14b** (64%), both possessing no Boc group (Table 1). In contrast, aminopyrazole **15** reacted with salt **1** as an N,N bis-nucleophile to provide the sole isomer **14b**. The structure of both isomers **14a/14b** was confirmed by directed synthesis of **14a** (Scheme 2). Cleavage of the *N*-sulfolanyl protecting group in **13a** afforded compound **14a**, identical to the isomer formed as the minor product in the reaction of the Boc-protected aminopyrazole **14** with salt **1**.

Table 1 Synthesis of 3-Formylpyridines and 5-Formylpyrimidines[a]

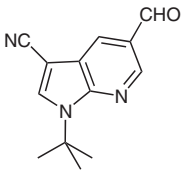
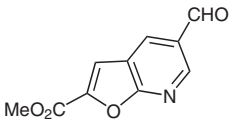
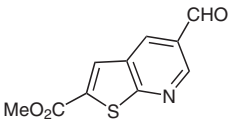
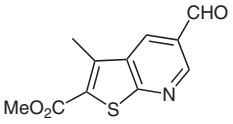
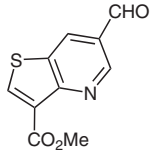
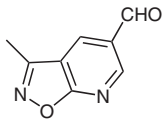
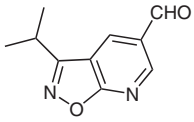
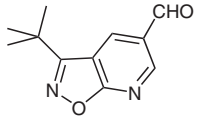
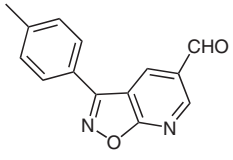
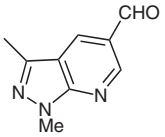
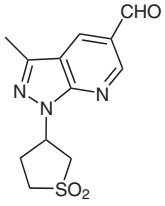
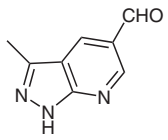
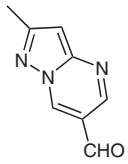
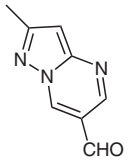
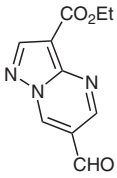
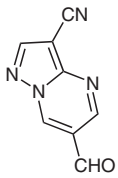
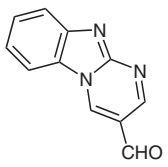
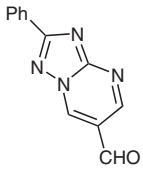
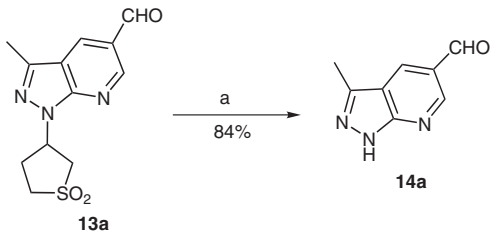
Starting amino heterocycle	Product		Yield (%)
3	**3a**		34
4	**4a**		38
5	**5a**		43
6	**6a**		57
7	**7a**		64
8	**8a**		57
9	**9a**		52
10	**10a**		61
11	**11a**		99
12	**12a**		80
13	**13a**		76

Table 1 Synthesis of 3-Formylpyridines and 5-Formylpyrimidines[a] (continued)

Starting amino heterocycle	Product		Yield (%)
			
		14a	
14	**14a + 14b**		**14a**: 32 **14b**: 64
			
		14b	
15	**14b**		44
16	**16b**		27
17	**17b**		53
18	**18b**		80
19	**19b**		39

[a] Reaction conditions: salt **1**, 0.4 N NaOMe, MeOH, reflux, 12 h.



Scheme 2 *Reagents and conditions*: a) 15% aq HCl, heating at reflux, 6 h.

Amino heterocycles **16–19** with an α-NH moiety reacted with salt **1** to give the corresponding fused 5-formylpyrimidines **16b–19b** in 27–80% yield (Figure 1 and Table 1).

In conclusion, the cyclization reaction of 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate (**1**) with various five-membered amino heterocycles is a facile method for the synthesis of fused 3-formylpyridines and 5-formylpyrimidines.

