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Studies on 1,3-Benzoxazines. VII.¹⁾ Formation of Diphenylpyrimidines by the Reaction of 4-Chloro-2*H*-1,3-benzoxazines with Ethyl 3-Aminobutyrate

RYUJI TACHIKAWA, KAZUYUKI WACHI* and ATSUSUKE TERADA

Central Research Laboratories, Sankyo Co., Ltd., Shinagawa-ku Tokyo, 140, Japan

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A new reaction mode for the formation of pyrimidine derivatives by the reaction of 4-chloro-2*H*-1,3-benzoxazines (**1a**–**f**) with ethyl 3-aminobutyrate is described. Treatment of chlorobenzoxazines (**1a**–**f**) with ethyl 3-aminobutyrate (**2**) gave pyrimidine derivatives (**4a**–**f**) possessing an *o*-hydroxyphenyl substituent. When 4-chloro-2-methyl-2-methoxycarbonylmethyl-2*H*-1,3-benzoxazine (**1g**) was treated with **2**, a pyrimidinone derivative (**7**) was isolated. A possible mechanism for the formation of these reaction products is discussed.

Keywords—1,3-benzoxazine; imidoyl chloride; pyrimidine derivative; ethyl 3-aminobutyrate; reaction mechanism

As part of study on 1,3-benzoxazines, we have recently developed a general synthetic method for heteroaromatic compounds such as benzoxazoles,²⁾ quinazolines and 3,1-benzoxazines¹⁾ bearing an *o*-hydroxyphenyl group from 4-chloro-2*H*-1,3-benzoxazines.

Various heteroaromatic derivatives containing an *o*-hydroxyphenyl substituent were investigated for use as protective agents against UV radiation.³⁾

In the present paper, we report the reaction of imidoyl chlorides of 1,3-benzoxazines with ethyl 3-aminobutyrate to give diphenylpyrimidines possessing a 2-hydroxy substituent on the benzene ring.

Treatment of 4-chloro-2,2-dimethyl-2*H*-1,3-benzoxazine (**1a**)⁴⁾ with ethyl 3-aminobutyrate (**2**) at 150–160°C for 4 h, followed by silica gel chromatography, gave two compounds (**3a** and **4a**) in 10 and 38% yields, respectively, in addition to ethyl crotonate (**5**) (Chart 1). The structure of the first reaction product (**3a**) was determined to be ethyl 3-(2,2-dimethyl-2*H*-1,3-benzoxazin-4-ylamino)butylate by consideration of the elemental analysis (C₁₆H₂₂N₂O₃), and mass (M^+ : m/e 290), infrared (IR) and nuclear magnetic resonance (NMR) spectral data. The structure of the second reaction product (**4a**) was deduced from its spectral properties and from mechanistic considerations. The elemental analysis and the mass spectrum (M^+ : m/e 278) of **4a** established its molecular formula to be C₁₇H₁₄N₂O₂. In the NMR spectrum of **4a**, the signals of the dimethyl ketal groups and ethyl ester group had disappeared, and a new singlet at 2.30 ppm (3H) due to the methyl group on the pyrimidine ring and another singlet at 8.10 ppm (1H) due to the proton of the 5-position on the pyrimidine ring had appeared. Furthermore, the presence of two hydroxyphenyl groups was indicated by the NMR spectrum, which showed an aromatic multiplet centered at 7.20 ppm (8H) in addition to a broad singlet at 10.35 ppm (2H) due to the hydroxyl groups on the benzene ring. The ultraviolet (UV) spectrum of **4a** in ethanol exhibited three absorption maxima at 214 (log ϵ 4.51), 266 (log ϵ 4.46) and 333 (log ϵ 4.21) nm. On the basis of these spectral data, the second reaction product (**4a**) was presumed to be 2,4-bis(2-hydroxyphenyl)-6-methylpyrimidine. The structure of **4a** was further confirmed by converting it to 2,4-bis(2-methoxyphenyl)-6-methylpyrimidine (**6**). Treatment of **4a** with methyl iodide in the presence of sodium hydride in dimethylformamide afforded the expected product, **6**, in 91% yield. The structure of **6** was unambiguously determined by comparison with an authentic sample prepared independently by the reaction of ethyl 2-methoxybenzalacetate with ammonia followed by oxidation, hydrolysis and decarboxylation, putting to practical use a reported method for the synthesis of unsubstituted

Chart 1

diphenylpyrimidine derivatives.⁵⁾ The final reaction product, **5**, was assigned on the basis of elemental analysis and the spectral (NMR, IR) data, and by comparison with an authentic specimen.⁶⁾

On the other hand, the reaction of 2-methyl-2-methoxycarbonylmethyl-4-chloro-2*H*-1,3-benzoxazine (**1g**) with **2** under similar reaction conditions afforded a different type of reaction product, 2-(2-hydroxyphenyl)-6-methyl-4(3*H*)-pyrimidinone in 26% yield, accompanied by **5**. Elemental analysis and mass spectrum (M^+ : m/e 202) of **7** were consistent with the empirical formula $C_{11}H_{10}N_2O_2$. The NMR spectrum of **7** showed no peaks due to ester groups and dimethyl ketal groups, but instead showed a singlet at 2.40 ppm (3H) due to the methyl group and another singlet at 6.40 ppm (1H) due to the proton of the 5-position on the pyrimidine ring. The IR spectrum showed a new amide absorption band at 1670 cm^{-1} .

