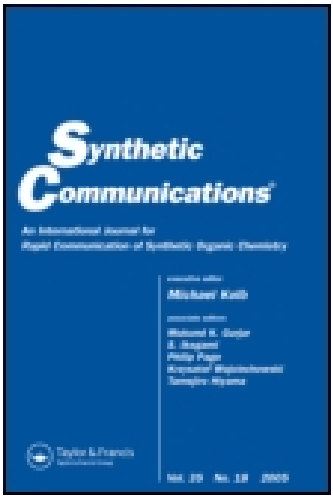

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REGIOSPECIFIC BROMINATION OF CEPHALOSPORIN SULFONES AT C-2 WITH CYANOGEN BROMIDE

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Abstract: 2α-Bromocephalosporin sulfones can be prepared very easily and in practically pure form by using commercial cyanogen bromide with base catalysis. The bromides can immediately be used for subsequent reactions.

2-Substituted cephalosprin sulfones are potent inhibitors of human leukocyte elastases (HLE) and they have been the subject of intensive recent studies, especially by the Alpegiani group, who probed their preparation.[1] These compounds can be prepared *via* bromination of the corresponding sulfones followed by nucleophilic substitution reactions. The preferred agent for bromination in the literature is NBS in combination with triethylamine (ionic bromination), but the C-2 bromides are always formed together with different side products. As the purification is difficult, this may cause various problems in the subsequent steps, especially because the C-Br bond has reversed polarity owing to the adjacent sulfone, and the bromine tends to take part in a

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reductive elimination instead of a clear nucleophilic substitution with thiolates.[1a,2] To overcome the problematic bromination step several other agents were tried, and we found that cyanogen bromide is excellent.

Cyanogen bromide is a seldom used reagent for direct bromination according to the literature, apart from a specific application in the well-known *von Braun* dealkylation reaction: in certain cases a dialkylamino group can be replaced with bromine.[7] The few recent examples for the direct bromination can be found in Table 1.

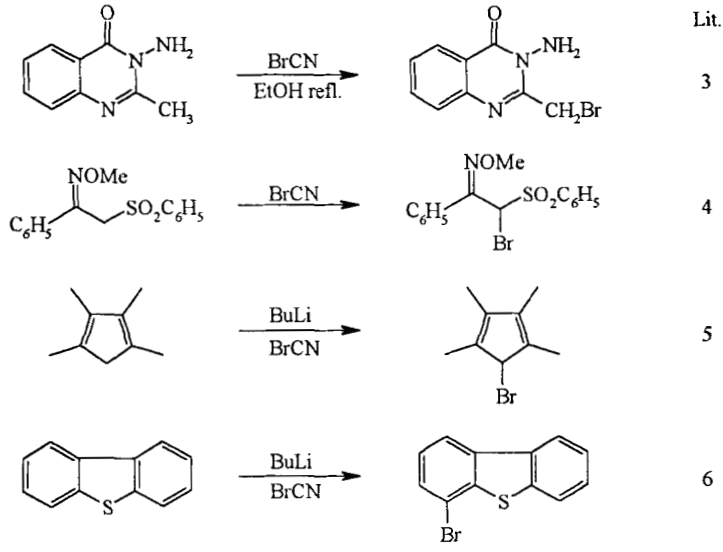
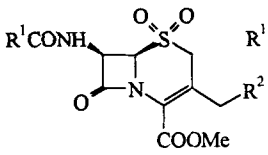


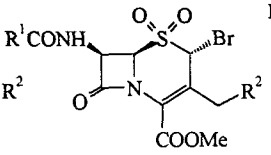
Table 1.

