A Novel Synthesis of 4H-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 4H-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 4H-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 paper3) we reported a novel synthesis of 3-ary1-5-tert-butyl-4-oxazolin-2-ones (3) through the reaction of ethyl N-ary1carbamates (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-ary1carbamates bearing an electron-withdrawing group at the 5 (or 3) position (4) with 1-bromo-3,3-dimethyl-2-butanone (2) afforded 4H-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 borohydride4) 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 method5) for the synthesis of 3-ary1-5-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 4H-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 C13H20ClNO5, lacking a fluorine atom. This was sup-

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ported by mass spectral analysis (m/z: 353 (M+)). In the
1H-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 de-
sired 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.59 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 4H-1,4-benzoaxine (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 4H-1,4-
benzoaxine (6b) via path b.60

In order to investigate the generality and the limitations
of this reaction, we performed the reaction using 2-fluooro-
5-nitroaniline (10c) as the starting material (Chart 6). The N-arylcarbamate (4e), prepared from 10e and ethyl chloroformate, reacted with the bromide (2) and LiN(TMS)$_2$ to give 6c in 64.8% yield. The acetanilide (13) prepared from 10e 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 4H-1,4-benzoazines (15) did not proceed.

Further, the reaction of N-(2,6-dichloro-4-fluoro-3-methoxy-carbonyloxypenyl)carbamate (4d and 4e) and 2 with LiN(TMS)$_2$ also afforded 4H-1,4-benzoazines (6d and 6e). The carbamates 4d and 4e were synthesized as shown in Chart 7. 2,6-Dichloro-4-fluorophenol (16) was
protected as the carbonate (8d), and nitrated to give 9d. Catalytic hydrogenation of 9d using PtO₂ 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) failed. But treatment of 10d with phosgene or diphosgene (trichloromethyl chloroformate) 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 4H-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 fluoride atom to be easily eliminated.

Several methods are known for the synthesis of 4H-1,4-benzoxazines. McKillop and Sayer reported the formation of 1,4-benzoxazine by Diels-Alder reaction between copper(II) complexes from o-nitrophenol and dimethyl acetylenedicarboxylate. But only 2,3-methoxy carbonyl derivatives were obtained using this method. Guillaumet et al. reported another synthetic method for 4H-1,4-benzoxazines, 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 4H-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 4H-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. 1H-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) SnCl₂:2H₂O (2.27g, 10.1 mmol) and NaH (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 NaHCO₃ and extracted with ethyl acetate (AcOEt) (3 times). The combined extracts were dried over MgSO₄ and concentrated in vacuo to give 0.20 g (48.9%) of 10a, which was subjected to the next reaction without further purification. 1H-NMR (CDCl₃): δ: 7.31 (1H, d, J = 9.3 Hz), 7.09 (1H, d, J = 10.6 Hz), 3.90 (3H, s), 3.90 (2H, brs). MS m/z: 203 (M⁺), 188, 172 (base), 144, 117, 42.

Methyl 2-Chloro-5-sulphonylaminobenzofuran-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 (50 ml) at 0°C and the resulting mixture was stirred at 0°C for 1 h. The reaction mixture was added with dilute HCl, extracted with AcOEt (3 times), dried over MgSO₄, 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. 1H-NMR (CDCl₃): δ: 8.67 (1H, d, J = 8.7 Hz), 7.31 (1H, d, J = 10.6 Hz), 6.83 (1H, brs), 4.27 (2H, q, J = 7.1 Hz), 3.92 (3H, s), 1.34 (3H, t, J = 7.1 Hz); IR (cm⁻¹): 3325, 1735, 1577, 1261, 1222, 1066. MS m/z: 275 (M⁺), 244, 216, 203 (base), 172. Anal. Calc. for C₁₈H₁₉Cl₂FNO₅: C, 47.85; 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-ethoxybenzyl-6-methoxybenzyl-4H-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 MgSO₄ 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. 1H-NMR (CDCl₃): δ: 8.44 (1H, brs), 6.90 (1H, s), 6.59 (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 (cm⁻¹): 2967, 1722, 1500, 1261, 1172, 1100. MS m/z: 353 (M⁺), 322, 294, 280 (base), 266, 253, 212, 69. Anal. Calc. for C₂₆H₂₅ClNO₅: 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 HNO₃ (19.3 mL, 258 mmol) was slowly added to a solution of 8b (20 g, 129 mmol) in concentrated H₂SO₄ (20 mL) at room temperature. After the addition was completed, the reaction mixture was neutralized with aqueous Na₂CO₃ and extracted with AcOEt (3 times). The combined extracts were dried over MgSO₄ and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexane/DCM (1:1) as the mobile phase. The combined extracts were dried over MgSO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography to give 51.6 g (85.8%) of 9b. 

