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SOLUBLE POLYMER TRACELESS LINKER INVESTIGATIONS: SOLVENT EFFECTS ON THE DESULFONYLATION OF POLYETHYLENE GLYCOL (PEG) SUBSTITUTED ARYL ALKYL SULFONES WITH SODIUM AMALGAM

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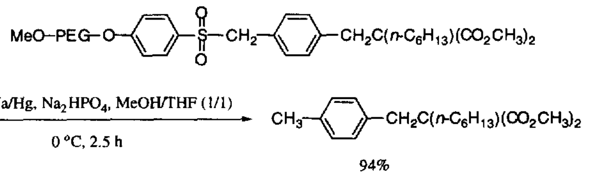
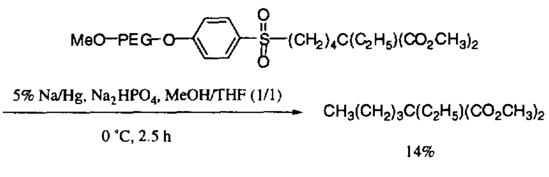
Abstract: The soluble polymer polyethylene glycol containing a traceless aryl alkyl sulfone linker was found to be resistant to reductive cleavage with sodium amalgam (Na/Hg). Detailed investigations revealed that the solvent plays an important role in the desulfonylation reaction; subsequently it was determined that MeOH/DMF (1/8) is an ideal solvent system for the cleavage of this traceless linker. © 1998 Elsevier Science Ltd. All rights reserved.

Previously, we reported a soluble polymer containing a traceless[1] linker that allowed for the synthesis of a variety of alkylated malonates following their detachment using Na/Hg.[2] During this investigation it was discovered that benzylic sulfones underwent smooth reductive cleavage (Equation 1), but, unfortunately, cleavage of a non-benzylic sulfone, under the same reaction conditions gave a less than adequate yield of the desired malonate (Equation 2). This result was in striking contrast to that obtained with a different sulfone linker that was described in an earlier report[3] (Equation 3). Here, the structural difference between the two linkers was that one had a strong electron donating group para to the aryl sulfone; we surmised that the reaction rate was being retarded by the alkoxy moiety. Thus, it was of great interest to see if it was possible to develop new reaction conditions under which less reactive sulfones would undergo smooth desulfonylation.



Equation 1



Equation 2

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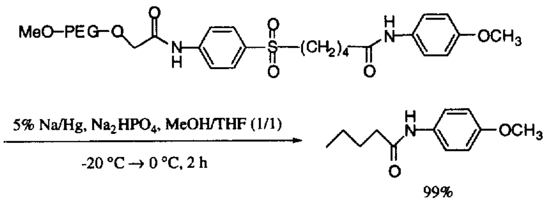
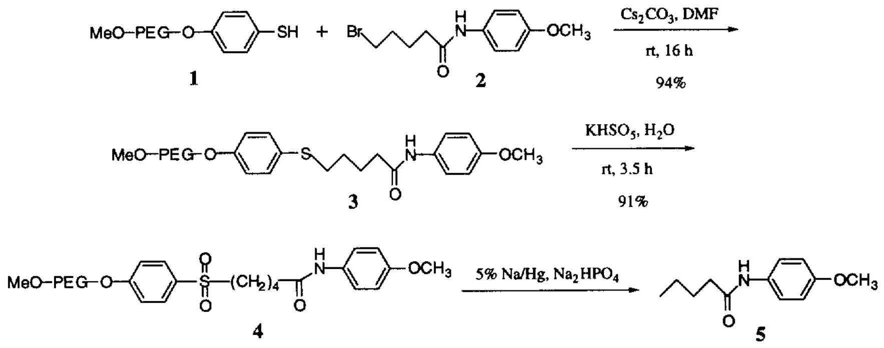


Equation 3

In our efforts to explore a new set of reaction conditions the easily identifiable polymeric sulfone **4** was synthesized (Scheme 1) and engaged in all our investigations. When MeOH/THF (1/1) was used as the solvent for desulfonylation of **4**, the yields of cleaved product **5** were in the range of 13–31% (Table 1, entries 1–5). Attempts to improve the yield by increasing the reaction temperature, prolonging the reaction times, increasing the amount of Na/Hg, or decreasing the amount of Na_2HPO_4 failed. Also, when the reaction was allowed to proceed overnight, the Na/Hg had totally decomposed (Table 1, entries 2, 3, and 5). From these observations it was hypothesized that MeOH may be promoting the decomposition of Na/Hg. Repeating the reaction in MeOH alone proved to give total decomposition of Na/Hg after 6 h, but improved yields of **5** were obtained (Table 1, entries 7, 8).

