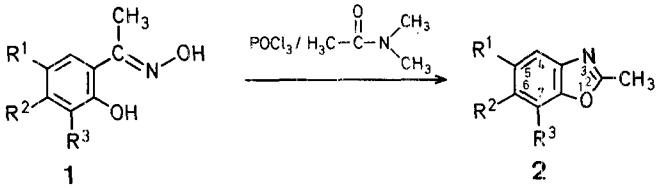
The Beckmann Rearrangement by Means of Phosphoryl Chloride/*N,N*-Dimethylacetamide; A Novel and Convenient Method for Preparing Benzoxazoles

Shinsaku FUJITA*, Koichi KOYAMA, Yoshio INAGAKI

Research Laboratories, Ashigara, Fuji Photo Film Co. Ltd., Minami-Ashigara, Kanagawa, 250-01 Japan

Benzoxazoles are important intermediates for the syntheses of polyether antibiotics[1], of fluorescent whitening agents[2], and of dye releasers in instant color photography[3,4]. Among several synthetic methods, the Beckmann rearrangement of *o*-acylphenol oximes has been reported to produce benzoxazoles as a result of an intramolecular ring closure. However, the conventional reagents used have been applied to a very limited range of starting oximes and often afford low yields of products[5]. Especially, no satisfactory methods have been introduced for preparing hydroxy-substituted benzoxazoles[6]. We report here that phosphoryl chloride/*N,N*-dimethylacetamide (DMA) is a convenient reagent for the preparation of benzoxazoles and, particularly, for hydroxy-substituted derivatives.

The results of our studies on the Beckmann rearrangement of *o*-acylphenol oximes **1** using phosphoryl chloride/*N,N*-dimethylacetamide are summarized in Table 1. The reaction proceeds smoothly at room temperature, and the conversion is almost complete when the addition of phosphoryl chloride is finished. Oximes of 2′,4′-dihydroxyacetophenone derivatives **(1a–g)** were converted into the corresponding 6-hydroxybenzoxazoles **(2a–g)** in good yields. This method was also applied to acylhydroquinone oximes **(1h–j)** to produce 5-hydroxybenzoxazoles **(2h–j)**. 6-Hexadecyloxy-2-methylbenzoxazole **(2k)** was obtained by the action of the reagent on **1k**, and was identical with the sample prepared by alkylation of 6-hydroxy-2-methylbenzoxazole **(2o)**.



1 2

The results of studies on the Beckmann rearrangement of **1a** under various conditions are summarized in Table 2 for comparison. The use of solvents (especially, acetonitrile) and a small excess of *N,N*-dimethylacetamide afforded the most satisfactory results (run 1). A large excess of the amide caused an undesired coloration of the product and a lowering of the yield (run 2). The Beckmann rearrangement also proceeded in the absence of *N,N*-dimethylacetamide (run 3–6). In these cases, however, 4-acetylaminoresorcinol (~40%) was formed as a by-product, and hence the yields were considerably lower as compared with cases in the presence of the amide. The different results in the presence and absence of the amide may be accounted for by presuming the attack of a Vilsmeier-type complex instead of the attack of phosphoryl chloride itself and the efficient solvation of carbocation intermediates in the presence of the amide.

Treatment of **1a** with hydrogen chloride in acetic acid also gave benzoxazole **2a** in a fair yield (run 7). However, the bubbling of hydrogen chloride gas was very tedious and the heating to about 90°C was necessary. Refluxing formic acid has been reported to be applicable to the rearrangement of **1a**, but the yield reported was only 44% (run 8)[6a]. Benzoxazole **2a** was obtained also by means of phosphoryl chloride/*N,N*-dimethylformamide. However, it should be noted that the latter reagent has been reported to cause undesired formylation of the active 2-methyl group of **2a**[6b]. The reagent reported in this work was more mild and chemoselective than phosphoryl chloride/dimethylformamide and did not cause such formylation even at a higher temperature.

The related reaction of the acetate of oxime **1a** with aqueous sodium hydroxide has been reported to give the same product **2a** in 75% yield[7]. However, the acetate of oxime **1h** has been found to afford no benzoxazole. In conclusion, the phosphoryl chloride/dimethylacetamide method of the present work is a versatile and convenient tool for preparation of benzoxazoles **2.**

6-Hydroxy-2-methylbenzoxazole (2a); Typical Procedure:
Phosphoryl chloride (2.4 ml, 0.026 mol) is added dropwise below 30°C during 15 min to a stirred solution of **1a** (4.20 g, 0.025 mol) in dimethylacetamide (5.0 ml) and acetonitrile (15 ml). The mixture is stirred for additional 30 min and poured into ice/water (200 ml) containing sodium acetate (6.00 g). The precipitates are collected by filtration to give **2a**; yield: 3.08 g (83%); m.p. 194–196°C. A single recrystallization from acetonitrile gives an analytically pure sample.

