5-Halo-1-phenyltetrazoles

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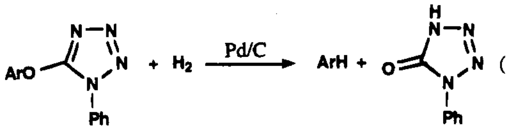
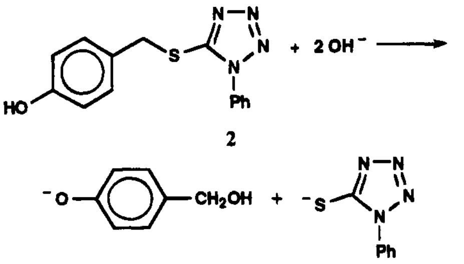
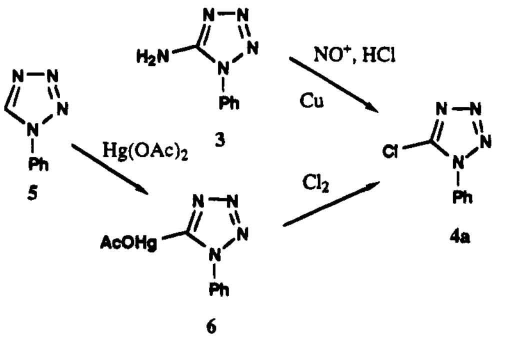
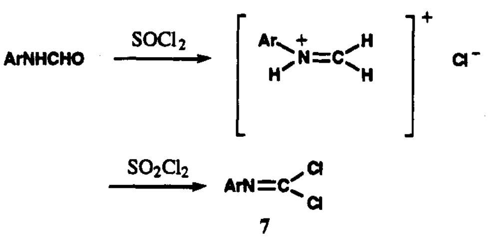
The 5-substituted-1-phenyltetrazolyl moiety has been shown to be of great utility as an activating group for the hydrogenolysis of phenolic hydroxy groups under mild conditions (eq 1).[1] It has further been exploited as a leaving group in the alkali-induced cleavage to the corresponding hydroxy compounds (eq 2).[2] Although the alkylation or the acylation of 5-hydroxy- or 5-mercapto-1-phenyl-tetrazoles gives the ring N-substituted products as well as the desired O- or S-substituted products,[3] the chlorine of 5-chloro-1-phenyltetrazole (**4a**) is sufficiently reactive to undergo nucleophilic substitution to yield synthetically useful compounds such as **1** and **2** *inter alia*.[4]





Until recently, 5-chloro-1-phenyltetrazole (**4a**) could only be prepared in low yields by the Sandmeyer reaction of 5-amino-1-phenyltetrazole (**3**)[5a] or by the chlorination of 5-acetoxymercurio-1-phenyltetrazole (**6**),[5b] itself obtained from the acetoxymercuration of 1-phenyltetrazole (**5**);[5c] furthermore, the starting materials **3** and **5** are not readily prepared. In 1962, Kühle reported an improved preparation of aryl isocyanide dichlorides (**7**) from the reaction of formanilides with thionyl chloride, followed by treatment of the resulting complex with sulfuryl chloride.[6] Reaction of phenyl isocyanide dichloride with azide ion thus provided a ready,[4] albeit risky[6] access to **4a**. More recently, Hassner and his group[7] obtained 5-iodo-1-phenyltetrazole (**4c**) from the addition of iodine azide to phenyl isocyanide.





Our finding that the reaction of *N*-halo compounds with nitrite ion led to an active nitrosating species (N_2O_4)[8] prompted us to explore the possibility that *N*-halosuccinimides could undergo similar displacement by other nucleophiles and thereby help in the preparation of **4a** and its congeners in improved yields.

We now report that the treatment of phenyl isocyanide with *N*-halosuccinimides in the presence of azide ion under PTC conditions has led to a simple and facile synthesis of the corresponding 5-halo-1-phenyltetrazoles (**4**) in good to excellent yields (69−90%). It is likely that in these reactions, the active species are the corresponding halogen azides[9] which add to phenyl isocyanide as suggested by Hassner and his group.[7] The utility of this procedure lies in fact that the putative halogen azides[9] are generated *in situ* and that *no* excess of sodium azide is used. The method thus results in improved convenience, yields, and safety.

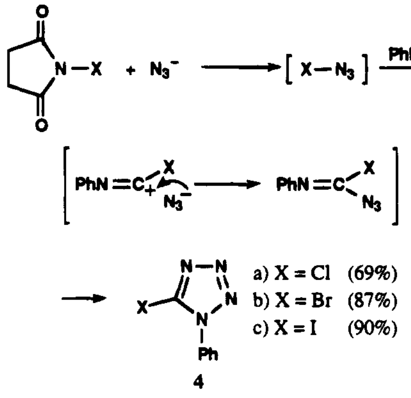


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Table 1. 5-Halo-1-phenyltetrazole (4)[a]

X	PhNC (wt, mmol)	N-Halosuccinimide (wt, mmol)	NaN_3 (wt, mmol)	yield of **4** (%)	mp (°C)	lit. mp (°C)
Cl	(2.00 g, 19.4)	(2.60 g, 19.5)	(1.26 g, 19.4)	69	120–121	124[b]
Br	(2.00 g, 19.4)	(3.46 g, 19.5)	(1.26 g, 19.4)	87	150–152	156[c]
I	(1.00 g, 9.7)	(2.18 g, 9.7)	(0.63 g, 9.7)	90	142–144	145–147[d]

[a] Tetramethylammonium bromide (0.10 g, 1 mmol) was used throughout. [b] Reference 5b. [c] Reference 5c. [d] Reference 7.

5-Halo-1-phenyltetrazoles (4). General Procedure. To a solution of the *N*-halosuccinimide (1 equiv) in 20 mL of chloroform at 0 °C was added a solution of sodium azide (1 equiv) in 10 mL of water. To this mixture kept at 0 °C was added the phase-transfer catalyst and the mixture was stirred for 5 min. Then a solution of phenyl isocyanide (1 equiv) in 10 mL of chloroform was added in one portion; the reaction mixture was stirred for 45 min at 0 °C and then the temperature was allowed to become ambient. The organic layer was separated, washed with water (2 × 250 mL), and dried (Na_2SO_4). Evaporation left a reddish semisolid to which was added ~10 mL of 95% ethanol. The off-white solid was collected and recrystallized.

Caution: Although we never experienced any problem in these reactions, all due precautions should be exercised in view of the possibility, remote as it may be, of the presence of halogen azides.

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