Pyridine-4-thiol and Amphoteric Analogs: Novel Protection of Aryl Bromides in Strong Alkali

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The use of pyridine-4-thiol (PT) to preserve certain aryl bromides in strong alkali is reported (*Scheme 1*). The presence of this additive or of some of its amphoteric analogs such as 3-hydroxypyridin-4(1*H*)-ones suppresses the replacement of the Br-substituent by hydroxide and alkoxide ions. A mechanistic interpretation of the effect is proposed.

Introduction. – Functional-group compatibility is a perennial problem that a synthetic chemist must face in dealing with the construction of complex molecules. As a testimonial for the many ways developed to solve such problems, a vast pool of literature on the use of protecting groups has accumulated [1]. Aryl bromides are often deemed stable under most reaction conditions, although they are excellent partners for transition metal-catalyzed processes [2]. But few literature reports deal with the protection of a halo group. In the present work, we describe a novel protection of aryl bromides by pyridine-4-thiol and amphoteric analogs such as 3-hydroxypyridin-4(1*H*)-ones under nucleophilic aromatic substitution condition.

Results and Discussion. – Previously, we attempted to convert compound **1** to **2** by hydrolytic cleavage of the exocyclic guanidine moiety (*Scheme 1*). Rather harsh reaction conditions such as treatment with KOH in refluxing ethylene glycol were required [3]. The results were unsatisfactory as the product mixture was complex, and the desired product was obtained in small yields (*Fig. 1*). The substituted quinazolinones **3** and **4** were identified as two major by-products by ^{1}H-NMR, MS, and HR-MS. It appears that the Br-substituent of **1** is susceptible to replacement in strong alkali, a fact which prompted us to undertake a series of experiments to avert the undesired reactions.

We were glad to find that the presence of pyridine-4-thiol (PT) has beneficial effects (*Scheme 1*). When a few mol-% of PT was added to the reaction mixture, dramatic changes were observed: the formation of the by-products was almost suppressed (*Fig. 2*).

To establish the optimal ratio of **1** and PT for the conversion to **2**, we carried out a series of experiments by varying the amount of PT from 0.1–100 mol-%, while

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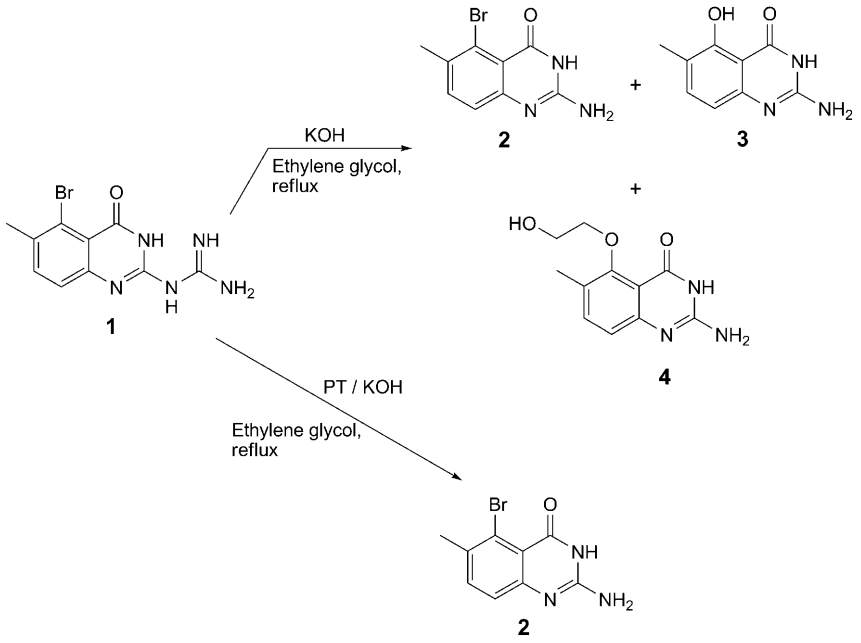
Scheme 1. *Reaction of* **1** *with KOH in the Absence or Presence of PT*



