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Silver(I) – Gelatin Complex : A Novel Reagent for Oxidative Phenol Coupling

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Silver(I) – gelatin complex, a mild, efficient and new reagent has been developed for phenol coupling. When applied to *p*-cresol naphth-2-ol and emodin (1) separately, it afforded Pummerer's ketone (2) and *o,o*-coupled dimer (3) for first compound, for naphth-2-ol we were left only with 1,1'-binaphth-2-ol (4) and emodin led to isoskyrin (5a) as the sole product. The method is highly selective and gifted with least polymerisation.

DURING the course on the synthetic investigation[1] of several dimeric naturally occurring compounds via oxidative phenol coupling, we have developed a new bioinorganic reagent silver(I) – gelatin complex[2] for the purpose. Oxidative phenol coupling reaction[3] is generally carried out with classical and trivial inorganic reagents, viz. $FeCl_3$, alkaline $K_3[Fe(CN)_6]$, MnO_2, VCl_4, $VOCl_3$, Ag_2O, manganic *tris*-acetylacetonate etc. many of which led to a complicated mixture of products[4,5] or extensive polymerisation[6]. The added complication has brought difficulties to achieve selectivity, rendering complications for natural product synthesis. The tempting advantage of the newly approached first order inner-metallic complex of gelatin is that it is mild and efficient and is very easy to prepare. The least polymerisation simply authenticates the mildness of the reagent. The silver(I) – gelatin complex has the added advantage over other classical simple compounds in terms of yield and selectivity. Controlled release of active silver species[2], owing to its binding through gelatin, may well be realised from the following equilibrium, is an efficient contributor to the reaction products.

$$Ag^+ + H_2N\ COOH + OH^- \rightleftharpoons H_2N \cdot COOAg + H_2O$$

and $H_2N \cdot COOAg + OH^- \rightleftharpoons AgHN\cdots COO^- + H_2O$

alternatively,

$$AgHN\ COO^- + OH^- \rightleftharpoons [Ag-N\ COO]^{2-} + H_2O$$

and $[Ag-N\cdots COO]^{2-} + H_2O \rightleftharpoons Ag^+OH^- + HN\ COO^-$

The picture is different, however, for simple oxide, nitrate or carbonate of silver used previously[7-9] which caused notable polymerisation and hence poor yield owing to the availability of huge reducible Ag^+ nuclei. The standard reduction potential for the silver complex is ~0.80 V. So oxidation by the active silver species is easily achieved which in extreme cases, may be based on either a purely ionic or a purely free radical generation via surface protrusions[10]. In addition, the recently developed method is very simple, neat and the reclaiming of silver is also very much quantitative. The idea of utilisation of such a cheaper bioinorganic reagent as a new alternative to oxidative phenol coupling was due to the fact that many natural polyphenolics are believed to be biosynthesised via such coupling process and to mimic the nature bioinorganic reagent probably should be the best choice. In this context we mention that it is incidentally the first attempt to exploit a proven analytically potential[2] bioinorganic reagent for such phenol coupling reaction. It should be noted that water-soluble silver(I) – gelatin complex or an impregnated reagent on an inert silica gel support can be used. In the second case separation of the reaction mixture from the solvent immiscible impregnated reagent thus becomes easy and vulnerable. This fact uncovers the possibility of using the reagent both in water and in organic solvent.

Results and Discussion

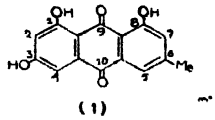
Reaction of *p*-cresol with silica-gel impregnated silver(I) – gelatin complex in dichloromethane on 48 h stirring at room temperature under nitrogen atmosphere led to the isolation of Pummerer's ketone (2) and *o,o*-coupled dimer (3) in 8 and 17% yield, respectively. The products are authenticated by direct comparison (co-tlc, co-ir and m.m.p.) with the authentic samples[11] and ^1H nmr spectra. ^{13}C nmr spectra ($CDCl_3$) for the *o,o*-coupled dimer done for the first time endorse the structure. The carbon chemical shifts of the dimer account for all the fourteen carbon atoms of the compound and assigned on the basis of the splitting observed in its SFORD spectrum and by comparison with the δ_c values of structurally related biphenyl compounds[11,12] and is best rationalised as δ_c 124.21 (C-1, C-1'), 150.94 (C-2, C-2'), 116.60 (C-3, C-3'),

130.25* (C-4, C-4'), 130.70 (C-5, C-5'), 131.72* (C-6, C-6') and 20.49 (ArMe).

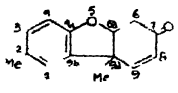
The same procedure, however, when applied to 2-naphthol afforded the only product 1,1'-binaphth-2-ol (**4**) as the only isolable product in 18% yield. The product has been authenticated by direct comparison (co-tlc, co-ir and m.m p.) with the authentic sample produced from naphth-2-ol using $FeCl_3$ method[13] and was further supported by its spectral data.

Isolation of a host of emodin dimers both natural[14-16] and synthetic[17], however, prompted a further extension of the work to achieve the successful application of silver(I) – gelatin complex on emodin (**1**), an uniquely functionalised anthraquinone system. Essential part of our study was to examine the mode of coupling to ascertain the selectivity and to nullify the polymerisation of rare-occurring starting materials with the new reagent.

