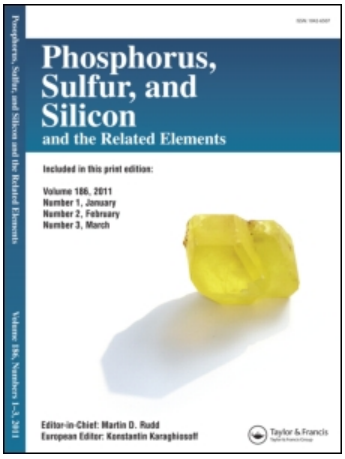

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Stephen D. Pastor[a]; Hareish K. Naraine[a]; Raj Sundar[a]
[a] Department of Chemistry and Physical Science, Pace University, Pleasantville, New York

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SUBSTITUTION OF HETEROARYL HALIDES BY THIOLATE ANIONS IN TETRAGLYME

STEPHEN D. PASTOR,† HAREISH K. NARAINE, and RAJ SUNDAR
Pace University, Department of Chemistry and Physical Science, Pleasantville, New York 10570

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The substitution of heteroaryl halides by alkanethiolate anions in tetraethyleneglycol dimethyl ether (tetraglyme) reaction medium is described. The 2-(alkylthio)-substituted quinolines **3a–c** were obtained by the reaction of 2-chloroquinoline, **1**, with the corresponding alkanethiolates **2a–c**, respectively, in tetraglyme solvent. The 2-(alkylthio)-substituted pyrimidines **5a–b** and pyrazines **7a–b** were prepared by the reaction of 2-chloropyrimidine and 2-chloropyrazine, respectively, with the corresponding alkanethiolates **2b–c**. The spectral data and elemental analyses were fully in accord with the proposed structures.

Key words: Tetraglyme; Heteroaryl substitution reactions; Thiolate anions, Substitution by.

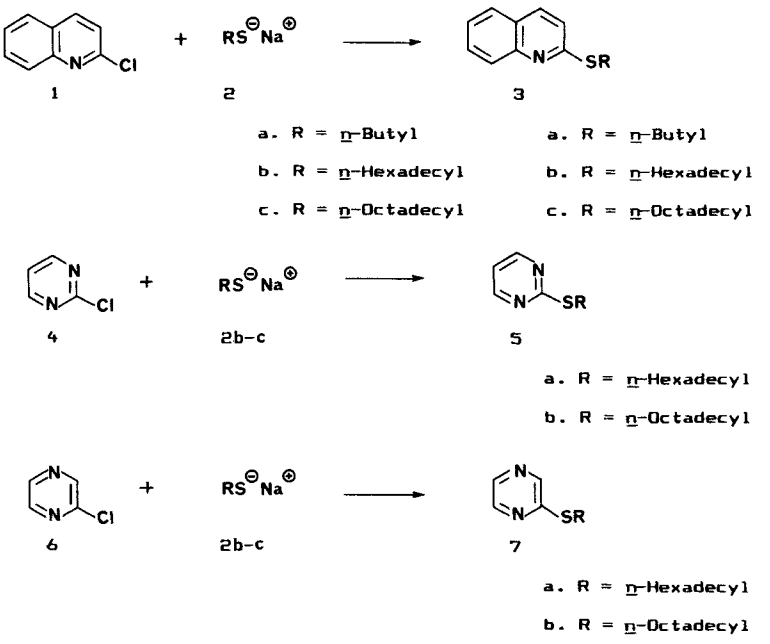
The substitution of aryl halides by aryl and alkanethiolate anions continues to be an active area of research from both a mechanistic and synthetic point of view. Recently, the dipolar aprotic solvents dimethylformamide (DMF),[1] dimethylacetamide (DMAC),[2] and hexamethylphosphoric triamide (HMPT),[3] have been advocated as the solvents of choice for the substitution of both activated and unactivated aryl halides by thiolate anions. Quite recently, we demonstrated that tetraethyleneglycol dimethyl ether was a suitable solvent for the substitution of unactivated aryl halides which avoids the use of the troublesome and in some cases carcinogenic dipolar aprotic solvents.[4]

Few systematic studies[5] of the substitution of heteroaryl halides by thiolate anions have been reported despite the importance of alkylthio- and arylthio-substituted heterocyclic compounds as pesticides,[6] antibacterial agents,[7] antiviral agents,[8] hosts for inclusion compounds,[9] and ligands for transition metals.[10] Many previous reports involve circumlocutory routes to the desired alkylthio- or arylthio- substituted heteroarenes.[11] We report in this paper the results of an investigation of the substitution of heteroaryl halides by alkanethiolate anion in a tetraglyme reaction medium.

RESULTS AND DISCUSSION

The substitution of 2-chloroquinoline, **1**, by sodium butanethiolate, **2a**, in DMF was reported by Bauer and Dickerhofe to give **3a** in modest yield.[12] In a related study Testaferri and co-workers have advocated the use of DMF as a solvent for the substitution of halopyridines by thiolate anions.[5d] Recently, Becher and

† Author to whom all correspondence should be addressed.



