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A novel synthesis of bis(benzoxazole) derivatives via tandem Claisen rearrangement

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Abstract

The one-pot thermal reaction of 1,3-bis(*o*-acylamino phenyloxy)-2-methylene propane derivatives gave either the bis(benzoxazole) derivatives or the benzodihydrofuran derivatives via tandem Claisen rearrangement in good yields. The reaction courses strongly depend upon the reaction conditions such as the solvent or the substituent of the carbamoyl moiety. The resulting bis(benzoxazole) derivative having a 2-aromatic substituent emits blue fluorescence and has almost the same fluorescence quantum yield as the model mono(benzoxazole) compound.

Keywords: bis(benzoxazole) derivatives; tandem Claisen rearrangement; fluorescence behaviors.

Much attention has been paid to benzoxazoles because they have a number of optical applications such as photoluminescents,[1] whitening agents,[2] and dye laser.[3] Furthermore, the benzoxazole units are used not only for optical application, but also for other important uses such as intermediates for organic syntheses[4] and therapeutic materials.[5] So far, a variety of synthetic methods of benzoxazoles have been reported. They are usually synthesized by the condensation of 2-aminophenols with benzaldehyde[6] or benzoic acid derivatives,[7] followed by intramolecular cyclization. However, there has been no report on versatile methods for the synthesis of bis(benzoxazole) derivatives. We attempted to prepare such compounds by utilizing a tandem Claisen rearrangement,[8] because they are of much interest from the viewpoint of optical behavior and so on. We have recently reported that isobutenyl bis(aryl ether) derivatives are easily converted into compounds having two phenolic hydroxyl groups via tandem Claisen rearrangement.

In this paper, we demonstrate a novel synthetic method of 2-substituted bis(benzoxazole) derivatives via tandem Claisen rearrangement of 1,3-bis(*o*-acylamino phenyloxy)-2-methylene propanes as a versatile synthetic application. We also describe the fluorescent properties of the resulting bis(benzoxazole)s.

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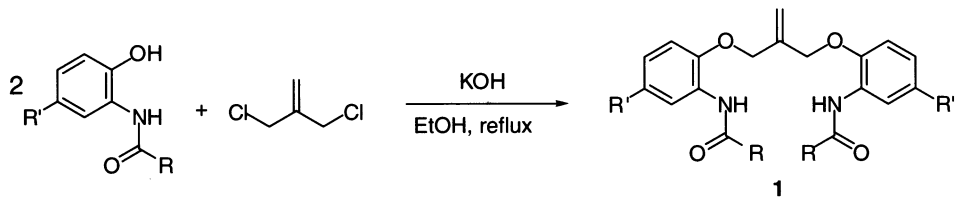
A series of bis(*o*-acylamino phenyloxy)-2-methylene propanes (**1a**–**d**)[9] as the precursors of bis(benzoxazole) derivatives, were easily prepared: 2-amino-4-methylphenols were treated with the corresponding acid chlorides in the presence of pyridine in dry DMF at 0–20°C for 12 h, followed by etherification with 3-chloro-2-chlorometyl-1-propene in the presence of a base (NaH in DMF, otherwise KOH in EtOH)[10] at 70°C for 12 h (Scheme 1).



Scheme 1.

	R	R′	Yield (%)
1a	CH_3	H	80
1b	C_6H_5	H	74
1c	CH_3	CH_3	70
1d	C_6H_5	CH_3	79

The reaction conditions and yields are summarized in Table 1.[11] The thermal bulk reaction of **1a** gave the corresponding bis(benzoxazole)s, **2a** (71%) and **4a** (5%), and benzodihydrofuran, **3a** (13%) (Table 1, run 1). It should be noted that in marked contrast to **1a**, the bulk reaction of **1b** gave preferentially the benzodihydrofuran derivatives (Table 1, run 2). In the cases of **1a** and

