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LETTERS

Radical-Polar Crossover Reactions with Polymer-Supported Tetrathiafulvalene

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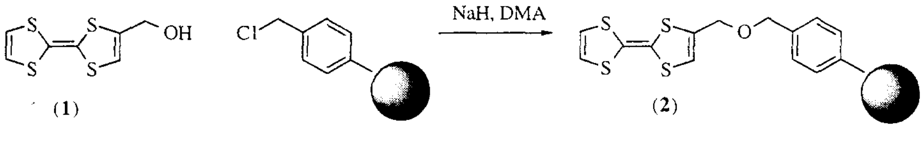
Abstract: Polymer-supported tetrathiafulvalene reagents have been prepared and their reactivity in radical-polar crossover reactions compared to tetrathiafulvalene itself. The reagents give easy separation of products. A regeneration step permits re-use of the polymer-supported reagent.

The necessity to develop environmentally acceptable chemistry has become very evident in recent years.[1] Preparation of carbon-carbon bonds by free radical chemistry was extensively developed using organotin reagents, but the toxicity of these reagents and the difficulty in separating organotin by-products from target molecules meant that they could not be employed in the pharmaceutical industry. Extensive efforts have been made to improve the process either by developing better separation methods[2] or by altering the polarity or solubility[3] of the tin reagent. Attaching the tin reagent to a polymer support[4] is an exciting alternative.

A great deal of effort has also been dedicated to finding alternative radical methods[5,6] for forming carbon-carbon bonds and to extending the range of functionalisation available to the final radical. Among the new reactions which have resulted, the radical-polar crossover reaction[7] affords a unique type of polar termination to radical chemistry, and this has been exploited in a recent synthesis of (±)-aspidospermidine.[8]

In an effort to make this reaction even more convenient to use, we have attached tetrathiafulvalene to polymer supports and now make an initial report on the reactivity of such reagents. The hydroxymethyltetrathiafulvalene (**1**) was prepared by the literature procedure.[9] Polymer-supported reagents resulted from reaction of this alcohol with sodium hydride in dimethylacetamide as solvent with two different polymer types - a macroporous resin [derived from 25% chloromethylstyrene, 65% divinylbenzene and 10% styrene with toluene as the porogen] and a gel-type resin [derived from 25% chloromethylstyrene, 2% divinylbenzene and 73% styrene] prepared using suspension polymerisation methodology.[10] After filtration, washing and drying, the degree of substitution was determined quantitatively by combustion analysis. The gel-type resin afforded 80-90% substitution of the benzylic chlorine atoms by TTF units (depending on the batch). On the other hand, only 40% substitution was observed for the macroporous beads. Hence, the gel-type beads were used for the radical-polar crossover reactions.



Scheme 1

Reaction of the gel-type beads with diazonium salt (**3**) in undried acetone afforded alcohol (**8**) (42%) as a 1:1 mixture of diastereoisomers. As expected, isolation of the product was a great deal easier than for

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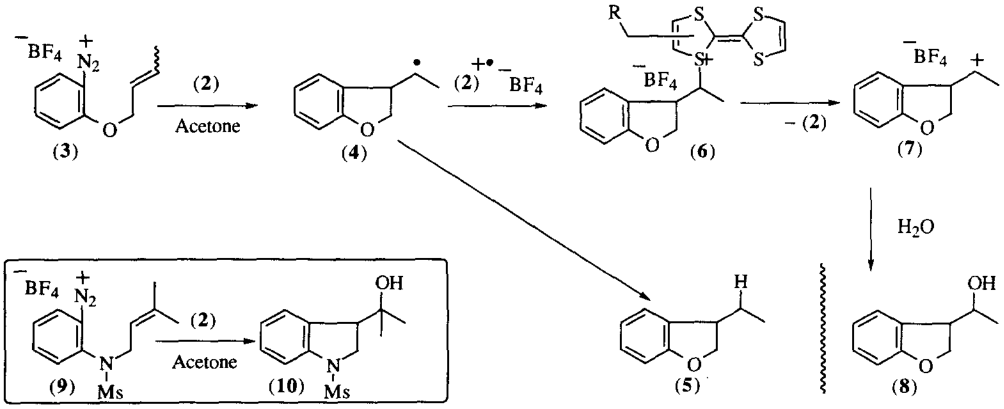
the corresponding solution-phase experiment since all TTF-related products were retained on the polymer. The recovered polymer was not directly capable of reacting efficiently with another batch of diazonium salt, but could be reactivated by treatment with sodium borohydride in methanol. This indicates that the TTF residues on the used polymer are substantially in the radical-cation state, which parallels our findings in solution. [The isolation process exposes the polymer to air, which can readily oxidise the TTF residues]. The regenerated polymer was put through two further cycles of radical-polar crossover reaction and regeneration and afforded 51% and 39% of alcohol (**8**) respectively. The robust nature of the polymer is indicated by combustion analysis, which showed very little decrease of sulfur content (from 13.26% for the polymer sample used in the initial radical-polar crossover reaction to 12.69% after the third such reaction.)