Solvents were purified according to standard procedures. All other materials were purchased from Aldrich and Enamine Ltd. Melting points are uncorrected. Analytical TLC was perfomed using Polychrom SI F_{254} plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9 and 124.9 MHz, respectively). Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument using chemical ionization (CI). 2-Dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate (**1**) was prepared according to the literature procedure.[5a]

Fused 3-Formylpyridines and 5-Formylpyrimidines; General Procedure

A soln of 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate (**1**; 3.82 g, 10 mmol) and an amino heterocycle **3–19** (10 mmol) in 0.4 N NaOMe in anhyd MeOH (50 mL) was heated at reflux for 12 h. Thereafter, the reaction mixture was cooled to r.t., which was followed by the addition of H_2O (10 mL). The formed suspension was concentrated under reduced pressure to remove the MeOH. The obtained residue was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude product **3a–13a**, **14a/14b**, **14b**, **16b–19b**. Crystallization (MeOH) afforded pure **3a–13a**, **14b**, **16b–19b**. The mixture **14a/14b** was separated by flash column chromatography. Elution with $CHCl_3$ provided isomer **14b** (1.04 g, 6.4 mmol, 64% yield); further elution with MeOH afforded isomer **14a** (0.52 g, 3.2 mmol, 32% yield).

1-*tert*-Butyl-5-formyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (3a)

Yellow solid; yield: 0.77 g (34%); mp 184 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (s, 9 H), 8.58 (s, 1 H), 8.69 (s, 1 H), 8.92 (s, 1 H), 10.17 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.9, 59.6, 84.1, 115.1, 120.9, 126.7, 129.8, 138.7, 145.85, 149.0, 192.2.

MS: m/z = 228 $[M + 1]^+$.

Methyl 5-Formylfuro[2,3-*b*]pyridine-2-carboxylate (4a)

Yellow solid; yield: 0.78 g (38%); mp 193 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 7.91 (s, 1 H), 8.76 (s, 1 H), 9.03 (s, 1 H), 10.18 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 53.2, 114.3, 119.9, 129.9, 134.7, 146.1, 150.8, 158.9, 163.9, 191.8.

MS: m/z = 206 $[M + 1]^+$.

Methyl 5-Formylthieno[2,3-*b*]pyridine-2-carboxylate (5a)

Yellow solid; yield: 0.95 g (43%); mp 180 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 8.37 (s, 1 H), 8.91 (s, 1 H), 9.18 (s, 1 H), 10.21 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 53.4, 129.2, 130.0, 132.3, 134.2, 135.5, 150.6, 162.2, 166.3, 192.2.

MS: m/z = 222 $[M + 1]^+$.

Methyl 5-Formyl-3-methylthieno[2,3-*b*]pyridine-2-carboxylate (6a)

Pale brown solid; yield: 1.34 g (57%); mp 197 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.72 (s, 3 H), 3.91 (s, 3 H), 8.75 (s, 1 H), 9.09 (s, 1 H), 10.20 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.0, 52.8, 127.3, 128.6, 133.2, 133.8, 140.1, 150.2, 162.5, 164.7, 191.8.

MS: m/z = 236 $[M + 1]^+$.

Methyl 6-Formylthieno[3,2-*b*]pyridine-3-carboxylate (7a)

Brown solid; yield: 1.42 g (64%); mp 169 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 9.10 (d, J = 2.0 Hz, 1 H), 9.21 (s, 1 H), 9.24 (d, J = 2.0 Hz, 1 H), 10.21 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.3, 127.3, 127.3, 133.5, 134.0, 147.0, 149.6, 155.4, 161.9, 192.0.

MS: m/z = 222 $[M + 1]^+$.

3-Methylisoxazolo[5,4-*b*]pyridine-5-carbaldehyde (8a)

Pale brown solid; yield: 0.93 g (57%); mp 139 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 8.90 (s, 1 H), 9.15 (s, 1 H), 10.19 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 10.8, 114.5, 129.2, 135.0, 154.0, 157.9, 171.2, 191.2.

MS: m/z = 163 $[M + 1]^+$.

3-Isopropylisoxazolo[5,4-*b*]pyridine-5-carbaldehyde (9a)

Yellow solid; yield: 0.99 g (52%); mp 75 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (d, J = 6.8 Hz, 6 H), 3.50 (m, J = 6.8 Hz, 1 H), 9.01 (d, J = 1.0 Hz, 1 H), 9.14 (d, J = 1.0 Hz, 1 H), 10.19 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9, 27.2, 112.9, 129.1, 135.7, 153.4, 165.3, 171.4, 191.3.