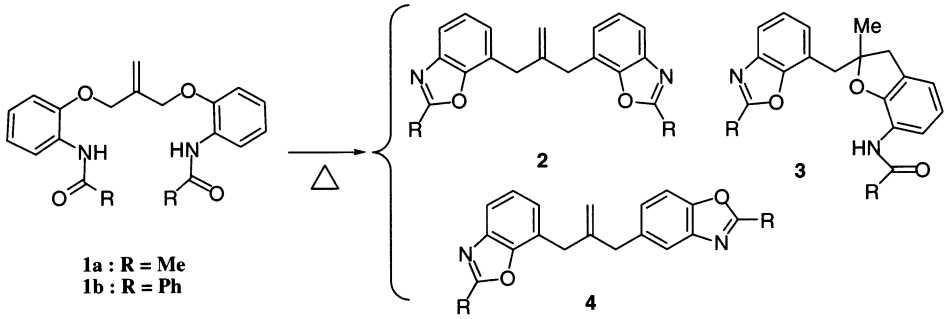
Table 1
Rearrangement of **1a**–**d**[a]

Run	Compound	Solvent	Yield (%)		
			2	**3**	**4**
1	**1a**	None	71	13	5
2	**1b**	None	15	82	Trace
3	**1c**	None	75	9	
4	**1d**	None	6	91	
5	**1a**	NMP	70	2	23
6	**1b**	NMP	81	9	Trace
7[b]	**1c**	NMP	95	5	
8	**1d**	NMP	85	13	

[a] Conditions: conc. in the case of use of solvent, 50 mg of substrate/0.4 ml of solvent; temperature, 180°C; reaction time, 24 h; under argon.

[b] **1c** was heated at 180°C for 84 h to complete the reaction.

1b that have no substituent at the *p*-position of the phenoxy group, tandem Claisen rearrangement proceeded at both the *o*- and *p*-position of the aromatic rings, thereby giving a mixture of **2**, **3**, and **4** as products (Scheme 2).



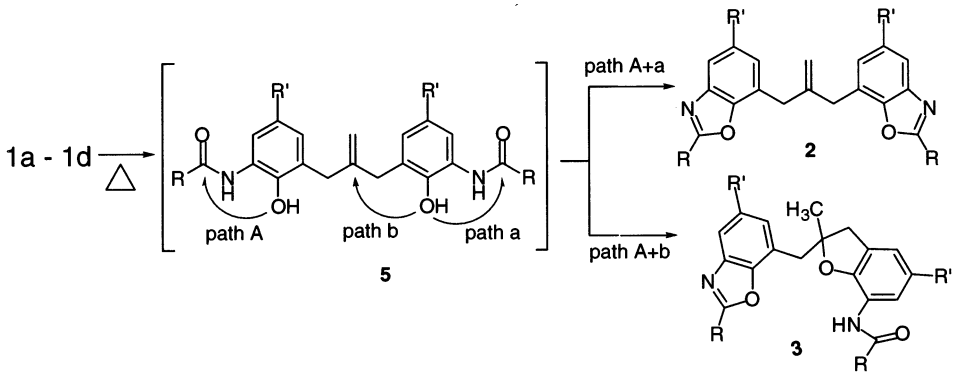
Scheme 2.

It is known that generally Claisen rearrangement of ally aryl ether proceeds preferentially at the *o*-position, but in some cases the rearrangement at the *p*-position without any substituent was observed.[12] In order to inhibit the rearrangement to the *p*-position, **1c** having a methyl group at the *p*-position of the aromatic rings was designed. The thermal reaction of **1c** was carried out under the same conditions as described for **1a** to give almost the same results as those of **1a** (Table 1, run 3). In marked contrast to **1c**, the bulk reaction of **1d** having an aryl group at R gave preferentially the benzodihydrofuran derivatives **3**, as in the case of **1b**. These results might suggest that the substituent R determined the direction of the reaction after the rearrangement: that is, an aliphatic substituent leads to the benzoxazole preferentially, while an aromatic substituent leads to the benzodihydrofuran.

In order to investigate the medium effect, the rearrangements were carried out in a solvent (*N*-methylpyrroridinone: NMP). The product ratios were dramatically changed after the rearrangement of **1b** and **1d** in NMP at 180°C under an argon atmosphere, that is to say, the bis(benzoxazole) derivatives **2** was preferentially obtained contrary to the bulk reaction. In the case of **1a** and **1c**, the predominant formation of **2a** and **2c** resulted almost the same as in the bulk reaction. This means that the direction of the intramolecular cyclization of **1b** and **1d** having the aryl group at R was greatly affected by the medium. Probably, NMP might work so as to protect the undesirable dehydrobenzodihydrofuran formation.

