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# ALKYLATION OF HETEROARYL ALKYL METALS BY BISTRIALKYLSILYLPEROXIDES

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Summary: Heteroaryl alkyl metals 3 undergo methylation and ethylation upon treatment with bistrimethylsilylperoxide 1a and bistriethylsilylperoxide 1b. Benzothiazolylderivatives 3c-d and 3h-j react with 1a giving trimethylsilyloxylation other than methylation products. The reaction of 3a-b with 1a leads also to the trimethylsilylation product 5. The reaction of 3g, 3c and 3k with 1b provides the ethylated derivatives 2h, 2d and 2n respectively. No reaction occurred when 3c was treated with 1c.

The easily available bistrimethylsilylperoxide (BTMSPO), a masked form of 100% hydrogen peroxide, is a useful oxidizing agent of several classes of organic substrates.[1] BTMSPO has also been described recently as a synthetic equivalent of $Me_3SiO^+$ and $OH^+$ in the reaction with C-nucleophiles.[2] In these reactions nucleophilic attack at silicon to give silanes may compete with that at oxygen to give silyl ethers. In no case has ever been observed demethylation of BTMSPO.

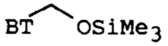
We have recently discovered that bistrimethylsilylperoxide 1a, when treated with 2-benzothiazolylalkyllithiums, undergoes demethylation other than desilyloxylation.[3] The demethylation reaction of 1a was unexpected in view of its well known tendency to undergo desilylation and desilyloxylation upon treatment with nucleophiles.[4]

In order to ascertain if BTMSPO methylates heterocyclic carbanions other than 2-benzothiazolylalkyllithiums and if other alkylsilylperoxides can be similarly dealkylated, we have investigated the reactions of silylperoxides 1 with heteroaryl alkyl metals 3.

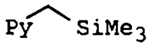
$(R_1R_2R_3SiO)_2$

1a : $R_1 = R_2 = R_3 = Me$
1b : $R_1 = R_2 = R_3 = Et$
1c : $R_1 = Me;\ R_2 = R_3 = Ph$

4a

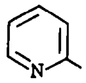


4b

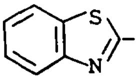


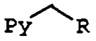
5

Py =



BT =

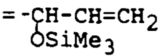




2a : R = H
2b : R = Me

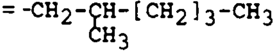
BT—R

2c : R = Et
2d : R = *n*-Pr
2i : R = -CH=CH-Et (trans)
2k : R =

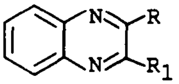


$-\underset{OSiMe_3}{CH}-CH=CH_2$

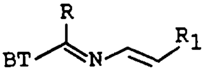
2r : R = -CH=CH-Me (cis)
2t : R = " (trans)
2v : R =



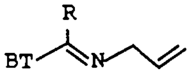
$-CH_2-\underset{CH_3}{CH}-[CH_2]_3-CH_3$



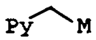
2e : R = H; $R_1$ = Et
2f : R = $R_1$ = Et
2g : R = Me; $R_1$ = Et
2h : R = Me; $R_1$ = *n*-Pr



2l : R = Me; $R_1$ = Et
2m : R = $R_1$ = Et
2n : R = Me; $R_1$ = *n*-Pr
2o : R = Ph; $R_1$ = Et

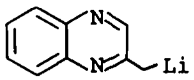


2p : R = Me
2q : R = Ph

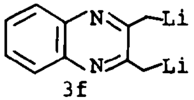


3a : M = Li
3b : M = MgBr

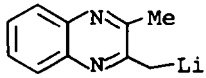
3c : M = Li
3d : M = MgBr



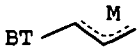
3e



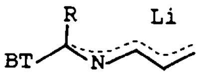
3f



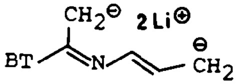
3g



3h : M = Li
3i : M = MgBr
3j : M = ZnBr



3k : R = Me
3m : R = Ph



3l

Treatment of 2-pyridylmethyllithium 3a, prepared by lithiation (LDA, THF, -78°) from α-picoline 2a with bistrimethylsilylperoxide 1a in THF at -78° and subsequent quenching with aqueous saturated $NH_4Cl$ afforded a mixture of 2-ethylpyridine 2b, 2-pyridylmethyl trimethylsilyl ether 4a and 2-pyridylmethyl trimethylsilane 5 which were separated by chromatography and characterized by IR, $^1H$-NMR and GC-MS spectrometry. The ratio between 2b, 4a and 5 was found to change on moving from THF to $Et_2O$ as the solvent (see Table). A comparable solvent dependence was observed in the reaction of 1a with 2-benzothiazolylmethyllithium 3c,[5] leading to a mixture of 1-ethylbenzothiazole 2c and 2-benzothiazolylmethyl trimethylsilyl ether 4b. In both cases the counterion dependence was poor.

