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A convenient synthesis of 1*H*-2,3-benzoxazines by an acid-catalyzed intramolecular Mitsunobu reaction

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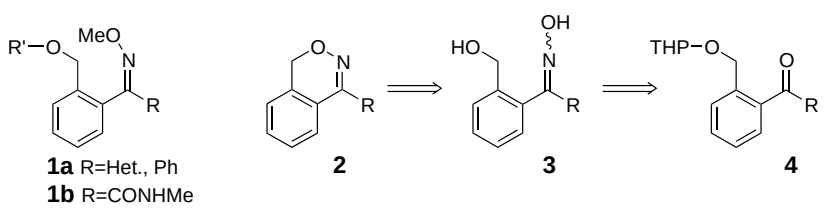
Abstract—A convenient, efficient method for the preparation of benzoxazines is described. 2-(Hydroxyiminomethyl)benzyl alcohols were cyclodehydrated to construct 1*H*-2,3-benzoxazines by acid-catalyzed intramolecular Mitsunobu reaction. This reaction depended on the geometry of the hydroxyimino moiety in the reaction precursor. © 2001 Elsevier Science Ltd. All rights reserved.

In our previous papers,[1] we reported the structure–activity relationship of fungicidal or acaricidal benzohydroximoyl derivatives (**1a**) designed by replacing the carbamoyl moiety in the known fungicidal methoxyiminoacetamide derivatives (**1b**)[2] with heterocycles (Het.) or a benzene ring. In our continuing study, we next designed 1*H*-2,3-benzoxazines (**2**) which have the essential elements for activity, that is, a methoxyimino moiety and *ortho* substitution (Scheme 1). A few synthetic methods of 1*H*-2,3-benzoxazines were reported. However, these were complicated and unsatisfactory.[3] So, we examined here a new and convenient method of constructing benzoxazines from 2-(hydroxyiminomonomethyl)benzyl alcohols (**3**), which are obtainable by oximation from ketone **4**, a key synthetic intermediate of **1a**.

First, for the investigation of cyclodehydration, 2-[4-chlorophenyl(hydroxyimino)methyl]benzyl alcohol (**3b**) was selected for optimization of the reaction conditions. Several attempts at ring closure by dehydration with thionyl chloride or *p*-toluene sulfonic acid led either to minimal or no reaction. However, using Mitsunobu conditions,[4] although the reaction was sluggish and did not continue to completion, 21% yield of the desired product (**2b**) was obtained (entry 1, Table 1).

We considered this cyclization on the basis of an ordinary Mitsunobu reaction illustrated in Scheme 2. Phosphonium salt (**8**) and oxime anion (**9**) are produced by the protonation of betaine **7** from oxime **3**. Then, the hydroxy moiety of **9** attacks **8** to produce alkoxyphosphonium salt (**10**). Finally, the desired product **2** is produced by intramolecular cyclization. We considered that the low yield of this reaction is due to the slow protonation of **7** from **3**. Therefore, it was expected that **7** is smoothly transformed to **8** by the addition of acid **13**. The intramolecular cyclization to produce **2** is faster than the attack of anion **14**, and anion **14** is simultaneously retransformed to **13** to work as a catalyst.



Scheme 1.

Keywords: benzoxazines; Mitsunobu reactions; catalysts; geometry.

