

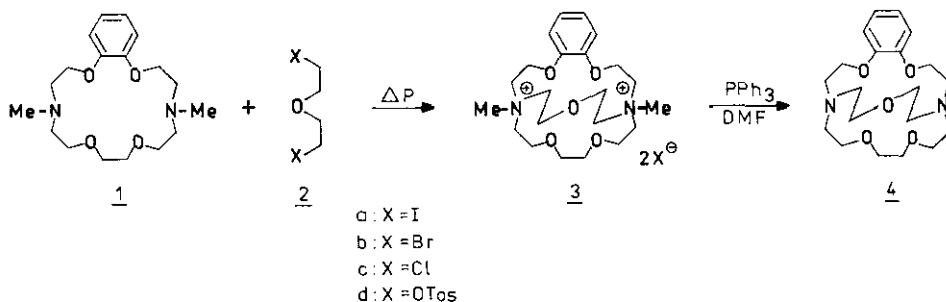
SYNTHESIS OF CRYPTANDS UNDER HIGH PRESSURE. THE ROLE OF SOLVENT
AND LEAVING GROUP IN DOUBLE QUATERNIZATION REACTIONS

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Abstract — The rate of double quaternization reaction of N,N'-dimethyldiaza-
coronand (1) with bis(2-iodoethyl) ether (2a) under high pressure strongly de-
pends on solvent polarity. The nature of the leaving group in bis(2-halogeno-
ethyl) ethers (2a-c) or in bis(2-tosyloxyethyl) ether (2d) influences the ra-
te of double quaternization reaction.

We have recently developed a high-yield synthesis of simple^{1,2} and chiral³⁻⁵ cryptands under high
pressure *via* double quaternization reaction of N,N'-dimethyldiazacoronands in acetone as solvent,
followed by demethylation. A representative example showing the formation of (2_B.2.1)cryptand (4)
is depicted in Scheme.



Scheme

Now we report on the influence of solvent and leaving group (X) on the yield of double quaterniza-
tion reactions. We selected N,N'-dimethyl-1,7,10,16-tetraoxa-4,13-diaza-(16)orthocyclophan (1) as a
model diazacoronand as well as four bridging components 2a-d. All reactions were performed in a high
pressure apparatus⁶ under 10 kbar at 30°C. The influence of solvent was studied for the reaction
1 + 2a → 3a (Scheme). Six different aprotic solvents were chosen as a reaction medium. The resulting
bisquaternary salt 3a was checked by ¹H NMR.⁷ The reaction course could be monitored by TLC on alu-
mina. The yields of bisquaternary salt 3a are compared in Table 1.

Table 1. The influence of solvent on double quaternization for 1 + 2a + 3a

| Solvent | Reaction time (h) | |
|--------------------|-------------------|-----|
| | 20 | 4 |
| | Yield (%) | |
| DMF | 100 | 100 |
| MeCN | 100 | 95 |
| Me ₂ CO | 100 | 65 |
| AcOEt | 100 | 53 |
| Et ₂ O | 100 | 30 |
| PhMe | 100 | 44 |

Table 2. The influence of leaving group on double quaternization

| Reaction | Solvent | |
|----------------------------------|--------------------|------|
| | Me ₂ CO | MeCN |
| | Yield (%) | |
| <u>1</u> + <u>2a</u> + <u>3a</u> | 100 | 100 |
| <u>1</u> + <u>2b</u> + <u>3b</u> | 85 | 100 |
| <u>1</u> + <u>2c</u> + <u>3c</u> | 8 | 52 |
| <u>1</u> + <u>2d</u> + <u>3d</u> | 70 | 100 |

In all cases, except dimethylformamide and acetonitrile, white microcrystalline salt precipitated during the reaction. All reactions were completed after 20 h. The yields differed substantially after 4 h indicating that the high-pressure double quaternization was accelerated in polar solvents like dimethylformamide or acetonitrile. From the practical point of view, it would be desirable to perform a double quaternization reaction in dimethylformamide within a short time and to demethylate the resulting compound directly, since DMF serves as good reaction medium for the following demethylation.⁸ The influence of the leaving group (X) was demonstrated in a set of experiments. Compound 1 was reacted with four bridging components 2a-d in acetone and acetonitrile under standard conditions: 10 kbar, 30°C, 20 h. The yields of the appropriate bisquaternary salts are listed in Table 2. It is clear that the results are in agreement with the well known order of reactivity giving by I>Br>Tos>>Cl. Evidently, the best bridging component is 2a. Not only it will give the best yield for 3a, but also it was found that bisquaternary diiodide is easier to demethylate than the corresponding dibromide (3b), dichloride (3c) or bistosylate (3d).

The final conclusion is drawn as follows: cryptands can be prepared in very good yield by the high pressure double quaternization method using highly polar solvents like DMF. The corresponding bisquaternary salts as intermediates need not to be isolated before demethylation to give the cryptands.

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7. ¹H NMR spectrum (100 MHz) of 3a in DMSO-d₆; δ (ppm): 7.2 (m, 4H, Ar), 4.6 - 3.1 (m, 32H, N-CH₂, O-CH₂), 3.4 (s, 6H, 2×CH₃).
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