A Novel Synthesis of 4*H*-1,4-Benzoxazines

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The reaction of methyl 2-chloro-5-ethoxycarbonylamino-4-fluorobenzoate (4a) and 1-bromo-3,3-dimethyl-2-butanone (2) in the presence of 2.2 eq of lithium bis(trimethylsilyl)amide afforded the 4*H*-1,4-benzoxazine (6a) in good yield instead of the expected 4-oxazolin-2-one (5a). The generality of the reaction and the mechanism are discussed.

Key words 4*H*-1,4-benzoxazine; 4-oxazolin-2-one; α-bromoketone; intramolecular cyclization; electron-withdrawing group

Heterocyclic compounds have received considerable attention because of their biological activities and synthetic utility.[1] Hence, our intense efforts have been directed toward the synthesis of heterocyclic compounds and the development of novel synthetic methods.[2] In the previous paper[3] we reported a novel synthesis of 3-aryl-5-*tert*-butyl-4-oxazolin-2-ones (**3**) through the reaction of ethyl *N*-arylcarbamates (**1**) and 1-bromo-3,3-dimethyl-2-butanone (**2**) in the presence of 2.2 eq of lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) (Chart 1). In order to examine the effect of functional group variations, the synthesis of a series of 3-aryl-4-oxazolin-2-ones (**5**) having an electron-withdrawing group at the 5 (or 3) position of the aryl group was designed. We now report that the reaction of *N*-arylcarbamates bearing an electron-withdrawing group at the 5 (or 3) position (**4**) with 1-bromo-3,3-dimethyl-2-butanone (**2**) afforded 4*H*-1,4-benzoxazines (**6**) instead of the desired 4-oxazolin-2-ones (Chart 2).

The carbamate (**4a**), the substrate for the reaction was prepared in five steps from **7a** as outlined in Chart 3. 2-Chloro-4-fluorobenzoic acid (**7a**) was esterified and nitrated to give **9a**. Reduction of **9a** using stannous chloride and sodium borohydride[4] afforded aniline (**10a**), which was treated with ethyl chloroformate to give the carbamate (**4a**) in 46.5% yield in two steps. Under conditions essentially identical to those of the previously reported method[3] for the synthesis of 3-aryl-5-*tert*-butyl-4-oxazolin-2-ones (**3**), a mixture of **4a** and 1-bromo-3,3-dimethyl-2-butanone (**2**) was treated with $LiN(TMS)_2$ in *N*,*N*-dimethylformamide (DMF). The product was the novel 4*H*-1,4-benzoxazine derivative (**6a**), in 81.5% yield after purification by silica gel column chromatography. The desired product (**5a**) was not found in the reaction mixture. The structure of **6a** was verified by combustion and spectral analysis. Elemental analysis gave the formula $C_{17}H_{20}ClNO_5$, lacking a fluorine atom. This was sup-

