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IMPROVED PREPARATION OF 5-CHLORO-1-PHENYL-1*H*-TETRAZOLE AND OTHER 5-CHLOROTETRAZOLES.

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Abstract: Reaction of aryldichloroisocyanides **1a–e** with sodium azide and a phase transfer agent has provided 5-chloro-1-aryl-1*H*-tetrazoles **2a–e** in good yield. In particular, the widely-used intermediate, 5-chloro-1-phenyl-1*H*-tetrazole **2a,** can be produced conveniently and safely in yields approaching 100%.

5-Chloro-1-aryl-1*H*-tetrazoles are widely used in several disparate areas of research and, commercially, in a variety of drug and herbicide manufactures.[1] Biological activity is encountered due to the special metabolism of disubstituted tetrazoles and also because, in 5-substituted tetrazolyl compounds, the heterocyclic ring is isosteric with a carboxy group and of similar acidity.[3] Some typical uses of such tetrazoles are in anti-inflammatory drugs,[2] herbicides,[4] rocket propellants[5] and photography and polymers.[6] 5-Chloro-1-phenyl-1*H*-tetrazole **2*a*** is valuable for the preparation of tetrazolyl ethers of phenols, which can be hydrogenolysed[7] to replace the original phenolic C–O bond by C–H or cross-coupled[8] to replace the same C–O bond by C–C in excellent yield.

Reaction of aryldichloroisocyanides **1*a–e*** with sodium azide to afford 5-chloro-1-aryl-1*H*-tetrazoles (**2*a–e***; scheme) has been reported.[9] However, isolated yields

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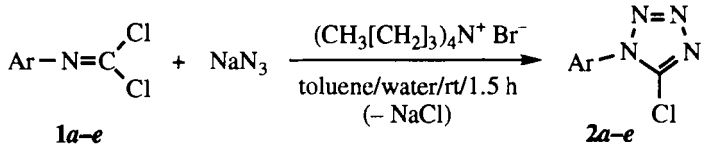
are not high and there are difficulties with this preparation because of the sodium azide, which must be activated[10] and used with expensive high boiling solvents such as 1,2-dimethoxyethane or ethylene glycol dimethyl ether.[11] It is not clear what this so-called 'activation' actually does but it requires the use of hazardous hydrazine. Activated sodium azide does not appear to be much more active than ordinary sodium azide.



1*a–e* **2*a–e***

Compound	Ar = substituted phenyl
a	phenyl
b	4-fluorophenyl
c	4-methylphenyl
d	4-nitrophenyl
e	3-chloro-4-methoxyphenyl

Scheme

Another difficulty with the existing method lies in the hazardous nature of inorganic azides. There is a reluctance to use almost any inorganic azide on a large scale because, although sodium azide itself is regarded as relatively safe, the possible concomitant formation of heavy metal azides during its use makes it a suspect reagent. Sodium azide has been used to prepare organic azides from organic halides or tosylates through use of a phase transfer agent in aqueous solution, thereby alleviating the potential hazards accompanying its use.[12] The method described here enables the preparation of 5-chloro-1-aryl-1*H*-tetrazoles **2** from aryl-1,1-dichloroisocyanides **1** and sodium azide to be carried at low temperatures and in high yield through use of a phase transfer reagent. Only one of the chloro groups is substituted, the halogen in the resulting 5-chloro-1-aryl-1*H*-tetrazoles remaining unreacted under the conditions described here. On a large scale, recovery of the phase transfer agent is simple, the recovered material being continually reusable. This method of preparation of the chlorotetrazoles **2** has been made even more convenient through a simplified method for the

preparation of the intermediate aryldichloroisocyanides **1**, which can be used without purification.

The general method of preparation is described below but mention is made here of the possibilities for large scale synthesis of the widely-used, expensive reagent and parent compound, 5-chloro-1-phenyl-1*H*-tetrazole **2*a***. After reaction of the starting material, phenyldichloroisocyanide **1*a*** with sodium azide in a water/toluene solvent mix, the organic layer is separated, dried (Na_2SO_4) and the solvent removed by rotary evaporation at about 35 °C. When the solid 5-chloro-1-phenyl-1*H*-tetrazole **2*a*** first starts to appear, the flask is removed from the evaporator and its contents are warmed until the solid just dissolves again; the resulting solution is set aside to cool to -5 to -10 °C. The crystals of pure 5-chloro-1-phenyl-1*H*-tetrazole that form are filtered off. The isolated yield is about 90%. However, the filtrate contains the original phase transfer agent and some residual 5-chloro-1-phenyl-1*H*-tetrazole. Rather than try to isolate the small amount of the latter, the mixture can be used in a new preparation of the tetrazole, without addition of more phase transfer agent. This second preparation then gives a 'yield' of the required tetrazole of almost 100%. The phase transfer agent plus some residual tetrazole is isolated and used again; this cycling can continue apparently indefinitely, making large-scale synthesis particularly easy. Yields of the other chlorotetrazoles **2*b–e*** have not been optimized.

