

# One-pot sequences of reactions with sol-gel entrapped opposing reagents. Oxidations and catalytic reductions

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*Received (in Montpellier, France) 14th August 2002, Accepted 12th November 2002  
First published as an Advance Article on the web 12th December 2002*

**An oxidant and a reducing catalyst are placed in a single pot without destroying each other, but are still capable of carrying out useful reactions, simultaneously. The oxidant, pyridinium dichromate, and an H<sub>2</sub>-reduction catalyst, RhCl[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>3</sub>, were entrapped in separate sol-gel matrices, and with these entrapped reagent and catalyst, three different flow-chart sequences of one-pot redox reactions were carried out—up to four reactions in one pot—without their mutual destruction and with no need for separation steps.**

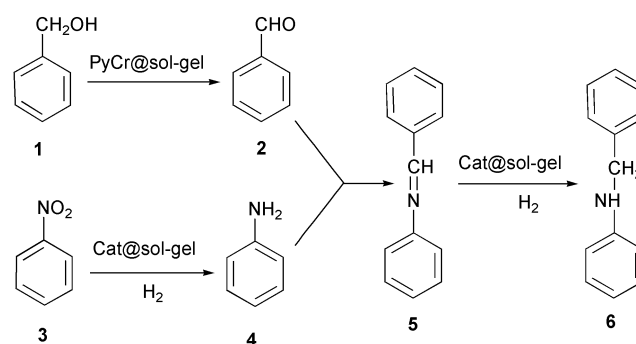
We report a new development of our sol-gel methodology for the non-destructive co-existence of sol-gel entrapped reagents and catalysts and their use in one-pot multistep syntheses.<sup>1–3</sup> In our previous studies we demonstrated the synthetic use of the one-pot co-existence of acids and bases,<sup>2</sup> of catalysts with acids and bases,<sup>1,3b</sup> and even of an enzyme in the presence of destructive catalysts,<sup>3a</sup> all of which were entrapped, separately, in SiO<sub>2</sub>-type porous sol-gel matrices but added together to one and the same reaction pot. Examples of such one-pot simultaneous or consecutive reactions carried out under these conditions include the use of the hydrogenation catalyst RhCl[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>3</sub> and a diamine (which poisons this catalyst under homogeneous conditions) for the preparation of ethylbenzene from iodoethylbenzene<sup>1</sup> and the one-pot acid-catalyzed pinacol–pinacolone rearrangement followed by base-catalyzed condensation with malononitrile.<sup>2</sup> To further generalize this methodology we report here its application for another key family of incompatible reactions, namely oxidations and catalytic reductions. Furthermore, we report here also an increase in the number of reactions we have been able to carry out by this one-pot methodology from two in our previous reports, to four.

Despite the inherent advantages of one-pot sequences of reactions, namely saving separation and purification steps, cutting down on the use of solvents and reagents and increasing yields by eliminating the need to separate intermediate products, one-pot reactions with opposing reagents are rare<sup>4</sup> and limited, to the best of our knowledge, to a few polymer-bound reagents (reduction/oxidation<sup>5–8</sup> and acid/base reactions<sup>9–11</sup>). It seems that the rarity of the one-pot approach has been due to cumbersome synthetic procedures for the preparation of derivatized polymers, to auto- and mutual destruction of the organic polymeric support by the bound reagents,<sup>12</sup> and to swelling in organic solvents, which increases local viscosity and opens the polymer network to further mutual destruction of the opposing active moieties. A discussion of these difficulties can be found in chapters 1 and 13 of ref. 12; see also refs. 13–15. Sol-gel matrices are devoid of these difficulties: straightforward covalent bonding can be used but is not always needed as reactive functionalization can be

introduced by direct physical entrapment; the inorganic matrix is very stable both to oxidizing and reducing conditions; SiO<sub>2</sub> sol-gel materials do not swell; they are characterized by very high surface areas and yet at the same time provide excellent dopant protection by their full isolation from another sol-gel entrapped reagent.