When **1a** was reacted with 1.5 eq. of BrCN in methylene chloride in the presence in triethylamine, one new compound (**2a**) was shown in the reaction mixture according to

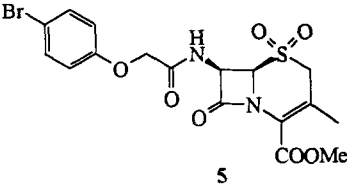
tlc, together with unreacted starting material in a ratio of ca. 1:2. On raising the amount of BrCN up to four equivalents and using 5 mol% of triethylamine as base catalyst, only a 1:1 mixture of **1a** and **2a** could be obtained. When the amount of the base was increased to above 0.8 eq., partial epimerization at C-7 of both the product and the starting material occurred, as it was revealed by the ^{1}H NMR spectra of the



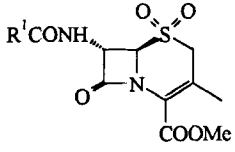
1a-c



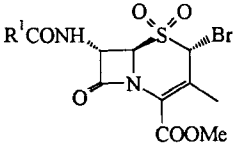
2a-c



5



3a



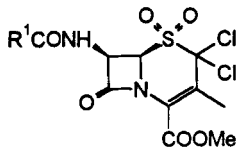
4a

a - $R^1 = C_6H_5OCH_2$- R^2 = -H
b - $R^1 = pNO_2C_6H_4$- R^2 = -H
c - R^1 = tBuO- R^2 = -OAc

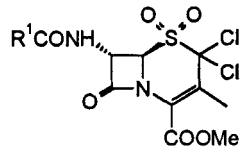
chromatographically separated compounds (**3a** and **4a**; the 6(7)-epimerization of the sulfoxides and sulfones of the ß-lactam antibiotics in the presence of anhydrous strong bases is a known phenomenon[8]). If the reaction was carried out at elevated temperature ($CHCl_3$, 60 °C), a substantial amount of **2a** was formed, but on longer reaction time its amount decreased, and a new compound appeared in the reaction mixture, chromatographically very near to the starting material. After separation of the components, this new compound suprisingly proved to be the starting material brominated in the aromatic 7β side chain in para position (**5**). In order to shed more light on the way of formation of **5**, the 2.2-dichloro derivative **6a** was synthesized and subjected to brominatian with cyanogen bromide. At room temperature with 1-3 eq. of

BrCN and 0.05 – 0.25 eq of triethylamine no reaction occurred. On raising the temperature to 60 °C and increasing the amount of the base only a small amount of the epimer **7a** has formed. According to this finding direct bromination of the aromatic ring in the case of **5** is improbable. We may speculate that because of the strongly reversed polarity of the C–Br bond in **2** this may result in the formation of Br^+, which is capable of an *in situ* electrophilic bromination of the aromatic ring.

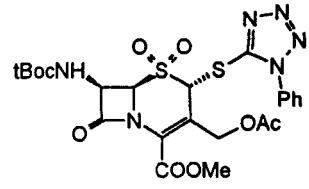
As a minor amount of unreacted starting material did not affect in the following reaction, and in turn, a small amount of **2** always decomposed to the starting material, striving after ca. 90% conversion was found to be more advantageous than forcing the



6a



7a



8

reaction to completion, when the byproducts mentioned above may also be easily produced. Thus, on optimizing the bromination reaction, we found that in absolute methylene chloride in the presence of 2 eq of BrCN and 0.66 eq of triethylamine the reaction is very clean at room temperature and almost complete conversion is achieved in short time. Compounds **2a** and **c** can be isolated in oily form with the aid of fast column chromatography, but owing to their instability in the presence of nucleophiles, it is advisable to use them immediately, whereas **2b** crystallizes easily. As an example **2c** was converted very cleanly to **8**, although some **1c** was always formed because of the possible reductive dehalogenation with thiols.

Experimental

M.p.s were determined on a Koffler-type hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer in KBr pellets. The ^{1}H NMR spectra were recorded at 200 MHz on a Bruker WP-SY instrument, with Me_4Si as internal standard.

Methyl 2-bromo-3-methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate 1.1-dioxide (2a) 0.394 g (0.001 M) of **1a** was dissolved in 40 ml of dry methylene chloride at 0 °C, 0.22 g (0.002 M) of BrCN was added followed by the dropwise addition of 10 ml of methylene chloride containing 0.092 ml (0.00067 M) of triethylamine. The mixture was allowed to stand for 1 hour at room temperature. According to tlc (toluene – ethyl acetate 1:1) the mixture contains beside the product only a small amount of starting material. The reaction mixture was evaporated to dryness in vacuum. The resulting oily material can be used immidiately for the subsequent steps. It can be purified with quick column chromatography on silicagel (toluene – ethyl acetate 4:1), yielding a solid foam.