5-Amino-2-chloro-4-fluorobenzonitrile (10b) SnCl₂·2H₂O (2.17 g, 9.62 mmol) was added to a solution of 9b (20 g, 131 mmol) in concentrated HCl (30 mL) at 100°C. The resulting mixture was stirred at 100°C for 1 h. The reaction mixture was poured into aqueous NaOH, and extracted with AcOEt (3 times). The organic solution was dried over MgSO₄ 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 (CH₂Cl₂)-hexane. 

4-Acetyl-2-tert-butyl-6-nitro-4H-1,4-benzoxazine (14) A solution of 13d (187.3 mmol) in DMF (2 mL) was added to a solution of LIN(TMS) in THF (1.2 mL, 1.5 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 MgSO₄, 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 CH₂Cl₂-hexane. IR νmax cm⁻¹: 3266, 1585, 1567, 1536, 1345, 1360, 1205, 1142, 1114, 1153, 1169, 1173. MS m/z: 276 (M⁺), 239 (base). HRMS Caled for C₇H₆N₄O₂: 276.0910. Found: 276.0912.

2-Methyl-6-Dichloro-4-fluorophenyl Carbamate (8d) Methyl chlorofomes (23.5 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 reaction 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 CH₂Cl₂-hexane. 

4-Acetyl-2-tert-butyl-6-nitro-4H-1,4-benzoxazine (9d) A mixture of concentrated HNO₃ (0.35 mL, 4.68 mmol) and concentrated H₂SO₄ (0.35 mL) was slowly added to a solution of 8d (371 mg, 1.55 mmol) in concentrated H₂SO₄ (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 425 mg (96.1%) of 9d. Light yellow needles, mp 50—51°C, from CH₂Cl₂-hexane. IR νmax cm⁻¹: 2750, 2650, 1580, 1575, 1550, 1450, 1380, 1205, 1180, 1150, 1130. MS m/z: 280 (M⁺), 253 (base), 236 (205), 191, 179 (160), 151. Anal. Caled for C₂₂H₁₄F₂NO₃: C, 40.20; H, 2.11; N, 0.00. Found: C, 40.06; H, 2.27; N, 0.01.
mp 121—122 °C, from AcOEt—hexane. 1H-NMR (CDCl3) δ: 7.26 (1H, s), 6.21 (1H, brs), 4.24 (2H, q, J = 7.1 Hz), 3.97 (3H, s), 1.31 (3H, t, J = 7.1 Hz). IR νmax cm⁻¹: 3234, 3128, 1778, 1711, 1253, 1190. MS m/z: 325 (M⁺), 223, 222 (base), 109, 194, 166, 57. Anal. Calcld. for C13H18Cl2FNO2: 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-methoxycarbonyl-4H-1,4-benzoazine (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 MgSO4 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. 1H-NMR (CDCl3) δ: 7.00 (1H, s), 6.05 (1H, brs), 3.96 (3H, s), 3.82 (3H, s), 1.16 (9H, s). IR νmax cm⁻¹: 2966, 1776, 1740, 1468, 1448, 1267, 1190, 1109. MS m/z: 389 (M⁺), 332 (base), 303, 259, 65, 57. Anal. Calcld. for C13H16Cl2N2O2: C, 45.25; 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-methoxycarbonyl-4H-1,4-benzoazine (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 MgSO4 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—122 °C, from AcOEt—hexane. 1H-NMR (CDCl3) δ: 7.00 (1H, s), 6.06 (1H, brs), 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 νmax cm⁻¹: 2979, 1780, 1720, 1467, 1307, 1256, 1193. MS m/z: 403 (M⁺), 330 (base), 296, 262, 69, 57. Anal. Calcld. for C13H18Cl2N2O2: C, 50.51; H, 4.74; Cl, 17.54; N, 3.46. Found: C, 50.24; H, 4.66; Cl, 17.62; N, 3.41.

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References and Notes