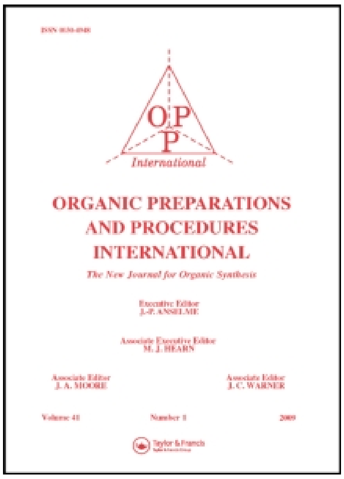

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A CONVENIENT AND EFFECTIVE METHOD FOR THE SYNTHESIS OF TETRAOXAQUATERENES

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A CONVENIENT AND EFFECTIVE METHOD FOR THE SYNTHESIS OF TETRAOXAQUATERENES

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There is a great interest in the synthesis of new types of ionophores; among others calixarenes[1,2] and cyclodextrins[3-5] are well known. Recent papers dealing with the synthesis of tetraoxaquaterenes show that this may be a very interesting scaffold in supramolecular chemistry. Among all quaterenes, the synthesis of octamethyltetraoxaquaterene (**3**) is documented very well. One of the best methods, already published by Chastrette *et al.*,[6,7] based on the one-pot reaction of furan (**1**) with acetone (**2**), carried out in the presence of hydrochloric acid and lithium perchlorate, afforded the desired product **3** in 25% yield. Several attempts at modification of the reaction conditions were unsuccessful.[8,9]

In this paper we present the effect of concentration of sulfuric acid on the yield of the cyclocondensation reaction of furan (**1**) with acetone (**2**) and with cyclohexanone (**4**), performed in dioxane (Scheme, Table).

We found that upon addition of concentrated sulfuric acid (Entry 9) to the mixture of furan (**1**) and acetone(**2**), the reaction mixture turned black (temperature of the reaction was kept below 10°C) and the crude product contained a large amount of polymeric material. After purification, the desired product **3** was obtained in a 20% yield.[10] When the concentration of sulfuric acid was decreased to 93.3% (Entry 8), the product **3** was obtained in a 51% yield, and supression of the polymerization reaction was observed. At a lower concentration of acid (Entry 7, 90.5%) the reaction yield was much higher (71% after recrystallization from toluene). Further experiments showed that the yield drops with decreased acid concentration (Entries 2-6), and below the acid concentration of 83%, no reaction occurred (Entry 1).

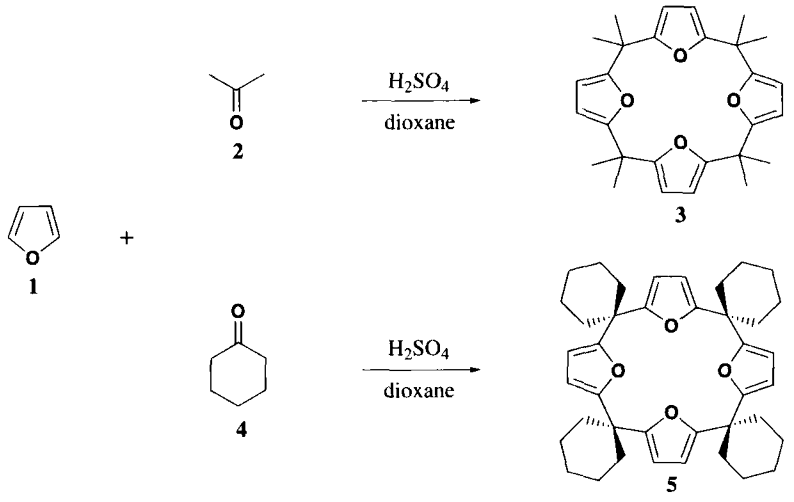

TABLE. Influence of the Concentration of Sulfuric Acid on the Yield of **3** and **5**