0039-7881/82/0132-0068 $ 03.00

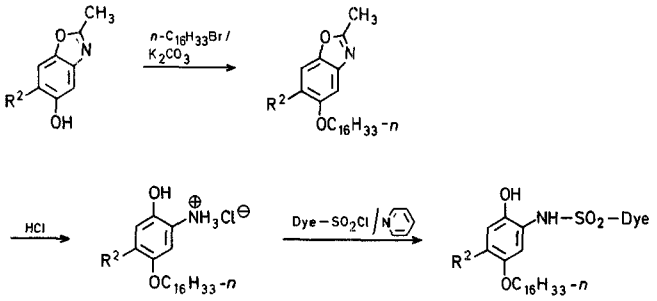
Table 1. Benzoxazoles **2** prepared by Beckmann Rearrangement of Oximes **1** with Phosphoryl Chloride/Dimethylacetamide at Room Temperature

Product No.	R^1	R^2	R^3	Yield [%][a]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	^{1}H-N.M.R. (DMSO-d_6, 90 MHz, r.t.)[c] δ [ppm]
2a	H	HO	H	83	194–196°	196°[7]	2.52 (s, ~3 H)[d]; 6.77 (dd, 1 H, J=9 Hz, 3 Hz); 6.98 (d, 1 H, J=3 Hz); 7.42 (d, 1 H, J=9 Hz); 9.63 (br s, 1 H)
2b	CH_3	HO	H	82	222–223°	$C_9H_9NO_2$ (163.2)	2.18 (s, 3 H); 2.49 (s, ~3 H)[d]; 6.94 (s, 1 H); 7.28 (s, 1 H); 9.48 (s, 1 H)
2c	t-C_4H_9	HO	H	85	264–266°[e]	$C_{12}H_{15}NO_2$ (205.3)	1.41 (s, 9 H); 2.49 (s, ~3 H)[d]; 6.96 (s, 1 H); 7.34 (s, 1 H); 9.56 (br s, 1 H)
2d	C_2H_5—$C(CH_3)_2$—	HO	H	62	237–238°[e]	$C_{13}H_{17}NO_2$ (219.3)	0.58 (t, 3 H, J=7 Hz); 1.35 (s, 6 H); 1.88 (q, 2 H, J=7 Hz); 2.50 (s, ~3 H)[d]; 6.95 (s, 1 H); 7.29 (s, 1 H); 9.50 (br s, 1 H)
2e	H_3C—$C(C_2H_5)_2$—	HO	H	87	217–218°[e]	$C_{14}H_{19}NO_2$ (233.3)	0.58 (t, 3 H, J=8 Hz); 1.27 (s, 3 H); 1.3–1.7 (m, 2 H); 2.0–2.4 (m, 2 H); 2.50 (s, ~3 H)[d]; 6.94 (s, 1 H); 7.24 (s, 1 H); 9.47 (s, 1 H)
2f	n-C_6H_{13}	HO	H	68	126–127°	$C_{14}H_{19}NO_2$ (233.3)	0.7–1.1 (m, 3 H); 1.1–1.8 (m, ~10 H); 2.51 (s, ~3 H)[d]; 6.97 (s, 1 H); 7.27 (s, 1 H); 9.46 (br s, 1 H)
2g	t-C_4H_9	HO	CH_3	85	166–168°	$C_{13}H_{17}NO_2$ (219.3)	1.41 (s, 9 H); 2.32 (s, 3 H); 2.51 (s, ~3 H)[d]; 7.24 (s, 1 H); 8.32 (s, 1 H)
2h	HO	H	H	68	164–165°	164°[8]	2.56 (s, ~3 H)[d]; 6.76 (dd, 1 H, J=9 Hz, 2 Hz); 7.00 (d, 1 H, J=2 Hz); 7.37 (d, 1 H, J=9 Hz); 9.33 (s, 1 H)
2i	HO	t-C_4H_9	H	88	203–205°	$C_{12}H_{15}NO_2$ (205.3)	1.42 (s, 9 H); 2.55 (s, ~3 H)[d]; 7.06 (s, 1 H); 7.39 (s, 1 H); 9.41 (s, 1 H)
2j	HO	4-H_3C—C_6H_4	H	92	195–196°	$C_{15}H_{13}NO_2$ (239.3)	2.34 (s, 3 H); 2.55 (s, ~3 H)[d]; 7.1–7.5 (m, 6 H); 9.42 (s, 1 H)
2k	H	n-$C_{16}H_{33}O$	H	76	56–57°	$C_{24}H_{39}NO_2$ (373.6)	1.88 (m, 3 H); 1.2–2.0 (m, 28 H); 2.57 (s, 3 H); 3.96 (t, 2 H); 6.87 (dd, 1 H, J=8 Hz, 2 Hz); 6.98 (d, 1 H, J=2 Hz); 7.48 (d, 1 H, J=8 Hz)[f]