Chart 2

A plausible mechanism for the formation of **4a** and **7** is shown in Chart 3.

The 4-amino compound (**8**) might be produced from the initially formed substituted compound (**3**) by the elimination of ethyl crotonate (**5**) as depicted in 3. After reaction of **8** with another molecule of **1a**, intramolecular cyclization might occur *via* **10** and **11** to give the spiro intermediate (**12**). Aromatization accompanying an elimination of isopropylideneimine might then lead to the pyrimidine derivative (**4a**). On the other hand, compound **7** might be produced by intramolecular cyclization of the equilibrium mixture (**8** and **9**).

TABLE I. Reaction of 4-Chloro-2*H*-1,3-benzoxazine Derivatives with Ethyl 3-Aminobutyrate

<div> </div>	Compd. No.	R ₁ R ₂	mp (°C)	Yield (%)	Formula	Analysis (%)	NMR (DMF- <i>d</i> ₇) δ: C-5 (H)	UV λ _{max} ^a nm (log ε)		
C	H	N	Calcd (Found)							
4a	CH ₃	H	144—146	38	C ₁₇ H ₁₄ N ₂ O ₂	73.36 (73.14)	5.07 4.90	10.07 10.20	8.10	214(4.51), 266(4.46), 333(4.21)
4b	C ₂ H ₅	H	127—129	36	C ₁₈ H ₁₆ N ₂ O ₂	73.95 (73.84)	5.52 5.31	9.58 9.66	8.17	214 266 333 ^a
4c	CH ₃	5-OCH ₃	169—171	32	C ₁₉ H ₁₈ N ₂ O ₄	67.44 (67.65)	5.36 5.35	8.28 8.37	8.10	219 247 269 364 ^a
4d	CH ₃	4-Cl	198—200	40	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₂	58.80 (59.05)	3.48 3.52	8.06 8.14	8.10	217(4.53), 271(4.49), 329(4.33)
4e	CH ₃	5-Cl	218—220	42	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₂	58.80 (59.00)	3.48 3.51	8.06 8.09	8.02	225(4.60), 263(4.44), 341(4.17)
4f	Ph	H	250—253	30	C ₂₃ H ₁₆ N ₂ O ₂	77.63 (77.35)	4.74 4.62	8.23 8.40	8.20	270(4.56), 340(4.24)

^a) The UV spectra of 4a and 4b were measured only qualitatively because of their poor solubility in the solvent.

Chart 3

In the reaction of various substituted 4-chloro-2*H*-1,3-benzoxazine (**1b–f**) with ethyl 3-aminobutyrate (**2**) under the same reaction conditions, 2,4-diphenylpyrimidine derivatives (**4b–f**) were obtained mainly, and the corresponding substituted reactilon compounds (**3**) were only detected on thin layer chromatography. The results are summarized in Table I.

Considering the reaction mechanism, we attempted to react 2,2-diethyl- or 2-spirocyclohexyl derivatives of 1,3-benzoxazine instead of **1a** with ethyl 3-aminobutyrate in order to obtain 5,6-disubstituted 2,4-diphenylpyrimidines such as A and B. Contrary to our expectation, these compounds gave no 5,6-disubstituted pyrimidine derivatives, but only a polymerized product. From these results, it is clear that the formation of pyrimidine compounds requires at least one methyl group on the ketal moiety of the benzoxazine derivatives.

Experimental

Melting points were determined with a Buchi melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrophotometer. NMR spectra were determined on a Varian A-60 or HA-100 instrument using tetramethylsilane as an internal standard; coupling constants are given in Hz. MS were taken on a JEOL JMS-01SG instrument.

4-Chloro-2-methyl-2-methoxycarbonylmethyl-2H-1,3-benzoxazine (1g)—A solution of methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,3-benzoxazine-2-acetate (23.5 g) and PCl_5 (21.1 g in POCl_3 (10 ml)) was stirred for 1 h at room temperature, and then heated at 50–60°C for 2 h. After the removal of POCl_3 *in vacuo*, the residue was distilled to give 9.9 g of **1g** as a colorless oil, 123–125°C/1.0 mmHg. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{ClNO}_3$: C, 56.81; H, 4.77; Cl, 13.97; N, 5.52. Found: C, 56.62; H, 4.58; Cl, 14.11; N, 5.41.

