Synthesis and Cytotoxicity of Silicon Containing Pyridine and Quinoline Sulfides

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ABSTRACT

Silicon containing pyridine and quinoline sulfides have been prepared using phase transfer catalytic system thiol /alkyl halide / solid KOH/18-crown-6 / toluene. The target S-ethers were isolated in yields up to 81%. The cytotoxicity of the synthesized compounds was studied. Among pyridine sulfides S-[3-(1-methyl-1-silacyclohexyl)propyl] derivatives 5e and 6e exhibit the highest cytotoxicity. Aliphatic silicon derivatives were considerably less active. 8-[(Trimethylsilylmethyl)thio]quinoline (8a) exhibits the highest activity among quinoline sulfides.

INTRODUCTION

Pyridine and quinoline sulfides and related compounds exhibit a wide range of biological activity /1/. Among these activities antitumor and cytotoxic activities of pyridine /2-8/ and quinoline /9-12/ sulfides were described.

The known methods for the preparation of sulfides are based on reaction of hetaryl thiols with alkyl or aryl halides in the presence of K$_2$CO$_3$ / Me$_2$Co /13/, NaOMe / DMF /14/ or NaH / Me$_2$SO$_4$ /15/ systems. Recently we described two simple phase transfer catalytic (PTC) methods for the preparation of hetaryl sulfides in the hetaryl thiol / alkyl halide / solid K$_2$CO$_3$ / 18-crown-6 / toluene /1/ or hetaryl S-acetate / alkyl halide / solid KOH / 18-crown-6 / benzene systems /16/.

We have found that 3-(hetarylthio)-1-propynyl(trimethyl)silanes exhibit high cytotoxicity /17/. In the present work the novel N-beterocyclic sulfides with trialkylsilyl and silacyclic substituents have been synthesized as potential antitumor agents.
MATERIALS AND METHODS

Chemistry

$^1$H NMR spectra were recorded on a Varian 200 Mercury instrument using CDCl$_3$ as a solvent and hexamethyldisiloxane (HMDSO) as an internal standard (0.055 ppm). Mass spectra were registered on a GC-MS HP 6890 (70 eV). GC analysis was performed on a Chrom-5 instrument equipped with flame-ionization detector using glass column packed with 5% OV-101 / Chromosorb W-HP (80-100 mesh) (1.2 m × 3 mm). Bromomethyltrimethylsilane, 3-iodopropyltrimethylsilane, 1-(3-iodopropyl)-1-methylsilacyclopentane and 1-(iodopropyl)-1-methylsilacyclohexane were obtained by Grignard reaction /18,19/ from corresponding chloropropylmethylidichlorosilane with the following exchange of chlorine atom by iodine using NaI/(CH$_3$)$_2$CO in excellent yields.

**General procedure for alkylation of thiols 1-4.**

Finely powdered dry K$_2$CO$_3$ (0.82 g, 6 mmol) was added to a suspension of thiol 1-4 (compound 4 was used as potassium salt) (2 mmol), silane (2 mmol) and 18-crown-6 (0.053 g, 0.2 mmol) in 1.5 ml of toluene. The mixture was refluxed with stirring to achieve the disappearance of the substrates, filtered over the thin silica gel layer and concentrated under reduced pressure. The residue was purified by column chromatography on silicagel (eluent benzene – ethyl acetate in different mixtures) to give products 5-8. The results are shown in Tables 1 – 3.

**In vitro cycotoxicity assay**

Monolayer cell lines were cultivated for 72 h in DMEM standard medium without an indicator and antibiotics. After the ampoule was defrozen not more than four passages were performed. The control cells and cells with tested substances in the range of 2·10$^4$ cell/mL concentration (depending on line nature) were placed on separate 96 wells plates. Solutions containing test compounds were diluted and added in wells to give the final concentrations of 50, 25, 12.5, and 6.25 μg/mL. Control cells were treated in the same manner only in the absence of test compounds. Plates were cultivated for 72 h. The quantity of survived cells was determined using crystal violet (CV) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolinium bromide (MTT) coloration that was assayed by multiscan spectrophotometer. The quantity of alive cells on the control plate was taken in calculations as 100% /20,21/. The concentration of NO was determined according to /20/.

RESULTS AND DISCUSSION

Chemistry

Alkylation of pyridine and quinoline thiols 1-4 has been carried out in the phase transfer catalytic system silyl alkyl halide / solid K$_2$CO$_3$ / 18-crown-6 / toluene at reflux. Sulfides 5-8 were isolated in 20-81% yield by column chromatography (Table 1).
The spectroscopic data of compounds 5c, 6b, 6c, 6e, 7b, 7c, 7e are presented in Tables 2, 3. Compounds 5b, 5e, 8a, 8d, 8e were described in /1/.