Lundsgaard reported the substitution of **1** by sodium *tert*-butanethiolate in tetrahydrofuran at reflux temperature.[5a–b]

The reaction of **1** with **2a** in tetraglyme reaction medium at 144°C (4 h) gave the *n*-butyl-sutstituted quinoline **3a** (58% distilled). The structure of **3a** rests on the following observations. In the ^{1}H NMR spectrum of **3a**, a triplet resonance was observed at δ 3.32 that was assigned to the two equivalent methylene protons adjacent to the sulfur atom. In the IR spectrum, absorptions were observed at 1615 and 1595 cm^{-1} which are associated with the C=N stretching frequencies of the quinoline ring. A molecular ion was observed at 217 mass units in the MS of **3a**. Both the spectral and elemental analyses were fully in accord with the proposed structure.

Similarly, the alkylthio-sutstituted quinolines **3b–c** were obtained in good yield by the reaction of **1** with the corresponding alkanethiolate anions **2b–c** in tetraglyme at 105–110°C (see Table I). A small quantity of di-*n*-octadecyl

TABLE I

Entry substrate	R in RSNa	M equiv of RSNa	Reaction temp, °C	Reaction time, h	Product	Percent yield[a]
1 2-chloroquinoline	*n*-butyl	1.0	144	4	**3a**	58%
2 2-chloroquinoline	*n*-hexadecyl	1.1	108	3	**3b**	70%
3 2-chloroquinoline	*n*-octadecyl	1.1	109	3	**3c**	65%
4 2-chloropyrimidine	*n*-hexadecyl	1.1	100	3	**5a**	42%
5 2-chloropyrimidine	*n*-octadecyl	1.1	100	2.5	**5b**	63%
6 2-chloropyrazine	*n*-hexadecyl	1.0	135	2	**7a**	69%
7 2-chloropyrazine	*n*-octadecyl	1.0	125	3	**7b**	43%

[a] All yields are of purified product.

disulfide, which was identified by its MS and ^{1}H NMR spectrum, was separated by preparative TLC from singly recrystallized **3c**.[13] The Disulfides **2a–c** that are usually present in the commercially-obtained starting thiols are difficult to remove by recrystallization from the final products **3a–c**. The formation of disulfides (other than that present in the starting thiol) by radical processes that are the result of an electron-transfer reaction pathway or oxidation of unreacted thiol during workup was not excluded. Quite recently, a $S_{RN}1$ mechanism was reported for the substitution of certain halonaphthalenes by alkanethiolate anions.[14]

The alkylthio-substituted pyrimidines **5a–b** were obtained by the reaction of 2-chloropyrimidine, **4**, with the corresponding thiolate anions **2b–c** in tetraglyme. Similarly, the alkylthio-substitituted pyrazines **7a–b** were prepared by the reaction of 2-chloropyrazine, **5**, with the corresponding thiolate anions **2b–c**.

In summary, tetraglyme was found to be a suitable reaction medium to effect the rapid substitution of a variety of heteroarylhalides by alkanethiolate anions. In particular, these findings demonstrate that tetraglyme is a suitable alternative to dipolar aprotic solvents such as DMF.

EXPERIMENTAL

All melting points were determined using a Fisher-Johns melting-point apparatus and are uncorrected. IR (1% solution in sodium chloride cells) were recorded on a Perkin–Elmer Model 1430 or 1300 spectrometer where the intensity of the absorption is reported using the convention s = strong, m = medium, and w = weak. ^{1}H NMR spectra were taken on either a Varian Model EM-360A or Jeol Model FX-90Q spectrometer. ^{13}C NMR spectra were taken on a Jeol Model FX-90Q spectrometer with full proton decoupling. ^{1}H and ^{13}C NMR spectra are reported in ppm relative to tetramethylsilane, where a positive sign is downfield from the standard. MS were obtained on a Finnegan Model 8200 mass spectrometer. MERCK precoated (0.25 mm) silica gel 60 F-254 plates were used for TLC. MERCK precoated (2.0 mm) silica gel 60 F-254 plates were used for preparative TLC. Whatman DSC-1F silica gel was used for dry column chromatography. All analytical samples were prepared by preparative TLC.

Tetraglyme was dried prior to use by passing through a column of alumina. Reagents were purchased from commercial laboratory supply houses and used without further purification. Reactions were carried out in flame-dried apparatus under an atmosphere of nitrogen. The preparation of compound **3b** is illustrative of the general procedure used. The molar equivalents of thiol used, reaction temperature, reaction duration, and yields (recrystallized or distilled) of substitution product are listed in Table I.