Judging from these results we infer that the reactions, including tandem Claisen rearrangement, proceed as follows: at the first step, the tandem Claisen rearrangement of **1** at the isobutenyl aryl ether group takes place to give the 2-carbamoyl phenol derivative **5**. At the second step, bis(benzoxazole) derivatives **2** were obtained by intramolecular cyclization between OH and amide groups accompanied by the dehydration (Scheme 3, paths A and a), while benzodihydrofuran derivatives **3** were formed by the attack of the OH group at the isobutenyl group (Scheme 3, paths A and b).

The emission spectrum of **2a**, **2c**, and **2d** and the corresponding precursors, **1a**, **1c**, and **1d**, in $CHCl_3$ (1×10^{-6} M) was measured, which is one of the most important properties of the benzoxazoles. The results are listed in Table 2. None of the precursors **1** emitted any fluorescence. In contrast, bis(2-arylbenzoxazole) **2d** emitted blue fluorescence at 369 and 374 nm upon excitation at 300 nm, while the fluorescence of bis(2-methylbenzoxazole)s **2a** and **2c** could not be observed. The fluorescence quantum yield of bis(benzoxazole) **2d** in $CHCl_3$ (conc. 1×10^{-6}



Scheme 3.

M) was compared with that of 2-phenyl-6-methylbenzoxazole **6d** as the model compound. As a result, the quantum yield of bis(benzoxazole) was somewhat smaller than that of the model compound ($\phi_{\mathbf{2d}} = 0.43$ versus $\phi_{\mathbf{6d}} = 0.63$). This might be caused by the self-quenching due to some possible orientation with the neighboring benzoxazole for quenching in the case of the bis(benzoxazole)s.

Table 2
Fluorescence spectra[a]

Run	Compound	λ_{max} (nm)	ϕ
1	**1c**	None	
2	**1d**	None	
3	**2c**	None	
4	**2d**	369	0.43
5	**6d**	362	0.63

[a] All samples were exited at 300 nm. The ϕs were calculated with quinine sulfate in 1N H_2SO_4 as a reference, which has a quantum yield of 0.51.

In conclusion, we have succeeded in the simple and convenient one-pot syntheses of bis(benzoxazole) derivatives from 1,3-bis(phenyloxy)-2-methylene propanes having carbamoyl groups at the *o*-position of the phenyl groups via tandem Claisen rearrangement in good yields. The yields of bis(benzoxazole) derivatives largely depend upon either the reaction conditions or the substituent of the carbamoyl groups of **1**. The heating of **1d** caused change in the fluorescent property digitally. It might be suggested that compounds including **1d** units are applicable to thermo-induced fluorescence materials. We are studying the fluorescence behavior of the macrocyclic system having two benzoxazole moieties in terms of the orientation dependency.