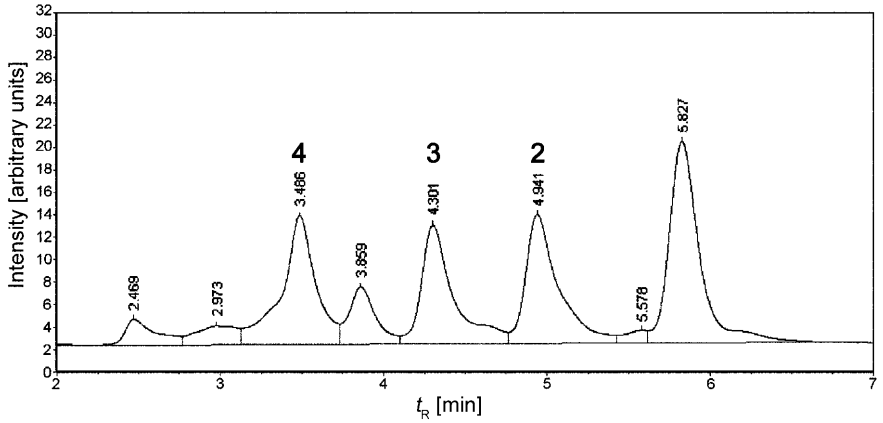


Fig. 1. *HPLC Plot of the reaction products in the absence of PT*

maintaining the concentration of KOH at 0.67 mM in ethylene glycol. Consistent improvements were achieved when the mol-% of PT was increased from 0.13 – 100 (*Fig. 3*). The use of a higher concentration of KOH (2.68 mM) did not affect the overall results (*Fig. 4*), and an optimal yield of **2** was reached when the reaction was carried out in the presence of 1 mol-equiv. of PT.

To establish the protective role played by PT, we subjected product **2** to the original reaction conditions. Within 2 h, about 58% of **2** was converted to give *ca.* 11% of **3** and

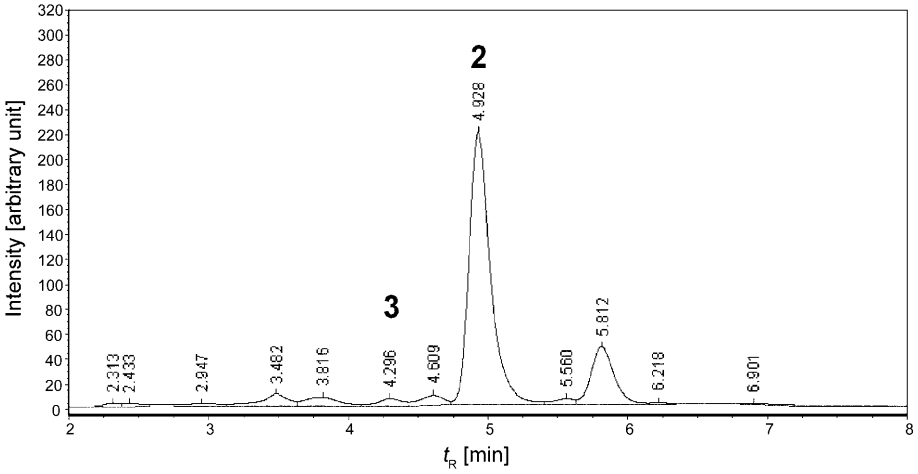


Fig. 2. *HPLC Plot of the reaction products in the presence of 10 mol-% of PT*

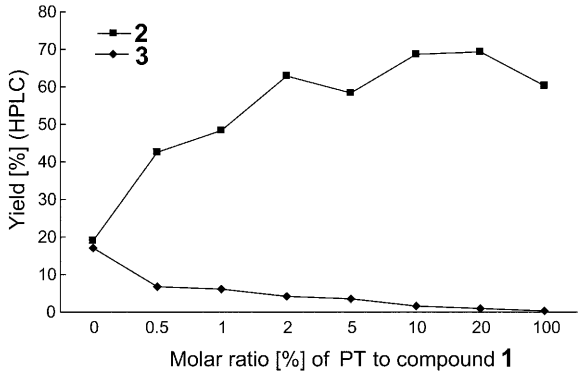


Fig. 3. *Effect of different molar ratios of PT on the production of* **2** *and* **3** (0.67 mM KOH)

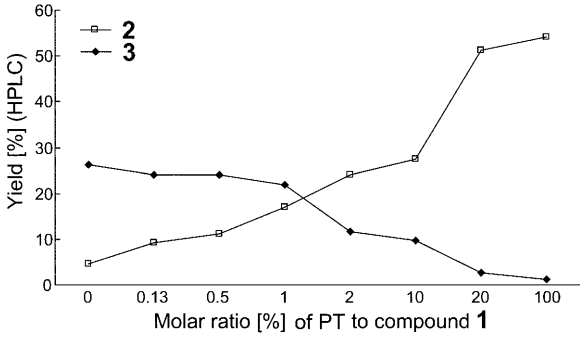
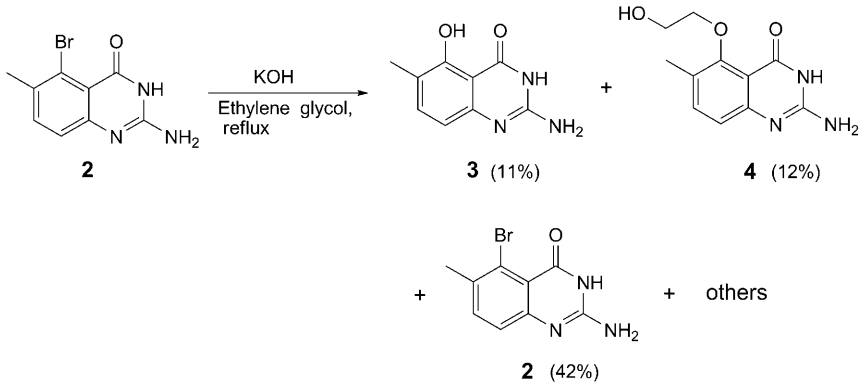