2-(n – Hexadecylthio)quinoline, **(3b)**. To a suspension of 0.53 g (22 mmol) of sodium hydride in 100 ml of tetraglyme was added portionwise 5.69 g (22 mmol) of **2b**. The reaction mixture was heated slowly to 40°C and was held at that temperature until hydrogen evolution was complete. To the heterogeneous reaction mixture was added 3.27 g (20 mmol) of 2-chloroquinoline and the reaction mixture was heated at 108°C for 3 h. The cooled reaction mixture was poured into a mixture of ice and water. The resultant solid was collected by filtration and the solid was recrystallized from 2-propanol to give 5.94 (70%) of a white solid. The analytical sample was prepared by preparative TLC (98:2 hexane:ethyl acetate eluent): mp 47°C; R_f (70:30 heptane:ethyl acetate eluent) 0.65; IR (CH_2Cl_2) 1615 (m), 1595 (s) cm^{-1} (C=N); ^{1}H NMR ($CDCL_3$) δ 0.87 (t, CH_3, 3 H), 1.23 (complex m, 28 H), 3.30 (t, SCH_2, $^3J_{HCCH}$ = 7.2 Hz, 2 H), 7.07–8.02 (complex m, ArH, 6 H). Anal. Calcd for $C_{25}H_{39}NS$: C, 77.9; 10.2; N, 3.6. Found: C, 78.0; 10.1; N, 3.7.

2-(n-Butylthio)quinoline, **(3a)**. Colorless liquid; Purified by dry-column chromatography followed by distillation; bp 133–135°C, 0.1 mm (lit[12] 120–122°C, 0.1 mm); R_f (70:30 heptane:ethyl acetate eluent) 0.56; IR (CH_2Cl_2) 1610 (s), 1585 (s) cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.67 (m, 4 H), 3.32 (t, SCH_2, 2 H), 7.57 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 21.9, 29.2, 31.3, 120.8, 124.8, 127.3, 127.8, 129.2, 134.8, 138.4, 148.3, 159.5; MS *m/z* 217 ($M^{+\cdot}$). Anal. Calcd for $C_{13}H_{15}NS$; C, 71.8; H, 7.0; N, 6.5. Found: C, 71.4; H, 7.1; N, 6.3.

2-(n-Octadecylthio)quinoline, **(3c)**. White solid; Purified by recrystallization from ethanol; mp 55.5–56.5°C; R_f (85:15 heptane:ethyl acetate eluent) 0.63; IR (CH_2Cl_2) 1600 (m), 1585 (s) cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H), 1.27 (complex m, 32 H), 3.36 (t, SCH_2, $^3J_{HCCH} = 7.4$ Hz, 2 H), 7.15–7.98 (complex m, 6 H). Anal. Calcd for $C_{27}H_{43}NS$: C, 78.4; H, 10.5; N, 3.4. Found: C, 78.7; H, 10.8; N, 3.2.

2-(n-Hexadecylthio)pyrimidine, **(5a)**. White solid; Purified by recrystallization from a mixture of acetone and ethanol; mp 47°C; R_f (95:5 heptane:ethyl acetate eluent) 0.63; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.28 (complex m, 28 H), 3.15 (t, SCH_2, $^3J_{HCCH} = 7.2$ Hz, 2 H), 6.93 (t, $^3J_{HCCH} = 4.8$ Hz, 1 H), 8.55 (d, $^3J_{HCCH} = 4.8$ Hz, 2 H). Anal. Calcd for $C_{20}H_{36}N_2S$: C, 71.4; H, 10.8; N, 8.3. Found: C, 71.8; H, 11.3; N, 8.2.[15]

2-(n-Octadecylthio)pyrimidine, **(5b)**. White solid; Purified by recrystallization from acetone; mp 53°C; R_f (99:1 heptane:ethyl acetate eluent) 0.47; ^1H NMR ($CDCl_3$)[16] δ 0.90 (t, 3 H), 1.27 (complex m, 32 H), 3.20 (t, SCH_2, $^3J_{HCCH} = 5.0$ Hz, 2 H). Anal. Calcd for $C_{22}H_{40}N_2S$: C, 72.5; H, 11.1; N, 7.7. Found: C, 72.7; H, 11.5; N, 7.6.

2-(N-Hexadecylthio)pyrazine, **(7a)**. White solid; Purified by recrystallization from acetone; mp 63°C; R_f (85:15 heptane:ethyl acetate eluent) 0.26; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.27 (complex m, 28 H), 3.20 (t, SCH_2, 2 H), 8.17–8.53 (complex m, 3 H). Anal. Calcd for $C_{20}H_{36}N_2S$: C, 71.4; H, 10.8; N, 8.3. Found: C, 71.0; H, 10.7; N, 8.1.

2-(n-Octadecylthio)pyrazine, **(7b)**. White solid; Purified by recrystallization sequentially from acetone and 2-butanone; mp 67°C; R_f (85:15 heptane:ethyl acetate eluent) 0.25; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.25 (complex m, 32 H), 3.17 (t, SCH_2, $^3J_{HCCH} = 6.8$ Hz, 2 H), 8.13–8.50 (complex m, 3 H). Anal. Calcd for $C_{22}H_{40}N_2S$: C, 72.5; H, 11.1; N, 7.7. Found: C, 72.7; H, 11.2; N, 7.6.

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