Note

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Lindlar catalyst mediated tritiation of a triazole substituted isoxazoline insecticide

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The radiolabelling of isoxazoline insecticide 1a employing a Lindlar catalyst tritium dehalogenation of a bromo precursor is described.

Keywords: tritium; Lindlar catalyst; selectivity; insecticide

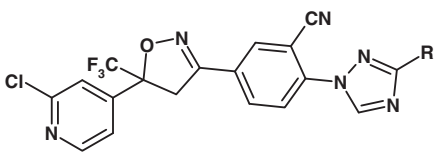
Introduction

Catalytic aromatic dehalogenation with tritium gas and other tritiated reagents remains an important and reliable method of high specific activity radiolabelling, but it can also be complicated by the unwanted reduction of other susceptible functional groups. Chemoselective variations of this aromatic dehalogenation procedure have recently been reported for tritium by Rousseau[1] and sodium borotritide by Tang.[2] In this note we now describe the tritiation of the isoxazoline insecticide[3] **1a**, highlighting another rather selective tritium dehalogenation approach employing Lindlar catalyst.

Results and discussion

Triazole **1a** is an isoxazoline insecticide that required tritiation for biological testing and access to bromo precursor **1b** suggested the possibility of employing some catalytic tritium debromination technique. However, complicating this option was the presence of other potentially reducible groups including a 2-chloropyridine, isoxazoline and nitrile. Previous investigators had dealt with the challenge of such competing side reactions by deliberate catalyst poisoning to diminish catalyst reactivity. For instance, Janssen and co-workers tritium labelled the natural product galantamine using a bromo precursor together with tritium and butanethiol deactivated 10% Pd/C to avoid concomitant olefin reduction.[4] Lindlar catalyst is palladium supported on calcium carbonate but further treated with lead additives for deactivation. Evidence exists that these lead poisons actually rearrange the catalyst surface structure.[5] Traditionally, Lindlar catalyst has been exploited to perform almost exclusively one remarkable and important transformation in natural product synthesis; namely, the reduction of an alkyne to an olefin. However, from previous tritiation work we had discovered that Lindlar catalyst could also be used to selectively accomplish tritium aromatic dehalogenation in the presence of other reducible groups.[6] To the best of our knowledge there is only one other literature report of using Lindlar catalyst for such an aromatic tritium dehalogenation.[7]

Tritiation of precursor **1b** using Lindlar catalyst over a period of several days smoothly produced a significant amount of desired product **1c**. The scale and longer tritiation time period were purposefully selected based on the past experience with Lindlar catalyst to ensure obtaining enough desired product, and no attempts at shorter reaction times were tried. Only minor amounts of tritiated side products (resulting from the over reduction of the other functional groups) were present in the crude reaction mixture by TLC analysis. However, some unreduced bromo precursor was evident as a higher R_f spot, suggesting that the tritiation was not entirely complete. As has been observed in the classic Lindlar catalyst alkyne hydrogenations, batch to batch variations in catalyst performance may also exist for Lindlar reductive dehalogenations as well. Purification of the crude product, first by the flash chromatography followed by the reverse phase HPLC, afforded **1c** at high specific activity. A proton decoupled tritium NMR ($CDCl_3$) of the product was obtained and is shown in Figure 1. It revealed that the majority of tritium installation had occurred as expected in the triazole position formerly occupied by bromine (8.27 ppm) and a small amount (~12%) of tritium had clearly been incorporated in the other open triazole position (8.96 ppm) by a general exchange process with the nearby Lindlar catalyst surface.



1a R = H
1b R = Br
1c R = ^{3}H

Scheme 1.