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, N ±0.20.
[c] Varian EM-390 spectrometer.
[d] Overlap with solvent signal.
[e] Measured in a sealed tube.
[f] $CDCl_3$ solution.

Table 2. Beckmann Rearrangement of 2′,4′-Dihydroxyacetophenone Oxime (**1a**)

Run	Reagent	Solvent	Reaction conditions temperature/time	Yield [%] of **2a**
1	$POCl_3$/DMA	CH_3CN	30 °C/0.5 h	83
2	$POCl_3$/DMA	(DMA)	30 °C/0.5 h	78
3	$POCl_3$	CH_3CN	30 °C/0.5 h	44
4	$POCl_3$	THF	30 °C/0.5 h	52
5	$POCl_3$	acetone	30 °C/0.5 h	54
6	$POCl_3$	sulfolane	40 °C/0.5 h	56
7	HCl	AcOH	reflux/2.5 h	68
8[6a]	HCOOH	(HCOOH)	reflux/4.5 h	44



Received: August 5, 1981

[1] D. A. Evans, C. E. Sacks, W. A. Kleschick, T. R. Taber, *J. Am. Chem. Soc.* **101**, 6789 (1979).

[2] A. Reiser, L. J. Leyshon, D. Saunders, M. V. Mijovic, A. Bright, J. Bogie, *J. Am. Chem. Soc.* **94**, 2414 (1972).

[3] (a) S. Fujita, *Yuki Gosei Kagaku Kyokai-Shi* **39**, 331 (1981).
(b) K. Koyama, Y. Maekawa, M. Miyakawa, *U. S. Patent* 4055428 (1977); *C. A.* **87**, 31917 (1977).
(c) S. Fujita, K. Koyama, Y. Inagaki, *Japan Kokai* 1981-16131 (1981)
(d) S. Fujita, *J. Chem. Soc. Chem. Commun.* **1981**, 425.

[4] The 5- and 6-hydroxybenzoxazoles can be converted to *o*-sulfonamidophenol dye-releasers, which are used as image-providing compounds in instant color photography. For example:

wherein Dye is a dye moiety and the *n*-hexadecyloxy group is a ballast group. The dye releasers are oxidized to the corresponding *o*-quinonemonosulfonimides in a photographic developing process and then hydrolyzed to release a diffusible Dye-SO_2—NH_2[3a,d].

[5] (a) E. P. Kohler, W. F. Bruce, *J. Am. Chem. Soc.* **53**, 1569 (1931).
(b) K. v. Auvers, O. Jordan, *Ber. Dtsch. Chem. Ges.* **58**, 26 (1925).
(c) A. H. Blatt, L. A. Russel, *J. Am. Chem. Soc.* **58**, 1903 (1936).
(d) Z. Witczak, M. Krolikowska, *Polish J. Chem.* **52**, 2479 (1978).

[6] (a) T. Sugiyama, H. Yamaguchi, S. Ishimoto, *Japan Kokai* 1976-54552 (1976).
(b) M. R. Jayanth, H. A. Naik, D. T. Tatke, S. Seschadri, *Indian J. Chem.* **11**, 1112 (1973).

[7] H. Lindemann, H. Könitzer, S. Romanoff, *Justus Liebigs Ann. Chem.* **456**, 284 (1927).

[8] R. Royer, G. Colin, P. Demerseman, S. Combrisson, A. Cheutin, *Bull. Soc. Chim. Fr.* **1969**, 2785.