

Synthesis and Herbicidal Activity of New Hexahydrobenzisoazole Derivatives

Hyoung Rae Kim · Hyun Ju Park¹ · Hyung Ki Kim · Jong Hwan Song · Dong Ju Jeon
Kyoung Mahn Kim · Tae Joon Kim and Eung K. Ryu*

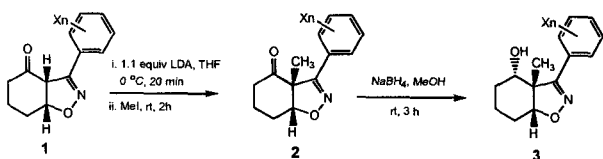
Korea Research Institute of Chemical Technology, P. O. Box 107 Yusong, Taejeon 305-600, Korea

¹Bioneer Co. Ltd., High-Tech Park, 124 Chuckbook-Rhi, Namee-Myun, Cheongwon, Chungbuk, 363-810, Korea

Abstract : Hexahydro-1,2-benzisoxazol-4-ols prepared from the diastereoselective reductions of 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones were reacted with benzyl chloride in the presence of sodium hydride to give new 4-benzyloxy-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazoles, which showed good herbicidal activity together with excellent selectivity on rice under submerged paddy conditions. (Received June 21, 1999; accepted September 30, 1999)

Key words : isoxazoline, diastereoselectivity, herbicide.

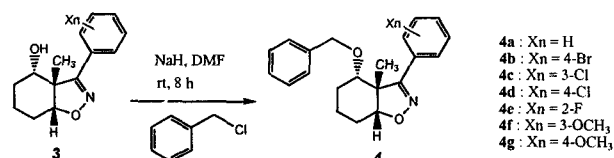
Various 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones (**1**) prepared from the 1,3-dipolar cycloadditions of substituted benzonitrile oxides with 2-cyclohexen-1-one showed significant herbicidal activity under the rice paddy condition (Kim *et al.*, 1997), the structures of which were designed as a modifications of triketone herbicides. In order to optimize the herbicidal activity of **1**, we variously modified the structures of **1** by methylation at 3a-position and reduction of carbonyl group at 4-position. The methylation at 3a-position of **1** could be achieved by treatment with LDA followed by methyl iodide at 0 °C in THF and only *cis*-isomers (**2**) were formed in fairly good yields with no trace amount of *trans*-isomers (Kim *et al.*, 1999). On reduction of carbonyl groups of **2** by NaBH₄, surprisingly, we could isolate only 3a,4-*cis*-3a,7a-*cis*-2-aryl-4-hydroxy-3a-methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazoles (**3**) as a single diastereomer (Kim *et al.*, 1999).



Scheme 1

The compounds **2** and **3** showed no herbicidal activity at all. We have further modified the hydroxyl

group of **3** with benzyloxy group by the reaction of **3** with benzyl chloride in the presence of sodium hydride in *N,N*-dimethylformamide (DMF) as shown in Scheme 2.



Scheme 2

To a solution of 3a,4-*cis*-3a,7a-*cis*-2-aryl-4-hydroxy-3a-methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole (**3**, 2 mmol) in DMF (20 ml) was added 60% sodium hydride (0.1 g, 2.4 mmol) at 0 °C and the reaction mixture was stirred for 10 min at that temperature. Benzyl chloride (0.28 ml, 2.4 mmol) was added to the mixture using a syringe, and followed by stirring for 8 h at room temperature. After the reaction mixture was poured into an ice-water (20 ml), it was extracted twice with methylene chloride (20 ml x 2). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give a crude product. The crude product was purified by a silica gel column chromatography (ethyl acetate/*n*-hexane, 1/10) to afford 3a,4-*cis*-3a,7a-*cis*-2-aryl-4-benzyloxy-3a-methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole (**4**) in good yield. The herbicidal activity of **4** was evaluated under paddy submerged

conditions according to the following methods. The sterilized paddy soil was filled in a test pot having a surface area of 140 cm² and test species were planted.

The test compounds were added on the surface using acetone as a solvent at proper rates. The pots were placed in a greenhouse and watered for 3 weeks. The herbicidal activity ratings were visually evaluated, wherein 0 signifies no herbicidal effect and 100 signifies complete kill. The results are summarized in Table 1.