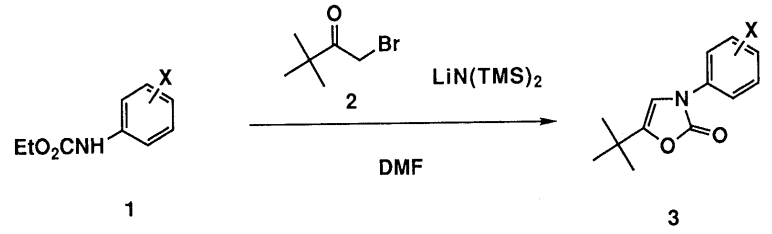

Chart 1

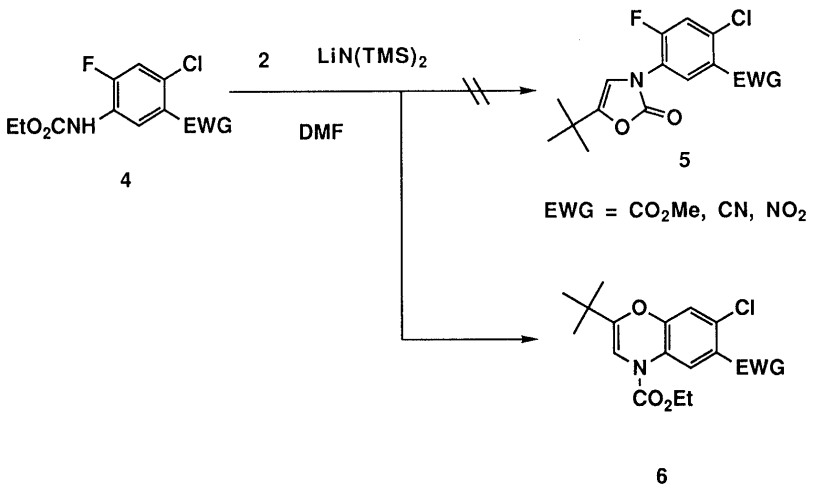

Chart 2

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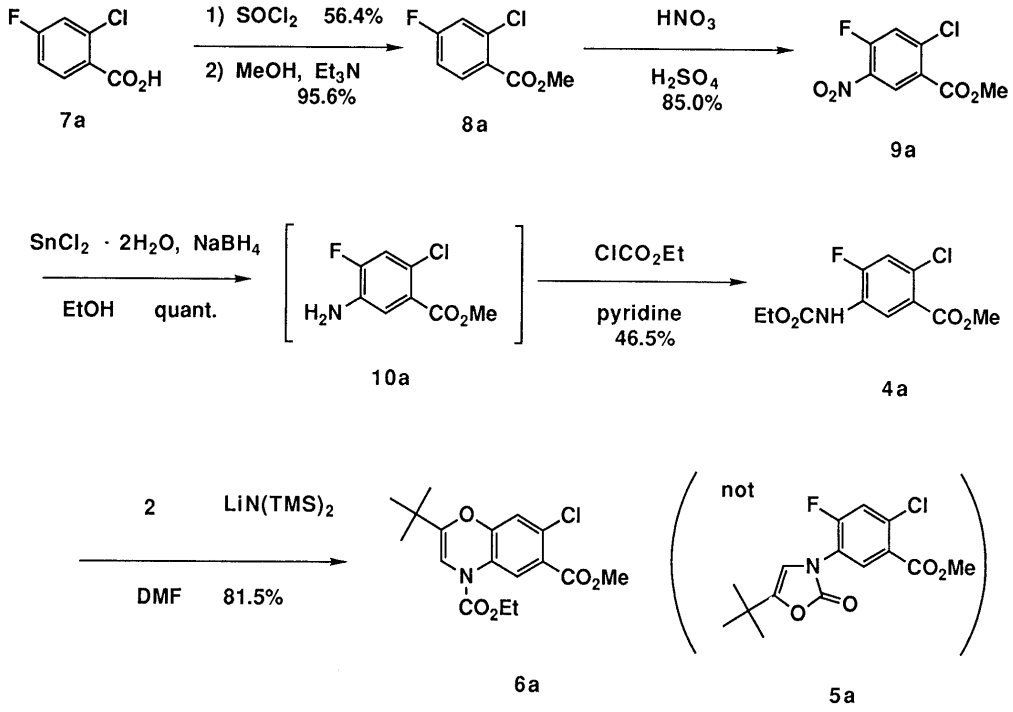

Chart 3

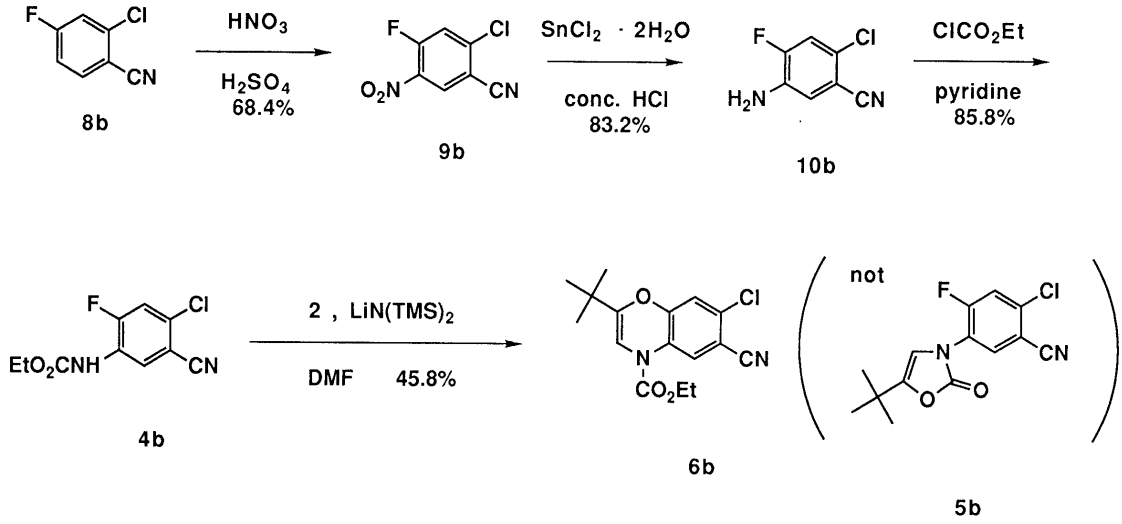

Chart 4

ported by mass spectral analysis (*m/z*: 353 (M^+)). In the ^{1}H-NMR spectrum (200 MHz), a triplet (δ 1.37, 3H, $J=7.1$ Hz) and a quartet (δ 4.31, 2H, $J=7.1$ Hz) due to the protons in the ethoxycarbonyl group, which indicated the presence of a carbamate moiety, and an olefinic proton (δ 6.09, 1H, s) were observed. Based on these results, the structure of the product was considered to be **6a**, and not the desired **5a**.

In an attempt to prepare the desired product (**5a**), the same reaction was run as shown in Chart 4 using cyano-substituted *N*-arylcarbamate (**4b**), because, after the desired cyclization, the cyano group could be transformed into an ester group in an acidic alcoholic media. Nitration of 2-chloro-4-fluorobenzonitrile (**8b**) gave **9b**, which was converted to aniline (**10b**) by using stannous chloride in concentrated hydrochloric acid.[5] Reaction of **10b** with ethyl chloroformate gave the carbamate (**4b**). Again, treatment of **4b** and the bromide (**2**) with 2.2 eq of $LiN(TMS)_2$ did not afford the desired 4-oxazolin-2-one (**5b**), but gave 4*H*-1,4-benzoxazine (**6b**) in 45.8% yield (Chart 4).