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9. **1a**: Colorless solid; mp 131.1–133.5°C; ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H, –CH_3), 4.72 (s, 4H, –CH_2–O–), 5.44 (s, 2H, CH_2=C), 6.91 (d, J=7.8 Hz, 2H, Ar), 6.98–7.02 (m, 4H, Ar), 7.75 (bs, 1H, NH), 8.32 (d, J=7.3, 2H, Ar). IR (KBr): 3296, 1660, 1600, 1260 cm^{-1}. HRMS calcd for $C_{20}H_{22}N_2O_4$ 354.1578, found 354.1574. **1b**: Colorless solid; mp 119.2–123.0°C; ^{1}H NMR ($CDCl_3$): δ 4.78 (s, 4H, Ar–CH_2–), 5.48 (s, 2H, CH_2=C), 7.18 (d, J=7.0, 2H, Ar), 7.27 (t, J=7.8, 2H, Ar), 7.42–7.48 (m, 6H, Ar), 7.62 (dd, J=0.9, 7.9, 2H, Ar), 8.06 (dd, J=1.4, 8.2, 4H, Ar). IR (KBr): 3431, 3338, 1656, 1602, 1258, cm^{-1}. HRMS calcd for $C_{30}H_{26}N_2O_4$ 478.1891, found 478.1803. **1c**: Colorless solid; mp 149.3–151.0°C; ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 3H, CH_3–C(=O)–), 2.30 (s, 3H, CH_3–Ar), 4.68 (s, 4H, –CH_2–O–), 5.40 (s, 2H, CH_2=C), 6.80 (s, 2H, Ar), 7.73 (bs, 1H, NH), 8.17 (s, 2H, Ar). IR (KBr): 3288, 1660, 1262 cm^{-1}. HRMS calcd for $C_{22}H_{26}N_2O_4$ 382.1891, found 382.1929. **1d**: Colorless solid; mp 131.8–133.7°C; ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H, CH_3–Ar), 4.73 (s, 4H, –CH_2–O–), 5.45 (s, 2H, CH_2=C), 6.79–6.80 (m, 4H, Ar), 7.40 (t, J=7.7, 4H, Ar), 7.49 (t, J=7.5, 2H, Ar), 7.78–7.80 (m, 4H, Ar), 8.36 (s, 2H, Ar), 8.49 (bs, 1H, NH). IR (KBr): 3444, 3425, 1669, 1595, 1253 cm^{-1}. HRMS calcd for $C_{32}H_{30}N_2O_4$ 506.2204, found 506.2249.
10. The reaction of 2-*N*-benzoyl aminophenol with 3-chloro-2-chlorometyl-1-propene in the presence of NaH did not give **1b**, but the [1+1] cyclic compound obtained in 70% yield by *O*- and *N*-alkylation of the isobutenyl dichloride with hydroxyl and amide groups, respectively. KOH could be also used as a base for the etherification in ethanol.
11. **2a**: Colorless solid; mp 94.7–96.7°C; ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 6H, C–CH_3), 3.59 (s, 4H, Ar–CH_2–), 4.93 (s, 2H, CH_2=C), 7.09 (d, J=7.4, 2H, Ar), 7.21 (t, J=7.7, 2H, Ar), 7.50 (d, J=7.9, 2H, Ar). IR (KBr): 1614, 1268 cm^{-1}. HRMS calcd for $C_{20}H_{18}N_2O_2$ 318.1367, found 318.1362. **3a**: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 3H, CH_3–C(–O–)), 2.09 (s, 3H, –C(=O)CH_3), 2.54 (s, 3H, CH_3), 2.96 (d, J=15.4, 1H, Ar–CH–), 3.11 (d, J=13.8, 1H, Ar–CH–), 3.19 (d, J=15.4, 1H, Ar–CH–), 3.28 (d, J=13.8, 1H, Ar–CH–), 6.75 (t, J=7.7, 1H, Ar), 6.79 (d, J=6.8, 1H, Ar), 7.07 (d, J=7.6, 1H, Ar), 7.17 (t, J=7.7, 1H, Ar), 7.47 (d, J=7.9, 1H, Ar), 8.00 (d, J=7.9, 1H, Ar). IR (KBr): 3277, 1671, 1624 cm^{-1}. HRMS calcd for $C_{20}H_{20}N_2O_3$ 336.1473, found 336.1478. **4a**: Colorless solid; mp 77.4–78.8°C; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, C–CH_3), 2.56 (s, 3H, C–CH_3), 3.37 (s, 2H, Ar–CH_2–), 3.45 (s, 2H, Ar–CH_2–), 4.81 (s, 1H, CH_2=C), 4.82 (s, 1H, CH_2=C), 7.00–7.02 (m, 4H, Ar), 7.15 (t, J=7.7, 1H, Ar), 7.38 (s, 1H, Ar), 7.43 (d, J=8.0, H, Ar). IR (KBr): 1613 cm^{-1}. HRMS calcd for $C_{20}H_{18}N_2O_2$ 318.1367, found 318.1405. **2b**: Colorless solid; mp 122.6–123.9°C; ^{1}H NMR ($CDCl_3$): δ 3.71 (s, 4H, Ar–CH_2–), 5.09 (s, 2H, CH_2=C), 7.18 (d, J=7.0, 2H, Ar), 7.27 (t, J=7.8, 2H, Ar), 7.42–7.48 (m, 6H, Ar), 7.62 (dd, J=0.9, 7.9, 2H, Ar), 8.06 (dd, J=1.4, 8.2, 4H, Ar). IR (KBr): 1615 cm^{-1}. HRMS calcd for $C_{30}H_{22}N_2O_2$ 442.1680, found 442.1704. **3b**: Colorless solid; mp 61.5–63.0°C; ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 3H, CH_3–C(–O–)), 3.16 (d, J=15.4, 1H, Ar–CH–), 3.22 (d, J=13.8, 1H, Ar–CH–), 3.36 (d, J=15.4, 1H, Ar–CH–), 3.53 (d, J=13.8, 1H, Ar–CH–), 6.92 (t, J=7.5, 1H, Ar), 6.95 (d, J=7.2, 1H, Ar), 7.22 (d, J=6.6, 1H, Ar), 7.30 (t, J=7.7, 1H, Ar), 7.43 (d, J=7.2, 1H, Ar), 7.48 (d, J=7.5, 1H, Ar), 7.61 (dd, J=1.2, 8.3, 1H, Ar), 7.69 (dd, J=1.1, 8.0, 1H, Ar), 7.84 (bs, 1H, NH), 8.10 (d, J=7.0, 2H, Ar), 8.27 (d, J=8.0, 1H, Ar). IR (KBr): 1675, 1626 cm^{-1}. HRMS calcd for $C_{30}H_{24}N_2O_3$ 460.1786,