**TABLE 1**

Synthesis of silyl derivatives of hetaryl thiols

| Thiol | Het                  | SiR'R"R''' | n | Reaction time, h | Product | Isolated yield, % |
|-------|----------------------|------------|---|-----------------|---------|-------------------|
| 1     | 2-pyridyl            | SiMe₃      | 3 | 8               | 5b      | 66                |
| 1     | 2-pyridyl            | SiMe₂Hp    | 3 | 7               | 5c      | 36                |
| 1     | 2-pyridyl            | 1-Me-1-silacyclohexyl | 3 | 9   | 5e      | 60                |
| 2     | 4-pyridyl            | SiMe₃      | 3 | 7               | 6b      | 62                |
| 2     | 4-pyridyl            | SiMe₂Hp    | 3 | 7               | 6c      | 32                |
| 2     | 4-pyridyl            | 1-Me-1-silacyclohexyl | 3 | 7   | 6e      | 38                |
| 3     | 2-quinolyl           | SiMe₃      | 3 | 7               | 7b      | 53                |
| 3     | 2-quinolyl           | SiMe₂Hp    | 3 | 7               | 7c      | 57                |
| 3     | 2-quinolyl           | 1-Me-1-silacyclohexyl | 3 | 7   | 7e      | 64                |
| 4     | 8-quinolyl           | SiMe₃      | 1 | 7               | 8a      | 45                |
| 4     | 8-quinolyl           | 1-Me1-silacyclopenty | 3 | 21  | 8d      | 20                |
| 4     | 8-quinolyl           | 1-Me1-silacyclohexyl | 3 | 9   | 8e      | 24                |
TABLE 2

| Compound | δ (ppm, CDCl₃ / HMDSO) |
|----------|------------------------|
| 5c       | -0.01 (s, 6H, SiCH₃), 0.51 (m, 2H, SiCH₂(CH₂)₃CH₃), 0.68 (m, 2H, SiCH₂), 0.8-1.7 (m, 15H, CH₂CH₂CH₂ and CH₂(CH₂)₃CH₃), 3.18 (t, 2H, J = 7.4 Hz, CCH₂), 6.98 (m, 1H, 5-H), 7.17 (m, 1H, 3-H), 7.44 (m, 1H, 4-H), 8.45 (m, 1H, 6-H) |
| 6b       | 0.00 (s, 8H, Si(CH₃)₂), 0.66 (m, 2H, CH₂Si), 1.70 (m, 2H, CH₂CH₂CH₂Si), 2.97 (t, 2H, J = 7.2 Hz, SCH₂), 7.09 (m, 1H, 3-H and 5-H), 8.37 (m, 1H, 2-H and 6-H) |
| 6c       | -0.03 (s, 6H, SiCH₃), 0.49 (m, 2H, SiCH₂(CH₂)₃CH₃), 0.66 (m, 2H, SiCH₂), 0.8-1.7 (m, 15H, CH₂CH₂CH₂ and CH₂(CH₂)₃CH₃), 2.97 (t, 2H, J = 7.4 Hz, CCH₂), 7.09 (m, 2H, 3-H and 5-H), 8.37 (m, 2H, 2-H and 6-H) |
| 6e       | 0.05 (s, 3H, SiCH₃), 0.60 (m, 6H, SiCH₂), 1.63 (m, 8H, CH₂(CH₂)₃CH₂ in silacycle and CH₂CH₂CH₂Si), 2.97 (t, 2H, J = 7.4 Hz, SCH₂), 7.09 (m, 2H, 3-H and 5-H), 8.37 (m, 2H, 2-H and 6-H) |
| 7b       | 0.02 (s, 9H, Si(CH₃)₃), 0.76 (m, 2H, CH₂Si), 1.80 (m, 2H, CH₂CH₂CH₂Si), 3.34 (t, 2H, J = 7.4 Hz, SCH₂), 7.22, 7.44, 7.67 and 7.90 (all m, 6H, quinoline ring protons) |
| 7c       | -0.02 (s, 6H, SiCH₃), 0.51 (m, 2H, SiCH₂(CH₂)₃CH₃), 0.72 (m, 2H, SiCH₂), 0.9-1.8 (m, 15H, CH₂CH₂CH₂ and CH₂(CH₂)₃CH₃), 3.34 (t, 2H, J = 7.4 Hz, CCH₂), 7.23, 7.40, 7.68 and 7.90 (all m, 6H, quinoline ring protons) |
| 7e       | 0.05 (s, 3H, SiCH₃), 0.57 and 0.67 (both m, 6H, SiCH₂), 1.64 (m, 8H, CH₂(CH₂)₃CH₂ in silacycle and CH₂CH₂CH₂Si), 3.36 (t, 2H, J = 7.0 Hz, SCH₂), 7.43, 7.69, 7.90 and 8.00 (all m, 6H, quinoline ring protons) |