Interestingly, most of the compounds **4** showed selectively tolerance against not only transplanted rice but also seeded rice. We observed that worthy tendency between the aromatic substituents and herbicidal activity, the *para*-substituted derivatives exhibited generally lower herbicidal activity than *ortho*- or *meta*-substituted derivatives. It is noteworthy that the unsubstituted analogues of **4a** and **4e** at 3a-position, for example, 3a,4-*cis*-3a,7a-*cis*-4-benzyloxy-2-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole (**5a**) and 3a,4-*cis*-3a,7a-*cis*-4-benzyloxy-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydrobenzisoxazole (**5e**) derived from 3a,4-*cis*-3a,7a-*cis*-4-hydroxy-2-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazoles (Kim *et al.*, 1999) did not show any herbicidal activity. The methyl group at 3a-position proved to be critical for their herbicidal activity.

In conclusion, new 3a,4-*cis*-3a,7a-*cis*-2-aryl-4-benzyloxy-3a-methyl-3a,4,5,6,7,7a-hexahydroben-1,2-zisoxazoles (**4**) were synthesized from 3a,4-*cis*-3a,7a-*cis*-2-aryl-4-hydroxy-3a-

methyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazoles (**3**) by *O*-benzylation and the herbicidal activities of **4** were evaluated under submerged paddy conditions. Among them **4a**, **4e**, and **4f** showed promising herbicidal activities with excellent rice tolerance at a rate of 4 Kg/ha.

Spectral data

4a : Yield: 88%, ¹H NMR (CDCl₃) δ 7.62-7.11 (10H, m), 4.57 (1H, d, J = 11.8 Hz), 4.28 (1H, d, J = 11.9 Hz), 4.21 (1H, dd, J = 3.9, 7.8 Hz), 3.73-3.72 (1H, m), 2.29-1.41 (6H, m), 1.39 (3H, s). ¹³C NMR (CDCl₃) δ 162.6, 137.8, 129.1, 128.3, 128.2, 128.0, 127.3, 113.0, 85.4, 72.0, 70.1, 54.6, 23.6, 22.8, 21.2, 13.9. FT-IR (cm⁻¹) 3036, 2938, 2866, 1734, 1454, 1111, 913, 697. MS m/z (relative intensity) 332 (1.4), 321 (3.2), 250 (37.1), 249 (7.9), 91 (100.0), 90 (22.8), 77 (14.8).

4b : Yield: 85%, ¹H NMR (CDCl₃) δ 7.77-7.76 (1H, m), 7.61-7.50 (2H, m), 7.23-7.08 (6H, m), 4.57 (1H, d, J = 11.2 Hz), 4.24 (1H, d, J = 11.3 Hz), 4.23-4.18 (1H, m), 3.20-3.12 (1H, m), 2.29-2.11 (1H, m), 2.09-1.40 (5H, m), 1.37 (3H, s). FT-IR (cm⁻¹) 2939, 2869, 1734, 1456, 1112, 919, 786, 696. MS m/z (relative intensity) 401 (2.1), 399 (3.5), 330 (20.5), 328 (18.4), 91 (100.0), 90 (82.4).

4c : Yield: 84%, ¹H NMR (CDCl₃) δ 7.61-7.54 (1H, m), 7.49-7.41 (1H, m), 7.34-7.05 (7H, m), 4.58 (1H, d, J = 12.1 Hz), 4.22 (1H, d, J = 12.0 Hz), 4.20 (1H, t, J = 4.2 Hz), 3.69-3.62 (1H, m), 2.14-1.33 (6H, m), 1.35 (3H,

Table 1. Herbicidal Activity^{a)} of the 3a,4-*cis*-3a,7a-*cis*-4-benzyloxy-3a-methyl-3a,4,5,6,7,7a-hexahydrobenzisoxazoles (4**) under Paddy Submerged Conditions**