We propose the reaction mechanism shown in Chart 5. The carbamate (**4**) is deprotonated by 1 eq of $LiN(TMS)_2$ and alkylated with the bromide (**2**) to give the intermediate **11**, which is then deprotonated with another 1 eq of $LiN(TMS)_2$ to give the enolate (**12**). It is considered that, instead of attack by the enolate oxygen on the carbonyl group of the carbamate moiety (path a), the fluorine atom was so activated by the electron-withdrawing group attached to the opposite site of the benzene ring that intramolecular cyclization occurred to form 4*H*-1,4-benzoxazine (**6**) *via* path b.[6]

In order to investigate the generality and the limitations of this reaction, we performed the reaction using 2-fluoro-

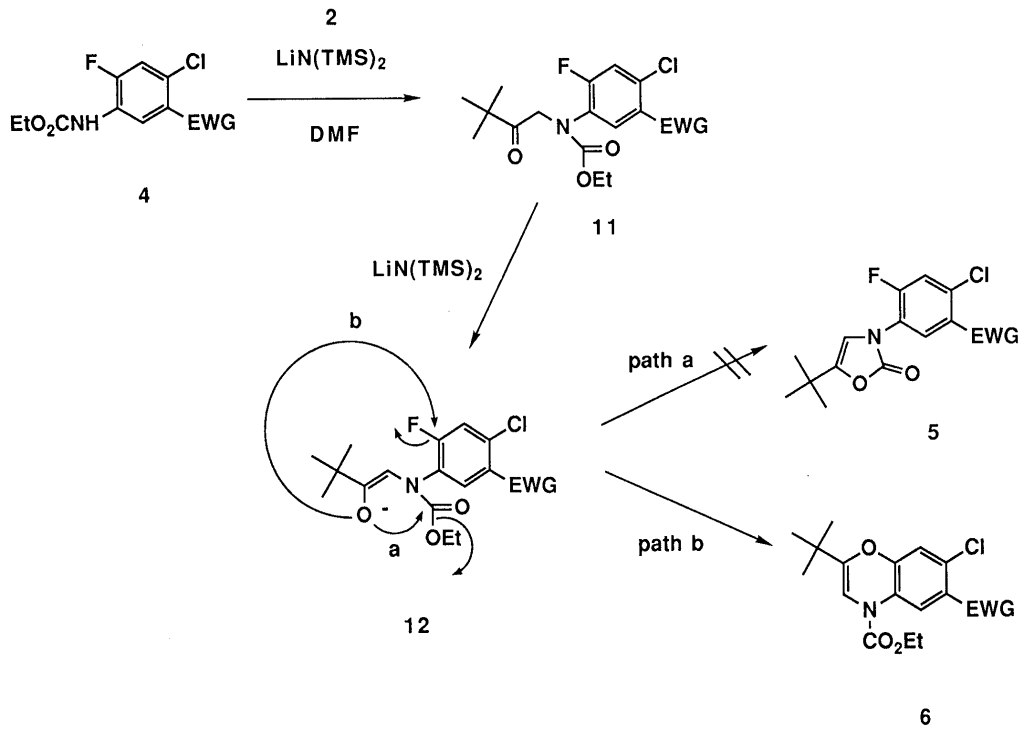

Chart 5

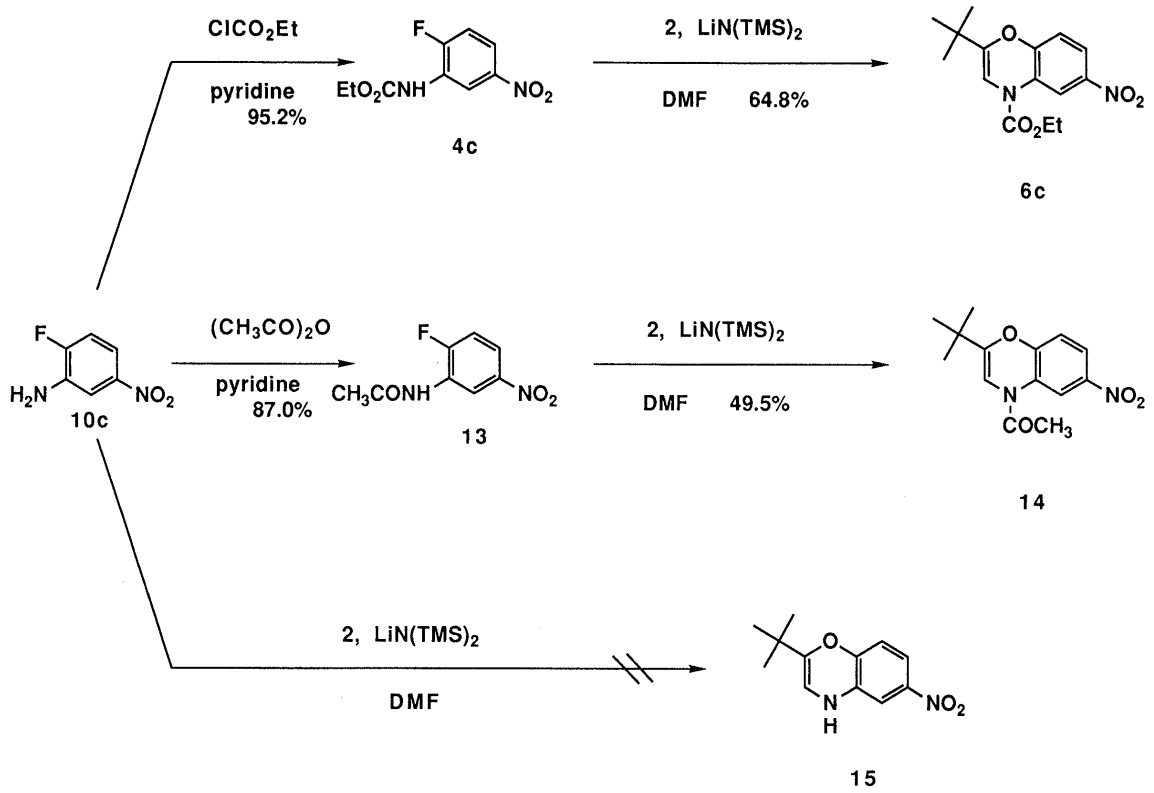

Chart 6

5-nitroaniline (**10c**) as the starting material (Chart 6). The *N*-arylcarbamate (**4c**), prepared from **10c** and ethyl chloroformate, reacted with the bromide (**2**) and $LiN(TMS)_2$ to give **6c** in 64.8% yield. The acetanilide (**13**) prepared from **10c** and acetic anhydride underwent a similar reaction to give **14** in 49.5% yield. However, direct reaction of **10c** with the bromide (**2**) and $LiN(TMS)_2$ to afford the 4-unsubstituted 4*H*-1,4-benzoxazine (**15**) did not proceed.

Further, the reaction of *N*-(2,6-dichloro-4-fluoro-3-methoxycarbonyloxyphenyl)carbamate (**4d** and **4e**) and **2** with $LiN(TMS)_2$ also afforded 4*H*-1,4-benzoxazines (**6d** and **6e**). The carbamates **4d** and **4e** were synthesized as shown in Chart 7. 2,6-Dichloro-4-fluorophenol (**16**) was