Interestingly, bistrimethylsilylperoxide 1a underwent exclusively demethylation upon treatment with 2-quinoxalinylmethyllithium 3e furnishing 2-ethylquinoxaline 2e. Similarly, the reaction of monolithioderivative 3g afforded 2-methyl-3-ethylquinoxaline 2g and dilithium derivative 3f[6] led to 2,3-diethyl-quinoxaline 2f.

Table. Reaction of silylperoxides 1 with carbanions 3.

| Carbanion | Solvent | Silylperoxide | Reaction Products (% yield)[a] |
|---|---|---|---|
| 3a | THF | 1a | 2b (12)<br>4a (28)<br>5 (38) |
| " | $Et_2O$ | " | 2b (—)<br>4a (25)<br>5 (7) |
| 3b[b] | THF | " | 2b (18)<br>4a (23)<br>5 (15) |
| 3c | " | " | 2c (40)<br>4b (30) |
| " | $Et_2O$ | " | 2c (traces)<br>4b ( " ) |
| 3d[c] | THF | " | 2c (44)<br>4b (26) |
| 3e | " | " | 2e (40) |
| 3g[6] | " | " | 2f (13)<br>2g (70) |
| " | " | 1b | 2h (40) |
| 3c | " | " | 2d (10) |
| " | " | 1c | — |
| 3h | " | 1a | 2i (47)<br>2k (32) |
| " | THF/HMPA | " | 2i (70)<br>2k (8) |
| " | $ET_2O$ | " | 2i (10)<br>2k (60) |
| 3i[d] | THF | " | 2i (44)<br>2k (26) |
| " | $ET_2O$ | " | 2i (16)<br>2k (65) |
| 3j[d] | THF | " | 2i (6)<br>2k (32) |
| 3k<br>3l | " | " | 2l (13)<br>2m (14) |
| 3k | " | 1b | 2n (40) |
| 3m |  | 1a | 2o (38) |

a) Yields are on isolated compounds. b) 3b was prepared in situ by transmetallation of 3a with $MgBr_2$. c) 3d was prepared from 3c by transmetallation with $MgBr_2$; d) 3i and 3j were prepared by transmetallation of 3h with $MgBr_2$ and $ZnBr_2$ respectively.

It was also interesting to find that bistriethylsilylperoxide 1b, behaves as an ethylating agent converting quinoxalinylmethyllithium 3g and 2-benzothiazolylmethyllithium 3c into 2-methyl-3-n-propylquinoxaline 2h and 2-n-propylbenzothiazole 2d respectively.

However, no reaction took place when 2-benzothiazolylmethyllithium 3c was treated with bismethyldiphenylsilylperoxide 1c under the same conditions in which 1a and 1b did react with 3c.

We have also checked the reactions of 1a with ambident and multidentate carbanions. The reaction of 2-benzothiazolylallyllithium 3h with 1a turned out to be either regioselective and stereoselective affording the trans 1-(2-benzothiazolyl)-1-butene 2i as the methylation product and 3-trimethylsilyloxy-3-(2-benzothiazolyl)propene 2k as the silyloxylation product. Exclusive demethylation of 1a occurred in the reaction with a multidentate carbanion such as the azahexadienyllithium 3k, producing regioselectively the methylated derivative 2l together with the dimethylated azahexadiene 2m, which likely derives from the dianion 3l, that probably forms together with 3k in the lithiation of 2p. Moreover, the azahexadienyllithium 3k reacted with bistriethylsilylperoxide 1b to give good yield of the ethylated derivative 2n. Highly regioselective appeared to be the reaction of the azapentadienyllithium 3l with 1a providing the methylated derivative 2o.

The reaction of 1a with the ambident carbanion 3h-j was found to be markedly solvent dependent and poorly counterion dependent (see Table). The demethylation of 1a was favored with respect to the desilyloxylation in THF, particularly when the reaction was carried out in the presence of a cosolvent such as HMPA.

Treatment of cis- and trans-1-(2-benzothiazolyl)propene 2r and 2t first with n-BuLi at -78°C and then with BTMSPO afforded 1-(2-benzothiazolyl)-2-methylhexane 2v, likely derived from addition of BuLi to the double bond of 2r (or 2t).