The previously reported preparations of aryldichloroisocyanides **1** by reaction of isothiocyanates with chlorine usually specify careful fractional distillation for isolation of the required product. It has been found in the present work that their preparation from arylisothiocyanates can be greatly simplified by simply monitoring the chlorination by GC. After the starting material has disappeared, the solvent is evaporated and the residue used either without further purification or after simple distillation without fractionation, with no noticeable effect on yields of the subsequent tetrazole. Synthesis of the required starting aryldichloroisocyanides **1*a–e*** is described in the experimental section. In the chlorination of 4-methoxyphenyldichloroisocyanide **1*e***, it was found that rapid chlorination took place into the aryl ring *ortho* to the methoxy group, as well as onto the isocyanide group. Thus, the isolated chlorotetrazole **2*e*** was not the

expected 5-chloro-1-(4-methoxyphenyl)-1*H*-tetrazole but 5-chloro-1-(3-chloro-4-methoxyphenyl)-1*H*-tetrazole.

The advantages of the present modification to the synthesis of the tetrazoles **2** are simplicity, good yields, application to large-scale work and relative lack of hazard when using large amounts of sodium azide, which does not need to be 'activated'. For aryl-1,1-dichloroisocyanides having electron-donating substituents in the aryl ring, cyclisation to the 5-chloro-1-aryl-1*H*-tetrazole proceeded well but with strongly electron-withdrawing substituents, such as nitro or trifluoromethyl, cyclisation was difficult to control and gave no or poor yields of the chlorotetrazole.

Experimental

Unless otherwise stated, all common reagents and solvents were used as supplied from commercial sources without further purification. Melting points were determined on a Reichert microscopic hotplate and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker ACE 200 spectrometer at 200 MHz in $CDCl_3$/TMS. Mass spectra were determined by electron ionization at 70 eV on a VG 7070E mass spectrometer. Gas chromatography was carried out on a Dani 3800 instrument, equipped with a flame ionization detector.

Aryldichloroisocyanides 1*a–e*; General procedure:
Chlorine gas was bubbled slowly into a solution of an arylisothiocyanate (0.5 mol) in CCl_4 (200 mL), cooled in an ice-bath. The progress of the reaction was monitored by taking occasional samples for gas chromatographic analysis. When all the starting material had disappeared, the solvent was removed by rotary evaporation to give a light yellow liquid. The following data give yield after distillation followed by bp in parentheses: **1*a***, 85% (90–92 °C/15 mm)[11] ; **1*b***, 52% (42–44 °C/0.4 mm); **1*c***, 56% (56 °C/0.6 mm); **1*d*** (120 °C); **1*e***, 92% (113–115 °C/5 mm).

5-Chloro-1-aryl-1*H*-tetrazoles 2*a–e*; General procedure:
In a typical reaction, a solution of sodium azide (24.7 g, 380 mmol) and tetra-*n*-butylammonium bromide (5.48 g, 17 mmol) in water (80 mL) was added to a

solution of phenyl-1,1-dichloroisocyanide (43.5 g, 250 mmol) in toluene (400 mL) and the whole was stirred at room temperature. The organic layer was monitored by tlc until the starting material had disappeared (normally about 90 min). The aqueous layer was saturated with NaCl and the organic layer was separated off; the aqueous layer was extracted with more toluene. The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was rotary evaporated at about 35 °C until crystals started to form and was then cooled to about -5 to -10 °C. The crystals of the chlorotetrazole **2*a*** that formed were filtered off; this process was repeated several times until the filtrate volume was about 10 mL, at which stage all of the residual solvent was removed by rotary evaporation and the residue, containing all of the phase transfer reagent, was used in the next preparation of more 5-chloro-1-phenyl-1*H*-tetrazole, to which no fresh tetra-*n*-butylammonium bromide needed to be added. Similarly, the tetrazoles **2*b–e*** were prepared. All gave satisfactory elemental analyses for C, H, N. Yields, melting points, ^{1}H NMR (δ) and mass spectra (*m/z*) are respectively as follows: **2*b***, 99%, 90–92 °C (lit.[11] 88 °C), δ 7.29–7.60(4H, m), m/z 198[M^+]; **2*c***, 21%, 101–102 °C, δ 2.46(3H, s), 7.41(4H, d, *J* = 8.8 Hz), *m/z* 194[M^+]; **2*d***, no cyclization of 1d was observed; **2*e***, 52%, 125–128 °C, δ 3.99(3H, s), 7.09(1H, d, *J* = 8.8 Hz), 7.43(1H, dd, *J* = 8.8, 2.8 Hz), 7.60(1H, d, *J* = 2.8 Hz), *m/z* 244, 246, 248[M^+, Cl isotopes].

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