Tetrahedron Letters, Vol. 33, No. 22, pp. 3155-3156, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

NITRATION OF 1,1-DIHALO-2-(4'-NITROPHENYL)CYCLOPROPANES: NEW METHOD TO PREPARE ISOXAZOLE

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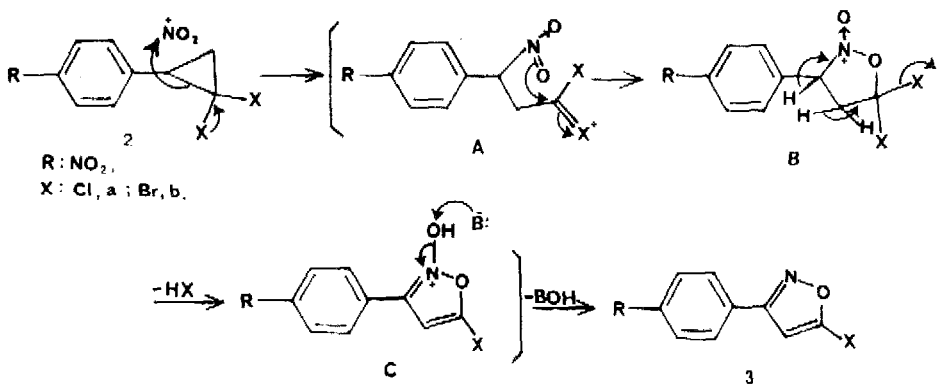
Abstract: 5-Halo-3-(4'-nitrophenyl)isoxazoles were prepared from the nitration of 1,1-dihalo-2-(4'-nitrophenyl)cyclopropanes in good yields.

The isoxazole derivatives demonstrate anticonvulsant,[1] antibacterial,[2] antiasthmatic, and pharmacological activities.[3] Reaction of nitrile oxides with alkynes is a typical process to prepare this series of compounds.[4] Herein, we would like to report a simple method to prepare 5-halo-3-(4'-nitrophenyl)isoxazoles (3), which could be an useful intermediate for functionalization.

1,1-Dichloro-2-(4'-nitrophenyl)cyclopropane (2a) was treated with HNO_3/H_2SO_4 at 273 K for 30 min, and then the reaction mixture was poured into ice to give white solid. Upon filtration, highly pure compound 3a was obtained in a good yield.[5] The ^1H NMR spectrum showed very simple patterns with two doublets (7.96 and 8.35 ppm, J=8.8 Hz) and a singlet at 6.58 ppm. Two sets of doublet at rather down field region indicate that the phenyl ring is substituted at the para-position with a strong electron-withdrawing group. Incorporating with the mass spectrum and elemental analysis, this compound was assigned as 5-chloro-3-(4'-nitrophenyl)isoxazole 3a.



Although the mechanism for the formation of compound 3 is not clear, no isoxazole derivatives were obtained during the nitration of 1,1-dichloro-2-phenylcyclopropane (1a). Therefore, the nitro group previously introduced at 4-position of phenyl ring of compound 2a is essential for the formation of isoxazole 3a. To form this isoxazole skeleton, the reaction mechanism is proposed in Scheme 1. The C(2) undergoes a nucleophilic attack torward nitronium ion by the assistance of chlorine atom with breaking of C(1)-C(2) bond to form A, in which the chlorine atom bears positive charge. The C(1) atom is then attacked by the oxygen atom of N=O to yield a cyclic intermediate B. It undergoes an elimination of HCl and followed by a hydrogen migration from C(2) to oxygen to result an intermediate C. Compound 3 is obtained after removal of the hydroxyl group with a conjugate base.

We thank the N.S.C. (R.O.C.) for financil assistance (NSC 80-0208-M-126-10).

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5. Upon nitration compound 2a and 2b, yielded compounds 3a and 3b in 81% and 85%, respectively. Compound 3a, mp. 167-169°C, ^{1}H NMR($CDCl_3$) δ 6.58 (s, 1H), 7.96 (d, 2H, J=8.8Hz), 8.35 (d, 2H, J=8.8Hz), EIMS: m/z(%) 224 (M^+, 23), 189 (100); Compound 3b, mp. 187-189°C, ^{1}H NMR ($CDCl_3$) δ 6.70 (s, 1H), 7.97 (d, 2H, J=8.5Hz), 8.36(d, 2H, J=8.5Hz), EIMS: m/z(%) 268 (M^+, 11), 189 (100). The satisfactory elemental analyses were obtained for both 3a and 3b.

(Received in Japan 15 February 1992)