In conclusion, bistrialkylsilylperoxides 1a and 1b do undergo demethylation and deethylation respectively upon treatment with a number of heteroaryl alkyl metals 3. In many cases the dealkylation reaction turned out to be the sole reaction. More work is under way in order to understand how this unprecedented dealkylation of bistrialkylsilylperoxides occurs and results will be published in due course.

## EXPERIMENTAL

$^1$H-NMR spectra were recorded on a Varian EM 360-A or Varian XL 200 spectrometers; chemical shifts are reported in parts per million (δ) from internal Me$_4$Si. $^{13}$C-NMR spectra were performed on a Varian XL-200 spectrometer. Melting points were determined on a Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer. Flash chromatographies were done with Merck 230-400 mesh silica gel. GC/mass spectrometry analysis were performed on a Hewlett-Packard 5890A Gas Chromatograph equipped with SE-30 capillary column, 30 m, and Hewlett Packard Mass Selective Detector MSD 5970B.

Materials: - Tetrahydrofuran (THF) end diethyl ether of commercial grade (RS, Carlo Erba) were purified by distillation (twice) from sodium wire in a $N_2$ atmosphere. Petroleum ether (RS, C.E.) refers to the 40-60° boiling fraction. α-Pycoline, 2-methylbenzothiazole, 2-methylquinoxaline, 2,3-dimethylquinoxaline were commercial grade (Fluka) and were purified by column chromatography. 2-Allylbenzothiazole[7] was prepared as reported. 1-(2-Benzothiazolyl)propene cis and trans 2r and 2t were prepared by isomerisation of 2-allylbenzothiazole[8] 2-Benzothiazolyl-3-aza-2,5-hexadiene 2p and 1-benzothiazolyl-1-phenyl-2-aza-1,4-pentadiene 2q were prepared from allylamine and 2-acetyl- and 2-benzoylbenzothiazole respectively in the presence of $TiCl_4$.[9] Bistriethylsilylperoxide 1b and bismethyldiphenylsilylperoxide 1c were prepared from the dried complex of $H_2O_2$ and 1,4-diaza[2,2,2]bicycloctane with triethylsilylchloride and methyldiphenylsilylchloride according to the procedure described for 1a.[10]

### Reaction of 2-pyridylmethyllithium 3a with bistrimethylsilylperoxide 1a.

To a THF (10 ml) solution of 3a, prepared by lithiation of α-picoline (2.0 mmol) with lithiumdiisopropylamide (LDA) (2.4 mmol of the commercial hexane solution of 2.5 M BuLi, 2.4 mmol of diisopropylamine), bistrimethylsilylperoxide (3.0 mmol) was added dropwise at -78°C and under $N_2$ atmosphere. The reaction mixture was kept at -78°C for about 2 h, then allowed to warm to room temperature and quenched with aqueous sat. $NH_4Cl$. Extraction with diethyl ether (3x25 ml), drying over $Na_2SO_4$ and solvent evaporation under reduced pressure left a residue that was a mixture of 2-ethylpyridine 2b, 2-pyridylmethyl-trimethylsilylether 4a and 2-pyridyltrimethylsilane 5, which were separated by flash chromatography (petroleum ether 8, diethyl ether 2) and characterized by IR, $^1H$ NMR and GC-Ms spectrometry. Data are reported below and yields are in the Table.

### Reaction of 2-quinoxalinylmethyllithium 3e with bistrimethylsilylperoxide 1a.

To a THF solution of 3e, prepared by lithiation of 2-methylquinoxaline (2.0 mmol) with LDA (2.4 mmol), 1a (3.0 mmol) was added dropwise at -78°C under $N_2$. Usual workup after 2h at -78°C and warming at RT yielded the 2-ethylquinoxaline 2e, that was purified by flash chromatography (petroleum ether 7, diethyl ether 3).

### Lithiation of 2,3-dimethylquinoxaline and reaction with bistrimethylsilylperoxide 1a.

A THF (5 ml) solution of 2,3-dimethylquinoxaline (2.0 mmol) was dropwise added to a solution of LDA (2.4 mmol) at -78°C. After about 15 min bistrimethylsilylperoxide (3.0 mmol) was added and the mixture was kept at -78°C for 2 h and then warmed at RT and quenched with aqueous sat. $NH_4Cl$. Usual workup afforded a mixture of 2-methyl-3-ethylquinoxaline 2g and 2,3-diethylquinoxaline 2f which were separated by flash chromatography (petroleum ether 9, diethyl ether 1) and characterized spectroscopically.

