

Synthesis and herbicidal activity of 3-aryltetrahydro-1,2-benzisoxazolin-4-one derivatives

Hyoung Rae Kim, Jong Hwan Song, Dong Ju Jeon, Kyung-Sik Hong and Eung K. Ryu*

Korea Research Institute of Chemical Technology P. O. Box 107 Yusong, Taejon 305-606, Korea

Abstract : 3-Aryltetrahydro-1,2-benzisoxazolin-4-one derivatives were prepared by regioselective 1,3-dipolar cycloaddition reactions of various aryl nitrile oxides with 2-cyclohexen-1-one. The structures of these compounds were designed as a modifications of triketone herbicides and showed good herbicidal activity. (Received December 1, 1997, accepted February 27, 1998)

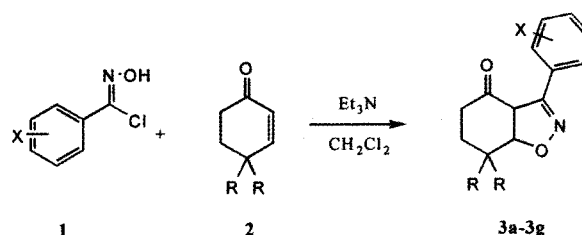
Key words : isoxazoline, herbicide, triketone.

Triketones have been focused by their excellent herbicidal activity and safety toward corn (Beraud, 1993; Prisbyll, 1993). Many trials to develop better herbicides with good selectivity for various crops have been performed by modifying their chemical structures, among them the most successful examples are the isoxazole derivatives (Bailey, 1995; Takashima, 1996; Sakhaikar, 1995) which have the shapes of the cyclized products of triketones with hydroxylamine. Though the isoxazole derivatives which have similar structures to our compounds isoxazolines were reported in a patent (Sakhaikar, 1995), the herbicidal activity of isoxazolines, reduced forms of isoxazoles have never been reported. Preparations of isoxazolines can usually be achieved by the 1,3-dipolar cycloaddition reactions of nitrile oxides with olefins (Bianchi, 1973), which exhibited regioselectivity and diastereoselectivity depending on the substituents of olefins. In most cases, the 1,3-dipolar cycloaddition reactions of nitrile oxides to α,β -unsaturated ketones afforded a mixture of two regioisomers, however the cycloadditions of aryl nitrile oxides to 2-cyclohexen-1-one could afford the corresponding 3-aryl-tetrahydro-1,2-benzisoxazolin-4-ones predominantly (Bianchi, 1973). 3-Aryltetrahydro-1,2-benzisoxazolin-7-ones were also formed as a minor regioisomers (around 10% of the major

products), which could easily removed by silica gel column chromatography.

We have prepared a new series of the 3-aryltetrahydro-1,2-benzisoxazolin-4-one derivatives by the 1,3-dipolar cycloadditions of aryl nitrile oxides to substituted 2-cyclohexen-1-ones (Scheme 1) as the mimics of the triketone herbicides and the results are summarized in Table 1 and the ^1H NMR Spectra of compound 3 were listed after the literature cited.

The substituted benzohydroxyiminoyl chlorides (1) were converted to the corresponding benzonitrile oxides by treatment of 1.0 equivalent of triethylamine in methylene chloride at 25 °C, and the resulting nitrile oxides reacted in situ with 1.2 equiv of 2-cyclohexen-1-ones (2) at 25 °C until the starting materials disappeared on TLC (EtOAc/n-Hexane, 3/1). The reaction mixture was poured into cold water, extracted with methylene chloride, dried over anhydrous



R = H, CH₃

Scheme 1

* Corresponding author

magnesium sulfate, and concentrated by a rotary evaporater to afford a sticky oil. The products 3 were separated from the oil by silica gel column chromatography (EtOAc/n-Hexane, 5/1) and identified by ¹H NMR spectra (see reference). The cycloaddition reactions of benzonitrile oxides toward 4,4-dimethyl-2-cyclohexen-1-one underwent much slower but showed a little cleaner reaction than those toward 2-cyclohexen-1-one. Practically, the cycloaddition

reaction to 4,4-dimethyl-2-cyclohexen-1-one showed a clean regioselectivity apparently owing to the steric effect of dimethyl group.