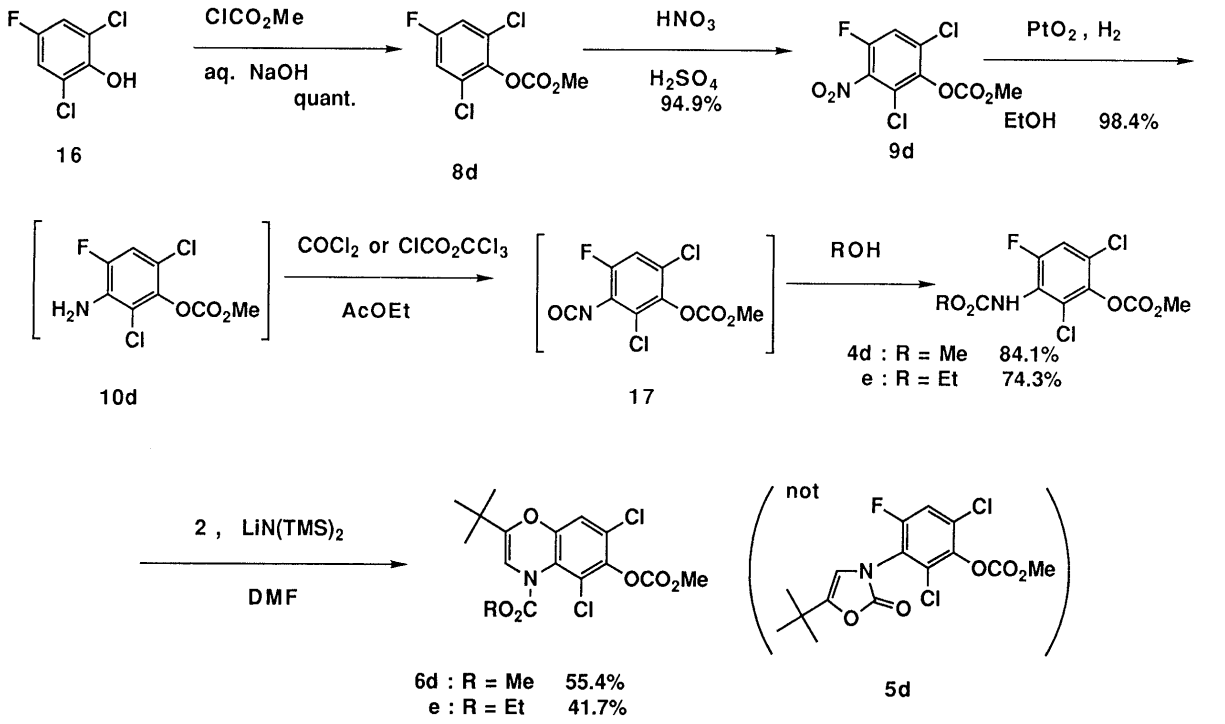

Chart 7

protected as the carbonate (**8d**), and nitrated to give **9d**. Catalytic hydrogenation of **9d** using PtO_2 afforded a crude aniline (**10d**) in 98.4% yield. Direct conversion of **10d** into the carbamate (**4e**) with ethyl chloroformate using the base (pyridine, triethylamine, or aqueous 10% NaOH[7]) failed. But treatment of **10d** with phosgene[8a] or diphosgene (trichloromethyl chloroformate)[8b] in refluxing ethyl acetate, followed by the addition of methanol or ethanol gave the corresponding methyl and ethyl carbamates (**4d** and **4e**), respectively. Reaction of the methyl or ethyl carbamate (**4d** and **4e**) and the bromide (**2**) in the presence of $LiN(TMS)_2$ afforded the corresponding 4*H*-1,4-benzoxazine (**6d** and **6e**), but not the 4-oxazolin-2-one (**5d**). This reaction may be attributed to the electron-withdrawing effect of the additional chlorine atom, which allows the fluorine atom to be easily eliminated.

Several methods are known for the synthesis of 4*H*-1,4-benzoxazines. McKillop and Sayer reported the formation of 1,4-benzoxazine by Diels–Alder reaction between copper(II) complexes formed from *o*-nitrosophenol and dimethyl acetylenedicarboxylate.[9] But only 2,3-methoxycarbonyl derivatives were obtained using this method. Guillaumet *et al.* reported another synthetic method for 4*H*-1,4-benzoxazines,[10] in which only 4-benzoyl-1,4-benzoxazine derivatives were obtained and multiple steps were required. In contrast, our synthetic method for the construction of novel 4*H*-1,4-benzoxazines (**6**) featured a single reaction step and the use of easily accessible *N*-arylcarbamate as the starting material.

In conclusion, a novel and an efficient synthetic method for 4*H*-1,4-benzoxazines from *N*-arylcarbamates and 1-bromo-3,3-dimethyl-2-butanone (**2**) has been established. Further applications of this reaction and a survey of the biological activities of the synthesized compounds are in progress.

Experimental

All melting points (mp) are uncorrected. IR spectra were measured on a Perkin Elmer 1600 spectrometer. ^{1}H-NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer with tetramethylsilane as an internal standard. MS and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer.