Scheme 1



It was also observed that THF suppresses the desulfonylation reaction. To resolve this problem solvents were investigated which would inhibit decomposition of Na/Hg, and still promote the desulfonylation of **4**. Aprotic, and extremely polar solvents such as DMF were considered, but the use of DMF alone gave none of the desired cleaved product (Table 1, entry 9). This result indicated that MeOH was essential for the reductive cleavage. Next a mixture of MeOH/DMF, with a minimum amount of MeOH in DMF was investigated. When MeOH/DMF (1/4) and 100 equiv Na/Hg were used, the reaction went to completion (Table 1, entry 10). If the amount of Na/Hg was reduced from 100 equiv to 50 equiv, and the ratio of MeOH/DMF remained the same at 1/4, only 70% of **5** was obtained (Table 1, entry 11). However, if the percentage of MeOH was diminished (MeOH/DMF, 1/8), again, a quantitative yield of **5** was obtained (Table 1, entry 12).[4] Further attempts to reduce the amount of Na/Hg from 50 equiv to 30 equiv, resulted in an 82% yield (Table 1, entry 13). The yield could not be further improved by decreasing of the percentage of MeOH (Table 1, entry 14).

Table 1

Entry	Solvent	Na/Hg (equiv)	Na_2HPO_4 (equiv)	Temp (°C)	Time (h)	Yield (%)[a]
1	MeOH/THF (1/1)	50	20	0–rt	2.5	13
2	MeOH/THF (1/1)	50	20	rt	22	17
3	MeOH/THF (1/1)	50	10	rt	22	19
4	MeOH/THF (1/1)	100	10	rt	2	25
5	MeOH/THF (1/1)	100	5	rt	22	31
6	MeOH	50	20	rt	2	41
7	MeOH	50	20	rt	6	55
8	MeOH	50	10	rt	6	53
9	DMF	100	10	rt	4.5	0
10	MeOH/DMF (1/4)	100	10	rt	18	95
11	MeOH/DMF (1/4)	50	5	rt	22	70
12	MeOH/DMF (1/8)	50	5	rt	22	97
13	MeOH/DMF (1/8)	30	5	rt	22	82
14	MeOH/DMF (1/20)	30	5	rt	22	81

[a]Isolated yields of **5**.

In summary, the reductive cleavage of polymeric sulfone **4** was found to be extremely solvent sensitive. Methanol is absolutely necessary for desulfonylation, and THF-MeOH is not a particularly good solvent system since THF suppresses the cleavage. In contrast, DMF promotes cleavage, and it was found that the combination of MeOH/DMF (1/8) is an excellent solvent system for desulfonylation. Because of the "solution" like properties that PEG bound molecules display,[5] we believe that this new solvent system may also facilitate desulfonylation in conventional organic synthesis, especially with less reactive sulfones.

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References and Notes

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4. In a typical experimental procedure, to a mixture of 5% Na/Hg (860 mg) and Na_2HPO_4 (27 mg, 0.19 mmol) at rt under Ar was added a solution of polymeric sulfone **4** (200 mg, 0.0374 mmol) in anhydrous DMF (4 mL) followed by absolute MeOH (0.5 mL). The resulting mixture was stirred at rt for 22 h wherein CH_2Cl_2 (35 mL) was added. The mixture was filtered through celite, and washed with CH_2Cl_2. The combined filtrate and washings were concentrated, redissolved in CH_2Cl_2 (5 mL), and triturated with anhydrous Et_2O (200 mL). The resulting suspension was filtered, and washed with Et_2O. The combined filtrate and washings were evaporated to dryness, redissolved in Et_2O (30 mL), and filtered through silica gel. The filtrate was evaporated, and further dried under vacuum to give **5** (7.5 mg, 97%).

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