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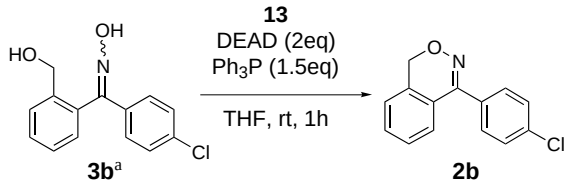
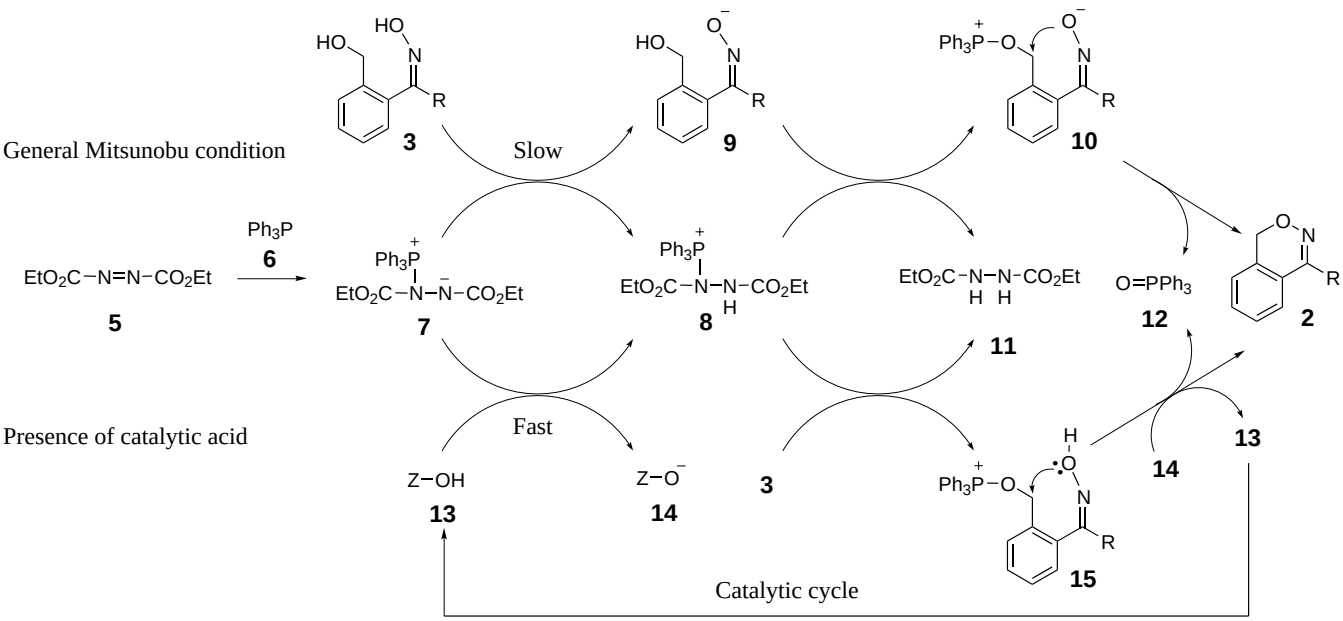
Table 1. Mitsunobu reaction with various acid catalysts



3b[a] **2b**

Entry	**13**	pK_a	Equiv.	Recovery	
				2b (%)[b]	**3b** (%)[b]
1	None	–	–	21	38
2	CH_3CO_2H	4.8	0.2	62	19
3	$C_6H_5CO_2H$	4.2	0.2	70	0
4	C_6H_5OH	10.0	0.2	66	15
5	4-$NO_2C_6H_4OH$	7.2	0.05	53	12
6	4-$NO_2C_6H_4OH$		0.2	82	0
7	4-$NO_2C_6H_4OH$		1.2	82	0
8	2,4-$(NO_2)_2C_6H_3OH$	4.0	0.2	70	10

[a] E/Z mixture (approximately 5:95 from ^{1}H NMR spectra).
[b] Isolated yields.

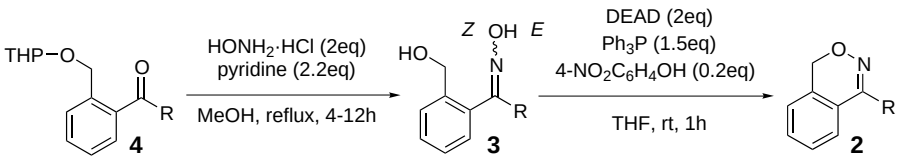


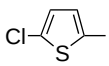
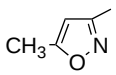
Scheme 2.

According to the above consideration, cyclodehydration of **3b** to form **2b** under Mitsunobu conditions by adding some acids was examined, and the results are listed in Table 1. The addition of a catalytic amount of acetic acid significantly increased the yield of **2b** (entry 2). Then, various acids were employed, and the influence of the acidity was examined. Among these acids, 4-nitrophenol gave the best result (entry 6).[5] And the optimal pK_a was approximately seven, although definitive reasons for this result have not been clarified. Decreasing the amount of 4-nitrophenol to 0.05 equiv. reduced the yield to 53% (entry 5), but the reaction of **3b** with 1.2 equiv. of the catalyst gave the same yield (entry 7). From this result, we confirmed that the acid works as a catalyst.

Next, we attempted to apply the optimal conditions obtained above (entry 6, Table 1) to the synthesis of various benzoxazines **2** from oximes **3**, which were afforded by oximation and subsequent in situ deprotection of ketones **4** with hydroxylamine hydrochloride and pyridine in methanol (Table 2). The electronic or steric effects of the substituents (R) did not affect cyclodehydration. However, when the geometry of the hydroxyimino moiety in the reaction precursor was *E*, no product was obtained (entries 8 and 9), and the