Methyl 5-Amino-2-chloro-4-fluorobenzoate (10a) $SnCl_2 \cdot 2H_2O$ (2.27 g, 10.1 mmol) and $NaBH_4$ (38 mg, 1.01 mmol) were added to a solution of **9a** (0.47 g, 2.01 mmol) in ethanol (EtOH, 20 ml) at 0 °C and the resulting mixture was stirred at 55 °C for 1 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ethyl acetate (AcOEt) (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 0.20 g (48.9%) of **10a**, which was subjected to the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.31 (1H, d, J=9.3 Hz), 7.09 (1H, d, J=10.6 Hz), 3.90 (3H, s), 3.90 (2H, br s). MS *m/z*: 203 (M^+), 188, 172 (base), 144, 117, 42.

Methyl 2-Chloro-5-ethoxycarbonylamino-4-fluorobenzoate (4a) Ethyl chloroformate (0.12 ml, 1.26 mmol) was added to a solution of **10a** (0.20 g, 0.98 mmol) in pyridine (30 ml) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was acidified with diluted HCl, extracted with AcOEt (3 times), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 0.20 g (73.9%) of **4a** as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 8.67 (1H, d, J=8.7 Hz), 7.21 (1H, d, J=10.6 Hz), 6.83 (1H, br s), 4.27 (2H, q, J=7.1 Hz), 3.92 (3H, s), 1.34 (3H, t, J=7.1 Hz); IR ν_{max}^{KBr} cm^{-1}: 3325, 1735, 1527, 1261, 1222, 1066. MS *m/z*: 275 (M^+), 244, 216, 203 (base), 172. *Anal.* Calcd for $C_{11}H_{11}ClFNO_4$: C, 47.93; H, 4.02; Cl, 12.86; F, 6.89; N, 5.08. Found: C, 47.71; H, 3.94; Cl, 13.04; F, 6.90; N, 5.13.

2-*tert*-Butyl-7-chloro-4-ethoxycarbonyl-6-methoxycarbonyl-4*H*-1,4-benzoxazine (6a) To a solution of **4a** (6.56 g, 23.8 mmol) and **2** (4.69 g, 26.2 mmol) in DMF (30 ml) was added a solution of $LiN(TMS)_2$ in tetrahydrofuran (THF) (54.6 ml, 54.6 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 1 h, then poured into water and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 6.86 g (81.5%) of **6a**. White needles, mp 102—104 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 8.44 (1H, br s), 6.90 (1H, s), 6.09 (1H, s), 4.31 (2H, q, J=7.1 Hz), 3.89 (3H, s), 1.37 (3H, t, J=7.1 Hz), 1.15 (9H, s). IR ν_{max}^{film} cm^{-1}: 2967, 1722, 1500, 1261, 1172, 1100. MS *m/z*: 353 (M^+), 322, 294, 280 (base), 266, 253, 212, 69. *Anal.* Calcd for $C_{17}H_{20}ClNO_5$: C, 57.71; H, 5.70; Cl, 10.02; N, 3.96. Found: C, 57.64; H, 5.69; Cl, 9.76; N, 3.95.