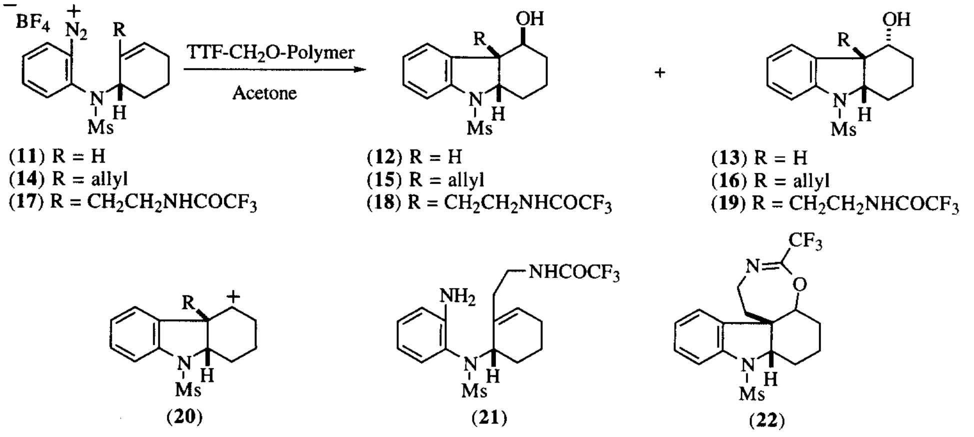


Scheme 2

The average yield for the above reactions is 44%, which is slightly lower than the corresponding solution-phase reaction. [A second diazonium salt (**9**) was converted to alcohol (**10**), also in a slightly lower yield (39%) than in the solution phase reaction (44%).] This could indicate a need to optimise parameters for the polymer-supported chemistry. However, we were concerned that the polymer could cause side-reactions not observed in solution. Thus the polymer contains many benzylic hydrogens. The intermediate radicals *e.g.* (**4**) could certainly abstract such hydrogens easily if collision occurs within the polymer cavity. However this would give rise to the reduced product, in this case, (**5**), and this compound was not observed. Moreover, no other product of substrate radical reduction has ever been detected in these reactions. The other factor which could cause lowering of yields would be difficulty of access for water to the hydrophobic polymer cavity to accomplish the hydrolysis step (**6**) → (**8**). Alternative reactions, *e.g.* Friedel-Crafts reactions with the aromatic rings of the polymer, or cation-induced rearrangement reactions, could occur if water were not present to intercept the ultimate carbocation (**7**). However, to test this proposal, the polymer recovered from the reaction with sulfonamide substrate (**9**) was subjected to combustion analysis. This assay showed no trace of nitrogen, within experimental error, indicating that Friedel-Crafts reactions were not a significant problem.

A major challenge to polymer-supported chemistry is the synthesis of complex, as opposed to simple, products. Accordingly, to test the ease with which a tricyclic product could be prepared, the diazonium salt (**11**) was subjected to the polymer-supported TTF reaction (48h, degassed acetone). This afforded a mixture of alcohols (**12**) and (**13**) in 37% (4:1 ratio), representing a 27% yield over two steps from the amine precursor of (**11**). The major isomer (**12**) had previously been identified, but the minor isomer was identified from this reaction only after acetylation of the mixture of isomers followed by hplc separation. When the experiment was repeated using solution-phase TTF, the same mixture of alcohols was isolated (35% yield from the parent amine) in the same ratio. Hence the polymer chemistry appeared to mirror chemistry in solution.

The chemistry was then extended to yet more hindered derivatives. The alkene-substituted derivatives (**14**) and (**17**) should feature slower aryl radical cyclisations, hence allowing a greater opportunity for interception of the aryl radical in side-reactions. If the radical cyclisation did occur, these substrates would lead to carbocations (**20**) (R = alkyl) where the opportunities for cationic rearrangement are considerable and where interception by water could be retarded by steric hindrance. The salt (**14**) afforded alcohols (**15**) and (**16**) in 40% yield (27% over two steps) as a 7:2 mixture of isomers. This was a markedly different ratio than had been observed with the solution-phase TTF (31% yield over two steps), where the two alcohol products were present 12:1. The reason for the different ratio of isomers is not completely clear; it is possible that one alcohol isomer could convert into another during the reaction (one equivalent of tetrafluoroboric acid is generated during the reaction). However, treatment of the major isomer with one equivalent of tetrafluoroboric acid in acetone, in an attempt to test this proposal, led solely to decomposition of the alcohol.



Scheme 3

Amine (**21**) was converted *in situ* into diazonium salt (**17**) which had been used in the synthesis of aspidospermidine. Curiously, reaction with (**2**) afforded the alcohol (**18**) [or (**19**)] as a single isomer (25%), just as in solution. The stereoselectivity observed in this case may result from an alteration in the mechanism of alcohol formation -*e.g.* by intramolecular interception by the trifluoroacetamide to form imidate (**22**), but this has not been determined. From the NMR spectrum it is not possible to say whether the observed isomer is (**18**) or (**19**).

In conclusion, the polymer-supported approach does afford easily isolated products from radical-polar crossover reactions, and the polymer can be re-used after regeneration. Although the yields are not very high, the sequence amine-diazonium salt-aryl radical-cyclised radical-TTF salt-alcohol is a useful and very complex conversion. An increase in our understanding of radical-polar crossover chemistry and the development of improved catalysts for polymer-supported TTF reactions will likely increase the utility of this approach. This paper marks the first efforts in adapting the reaction *via* polymer-supported reagents.

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