MS: m/z = 191 $[M + 1]^+$.

3-*tert*-Butylisoxazolo[5,4-*b*]pyridine-5-carbaldehyde (10a)

Yellow solid; yield: 1.25 g (61%); mp 48 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 9.07 (s, 2 H), 10.19 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.8, 34.3, 112.1, 129.0, 136.9, 152.5, 167.2, 171.6, 191.3.

MS: m/z = 205 $[M + 1]^+$.

3-(4-Methylphenyl)isoxazolo[5,4-*b*]pyridine-5-carbaldehyde (11a)

Yellow solid; yield: 2.36 g (99%); mp 152 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 7.38 (d, J = 6.6 Hz, 2 H), 7.89 (d, J = 6.6 Hz, 2 H), 9.07 (s, 1 H), 9.14 (s, 1 H), 10.20 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.5, 112.2, 124.6, 127.9, 129.6, 130.4, 136.4, 141.8, 153.0, 158.0, 171.7, 191.2.

MS: m/z = 239 $[M + 1]^+$.

1,3-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (12a)

Pale yellow solid; yield: 1.40 g (80%); mp 110 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 3.95 (s, 3 H), 8.55 (s, 1 H), 8.86 (s, 1 H), 10.05 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.2, 33.7, 114.4, 125.4, 132.9, 143.0, 150.3, 152.0, 191.3.

MS: m/z = 176 $[M + 1]^+$.

1-(1,1-Dioxidotetrahydro-3-thienyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (13a)
Yellow solid; yield: 2.13 g (76%); mp 138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 3.38–3.42 (m, 2 H), 3.49–3.56 (m, 2 H), 3.76–3.81 (m, 2 H), 5.82–5.88 (m, 1 H), 8.74 (d, *J* = 1.4 Hz, 1 H), 8.98 (d, *J* = 1.4 Hz, 1 H), 10.09 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.8, 29.0, 51.3, 52.1, 54.5, 115.5, 126.4, 133.7, 144.7, 151.0, 152.0, 191.7.

MS: *m*/*z* = 280 $[M + 1]^+$.

3-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (14a)
Yellow solid; yield: 0.52 g (32%); mp 196 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 8.68 (d, *J* = 1.5 Hz, 1 H), 8.93 (d, *J* = 1.5 Hz, 1 H), 10.07 (s, 1 H), 13.67 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.6, 114.3, 125.7, 133.1, 144.3, 150.7, 154.4, 191.8.

MS: *m*/*z* = 162 $[M + 1]^+$.

2-Methylpyrazolo[1,5-*a*]pyrimidine-6-carbaldehyde (14b)
Yellow solid; yield: 1.04 g (64%); mp 154 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 6.67 (s, 1 H), 8.76 (s, 1 H), 9.61 (s, 1 H), 9.94 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9, 98.1, 118.2, 142.0, 147.6, 149.9, 159.1, 189.4.

MS: *m*/*z* = 162 $[M + 1]^+$.

Ethyl 6-Formylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (16b)
Yellow solid; yield: 0.59 g (27%); mp 199 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 6.9 Hz, 3 H), 4.32 (q, *J* = 6.9 Hz, 2 H), 8.81 (s, 1 H), 9.13 (s, 1 H), 9.93 (s, 1 H), 10.06 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.8, 60.4, 103.9, 120.3, 143.4, 148.3, 150.5, 151.4, 161.7, 189.4.

MS: *m*/*z* = 220 $[M + 1]^+$.

6-Formylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (17b)
Brown solid; yield: 0.92 g (53%); mp 218 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95 (s, 1 H), 9.14 (s, 1 H), 9.97 (s, 1 H), 10.08 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 83.3, 113.0, 121.1, 143.6, 150.7, 151.3, 152.3, 189.2.

MS: *m*/*z* = 173 $[M + 1]^+$.

Pyrimido[1,2-*a*]benzimidazole-3-carbaldehyde (18b)
Brown solid; yield: 1.58 g (80%); mp 266 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (t, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 1 H), 9.18 (s, 1 H), 10.06 (s, 1 H), 10.26 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 113.4, 117.3, 120.1, 123.1, 127.5, 127.9, 142.7, 144.8, 154.5, 154.7, 188.4.