2-Chloro-4-fluoro-5-nitrobenzonitrile (9b) Concentrated HNO_3 (19.3 ml, 258 mmol) was slowly added to a solution of **8b** (20 g, 129 mmol) in concentrated H_2SO_4 (20 ml) at room temperature. After the addition was completed, the reaction mixture was neutralized with aqueous Na_2CO_3 and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography to give 17.68 g (68.4%) of **9b**. White powder, mp 84—85 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 8.47 (1H, d, J=7.3 Hz), 7.56 (1H, d, J=9.6 Hz). IR ν_{max}^{KBr} cm^{-1}: 3111, 2245, 1615, 1579, 1537, 1476, 1352, 991, 906. MS *m/z*: 200 (M^+, base), 170, 154, 142, 131. HRMS Calcd for $C_7H_2ClFN_2O_2$: 199.9789. Found: 199.9791.

5-Amino-2-chloro-4-fluorobenzonitrile (10b) $SnCl_2 \cdot 2H_2O$ (2.17 g, 9.62 mmol) was added to a solution of **9b** (639 mg, 3.19 mmol) in concentrated HCl (30 ml) and the resulting mixture was stirred at 70 °C for 1 h. The reaction mixture was poured into aqueous NaOH, and extracted with AcOEt (3 times). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give 452 mg (83.2%) of **10b**. White needles, mp 114—115 °C, from dichloromethane (CH_2Cl_2)–hexane. ^{1}H-NMR ($CDCl_3$) δ: 7.15 (1H, d, J=10.3 Hz), 7.04 (1H, d, J=8.7 Hz), 3.98 (2H, br s). IR ν_{max}^{KBr} cm^{-1}: 3468, 3374, 2236, 1645, 1499, 1205, 867. MS *m/z*: 170 (M^+, base), 143, 135, 108. *Anal.* Calcd for $C_7H_4ClFN_2$: C, 49.29; H, 2.36; N, 16.42. Found: C, 49.45; H, 2.46; N, 16.72.

Ethyl *N*-(4-Chloro-5-cyano-2-fluorophenyl)carbamate (4b) Ethyl chloroformate (0.3 ml, 3.14 mmol) was added to a solution of **10b** (465 mg, 2.72 mmol) in pyridine (15 ml) at 0 °C and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was acidified with diluted HCl (to pH 1) and extracted with AcOEt (3 times). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 568 mg (85.8%) of **4b**. White needles, mp 105—106 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 8.57 (1H, d, J=8.1 Hz), 7.27 (1H, d, 10.4 Hz), 6.89 (1H, br s), 4.28 (2H, q, J=7.1 Hz), 1.34 (3H, t, J=7.1 Hz). IR ν_{max}^{KBr} cm^{-1}: 3369, 2236, 1716, 1529, 1399, 1258. MS *m/z*: 242 (M^+), 183, 170 (base). *Anal.* Calcd for $C_{10}H_8ClFN_2O_2$: C, 49.50; H, 3.32; Cl, 14.61; F, 7.83; N, 11.55. Found: C, 49.52; H, 3.61; Cl, 14.63; F, 7.96; N, 11.57.

2-*tert*-Butyl-7-chloro-6-cyano-4-ethoxycarbonyl-4*H*-1,4-benzoxazine (6b) To a solution of **4b** (98 mg, 0.405 mmol) and **2** (87 mg, 0.486 mmol) in DMF (10 ml) was added a solution of $LiN(TMS)_2$ in THF (0.89 ml, 0.89 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 20 min, then poured into water and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to preparative thin layer chromatography (PTLC) to give 59.4 mg (45.8%) of **6b**. Yellow powder, mp 75—77 °C, from CH_2Cl_2–hexane. ^{1}H-NMR ($CDCl_3$) δ: 8.22 (1H, br s), 6.91 (1H, s), 6.08 (1H, s), 4.32 (2H, q, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 1.14 (9H, s). IR ν_{max}^{KBr} cm^{-1}: 2231, 1722, 1704, 1496, 1382, 1266, 1103. MS *m/z*: 320 (M^+), 292, 247 (base), 233, 220, 149, 69, 57. HRMS Calcd for $C_{16}H_{17}ClN_2O_3$: 320.0928. Found: 320.0928.

Ethyl *N*-(2-Fluoro-5-nitrophenyl)carbamate (4c) Ethyl chloroformate (0.33 ml, 3.45 mmol) was added to a solution of **10c** (500 mg, 3.20 mmol) in pyridine (3 ml) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was acidified with diluted HCl (to pH 1) and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 696 mg (95.2%) of **4c**, mp 87—88 °C (lit. 90—92 °C[11]). ^{1}H-NMR ($CDCl_3$) δ: 9.10 (1H, dd, J=6.9, 2.8 Hz), 7.93 (1H, ddd, J=9.1, 4.4, 2.8 Hz), 7.20 (1H, d, J=9.1 Hz), 6.96 (1H, br s), 4.31 (2H, q, J=7.1 Hz), 1.36 (3H, t, J=7.1 Hz). MS *m/z*: 228 (M^+), 169, 156 (base), 109.

