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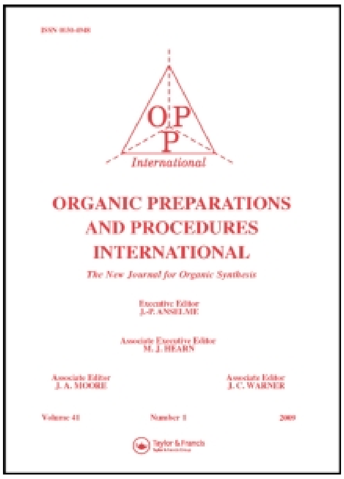

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

3-ARYL-5-CHLOROISOXAZOLES

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To cite this Article Micetich, R. G.(1970) '3-ARYL-5-CHLOROISOXAZOLES', Organic Preparations and Procedures International, 2: 3, 225 — 227

To link to this Article: DOI: 10.1080/00304947009458663

URL: http://dx.doi.org/10.1080/00304947009458663

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ORGANIC PREPARATIONS AND PROCEDURES 2(3), 225-227 (1970)

3-ARYL-5-CHLOROISOXAZOLES

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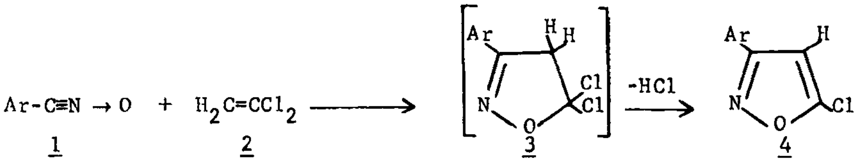

Various 3-aryl-5-chloroisoxazoles were required, as intermediates in the preparation of semisynthetic penicillins.[1] 3-Phenyl-5-chloroisoxazole has been made by Adembri and Tedeschi[2], by the action of phosphorus oxychloride on 3-phenylisoxazole-5-one. A convenient alternate method of preparing 5-chloroisoxazoles is the 1,3-dipolar cycloaddition of an arylnitrile oxide 1 to 1,1-dichloroethylene 2. The 3-aryl-5,5-dichloroisoxazoline 3, thus formed, loses hydrogen chloride spontaneously to form the 3-aryl-5-chloroisoxazole 4.

The nitrile oxide can be made from the oxime by the method of Grundmann and Dean[3] or generated in situ, in the presence of 1,1-dichloroethylene, by the action of triethylamine on the arylchloraldoxime. Since the arylchloraldoximes are formed in excellent yields by the action of chlorine[4] or better, nitrosyl chloride[5] on the readily available arylaldoximes, this method offers a convenient route to the 5-chloroisoxazoles. Ether or tetrahydrofuran or excess 1,1-dichloroethylene can be used as solvents for this reaction.

EXPERIMENTAL

3-Phenyl-5-chloroisoxazole, 4a. Benzohydroxamoyl chloride[4] (38.9g, 0.25 mole) and 1,1-dichloroethylene (33.9 g, 0.35 mole) were dissolved in ether (500 ml) and stirred in an ice bath, while triethylamine (30.3 g, 0.3 mole) was added slowly. After the addition was complete, the mixture was heated with stirring under reflux for 2 hours, water (200 ml) added and the mixture stirred well and the layers separated. The aqueous layer was extracted with ether (2 x 100 ml). The combined ethereal extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with hexane-ether (1:1) and filtered. The white solid thus obtained weighed 11 g (18%) and was 3,4-diphenylfuroxan mp. 118-120°, lit.[4] mp. 118°.

The filtrate was concentrated and the residue chromatographed on a silica gel column (Fisher grade Silica gel, 1 L) using hexane containing 5% ether as eluant. The 3-phenyl-5-chloroisoxazole (19.4 g) thus obtained was distilled under reduced pressure, when 18.4 g (41%) of an oil, bp. 90°/0.3 min, which crystallized mp. 45-47°, and was identical with an authentic sample[1] was obtained. $\text{Ir}_{\nu\max}^{\text{film}}$ 1580 (sh), 1550. Nmr ($CDCl_3$, 60-Mc, TMS) τ2.35 (m, 2H), 2.67 (m, 3H), 3.68 (s, 1H).

3-o-Chlorophenyl-5-chloroisoxazole, 4b. Crude o-chlorobenzohydroxamoxyl chloride made by the action of nitrosyl chloride on an ether solution of o-chlorobenzaldoxime, was treated with 1.2 equivalent of triethylamine in the presence of 2 equivalents of 1,1-dichloroethylene as described above, to give 4b, bp. 90-91°/0.5 mm (identical with an authentic sample[1]) in 40% yield. $\text{Ir}_{\nu\max}^{\text{film}}$ 1560 (sh), 1540. Nmr (CCl_4) τ2.17 to 2.75 (m, 4H), 3.35 (s, 1H).

3-(2,6-Dichlorophenyl)-5-chloroisoxazole, 4c. 2,6-Dichlorobenzonitrile oxide[3] (21.3 g, 0.113 mole) and 1,1-dichloroethylene (46.6 g, 0.48 mole) were stirred and heated under reflux for 3 hours (until the disappearance of the $-C\equiv N \rightarrow O$ band in the infrared spectrum). The reaction mixture was concentrated under reduced pressure, and the residue chromatographed on a silica gel column as described above. 3-(2,6-Dichlorophenyl)-5-chloroisoxazole bp. 119°/0.8 mm, mp. 34-37° was obtained in 60% yield (16.8 g). Irν_{max}^{film} 1580 (sh), 1550. Nmr (CCl_4) τ2.59 (s, 3H), 3.65 (s, 1H). Anal. Calcd. for $C_9H_4Cl_3NO$: C, 43.45; H, 1.61; N, 5.63. Found: C, 43.59; H, 1.71; N, 5.41.

ACKNOWLEDGEMENTS

The author thanks Dr. R. U. Lemieux, director of research, for his advice and interest in this work and Mr. R. A. Fortier for his capable technical assistance.

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(Received April 17, 1970)