found 460.1761. **2c**: Colorless solid; mp 104.2–106.3°C; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 6H, C–CH_3), 2.54 (s 6H, CH_3–Ar), 3.53 (s, 4H, Ar–CH_2–), 4.93 (s, 2H, CH_2=C), 6.87 (s, 2H, Ar), 7.28 (s, 2H, Ar). IR (KBr): 1617 cm^{-1}. HRMS calcd for $C_{22}H_{22}N_2O_2$ 346.1680, found 346.1711. **3c**: Colorless solid; mp. 57.0–58.0°C; ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 3H, CH_3–C(–O–)), 2.09 (s, 3H, –C(=O)CH_3), 2.28 (s, 3H, CH_3–Ar), 2 43 (s, 3H, CH_3–Ar), 2.58 (s, 3H, –CH_3), 2.99 (d, J=15.5, 1H, Ar–CH–), 3.10 (d, J=13.8, 1H, Ar–CH–), 3.20 (d, J=15.5, 1H, Ar–CH–), 3.27 (d, J=13.8, 1H, Ar–CH–), 6.69 (s, 1H, Ar), 6.94 (s, 1H, Ar), 7.10 (bs, 1H, NH), 7.32 (s, 1H, Ar), 7.90 (s, 1H, Ar). IR (KBr): 1685, 1625 cm^{-1}. HRMS calcd for $C_{22}H_{24}N_2O_3$ 364.1786, found 364.1805. **2d**: Colorless solid; mp 158.1–160.8°C; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 6H, CH_3–Ar), 3.65 (s, 4H, Ar–CH_2–), 5.10 (s, 2H, CH_2=C), 6.94 (s, 2H, Ar), 7.37 (s, 2H, Ar), 7.41–7.50 (m, 6H, Ar), 8.04 (d, J=6.1, 4H, Ar). IR (KBr): 1615 cm^{-1}. HRMS calcd for $C_{32}H_{26}N_2O_2$ 470.1993, found 470.2017. **3d**: Colorless solid; mp 197.5–199.0°C; ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 3H, CH_3–C(–O–)), 2.36 (s, 3H, CH_3–Ar), 2.42 (s, 3H, CH_3–Ar), 3.11 (d, J=15.3, 1H, Ar–CH–), 3.15 (d, J=13.7, 1H, Ar–CH–), 3.29 (d, J=15.4, 1H, Ar–CH–), 3.44 (d, J=13.8, 1H, Ar–CH–), 6.78 (s, 1H, Ar), 7.02 (s, 1H, Ar), 7.36–7.49 (m, 7H, Ar), 7.63 (t, J=7.2, 2H, Ar), 7.83 (bs, 1H, NH), 8.10 (d, J=7.0, 2H, Ar), 8.12 (s, 1H, Ar). IR (KBr): 1677, 1627 cm^{-1}. HRMS calcd for $C_{32}H_{28}N_2O_3$ 488.2098, found 488.2052.

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