2-*tert*-Butyl-4-ethoxycarbonyl-6-nitro-4*H*-1,4-benzoxazine (6c) To a solution of **4c** (109.4 mg, 0.479 mmol) and **2** (94.3 mg, 0.527 mmol) in DMF (1 ml) was added a solution of $LiN(TMS)_2$ in THF (1.05 ml, 1.05 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 95.1 mg (64.8%) of **6c**. Yellow needles, mp 56—57 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 8.75 (1H, br s), 7.90 (1H, dd, J=8.9, 2.6 Hz), 6.86 (1H, d, J=8.9 Hz), 6.11 (1H, s), 4.33 (2H, q, J=7.1 Hz), 1.38 (3H, t, J=7.1 Hz), 1.16 (9H, s). IR ν_{max}^{KBr} cm^{-1}: 1722, 1525, 1346, 1256, 1112. MS *m/z*: 306 (M^+), 233, 217, 69 (base), 41. *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.93; H, 6.00; N, 9.38.

2′-Fluoro-5′-nitroacetanilide (13) Acetic anhydride (0.33 ml, 3.50 mmol) was added to a solution of **10c** (500 mg, 3.20 mmol) in pyridine (3 ml) at 0 °C and the resulting mixture was stirred at 0 °C for 5 h. The reaction mixture was acidified with diluted HCl (to pH 1) and extracted with AcOEt (3 times). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 513 mg (87.0%) of **13**, mp 179—180 °C (lit. 179—180 °C[12]). ^{1}H-NMR ($CDCl_3$) δ: 9.33—9.28 (1H, m), 8.03—7.95 (1H, m), 7.48 (1H, br s), 7.24 (1H, t, J=9.5 Hz), 2.28 (3H, s). MS *m/z*: 198 (M^+), 156 (base), 110, 43.

4-Acetyl-2-*tert*-butyl-6-nitro-4*H*-1,4-benzoxazine (14) To a solution of **13** (148.1 mg, 0.804 mmol) and **2** (187.1 mg, 1.04 mmol) in DMF (2 ml) was added a solution of $LiN(TMS)_2$ in THF (1.77 ml, 1.77 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 30 min, then poured into water and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$, washed with brine, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 110 mg (49.5%) of **14**. Yellow powder, mp 104—105 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 8.89 (1H, br s), 7.99 (1H, dd, J=8.9, 2.6 Hz), 6.96 (1H, d, J=8.9 Hz), 5.90 (1H, br s), 2.30 (3H, s), 1.20 (9H, s). IR ν_{max}^{KBr} cm^{-1}: 2976, 1681, 1523, 1341, 1283, 1114. MS *m/z*: 276 (M^+), 234, 219 (base). HRMS Calcd for $C_{14}H_{16}N_2O_4$: 276.1110. Found: 276.1112.

Methyl 2,6-Dichloro-4-fluorophenyl Carbonate (8d) Methyl chloroformate (23 ml, 298 mmol) was added to a solution of **16** (41.8 g, 231 mmol) and NaOH (11.3 g, 282 mmol) in water (100 ml) at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The resulting precipitate was collected, washed with water, and dried to give 57.8 g (quantitative) of **8d**. White columns, mp 48—49 °C, from CH_2Cl_2–hexane. ^{1}H-NMR ($CDCl_3$) δ: 7.15 (2H, d, J=7.7 Hz), 3.97 (3H, s). IR ν_{max}^{KBr} cm^{-1}: 3101, 1779, 1591, 1471, 1441, 1258, 1197. MS *m/z*: 238 (M^+), 205, 191, 179, 160 (base), 151. *Anal.* Calcd for $C_8H_5Cl_2FO_3$: C, 40.20; H, 2.11; N, 0.00. Found: C, 40.06; H, 2.27; N, 0.00.

Methyl 2,6-Dichloro-4-fluoro-3-nitrophenyl Carbonate (9d) A mixture of concentrated HNO_3 (0.35 ml, 4.68 mmol) and concentrated H_2SO_4 (0.35 ml) was slowly added to a solution of **8d** (371 mg, 1.55 mmol) in concentrated H_2SO_4 (0.5 ml) at room temperature. After addition was completed, the reaction mixture was diluted with water. The resulting precipitate was collected, washed with water, and dried to give 423 mg (96.1%) of **9d**. Light yellow needles, mp 50—51 °C, from CH_2Cl_2–hexane. ^{1}H-NMR ($CDCl_3$) δ: 7.40 (1H, d, J=8.5 Hz), 4.00 (3H, s). IR ν_{max}^{KBr} cm^{-1}: 3090, 1790, 1585, 1550, 1440, 1352, 1252, 1194, 931, 858. MS *m/z*: 283 (M^+), 239, 181, 115, 59 (base). *Anal.* Calcd for $C_8H_4Cl_2FNO_5$: C, 33.83; H, 1.42; N, 4.93. Found: C, 34.00; H, 1.55; N, 4.94.