Fig. 4. *Effect of different molar ratios of PT on the production of* **2** *and* **3** (2.68 mM KOH)

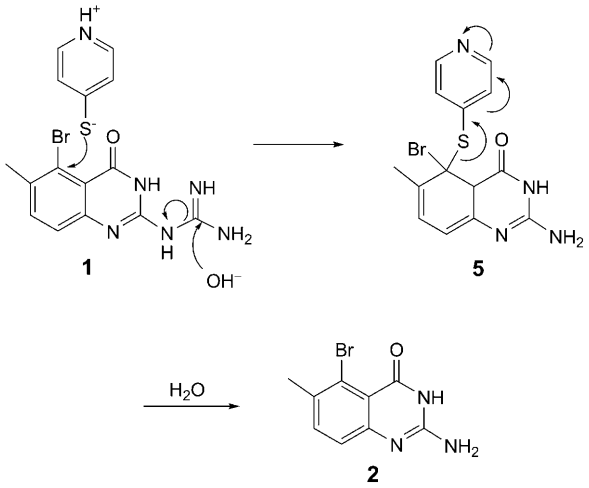
12% of **4** (*Scheme 2*). On the contrary, in the presence of 1 equiv. of PT, no noticeable change of **2** was observed by HPLC analysis after 2 h under reflux. In addition, treatment of **1** in the presence of PT for up to 4 h did not alter the production of **2** significantly as compared to the reaction time of 2 h.

Scheme 2. *Reaction of* **2** *with KOH in the Absence of PT*



The following rationale for our results is proposed. Both the displacement of the Br-substituent of **1** by hydroxide or alkoxide and its retention in the presence of PT presumably involve an initial *Michael* addition (*Scheme 3*). The intermediate adducts are reminiscent of the *Meisenheimer* complexes [4] although the two types of adducts, *i.e.*, with geminal Br and OH substituents and with geminal Br and SPy substituents, necessarily have different decomposition rates. Considering the symbiotic effect [5], the geminal Br,SPy adduct **5** is inherently more stable than the geminal Br,OH counterpart because of the hard–soft differences [6]. One can also speculate that the

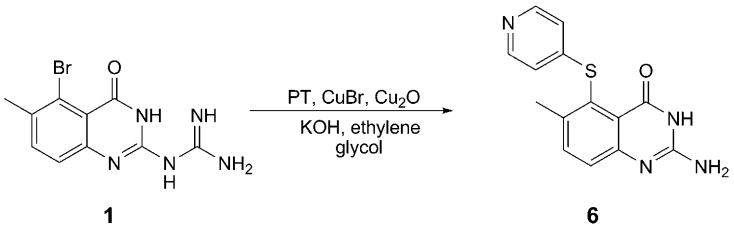
Scheme 3. *Mechanism of Protection by PT*



addition rate of PT is much higher (kinetically more favorable) so that OH^- ions (and ethylene glycolate) could hardly compete. On the other hand, once the geminal Br,OH adduct is formed, extrusion of the Br-substituent would be more rapid.

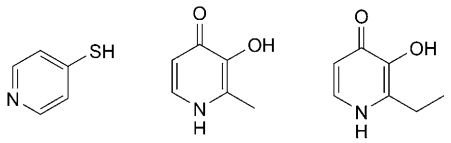
One might also argue that the elimination should proceed in the strictly reversed sense to generate the bromo compound from the geminal Br,SPy adduct **5** because the pyridinethiolate is a better leaving group. This behavior of the geminal Br,SPy adduct can be changed by adding CuBr and Cu_2O to the reaction (*Ullmann* reaction) [3][7], and indeed, in this event, the pyridinylsulfanyl-substituted derivative **6** was produced (*Scheme 4*).

Scheme 4. *Reaction of* **1** *with KOH in the Presence of PT, CuBr, and* Cu_2O



1 **6**

Besides PT, hydroxypyridinones are also amphoteric in nature [8]. For this reason, the presence of 3-hydroxy-2-methylpyridin-4(1*H*)-one (**7**) and 2-ethyl-3-hydroxypyridin-4(1*H*)-one (**8**) (*Fig. 5*) in the conversion of **1** to **2** was tested, and indeed, compounds **7** and **8** had a similar effect as PT (see *Fig. 6*).