MS: *m*/*z* = 198 $[M + 1]^+$.

2-Phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbaldehyde (19b)
White solid; yield: 0.88 g (39%); mp 263 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (m, 3 H), 8.25 (m, 2 H), 9.21 (s, 1 H), 10.00 (s, 1 H), 10.11 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 120.9, 127.6, 129.6, 130.1, 131.7, 142.4, 154.7, 157.2, 167.3, 189.1.

MS: *m*/*z* = 225 $[M + 1]^+$.

3-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (14a) from 1-(1,1-Dioxidotetrahydro-3-thienyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (13a)
A suspension of compound **13a** (0.56 g, 2.00 mmol) in 15% aq HCl (20 mL) was heated at reflux for 6 h. Thereafter, the reaction mixture was cooled to r.t. and neutralized with aq K_2CO_3 soln to pH 7. The formed precipitate was collected by filtration to provide pure **14a** (0.27 g, 1.68 mmol, 84% yield).

References

(1) (a) Yan, H.; Boehm, J. C.; Jin, Q.; Kasparec, J.; Li, H.; Zhu, C.; Widdowson, K. L.; Callahan, J. F.; Wan, Z. *Tetrahedron Lett.* **2007**, *48*, 1205. (b) Bennett, L. R.; Blankley, C. J.; Fleming, R. W.; Smith, R. D.; Tessman, D. K. *J. Med. Chem.* **1981**, *24*, 382. (c) Angiolini, M.; Bassini, D. F.; Gude, M.; Menichincheri, M. *Tetrahedron Lett.* **2005**, *46*, 8749. (d) Vanlaer, S.; Compernolle, F.; Voet, A.; Gielens, C.; De Maeyer, M. *Eur. J. Org. Chem.* **2009**, 643. (e) Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 7761.

(2) (a) Nishikawa, Y.; Shindo, T.; Ishii, K.; Nakamura, H.; Kon, T.; Uno, H. *J. Med. Chem.* **1989**, *32*, 583. (b) Bleloch, A.; Johnson, B. F. G.; Ley, S. V.; Price, A. J.; Shephard, D. S.; Thomas, A. W. *Chem. Commun.* **1999**, 1907. (c) Pham, V.; Zhang, W.; Chen, V.; Whitney, T.; Yao, J.; Froese, D.; Friesen, A. D.; Diakur, J. M.; Haque, W. *J. Med. Chem.* **2003**, *46*, 3680. (d) VanderWel, S. N.; Harvey, P. J.; McNamara, D. J.; Repine, J. T.; Keller, P. R.; Quin, J.; Booth, R. J.; Elliott, W. L.; Dobrusin, E. M.; Fry, D. W.; Toogood, P. L. *J. Med. Chem.* **2005**, *48*, 2371. (e) Stuart, A.; Paterson, T.; Roth, B.; Aig, E. *J. Med. Chem.* **1983**, *26*, 667.

(3) (a) Gupton, J. T.; Gall, J. E.; Riesinger, S. W.; Smith, S. Q.; Bevirt, K. M.; Sikorski, J. A.; Dahl, M. L.; Arnold, A. *J. Heterocycl. Chem.* **1991**, *28*, 1281. (b) Ragan, J. A.; McDermott, R. E.; Jones, B. P.; Ende, D. J.; Clifford, P. J.; McHardy, S. J.; Heck, S. D.; Liras, S.; Segelstein, B. E. *Synlett* **2000**, 1172.

(4) Tom, N. J.; Ruel, E. M. *Synthesis* **2001**, 1351.

(5) For the reactions of vinamidinium salts **1** and **2**, see: (a) Jameleddine, K.; Adnen, H. A. M.; Bechir, B. H. *Tetrahedron Lett.* **2006**, *47*, 2973. (b) Thouraya, G.; Jameleddine, K.; Adnen, H. A. M.; Bechir, B. H. *Synth. Commun.* **2007**, *37*, 1053. (c) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W. *J. Org. Chem.* **1990**, *55*, 4735. (d) Angus, R. O.; Bryce, M. R.; Keshavarz, B.; Wudl, F. *Synthesis* **1998**, 746.