One specific system we studied (Scheme 1) was composed of SiO<sub>2</sub> sol-gel entrapped pyridinium dichromate<sup>16</sup> as an oxidant (PyCr@sol-gel), and hydrogen as a reductant, the activity of which was catalyzed by entrapped RhCl[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>3</sub> (Cat@sol-gel)<sup>17</sup>. The two precursors, benzyl alcohol, **1** (to be oxidized to benzaldehyde **2**), and nitrobenzene, **3** (to be reduced to aniline **4**), and the granules of PyCr@sol-gel and of Cat@sol-gel were dissolved/dispersed in 1,2-dichloroethane in a hydrogen-purged (atmospheric pressure) autoclave. Since the reduction product of nitrobenzene, **3**, namely aniline, **4**, is prone to oxidation by PyCr@sol-gel, pressurizing the autoclave with hydrogen was delayed for 1 h, during which PyCr@sol-gel selectively oxidized the alcohol to benzaldehyde, **2**. The pressure of the hydrogen was then increased to 13 atm and the reduction of nitrobenzene to aniline was carried out for 6 h. (The reduction is negligible with the 1 atm hydrogen present during the oxidation stage). After being formed the aniline was trapped by the aldehyde in a spontaneous condensation reaction to form the Schiff base **5** (thus avoiding aniline oxidation) in 91% yield. Formed as well was 9% of the further reduction product of **5**, namely *N*-benzylaniline, **6**. Its yield can be increased if desired by extension of the reaction time: after an additional 10 h reaction time the yield of **6** increased to 23%. Thus, the use of two different sol-gel entrapped reagents allowed one to carry out *four reactions* in the same reaction flask without any separation of intermediate products. When non-entrapped RhCl[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>3</sub> was used in the presence of the entrapped oxidant, only benzaldehyde, **2**, was formed.

The non-destructive co-existence of this oxidation-reduction pair and its utilization for one-pot reactions was further

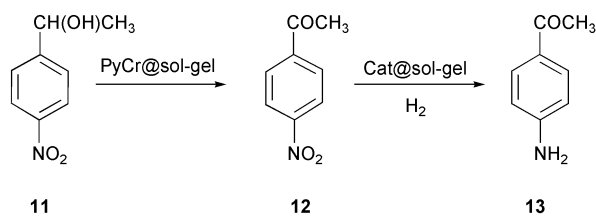
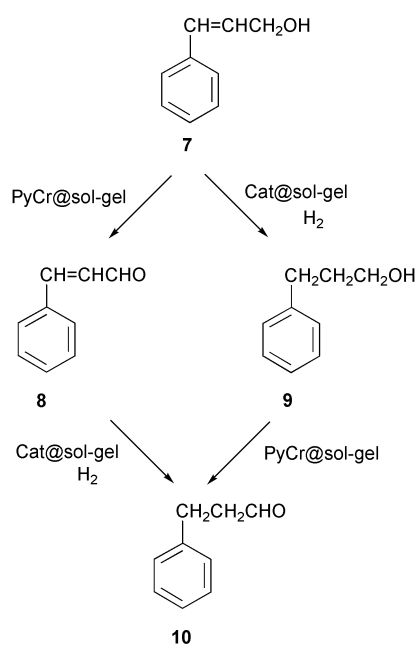


Scheme 1

proven with two additional sequences. These additional sequences also demonstrate the possibility of employing various flow charts in this one-pot method. Thus, whereas in Scheme 1 the flow chart is of parallel reactions that form products that react with each other, our next sequence (Scheme 2) is a flow-chart that leads from a starting material to a product in two parallel routes: cinnamyl alcohol (3-phenylpropenol), **7**, dissolved in 1,2-dichloroethane was converted into 3-phenylpropionaldehyde, **10**, as the result of the double bond reduction by  $\text{H}_2/\text{Cat@sol-gel}$  and the oxidation of the alcohol moiety by the  $\text{PyCr@sol-gel}$ . After 18 h at  $60^\circ\text{C}$  and 13 atm  $\text{H}_2$ , 32% of **10** was obtained, along with some residual polymeric material. The reaction proceeds both *via* the aldehyde **8** (3-phenylprop-2-enal) and *via* the reduced alcohol (3-phenylpropanol, **9**), as was evident from NMR follow-up.

The third system (Scheme 3) provides the most elementary flow-chart, namely of two consecutive steps: 1-(4-nitrophenyl)-ethanol, **11**, dissolved in 1,2-dichloroethane was converted by the same pair of reactive sol-gel materials (16 h,  $70^\circ\text{C}$ , 21 atm  $\text{H}_2$ ) to 42% of 4-aminoacetophenone, **13**<sup>8</sup> (along with some 4-aminostyrene and 4-aminoethylbenzene). To avoid possible oxidation of the amino group the same routine as in Scheme 1 was employed: first the conversion of **11** to **12** was affected, and after 2 h hydrogen was injected, converting **12** to **13**. A similar one-pot reaction with the non-entrapped catalyst  $\text{RhCl}[\text{P}(\text{C}_6\text{H}_5)_3]_3$  resulted in the oxidation of **11** to 4-nitroacetophenone, without any reduction products.