Reaction of 4-Chloro-2H-1,3-benzoxazines (1a–f)⁴⁾ with Ethyl 3-Aminobutyrate (2)—General Procedure: A mixture of chlorobenzoxazine (0.01 mol) and ethyl 3-aminobutyrate (0.015 mol) was heated at 150–170°C for 2–4 h with stirring. The reaction mixture was dissolved in ethyl acetate (100–150 ml) and the solution was washed with 2.8% NH_4OH and dried over Na_2SO_4 . After removal of ethyl acetate by evaporation, the residue was chromatographed on silica gel with benzene–hexane (1:1) to give 2,4-bis(2-hydroxyphenyl)pyrimidines (**4a–f**) (Table I). The second fraction, eluted with benzene, afforded ethyl crotonate (**5**), bp 80–82°C/150 mmHg. This was identical with an authentic sample. The last fraction, eluted with benzene–ethyl acetate (3:1), gave a substituted product (**3a**) as a colorless oil, *Anal.* Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.48; H, 7.68; N, 9.60. NMR (CDCl_3) δ : 1.23 (3H, t, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.30 (3H, d, $J=7$ Hz, $\text{CH}_3\text{CH}<$), 1.50 (6H, s, $<\text{CH}_3$), 2.63 (2H, d, $J=6$ Hz, $>\text{CHCH}_2\text{CO}$), 4.17 (2H, q, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.33 (1H, br m, $-\text{CH}<$). IR $\lambda_{\text{max}}^{\text{liquid}}$ cm^{-1} : 3420 ($-\text{NH}$), 1730 ($-\text{CO}_2\text{C}_2\text{H}_5$).

2,4-Bis(2-methoxyphenyl)-6-methylpyrimidine (6)—a) From **4a**: A solution of **4a** (0.5 g) in 15 ml of DMF was treated with 0.2 g of NaH (50% oily mixture) at 5–10°C, and then a solution of methyl iodide (0.8 g) in 15 ml of DMF was added. The reaction mixture was stirred for 3 h at room temperature, then poured into ice-water and extracted with ethyl acetate. The extracts were washed with water, dried over Na_2SO_4 and concentrated. The resulting solid material was recrystallized from methylene chloride–hexane to give 0.5 g of **6** as colorless needles, mp 100–102°C. *Anal.* Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.38; H, 5.88; N, 9.09. NMR ($\text{DMF}-d_7$) δ : 2.55 (3H, s, CH_3-), 3.80 (3H, s, $\text{CH}_3\text{O}-$), 3.95 (3H, s, $\text{CH}_3\text{O}-$), 7.85 (1H, s, C-5H).

b) Preparation of an Authentic Sample of **6**: A mixture of ethyl 2,4-bis(2-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (1.5 g) (synthesized by the method of Asahina and Kuroda⁵⁾), KOH (0.5 g) and 50% CH_3OH (50 ml) was heated under reflux for 3 h. After cooling, the reaction mixture was acidified with dil. HCl and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and evaporated off. The residual solid was recrystallized from methylene chloride–hexane to give 0.8 g of 2,4-bis(2-methoxyphenyl)-6-methylpyrimidine-5-carboxylic acid, mp 198–200°C. *Anal.* Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.65; H, 5.28; N, 7.73. NMR ($\text{DMF}-d_7$) δ : 2.70 (3H, s, CH_3-), 3.77 (3H, s, $\text{CH}_3\text{O}-$), 3.83 (3H, s, $\text{CH}_3\text{O}-$), 6.90–7.80 (8H, m, aromatic H). MS m/e : 350 (M^+). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1720 ($-\text{CO}_2\text{H}$).

This compound (0.6 g) was heated at 210–220°C for 20 min under reduced pressure (100 mmHg). The resulting solid was recrystallized from methylene chloride–hexane to give 0.2 g of **6**, mp 100–102°C, which showed no depression of mp on admixture with the product obtained from **4a**.

Reaction of 4-Chloro-2-methyl-2-methoxycarbonylmethyl-2H-1,3-benzoxazine (1g) with 2—A mixture of **1g** (5.0 g) and ethyl 3-aminobutyrate (**2**, 4.0 g) was heated at 170–180°C for 3 h with stirring. The reaction mixture was then poured into ethyl acetate (200 ml), washed with 2.8% NH_4OH and dried over Na_2SO_4 . The ethyl acetate layer was concentrated under reduced pressure and the residue was chromatographed on silica gel with benzene to give ethyl crotonate (**5**). The second fraction, eluted with benzene–ethyl acetate (5:1), afforded the pyrimidinone derivative (**7**) as yellow needles (1.0 g), mp 241–243°C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.31; H, 4.89; N, 13.71.

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