TABLE 3

| Compound | m/z (intensity, %) |
|----------|-------------------|
| 5c       | 294 (M⁺ - Me, 10), 262 (5), 210 (100), 168 (52), 154 (7), 138 (13), 111 (53), 78 (17), 59 (38) |
| 6b       | 225 (M⁺, 5), 210 (97), 183 (9), 168 (57), 151 (7), 73 (100), 59 (14), 51 (15), 45 (23), 39 (13) |
| 6c       | 308 (M⁺-1, <1), 294 (5), 210 (100), 168 (42), 154 (7), 138 (4), 73 (5), 59 (31), 43 (7) |
| 6e       | 265 (M⁺, 26), 222 (100), 209 (12), 195 (12), 180 (41), 166 (28), 152 (15), 138 (10), 113 (27), 85 (42), 59 (17), 51 (16), 43 (20) |
| 7b       | 275 (M⁺, 3), 260 (8), 228 (8), 218 (18), 188 (15), 175 (21), 161 (100), 128 (38), 101 (12), 73 (33), 45 (12) |
| 7c       | 360 (M⁺, 1), 344 (4), 312 (5), 260 (37), 218 (33), 188 (11), 175 (13), 161 (100), 143 (12), 128 (29), 59 (36) |
| 7e       | 315 (22), 272 (83), 244 (28), 231 (38), 217 (33), 188 (18), 174 (13), 161 (100), 143 (13), 128 (67), 101 (14), 85 (32), 59 (21), 43 (20) |

In vitro cytotoxicity

Cytotoxic activity of synthesized silicon-containing sulfides 5-8 was tested in vitro on two monolayer tumor cell lines: MG-22A (mouse hepatoma) and HT-1080 (human fibrosarcoma). Concentrations providing 50% of tumor death effect were determined according to the known procedure /22/ using 96 well plates.

The experimental evaluations of cytotoxic properties are presented in Table 4. A preliminary analysis of the structure-activity relationship for the cytotoxic action clearly indicates the strong influence of the silylalkyl substituent structure.
# TABLE 4

In vitro cell cytotoxicity and the ability of intracellular NO generation caused by silicon and containing pyridine and quinoline sulfides

| N°  | Compound | HT-1080 | MG-22A |
|-----|----------|---------|--------|
|     |          | TD\(_{50}\) | NO, % CV\(^a\) | TD\(_{50}\) | NO, % CV\(^b\) |
| 5b  | ![Structure](image) | 4 | 400 | 4 | 300 |
| 5c  | ![Structure](image) | 78 | 44 | 39 | 650 |
| 5e  | ![Structure](image) | 6.5 | 500 | 4.5 | 400 |
| 6b  | ![Structure](image) | 67 | 167 | 1.2 | 250 |
| 6c  | ![Structure](image) | 52 | 114 | 15.5 | 275 |
| 6e  | ![Structure](image) | 3 | 500 | <1 | 450 |
| 7b  | ![Structure](image) | 73 | 250 | 3.8 | 200 |
| 7c  | ![Structure](image) | >100 | 33 | >100 | 36 |
| 7e  | ![Structure](image) | 47 | 30 | 34 | 157 |
| 8a  | ![Structure](image) | 2.5 | 350 | 3.5 | 200 |
| 8d  | ![Structure](image) | 17 | 300 | 22 | 200 |
| 8e  | ![Structure](image) | 21.5 | 350 | 8.5 | 400 |

\(^a\) Concentration (µg/mL) providing 50% cell killing effect [(CV+MTT)/2]

\(^b\) NO concentration (%) (CV: coloration).
Pyridine and quinoline sulfides bearing dimethylheptylsilyl group at the sulfur atom (5c, 6c, and 7c) have a slight cytotoxic effect (> 15.5 μg/mL). The substitution of dimethylheptylsilyl group by trimethylsilyl (5b, 6b, and 7b) or silahexyl group (5e, 6e, and 7e) results in considerable increase of the cytotoxic activity. It must be noted that the activity of studied compounds depends on the tumor type. In general, all silicon containing sulfides (5-8) show the expressed selectivity on mouse hepatoma MG – 22A cell line. However, 8-trimethylsilylmethylmercaptoquinoline 8a exhibits a greater toxicity on HT – 1080 cells (2.5 μg/mL) contrary to MG – 22A (3.5 μg/mL). Comparison of the tumor growth inhibition for derivatives 5 – 7b and 5 – 7c shows a higher cytotoxic activity of the trimethylsilylpropyl group containing sulfides with respect to dimethylheptylsilylpropyl substituted sulfides. Among pyridine derivatives 4-[3-(1-methyl-1-silacyclohexyl)propyl]pyridine sulfide 6e exhibits the highest cytotoxicity on MG – 22A (<1 μg/mL). The most active in the series of quinoline sulfides is 8-[(trimethylsilylmethyl)thio]quinoline 8a (2.5 μg/mL on human fibrosarcoma HT – 1080 cell line). Studied pyridine and quinoline derivatives have a medium NO-induction ability, 2-(3’-dimethylheptylsilyl)propylpyridine sulfide 5e being the most active (650% on MG – 22A test).

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