Finally, it should be noted that in designing one-pot flow-charts of redox reactions, one should consider the possibility that the final products might be further reduced or oxidized. Thus, the selection of the reagents should be tailored to the desired product. For instance, in our case,  $\text{PyCr@sol-gel}$  is mild enough to avoid oxidation of the nitrogen in **6** or **13**,



while  $\text{H}_2/\text{Cat@sol-gel}$  is mild enough not to reduce the carbonyls of **10** and **13**.

Beyond the proof-of-concept reported here, work towards faster reaction rates and higher yields is still needed. An approach towards these goals that proved useful in other sol-gel studies has been to reduce the size of the material, that is to work with micro- and nanoparticles. In any event, taking into account our earlier reports on other one-pot incompatible systems,<sup>1-3</sup> we believe that evidence has been now accumulated that the sol-gel methodology is a convenient approach for heterogenizing a wide range of opposing chemicals for multistep one-pot syntheses.

## Experimental

### Procedure for preparation of sol-gel entrapped pyridinium dichromate ( $\text{PyCr@sol-gel}$ )

A mixture of 3.7 g (24.3 mmol) tetramethoxysilane (TMOS), 1.3 g (5.7 mmol) of 2-(trimethoxysilyl)ethylpyridine (Gelest) and 10 ml of methanol was stirred for 10 min. Then 2.2 ml of water was added and the solution stirred at  $40^\circ\text{C}$  until gelation occurred (within a few hours). The gel was kept at  $40^\circ\text{C}$  for 3 days and then dried at that temperature for 40 h. The resulting material was stirred with 20 ml of an aqueous solution of 0.6 g (6 mmol) of  $\text{CrO}_3$  for 4 h and then washed with water portions until the water was colorless. The material was then dried under vacuum (1 mm) at room temperature for 20 h. The weight of the final material was 3.0 g.

### Procedure for preparation of sol-gel entrapped $\text{RhCl}[\text{P}(\text{C}_6\text{H}_5)_3]_3$ ( $\text{Cat@sol-gel}$ )<sup>17</sup>

A mixture of 18 mg ( $1.95 \times 10^{-2}$  mmol) of chlorotris(triphenylphosphine)rhodium, 3.2 ml of peroxide-free THF, 0.4 ml degassed water and 1.0 ml (6.8 mmol) TMOS was stirred under Ar atmosphere until a clear solution was obtained, and then allowed to stand at room temperature until the solution gelled (2 days). The gel was dried under a vacuum of 0.1 mm Hg, washed and sonicated for 1 h with 30 ml dichloromethane and dried again under 0.1 mm vacuum until constant weight was achieved. The Rh content in the  $\text{CH}_2\text{Cl}_2$  washings was determined by atomic absorption analysis and was found to be less than 1 ppm.

### Procedure for the one-pot reaction

Following Scheme 1, a mini autoclave was charged with a solution of equimolar amounts of benzyl alcohol (0.16 g, 1.45 mmol) and nitrobenzene (0.2 g, 1.45 mmol) dissolved in 6 ml of 1,2-dichloroethane. After addition of 1.5 g of a sol-gel matrix containing 3 mmol of entrapped pyridinium dichromate and 1.3 g of a sol-gel matrix containing  $1.95 \times 10^{-2}$  mmol of  $\text{RhCl}[\text{P}(\text{C}_6\text{H}_5)_3]_3$ , the autoclave was purged three times with hydrogen and heated in a thermostated oil bath to  $70^\circ\text{C}$ . After 1 h the autoclave was pressurized to 13 atm  $\text{H}_2$  and heated at  $70^\circ\text{C}$  for an additional 6 h. The reaction was then stopped and the mixture cooled to room temperature. The sol-gel matrices were filtered out and the products, all known compounds (Scheme 1), were characterized and analyzed by NMR, GC-MS and GC. The transformations of cinnamyl alcohol (Scheme 2) and 4-nitrobenzyl alcohol (Scheme 3) were carried out by similar procedures; the products are all known.

## Acknowledgements

We thank the Ministry of Science, Arts and Sport for supporting this project under the special Tashtiot project, as well as the Israel Science Foundation (grant # 143/00-12) for financial aid.

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