The herbicidal activity of 3 were evaluated under paddy submerged conditions according to the following methods. The sterilized paddy soil was filled in test pot having a surface area of 140 cm² and test species were planted. The test compounds were added on the surface as an acetone solutions by proper rate. The pots were placed in a greenhouse and watered for 3 weeks. The herbicidal activity data were taken visually by percent control, wherein 0 signifies no herbicidal effect and 100 signifies complete kill. The results are summarized in Table 2. As shown in Table 2, it is interested to note that para-substituted derivatives exhibited significant herbicidal activity, while ortho-substituted derivative 3d was totally inactive, and most of the compounds showed selectively tolerance against rice (ORYSA). These observations are a little different from those of triketones. The triketone derivatives were the most active when the electron-withdrawing groups were substituted at ortho-position as well as para-

Table 1. The 1,3-dipolar cycloaddition reactions of aryl nitrile oxides with 2-cyclohexen-1-ones

| Entry | X | R | Reaction Time | Product | Yield (%) |
|-------|-------------------|-----------------|---------------|---------|-----------|
| 1 | 4-Br | H | 18 h | 3a | 80 |
| 2 | 4-CF ₃ | H | 18 h | 3b | 78 |
| 3 | 4-Cl | H | 18 h | 3c | 84 |
| 4 | 2-Br | H | 18 h | 3d | 80 |
| 5 | 4-Br | CH ₃ | 42 h | 3e | 80 |
| 6 | 4-CF ₃ | CH ₃ | 42 h | 3f | 76 |
| 7 | 4-Cl | CH ₃ | 42 h | 3g | 70 |

Table 2. Herbicidal activity^{a)} of the 3-aryltetrahydro-1,2-benzisoxazolin-4-ones under paddy submerged conditions

| Compound | Rate (kg/ha) | ORYSA ^{b)} (3 leaf) | ORYSA (seed) | ECHOR ^{c)} | SCPJU ^{d)} | MOOVA ^{e)} | CYPSE ^{f)} | SAGPY ^{g)} |
|----------|--------------|------------------------------|--------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| 3a | 4.0 | 70 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 1.0 | 30 | 50 | 100 | 60 | 100 | 100 | 0 |
| 3b | 4.0 | 30 | 100 | 100 | 90 | 100 | 100 | 50 |
| | 1.0 | 0 | 40 | 100 | 50 | 100 | 30 | 50 |
| 3c | 4.0 | 10 | 60 | 100 | 80 | 100 | 100 | 100 |
| | 1.0 | 0 | 10 | 100 | 50 | 100 | 0 | 100 |
| 3d | 4.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3e | 4.0 | 0 | 0 | 30 | 50 | 100 | 0 | 0 |
| 3f | 4.0 | 0 | 30 | 30 | 0 | 0 | 0 | 0 |
| 3g | 4.0 | 0 | 30 | 50 | 100 | 100 | 90 | 0 |

^{a)} Herbicidal ratings: 0 = no activity, 100 = completely killed. ^{b)} ORYSA: *Oryza sativa* L. (rice).

^{c)} ECHOR: *Echinochloa oryzicola* (barnyardgrass), ^{d)} SCPJU: *Scirpus juncoides* ROXB. (bulrush).

^{e)} MOOVA: *Monochoria vaginalis* PRESL. (monochoria).

^{f)} CYPSE: *Cyperus serotinus* ROTTB. (flatsedge).

^{g)} SAGPY: *Sagittaria pygmaea* MIQ. (arrowhead).

position, and they did not show the selectivity against rice but against corn. The methyl-substituted compounds 3e-3g showed much weaker herbicidal activity as compared with 3a-3c (Table 2).

In conclusion we found that the structural modifications of the triketones leading to 3-aryltetrahydro-1,2-benzisoxazolin-4-ones (3) showed more promising rather than the corresponding isoxazoles having a double bond at C7 and C8 positions on the basis of their herbicidal activity as well as their selectivity in rice.