PT **7** **8**

Fig. 5. *PT and amphoteric analogs*

In conclusion, we found a method for preserving a 'labile' Br-substituent at an aromatic ring such as that existing in **1** by using pyridine-4-thiol (PT) as an additive. We are continuing to investigate the applicability of this technique to other chemical conversions.

This work was partially supported by a grant (No. 30572237) from the *National Natural Science Foundation of China*. We also thank Miss *Hui-Xin Chen* and *Yu-Qi Liang* who participated in some preliminary work.

Experimental Part

General. The solvents were available commercially and were purified according to conventional methods. Starting materials were prepared according to a previous procedure [3]. HPLC: *Shimadzu LC-10-AT* chromatograph; *Kromasil-C18* column; elution with MeOH/H_2O 3 : 1, flow rate 0.8 ml/min. NMR Spectra: *Bruker* 400-MHz instrument; (D_6)DMSO soln.; chemical shifts δ in ppm, coupling constants

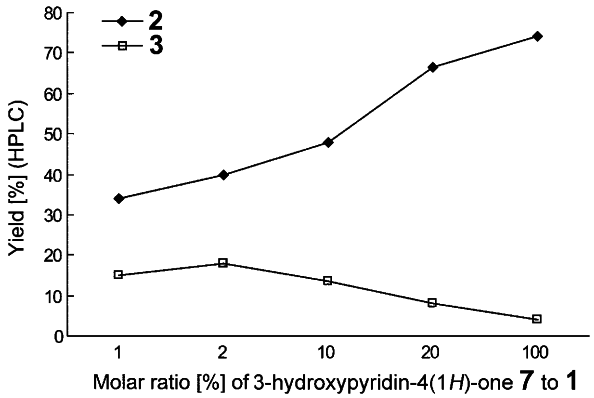


Fig. 6. *Effect of different molar ratios of 3-hydroxy-2-methylpyridin-4(1*H*)-one* (**7**) *on the production of* **2** *and* **3** (0.67 mM KOH)

J in Hz. MS: *ABI-4000-Q-TRAP* (ESI) and *VG-ZAB-HS* spectrometer (FAB); in *m*/*z* (rel. %). HR-MS: *MAT-95XP* (*Thermo*) spectrometer at the Zhongshan University Analyses Center, China.

Reaction of Compound **1** *with KOH in the Presence or Absence of Pyridine-4-thiol* (PT): *General Procedure.* A mixture of **1** (0.5g, 1.69 mmol), KOH (0.75g, 13.4 mmol; or 3.0g, 53.6 mmol), and PT (0–100 mol-% rel. to **1**) in ethylene glycol (20 ml) was refluxed for 2 h. After cooling, the mixture was diluted with H_2O (80 ml), neutralized with conc. HCl soln., and filtered. After washing with H_2O, the tan solid was dried. Products **3** and **4** were isolated by prep. HPLC from the products of the reaction which was carried out in the absence of PT.

*Data of 2-Amino-5-hydroxy-6-methylquinazolin-4(3*H*)-one* (**3**): ^{1}H-NMR ((D$_6$)DMSO): 2.35 (*s*, 3 H); 6.37 (*s*, 2 H); 7.08 (*d*, J = 8.4, 1 H); 7.46 (*d*, J = 8.5, 1 H); 11.0 (br., 1 H). MS: 192 (100, $[M+1]^+$). HR-MS: 192.0768 ($[M+H]^+$, $C_9H_{10}N_3O_2^+$; calc. 192.0768).

*Data of 2-Amino-5-(2-hydroxyethoxy)-6-methylquinazolin-4(3*H*)-one* (**4**): ^{1}H-NMR ((D$_6$)DMSO): 2.20 (*s*, 3 H); 3.29 (*s*, 1 H); 3.68 (*q*, J = 5.1, 2 H); 3.90 (*t*, J = 5.0, 2 H); 4.92 (*s*, 1 H); 6.22 (*s*, 1 H); 6.87 (*d*, J = 8.3, 1 H); 7.36 (*d*, J = 8.4, 1 H); 10.70 (*s*, 1 H). MS: 236 (100, $[M+1]^+$). HR-MS: 236.1040 ($[M+H]^+$, $C_{11}H_{14}N_3O_3^+$; calc. 236.1030).

When 3-hydroxy-2-methylpyridin-4(1*H*)-one (**7**) or 2-ethyl-3-hydroxypyridin-4(1*H*)-one (**8**) was used as an additive, the procedure was the same as that described above for PT.

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Received April 20, 2008