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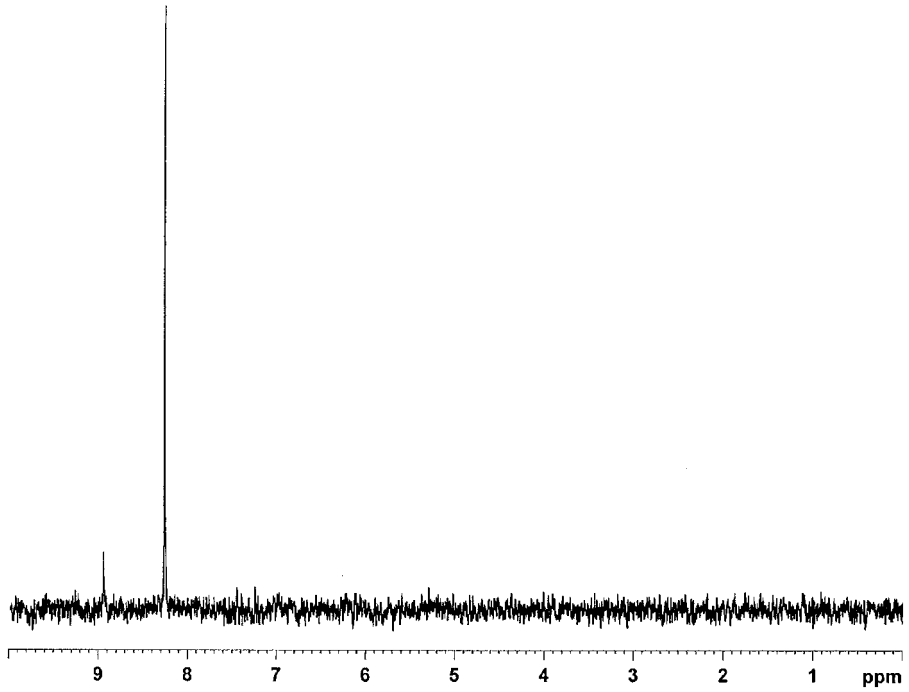

Figure 1. Proton decoupled tritium NMR ($CDCl_3$) of **1c**.

Lindlar catalyst can serve as a complimentary and selective method of catalytic tritium aromatic debromination in the presence of other potentially reducible functional groups to afford useful amounts of tritiated products.

Experimental

General

All chemicals used were reagent grade. Evaporations were carried out on a Buchi rotary evaporator at bath temperatures less than 40°C. Analytical TLC was performed on Analtech 5 × 15 cm glass plates coated with silica gel. Autoradiography was performed at 0°C after spraying with PPO and exposing plates to X-ray film. TLC plates were also scanned for applied radioactivity. Preparative and analytical HPLC were performed on a Waters instrument and peak detection was done simultaneously by UV (280 nm–Waters 440 UV detector) and liquid scintillation flow monitor. NMR spectra were obtained on a Bruker 300 MHz instrument and chemical shift values are expressed in parts per million (ppm) downfield from TMS.

*[Triazole-^{3}H] (**1c**): 5-[5-(2-Chloro-pyridin-4-yl)-5-trifluoromethyl-4,5-dihydroisoxazol-3-yl]-2-[1,2,4]triazol-1-yl-benzonitrile*

Bromo precursor **1b** (116 mg, 0.23 mmol) in 5 ml of ethanol with 116 mg of Lindlar catalyst (Alfa Aesar, catalogue 11723 lot 10107309) was rapidly stirred and reduced with 60 Ci of tritium gas for 4 days at ambient temperature. After this time, the catalyst was filtered and volatile tritium was removed with several evaporations of ethanol to afford 661 mCi of crude product. It was initially purified by silica gel flash chromatography, eluting first with methylene chloride followed by methanol:methylene chloride (2:98), collecting fractions and monitoring progress by TLC (silica gel—methanol:methylene chloride (2:98)). Several column fractions were combined to obtain 360 mCi of material. The product was further purified by reverse phase HPLC eluted with a gradient of 0.1% aqueous formic acid to acetonitrile:methanol (1:1). Pooling of appropriate fractions, solvent evaporation under reduced pressure and reconstitution in ethanol afforded 148 mCi (an extrapolated 2.2% radiochemical yield based on precursor **1b**) of product **1c** which was greater than 99% radiochemically pure and completely co-chromatographed with authentic **1a** on reverse phase HPLC (same system as above). The specific activity of product **1c** was measured to be 29 Ci/mmol by integration of its proton NMR ($CDCl_3$) in the aromatic region. A proton decoupled tritium NMR ($CDCl_3$) is shown in Figure 1.

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