^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 3.89 (s, 3H), 4.58 (s, 2H), 4.98 (s, H), 5.49 (d, H, J = 5.0 Hz), 6.25 (dd, H, J = 5.0 and 10.6 Hz), 6.9-7.4 (m, 5H), 7.83 (d, H, J = 10.6 Hz). The observed NOE verifies the 2α position of the bromine: the 6α-H (5.49 ppm) exhibited NOE only with 7α-H (6.25 ppm, 10%), whereas the 2β-H (4.98 ppm) only with the 3-Me protons (3%).

Similarly were prepared:

Methyl 2-bromo-3-methyl-7β-(4-nitrophenyl)acetamido-3-cephem-4-carboxylate 1.1-dioxide (2b) 74% crystalline compound after quick column chromatography, mp.: 174-6 °C (dec); ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 3.94 (s, 3H), 5.03 (s, H), 5.59 (d, H, J = 5.2 Hz), 6.40 (dd, H, J = 5.2 and 11.0 Hz), , 8.0-8.4 (AB, 4H) 7.91 (d, H, J = 11.0 Hz); IR (KBr) ν 1806, 1732, 1670, 1528 cm^{-1}; Analysis: ($C_{16}H_{14}N_3O_8SBr$, 488.28) Br calculated: 18.44%, found: 18.8%

Methyl 2-bromo-3-methyl-7β-t-butoxycarbonylamino-3-cephem-4-carboxylate 1.1-dioxide (2c) ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.15 (2, 3H), 3.91 (s, 3H), 4.91 – 5.10 (ABq, 2H), 5.42 (s, H), 5.55 (d, H, J = 5.0 Hz), 5.96 (dd, H, J = 5.0 Hz and 11.1 Hz), 5.83 (d, H, J = 11.1 Hz)

When the above reaction of **1a** was carried out in the presence of 2-2 eqs of cyanogen bromide and triethylamine, the work-up (column chromatography, SiO_2, toluene – ethyl acetate 4:1) yielded beside **2a** a small amount of 7α-epimers **3a** and **4a**:

Methyl 3-methyl-7α-phenoxyacetamido-3-cephem-4-carboxylate 1.1-dioxide (3a) M.p. 206-7 °C; ^{1}H NMR (DMSO-d_6) δ 1.95 (s, 3H), 3.70 (s, 3H), 4.14 – 4.45 (ABq, 2H), 4.62 (s, 2H), 5.29 (dd, H, J = 2.1 and 8.5 Hz), 5.38 (d, H, J = 2.1 Hz), 6.9-7.4 (m, 5H), 9.22 (d, H, J = 8.5 Hz); IR (KBr) ν 1778, 1726, 1678, 1524, 1232 cm^{-1}

Methyl 2-bromo-3-methyl-7α-phenoxyacetamido-3-cephem-4-carboxylate 1.1-dioxide (4a) M.p. 163-4 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 3.91 (s, 3H), 4.57 (s, 2H), 4.97 (s, H), 5.28 (dd, H, J = 2.3 and 7.5 Hz), 5.67 (d, H, J = 2.3 Hz), 6.78-7.3 (m, 5H), 7.5 (d, H, J = 7.5 Hz)

When the above reaction of **1a** was carried out in the presence of 2 eq of cyanogen bromide and 0.5 eq of triethylamine in $CHCl_3$ at 60 °C for 8 hours, the work-up (column chromatography, SiO_2, (toluene – ethyl acetate 4:1)) yielded beside **2a** 35% of **5**.