### Reaction of 3-methyl-2-lithiomethylquinoxaline 3g with bistriethylsilylperoxide 1b.

To a THF (10 ml) solution of 3g (2.0 mmol), prepared by lithiation of 2,3-dimethylquinoxaline (2.0 mmol) with LDA, 1b (3.0 mmol) was added dropwise at -78°C under $N_2$. The reaction mixture was kept at -78°C for 2h and then allowed to warm to RT. After 2h at this temperature the reaction was quenched with aq. sat. NH$_4$Cl. Usual workup led to 2-methyl-3-n-propylquinoxaline 2h.

### Reaction of 2-benzothiazolylmethyllithium 3c with bistriethylsilylperoxide 1b.

The reaction of 3c with 1b carried out as described above, afforded only 10% of 2-n-propylbenzothiazole 2d together with much 2-methylbenzothiazole.

### Reaction of 2-benzothiazolylallyllithium 3h with bistrimethylsilylperoxide 1a.

To a THF (10 ml) solution of 3h (2.0mmol), prepared as described,[11] BTMSPO (3.0 mmol) was added dropwise at -78°C under N$_2$. The reaction mixture was kept there for 2 h and then allowed to warm to RT. Quenching after 1 h with aq. sat. NH$_4$Cl and usual workup yielded a mixture of trans-1-(2-benzothiazolyl)-1-butene 2i and 3-trimethylsilyloxy-3-(2-benzothiazolyl)propene 2k, which were separated by flash chromatography (petroleum ether 8, diethyl ether 2) and characterized spectroscopically.

### Reaction of 2-benzothiazolyl-3-aza-hexadienyl-lithium 3k, dilithium 3l and 1-benzothiazolyl-1-phenyl-2-aza-pentadienyllithium 3m with 1a.

To a THF (10 ml) solution of 3k, containing also 3l, prepared by lithiation of 2p (2.0 mmol) with LDA (2.4 mmol), 1a (3.0 mmol) was added dropwise at -78°C under N$_2$. The mixture was kept there for 2h and then warmed to RT. Quenching with aq. sat. NH$_4$Cl after 1h and usual workup afforded a mixture of 2-benzothiazolyl-3-aza-2,4-heptadiene 2l and 3-benzothiazolyl-4-aza-3,5-octadiene 2m, which were separated by flash chromatography (petroleum ether 8, diethyl ether 2) and characterized spectroscopically.
Similarly the reaction of 3m with 1a afforded 1-benzothiazolyl-1-phenyl-2-aza- -1,3-hexadiene 2o.

### Reaction of 2-benzothiazolyl-3-aza-hexadienyllithium 3k with 1b.

To a THF solution of 3k (2.0 mmol) prepared as above, 1b (3,0 mmol) was added dropwise at -78°C under N$_2$. The mixture was kept there for 3 h and then warmed to RT. Quenching and usual workup afforded 2-benzothiazolyl-3-aza-2,4-octadiene 2n.

### Reaction of 1-(2-benzothiazolyl)propene (cis or trans) 2r and 2t with BuLi and BTMSPO.

To a THF solution of 2r (or 2t) (1.5 mmol) an hexane solution of 2.5 M BuLi (1.7 mmol) was added at -78°C under N$_2$. After 30 min to the resulting red solution BTMSPO (2.2 mmol) was added dropwise. The mixture was kept at -78° and then allowed to warm to RT. Quenching with aq. sat. NH$_4$Cl and usual workup afforded 1-(2-benzothiazolyl)-2-methylhexane 2v (55% yield).

Spectroscopic data for the new compounds are here reported:

2e, oil. $^1$H-NMR (CDCl$_3$): δ 1.45 (t, 3H, J = 7 Hz), 3.1 (q, 2H, J = 7 Hz), 7.62-8.28 (m, 4H), 8.75 (s, 1H). Ms m/e (rel. int.): 158 (66), 157(100), 144 (30), 130 (26), 117 (21), 103 (16), 102 (14), 76 (30).

2f, m.p. 60-61° (petroleum ether 40-70). $^1$H-NMR (CDCl$_3$): δ 1.45 (t, 6H, J=7 Hz), 3.12 (q, 4H, J = 7Hz), 7.6-8.3 (m, 4H). Ms m/e (rel. int.): 186 (100), 185 (32), 171 (100), 157 (19), 130(35), 103(17), 102(14), 76(18).