Methyl 3-Amino-2,6-dichloro-4-fluorophenyl Carbonate (10d) A solution of **9d** (30.0 g, 106 mmol) in ethanol (200 ml) was hydrogenated using PtO_2 as a catalyst for 2 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give 26.1 g of **10d** (98.4%), which was used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.07 (1H, d, J=10.3 Hz), 4.19 (2H, br s), 3.96 (3H, s). MS *m/z*: 253 (M^+), 209, 194, 166 (base), 96, 57.

Methyl *N*-(2,6-Dichloro-4-fluoro-3-methoxycarbonyloxyphenyl)carbamate (4d) A solution of **10d** (12.7 g, 50.1 mmol) in AcOEt (300 ml) was treated with 115 ml (250 mmol) of phosgene in toluene (2.17 M solution) and the reaction solution was heated under reflux for 2 h. After the mixture had cooled, methanol was added to it, and stirring was continued for 2 h. The reaction mixture was poured into water and extracted with AcOEt (3 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from toluene–hexane to give 13.1 g (84.1%) of **4d**. White columns, mp 142—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.26 (1H, s), 6.27 (1H, br s), 3.97 (3H, s), 3.80 (3H, s). IR ν_{max}^{KBr} cm^{-1}: 3362, 3058, 1770, 1737, 1511, 1270, 1236, 1202. MS *m/z*: 311 (M^+), 267, 232 (base), 220, 180, 57. *Anal.* Calcd for $C_{10}H_8Cl_2FNO_5$: C, 38.49; H, 2.58; N, 4.49. Found: C, 38.55; H, 2.80; N, 4.48.

Ethyl *N*-(2,6-Dichloro-4-fluoro-3-methoxycarbonyloxyphenyl)carbamate (4e) A solution of **10d** (0.99 g, 3.90 mmol) and diphosgene (1.5 ml, 12.4 mmol) in AcOEt (30 ml) was heated under reflux for 2.5 h. After the mixture had cooled, ethanol was added to it and stirring was continued for 12 h. The reaction mixture was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 0.94 g (74.3%) of **4e**. White columns,

mp 121—122 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 7.26 (1H, s), 6.21 (1H, br s), 4.24 (2H, q, J=7.1 Hz), 3.97 (3H, s), 1.31 (3H, t, J=7.1 Hz). IR ν_{max}^{KBr} cm^{-1}: 3234, 3128, 1778, 1711, 1253, 1190. MS m/z: 325 (M^+), 253, 222 (base), 209, 194, 166, 57. *Anal.* Calcd for $C_{11}H_{10}Cl_2FNO_5$: C, 40.52; H, 3.09; Cl, 21.74; F, 5.83; N, 4.30. Found: C, 40.77; H, 3.19; Cl, 21.58; F, 5.78; N, 4.35.

2-*tert*-Butyl-5,7-dichloro-4-methoxycarbonyl-6-methoxycarbonyloxy-4*H*-1,4-benzoxazine (6d) To a solution of **4d** (3.13 g, 10.0 mmol) and **2** (2.40 g, 13.4 mmol) in DMF (21 ml) was added a solution of $LiN(TMS)_2$ in THF (23 ml, 23 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 3 h, then poured into water and extracted with AcOEt (4 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 2.17 g (55.4%) of **6d**. White needles, mp 107—109 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 7.00 (1H, s), 6.05 (1H, br s), 3.96 (3H, s), 3.82 (3H, s), 1.16 (9H, s). IR ν_{max}^{KBr} cm^{-1}: 2966, 1776, 1740, 1468, 1448, 1267, 1190, 1109. MS m/z: 389 (M^+), 332 (base), 303, 255, 69, 57. *Anal.* Calcd for $C_{16}H_{17}Cl_2NO_6$: C, 49.25; H, 4.39; Cl, 18.17; N, 3.59. Found: C, 49.00; H, 4.50; Cl, 18.39; N, 3.56.

2-*tert*-Butyl-5,7-dichloro-4-ethoxycarbonyl-6-methoxycarbonyloxy-4*H*-1,4-benzoxazine (6e) To a solution of **4e** (1.19 g, 3.65 mmol) and **2** (0.90 g, 5.03 mmol) in DMF (7.5 ml) was added a solution of $LiN(TMS)_2$ in THF (8.4 ml, 8.4 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 3 h, then poured into water and extracted with AcOEt (4 times). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to give 615 mg (41.7%) of **6e**. White needles, mp 121—123 °C, from AcOEt–hexane. ^{1}H-NMR ($CDCl_3$) δ: 7.00 (1H, s), 6.06 (1H, br s), 4.27 (2H, q, J=7.1 Hz), 3.97 (3H, s), 1.31 (3H, t, J=7.1 Hz), 1.16 (9H, s). IR ν_{max}^{KBr} cm^{-1}: 2979, 1780, 1720, 1467, 1307, 1256, 1193. MS m/z: 403 (M^+), 330 (base), 296, 262, 69, 57. *Anal.* Calcd for $C_{17}H_{19}Cl_2NO_6$: C, 50.51; H, 4.74; Cl, 17.54; N, 3.46. Found: C, 50.24; H, 4.86; Cl, 17.62; N, 3.41.

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References and Notes

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