Compound	Rate (Kg/ha)	ORYSA ^{b)} (3 leaf)	ORYSA (seed)	ECHOR ^{c)}	SCPJU ^{d)}	MOOVA ^{e)}	CYPSE ^{f)}	SAGPY ^{g)}
4a	4.0	0	20	100	100	100	0	70
4b	4.0	0	0	0	50	0	80	0
4c	4.0	0	0	50	20	80	0	0
4d	4.0	0	0	50	0	0	0	0
4e	4.0	0	0	100	100	80	100	10
4f	4.0	0	0	100	100	100	80	40
4g	4.0	0	0	0	30	60	20	0
5a	4.0	0	0	0	0	0	0	0
5e	4.0	0	0	0	0	0	0	0

^{a)}Herbicidal ratings : 0 = no activity, 100 = completely killed. ^{b)}ORYSA : *Oryza sativa* L. (rice); ^{c)}ECHOR : *Echinochloa oryzicola* (barnyardgrass); ^{d)}SCPJU : *Scirpus juncooides* ROXB. (bulrush); ^{e)}MOOVA : *Monochoria vaginalis* PRESL. (monochoria); ^{f)}CYPSE : *Cyperus serotinus* ROTTB. (flatsedge); ^{g)}SAGPY: *Sagittaria pygmaea* MIQ. (arrowhead).

s).

4d : Yield: 88%, ^1H NMR (CDCl_3) δ 7.53-7.42 (2H, m), 7.32-7.32 (7H, m), 4.55 (1H, d, $J = 13.0$ Hz), 4.22 (1H, d, $J = 13.1$ Hz), 4.21-4.15 (1H, m), 3.68-3.61 (1H, m), 2.29-1.25 (6H, m), 1.35 (3H, s).

4e : Yield: 80%, ^1H NMR (CDCl_3) δ 7.52-6.92 (9H, m), 4.52 (1H, d, $J = 12.0$ Hz), 4.27 (1H, d, $J = 12.0$ Hz), 4.24 (1H, m), 3.59 (1H, m), 2.21-1.33 (6H, m), 1.28 (3H, s).

4f : Yield: 85%, ^1H NMR (CDCl_3) δ 7.62-7.11 (10H, m), 4.57 (1H, d, $J = 11.8$ Hz), 4.28 (1H, d, $J = 11.9$ Hz), 4.21 (1H, dd, $J = 3.9, 7.8$ Hz), 3.73-3.72 (1H, m), 2.29-1.41 (6H, m), 1.39 (3H, s).

4g : Yield: 73%, ^1H NMR (CDCl_3) δ 7.54 (2H, d, $J = 8.9$ Hz), 7.19-7.06 (5H, m), 6.83 (2H, d, $J = 8.9$ Hz), 4.53 (1H, d, $J = 12.0$ Hz), 4.18 (1H, d, $J = 12.0$ Hz), 4.15-4.13 (1H, m), 3.78 (3H, s), 3.67-3.65 (1H, m), 2.35-1.16 (6H, m), 1.34 (3H, s).

5a : Yield: 76%, ^1H NMR (CDCl_3) δ 7.76-6.86 (10H, m), 4.57 (1H, d, $J = 11.8$ Hz), 4.10 (1H, d, $J = 11.8$ Hz), 3.85 (1H, m), 3.51 (1H, m), 2.39-1.22 (6H, m).

5e : Yield: 78%, ^1H NMR (CDCl_3) δ 7.94-6.84 (9H, m), 4.60 (1H, m), 4.39 (1H, d, $J = 11.0$ Hz), 4.06 (1H, d, $J = 11.0$ Hz), 3.70 (1H, m), 1.95-1.15 (6H, m).

Acknowledgement

Financial support by the Ministry of Science and Technology of Korea is gratefully acknowledged.

References

- Kim, H. R., H. J. Park, S. I. Shin, B. H. Lee, J. N. Kim, and E. K. Ryu (1999) Diastereoselective methylation and reduction of 3-aryl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazol-4-ones. *Heterocycles* 51:639-647.
- Kim, H. R., J. H. Song, D. J. Jeon, K. S. Hong, and E. K. Ryu (1997) Synthesis of 3-Aryltetrahydro-1,2-benzisoxazolin-4-one derivatives and their herbicidal activity. *Korean J. Pesticide Science* 2:104-106.