Methyl 3-methyl-7β-(4-bromo-phenoxy)acetamido-3-cephem-4-carboxylate 1.1-dioxide (5) M.p. 223-5 °C; ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 3.77 (s, 3H), 4.17 - 4.31 (ABq, 2H), 4.56 - 4.75 (ABq, 2H), 5.31 (d, H, J = 5.2 Hz), 5.00 (dd, H, J = 5.2 and 9.2 Hz), 6.84-7.45 (AA'BB', 4H, characteristic of para disubstituted benzenes, J = 8.8 Hz); IR (KBr) ν 1798, 1732, 1700, 1488, 1330, 1232 cm^{-1}; MS (EI) ($C_{17}H_{17}N_2O_7SBr$, 473.30) m/e: 472 (1.1%, M), 155 (71%, $BrC_6H_4^+$).

Attempted bromination of **6a**:

Methyl 2.2-dichloro-3-methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate 1.1-dioxide (6a) To a solution of 0.788 g of **1a** in 30 ml of methylene chloride 0.534 g of N-chloro-succinimide and 0.4 ml of Et_3N was added. Having allowed to react for 40 minutes at room temperature, the mixture was washed with 10% aq. $NaHCO_3$ and water. After evaporation the row product was purified by column chromatography (SiO_2, toluene – ethyl acetate 3:1), and crystallized from iPrOH, m.p. 133-4 °C; m.p. 223-5 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (s, H); 3.79 (s, 3H), 4.58 – 4.78 (ABq, 2H), 6.19 (dd, H, J = 4.9 and 8.0 Hz), 6.28 (d, H, J = 4.9 Hz), 6.8 – 7.3 (m, 5H), 9.4 (d, H., J = 8.0 Hz); IR (KBr) ν 1806, 1758, 1696, 1496, 1230 cm^{-1}; Analysis: ($C_{17}H_{16}N_2O_7SCl_2$, 463.29) Cl calculated: 15.30%, found: 15.15%

Under the same reaction conditions used for preparing **2a** no changes were detected.

When using forced conditions, raising the temperature (refluxing $CHCl_3$) and the amount of triethylamine only partial epimerization at C-7 occured:

Methyl 2.2-dichloro-3-methyl-7α-phenoxyacetamido-3-cephem-4-carboxylate 1.1-dioxide (**7a**) M.p. 175-7 °C; ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 8.86 (s, 3H), 4.64 (s, 2H), 5.51 (dd, H, J = 2.4 and 7.6 Hz), 6.26 (d, H, J = 2.4 Hz), 7.0 – 7.4 (m, 5H), 9.23 (d, H, J = 7.6 Hz); IR (KBr) ν 1806, 1740, 1698, 1512, 1350, 1228 cm^{-1}.

Reaction of **2c** with thiol:

Methyl 2-(5-phenyl-1-tetrazolylmerkapto)-3-methyl-7β-t-butoxycarbonylamino-3-cephem-4-carboxylate 1.1-dioxide (**8**) The bromo derivative **2c** (from 0.001 M of **1c**) was obtained as described above and evaporated to dryness. The resulting oil was taken up in a solution of 0.356 (0.002 M) 1-merkapto-5-phenyl-tetrazole, 0.26 ml (0.002 M) of triethylamine in 35 ml of abs. acetonitrile. The reaction mixture was allowed to stay overnight in the cold. The solvent was changed to methylene chloride, was thoroughly washed with 5% aq. $NaHCO_3$ and water. According to tlc (toluene – ethyl acetate 1:1) it contains a small amount of **1a** too. Fast column chromatography on SiO_2 (toluene – ethyl acetate 3:1) yielded 260 mg of pure **8** (44 %). M.p.179-80 °C; NMR ($CDCl_3$), δ 1.44 (s, 9H), 2.13 (s, 3H), 3.91 (s, 3H), 5.01-5.20 (ABq, 2H), 5.15 (d, H, J = 4.8 Hz), 6.01 (s, H), 5.71 (d,H, J = 10.8 Hz), 5.95 (dd, H, J = 10.8, 4.8 Hz); IR (KBr) ν 1800, 1744, 1714, 1501, 1234 cm^{-1}.

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