Table 2. Synthesis of 4-substituted 1*H*-2,3-benzoxazines **2**



Entry	R	Oxime	Yield (%)[b]	*E*/*Z*[a]	Benzoxazine	Yield (%)[b]	Mp (°C)
1	C_6H_5	**3a**	97	7/93	**2a**	85	74–75[d]
2	4-ClC_6H_4	**3b**	98	5/95	**2b**	82	135.5–136.5
3	2-$CH_3C_6H_4$	**3c**	92	70/30	**2c**	25	68–70
4	4-$CH_3C_6H_4$	**3d**	76	7/93	**2d**	90	111.5–112.5
5	3-HOC_6H_4	**3e**	53	0/100	**2e**	92	154–155
6	3-$NO_2C_6H_4$	**3f**	67	7/93	**2f**	71	148–150
7	3,4-$(CH_3O)_2C_6H_4$	**3g**	69	0/100	**2g**	71	105–106
8	CH_3	**3h**	61	100/0	**2h**	0	–
9		**3i**	23	0/100[c]	**2i**	54	66–67
			54	100/0[c]	**2i**	0	–
10		**3j**	93	0/100[c]	**2j**	54	67–68

[a] ^{1}H NMR spectra.
[b] Isolated yields.
[c] The name of the geometrical isomer is disregarded IUPAC nomenclature.
[d] Lit.[3] mp 76.5–77°C.

reaction of the *E*/*Z* mixture containing predominantly the *E* isomer resulted in a low yield (entry 3). Apparently, this reaction was dependent on the geometry of the hydroxyimino moiety in the reaction precursor.

In conclusion, we have developed a convenient and efficient method for the synthesis of benzoxazines **2** from 2-(hydroxyiminomethyl)benzyl alcohols **3** by an acid-catalyzed intramolecular Mitsunobu reaction. The biological assay showed that several compounds of synthesized **2** have herbicidal activity. The structure–activity relationships of **2** will be reported elsewhere.

References

1. (a) Kai, H.; Ichiba, T.; Miki, M.; Takase, A.; Masuko, M. *J. Pesticide Sci.* **1999**, *24*, 130–137; (b) Kai, H.; Ichiba, T.; Tomida, M.; Masuko, M. *J. Pesticide Sci.* **1999**, *24*, 149–155; (c) Kai, H.; Ichiba, T.; Takase, A.; Masuko, M. *J. Pesticide Sci.* **2000**, *25*, 24–30; (d) Kai, H.; Tomida, M.; Nakai, T.; Kumano, K.; Hirose, S.; Morita, K. *J. Pesticide Sci.* **2001**, *26*, 121–126.
2. (a) Takenaka, H.; Ichinari, M.; Tanimoto, N.; Hayase, Y.; Niikawa, M.; Ichiba, T.; Masuko, M.; Hayashi, Y.; Takeda, R. *J. Pesticide Sci.* **1998**, *23*, 107–112; (b) Takenaka, H.; Hayase, Y.; Hasegawa, R.; Ichiba, T.; Masuko, M.; Murabayashi, A.; Takeda, R. *J. Pesticide Sci.* **1998**, *23*, 379–385.
3. (a) Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 1372 H374; (b) Pifferi, G.; Consonni, P.; Testa, E. *Tetrahedron* **1968**, *24*, 4923–4932; (c) Pifferi, G.; Monguzzi, R. *J. Heterocycl. Chem.* **1972**, *9*, 1445–1447.
4. Mitsunobu, O. *Synthesis* **1981**, 1–28.
5. Typical procedure: **3b→2b**: diethyl azodicarboxylate (DEAD, 0.31 ml, 2.0 mmol) was added to a mixture of **3b** (0.26 g, 1.0 mmol), 4-nitrophenol (0.02 g, 0.2 mmol), triphenylphosphine (0.39 g, 1.5 mmol) and tetrahydrofuran (3 ml) in an ice bath, and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into toluene (100 ml) and washed with 0.1N sodium hydroxide (80 ml). The organic layer was washed with brine (80 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane: 1/9 v/v) to give 0.20 g (82%) of 4-(4-chlorophenyl)-1*H*-2,3-benzoxazine (**2b**) as a white solid. The product was recrystallized from hexane and ethyl acetate to give colorless prisms, mp 135.5–136.5°C. ^{1}H NMR (270 MHz, $CDCl_3$) δ ppm: 5.04 (s, 2H), 7.20 (d, J=7.1 Hz, 1H), 7.27 (d, J=7.1 Hz, 1H), 7.35–7.63 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 67.2, 122.4, 124.5, 125.7, 128.4, 128.9, 130.3, 131.6, 132.2, 132.7, 136.0, 160.0. IR (KBr) cm^{-1}: 2836, 1592, 1486, 1397, 1335, 1090, 975, 860. Anal. calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; Cl, 14.55; N, 5.75. Found: C, 68.93; H, 3.99; Cl, 14.63; N, 5.73.