	Product **3**			Product **5**	
Entry [%]	Conc.of H_2SO_4 [%]	Yield [%]	Entry	Conc.of H_2SO_4 [%]	Yield [%]
1	81.3	0	10	70.5	40
2	83.2	57	11	74.3	40
3	84.5	53	12	77.8	46
4	85.7	50	13	81.3	44
5	87.6	51	14	84.5	46
6	88.8	62	15	87.6	49
7	90.5	71	16	90.5	45
8	93.3	51	17	93.3	44
9	96.0	20	18	96	40

When acetone (**2**) was replaced with cyclohexanone (**4**), tetracyclohexyltetraoxaquaternene (**5**) was obtained under above-mentioned conditions (Scheme 1, Table 1). Previous synthetic routes for this compound were not very successful, and yields of 9%[11] and 16%[9] were reported.

The highest yield was obtained for concentration of sulfuric acid 87.6% (Entry 15) similarly as in the case of the synthesis of tetraoxaquaterene **3** (Entry 7). Further experiments showed that the yield drops with decreased acid concentration (Entries 10-14) as well as with increased acid concentration (Entries16-18).

The compound **5** precipitated from the reaction mixture, and after few attempts we managed to obtain the well-shaped monocrystals suitable for X-ray analysis, which finally confirmed the assumed structure.[12]

In summary, there is presented a one-step procedure for the synthesis of tetraoxaquaterenes **3** and **5**, characterized by relatively high yield and selectivity. A substantial effect of sulfuric acid concentration on the reaction yield is observed. An extension of this procedure to more complex systems which may be of interest as new scaffolds in supramolecular chemistry is now in progress.

EXPERIMENTAL SECTION

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a Varian Gemini 200BB (200 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (d, 0.00 ppm). IR spectra were obtained on Perkin-Elmer 1640 FTIR spectrophotometer as KBr pellets. Mass spectra were recorded on an AMD 604 Intectra instrument using the electron impact (EI) technique. Single-crystal X-ray diffraction analysis was performed on an Enraf-Nonius MACH 3 diffractometer.

Synthesis of Octamethyltetraoxaquaterene (3). Typical Procedure.- A precooled 90.5% sulfuric acid (5 mL) was added dropwise to a stirred precooled (0-5°) mixture of acetone (1.46 mL, 20 mmol), furan (1.44 mL, 20 mmol), and dioxane (30 mL). Upon addition of sulfuric acid, the reaction mixture turned red and some precipitation of product was observed. The reaction mixture was stirred overnight at room temperature, then water (50 mL) was added and the acid was neutralized by a sodium hydroxide aqueous solution (20%). Crude product was filtered off, washed with water (2 x 10 mL), methanol (2 x 10 mL) and recrystallized from toluene to give 1.54 g (71% yield) of colorless needles, m.p. 241.5-242° (*lit.*[13] 243°); R_f=0.51 (hexane-ethyl acetate, 95:5 v/v). IR (KBr pellets): 2983, 2871, 1651, 1602, 1559, 1449, 1365, 1262, 1207, 1156, 1112, 1027, 955, 775, 732, 671, 562 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 24H), 5.88 (s, 8H). ^{13}C NMR: d 25.5, 36.6, 103.1, 158.6. EI-MS: m/z 433[M+H]$^+$, 432[M]$^+$, 419, 418, 417, 402, 387, 372, 201, 186.

Synthesis of Tetracycloheksyltetraoxaquaterene (5).- For this preparation the above procedure was applied to afford compound **5** in 45% yield, colorless needles, m.p. 268-269°, (*lit.*[13] 268°). R_f=0.43 (hexane-ethyl acetate 95:5 v/v). IR (KBr pellets): 2944, 2855, 2662, 1649, 1602, 1554, 1446, 1240, 1124, 1020, 1014, 969, 903, 874, 768, 709, 666, 573 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (bs, 24H), 2.01 (bs, 16H), 5.86 (s, 8H). ^{13}C NMR: d 22.31, 26.12, 33.43, 40.75, 103.91, 157.45. EI-MS: m/z 594, 593[M+H]$^+$, 592[M]$^+$, 564, 549, 445, 377, 297, 229.

Anal. Calc. for $C_{10}H_{48}O_4$: C, 81.08; H, 8.11. Found C, 80.95; H, 8.18

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