Literature cited

- Bailey, A. J., M. Gingell and D. W. Hawkins (1995) WO 9516678 A1.
- Beraud, J. M. and J. M. Compagnon (1993) A selective postemergence herbicide for corn. *Phytoma* 456:55-57.
- Bianchi, G., C. De Micheli, R. Gandolfi, P. Grunanger, P. V. Finzi, and O. V. de Pava (1973) Isoxazoline derivatives. part VI.
- Regioselectivity in 1,3-dipolar cycloaddition of nitrile oxides to α , β -unsaturated ketones. *J. C. S. Perkin I.* 1148-1155.
- Prisbylla, M. P., B. C. Onisko, J. M. Shribbs, D. O. Adams, Y. Liu, M. K. Ellis, T. R. Hawkes, and L. C. Mutter (1993) The novel mechanism of action of the herbicidal triketones.
- Brighton Crop Protection Conference-Weeds, Vol. 2, 731-738.
- Sakhaikar, S. S., G. M. Khandekar, S. D. Sahasrabudhe, C. K. Rao, and D. C. Lathbury (1995) Herbicidal 3-(hetero)aryl-4-acylisoxazole compositions and compounds. GB 2 284 600.
- Takashima, Y., K. Koike, M. Yoshikawa, and K. Nakamura (1996) WO 9625413 A1.

Spectral Data :

¹H NMR Spectra of compounds 3 were recorded at Varian Gemini 200 MHz NMR spectrometer using TMS as a internal standard.

3-(4-Bromophenyl)tetrahydro-1,2-benzisoxazolin-4-one (3a): ¹H NMR (CDCl₃) δ 1.9 (m, 3H), 2.2 (m, 3H), 4.2 (d, 1H), 5.1 (m, 1H), 7.5 (d, 2H), 7.6 (d, 2H).

3-(4-Trifluoromethylphenyl)tetrahydro-1,2-benzisoxazolin-4-one (3b): ¹H NMR (CDCl₃) δ 1.9 (m, 3H), 2.2 (m, 3H), 4.3 (d, 1H), 5.2(m, 1H), 7.1 (d, 2H), 7.8 (d, 2H).

3-(4-Chlorophenyl)tetrahydro-1,2-benzisoxazolin-4-one (3c): ¹H NMR (CDCl₃) δ 1.9 (m, 3H), 2.2 (m, 3H), 4.2 (d, 1H), 5.1 (m, 1H), 7.5 (d, 2H), 7.6 (d, 2H).

3-(2-Bromophenyl)tetrahydro-1,2-benzisoxazolin-4-one (3c): ¹H NMR (CDCl₃) δ 1.9 (m, 3H), 2.2 (m, 3H), 4.2 (d, 1H), 5.1 (m, 1H), 7.2-7.5 (m, 4H).

3-(4-Bromophenyl)-6,6-dimethyltetrahydro-1,2-benzisoxazolin-4-one (3d): ¹H NMR (CDCl₃) δ 1.2 (s, 6H), 2.0 (m, 2H), 2.3 (m, 2H), 4.2 (d, 1H), 4.5 (dd, 1H), 7.5 (d, 2H), 7.7 (d, 2H).

3-(4-Trifluoromethylphenyl)-6,6-dimethyltetrahydro-1,2-benzisoxazolin-4-one (3e): ¹H NMR (CDCl₃) δ 1.4 (s, 6H), 2.0 (m, 2H), 2.3 (m, 2H), 4.3 (d, 1H), 4.5 (dd, 1H), 7.1 (d, 2H), 7.7 (d, 2H).

3-(4-Chlorophenyl)-6,6-dimethyltetrahydro-1,2-benzisoxazolin-4-one (3f): ¹H NMR (CDCl₃) δ 1.2 (s, 6H), 2.0 (m, 2H), 2.3 (m, 2H), 4.2 (d, 1H), 4.5 (dd, 1H), 7.3 (d, 2H), 7.6 (d, 2H).