2g, m.p. 50-52° (petroleum ether 40-70). $^1$H-NMR (CDCl$_3$): δ 1.45 (t, 3H, J=7 Hz), 2.83 (s, 3H), 3.12 (q, 2H, J = 7Hz), 7.6-8.3 (m, 4H). Ms m/e (rel. int.): 172 (100), 171 (98), 144 (17), 130 (26), 117 (12), 103 (9), 102 (11), 76 (19).

2h, m.p. 60-61° (petroleum ether 40-70). $^1$H-NMR ($CDCl_3$): δ 1.1 (t, 3H, J = 7.5 Hz), 1.5-2.3 (m, 2H), 2.80 (s, 3H), 3.05 (t, 2H, J=7 Hz), 7.55-8.15 (m, 4H). Ms m/e (rel. int.): 186 (10), 185 (5), 171 (21), 158 (100), 102 (6), 76 (11).

2i, oil. $^1$H-NMR ($CDCl_3$) : δ 1.2 (t, 3 H, J = 7 Hz), 2.33 (m, 2H), 6.80 (m, 2H), 7.2-8.1 (m, 4H). Ms m/e (rel. int.): 189 (100), 188 (71), 174(51), 173 (45), 149 (15), 108(12), 109(13), 69 (30), 63 (18), 45(16).

2k, oil. $^1$H-NMR ($CDCl_3$): δ 0.15 (s, 9H), 5.1-6.5 (m, 4H), 7.3-8.2 (m, 4H). Ms m/e (rel. int.): 263 (59), 248 (90), 192 (21), 174 (68), 129 (19), 124 (13), 73 (100), 45 (45), 43 (13).

2l, oil. $^1$H-NMR ($CDCl_3$): δ 1.12 (t, 3H, J= 7 Hz), 2.0-2.6 (m, 2H), 2.55 (s,3H), 6.35 (dt, 1H, J=7, J=13 Hz), 7.2 (d,1H, J=13 Hz), 7.3-8.4 (m,4H).

2m, oil. $^1$H-NMR ($CDCl_3$): δ 1.1 (t, 3H, J = 8 Hz), 1.25 (t, 3H, J = 8 Hz), 2.34 (dq, 2H, J= 7, J= 8 Hz), 3.1 (q, 2H, J = 8 Hz), 6.5 (dt, 1H, J= 7, J = 13 Hz), 7.4 (d, 1H, J = 13 Hz), 7.5-8.4 (m, 4H).

2n, $^1$H-NMR ($CCl_4$): δ 0.9 (t, 3H, J = 6 Hz), 1.0-2.2 (m, 4H), 2.4 (s,3H), 5.9-6.4 (m, 1H), 6.9-8.1 (m, 5H). Ms m/e (rel. int.): 244 (2), 201(100), 187 (2), 162 (13), 136 (4), 109 (6),80 (3), 41 (6).

2o, m.p. 123-125° (petroleum ether 40-70). $^1$H-NMR ($CCl_4$): δ 1.1 (t, 3H, J= 8 Hz), 2.4 (dq, 2H, J = 8, J= 7 Hz), 6.73 (dt, 1H, J= 7, J = 14 Hz), 7.3 (d, 1H, J = 14 Hz), 7.6-8.6 (m, 9H).

2v, oil. $^1$H-NMR ($CDCl_3$): δ 0.84-1.45 (m, 12H), 2.05 (m. 1H), 2.82-3.14 (m, 2H) 7.25-8.0 (m. 4H). $^{13}$C-NMR ($CDCl_3$): δ 14.11, 19.54, 22.83, 29.16, 34.45, 36.39, 41.75, 121.43, 122.53, 124.59, 125.80, 135.26, 153.25, 171.50. Ms m/e (rel. int.): 233 (6), 190 (8), 176 (24), 162 (11), 149 (100), 148 (29), 108 (12), 69 (12), 41 (26).

4a, oil. $^1$H-NMR ($CDCl_3$): δ 0.15 (s, 9H), 4.82 (s, 2H), 6.90-8.70 (m, 4H). Ms m/e (rel. int.): 181 (7), 166 (100), 136 (10), 92 (10), 73 (10), 65 (15), 45 (11).

5, oil. $^1$H-NMR ($CDCl_3$): δ 0.0 (s,9H), 2.33 (s, 2H), 6.95-8.65 (m, 4H). Ms m/e (rel. int.): 165 (19), 164 (13), 150 (100), 73 (44), 45 (16).

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## References

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5) The experimental procedure is described in Ref. 3.

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8) The details of such an isomerisation will be reported elsewhere in due course.

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