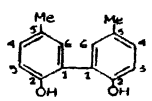
Unlike the simple model compounds, emodin failed to undergo coupling under room temperature stirring with silica gel impregnated silver(I) – gelatin



(1)

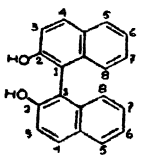


(2)



(3)

complex, probably due to steric crowding existing in the molecule. On the other hand, it required a rather drastic treatment. Reaction of emodin (**1**) in alcoholic medium with silver(I) – gelatin solution in aqueous phase under refluxing condition afforded isoskyrin (**5a**), a 4,2'-coupled emodin dimer, m.p. >300°, of very poor solubility in 15% yield with quantitative recovery of the unconverted emodin. The structure of the dimeric emodin was evidenced from ^1H nmr spectra of its hexamethyl ether (**5b**), m.p. 280°, and also by the direct comparison with the authentic samples obtained[1] by $K_3[Fe(CN)_6]$ or AgOH oxidation followed by methylation.



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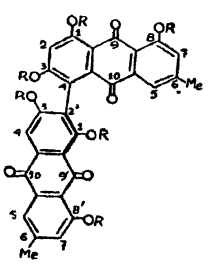

5a ; R=H
5b ; R=Me

* Values are interchangeable.

Experimental

Melting points reported are uncorrected. Silica gel (60 – 120 mesh) was used both for column chromatography and silver(I) – gelatin complex impregnation and silica gel G for tlc. Ir spectra (KBr) were run on a Beckman 20 spectrophotometer, ^1H nmr and ^{13}C nmr spectra ($CDCl_3$) on a Varian CFT-20 instrument operating at 80 MHz and 20 MHz, respectively, using TMS as the internal standard, and mass spectra on a DS-55 instrument equipped with a direct inlet system and operating at 70 eV. All the analytical samples were routinely dried over P_2O_5 at 80° for 24 h under reduced pressure. The petrol used had b.p 60 – 80°.

Preparation of silver(I) – gelatin complex : The reagent solution was prepared by dissolving gelatin powder (12.0 g) (E. Merck) in boiled distilled water (360 ml) with continuous stirring and adding 0.2 *M* silver nitrate solution (20 ml). Turbidity, if any, was removed by adding a few drops of 2 *M* sodium hydroxide solution. The solution was warmed to ~50°, the pH adjusted to about 8 and the volume made upto 400 ml. The binding of sliver(I) was authenticated from the dialysis-bag experiment and was noted that 1 ml of 0.5% gelatin solution effectively complexes 453 μg of silver(I) ion.

Silica gel impregnation : Silica gel (60 – 120 mesh ; 100 g) was impregnated with the silver(I) – gelatin complex (400 ml) and dried in a vacuum desiccator and stored in the dark.

Coupling of p-*cresol using silver(I) – gelatin complex impregnated on silica gel. Formation of Pummerer's ketone* (**2**) *and* o,o-*coupled dimer* (**3**) *:* A mixture of *p*-cresol (1.0 g) in CH_2Cl_2 (100 ml) and silica gel impregnated silver(I) – gelatin complex (50.0 g) was stirred under N_2 for 48 h. Silica gel was filtered out and the solvent on distillation gave a residue which was chromatographed. The petrol – EtOAc eluate (50 : 1) gave unconverted *p*-cresol (0.6 g). Further elution of the column with petrol – EtOAc (20 : 1) gave **2** (0.08 g ; $M^{+\cdot}$ 214), m.p. 125° (hot petrol) ; ν_{max} 1 665 (conjugated C=O) cm^{-1} ; ^1H δ 1.49 (9a-Me), 2.24 (2-Me), 2.80 (H_2-6), 4.60 (H-5a), 5.82 (H-8), 6.35 (H-3), 6 60 (H-9), 6.86 (H-4) and 6.90 (H-1).

Further elution of the column with petrol – EtOAc (10 : 1) afforded **3** (0.17 g, $M^{+\cdot}$ 214), m.p. 153°, crystallised from the same solvent mixture ; ν_{max} 3 100 (OH) cm^{-1} ; ^1H δ 2.25 (Ar – Me), 5.75 (disappeared on deuteration, ArOH), 6.83 (H-4, H-4'), 6.93 (H-3, H-3') and 7.05 (H-6, H-6').

Coupling of naphth-2-ol using silver(I) – gelatin complex impregnated on silica gel. Formation of 1,1'-binaphth-2-ol (**4**) *:* The same procedure was carried out as above using naphth-2-ol (1.4 g) in CH_2CH_2 (100 ml) with silica gel impregnated silver(I) – gelatin complex (50.0 g). The usual workup and column chromatography gave in the petrol – EtOAc eluate (20 : 1) the unconverted naphth-2-ol (0.8 g) while the petrol – EtOAc (10 : 1) eluate

afforded **4** (0.18 g, $M^{+\cdot}$ 286), m.p. 260° (petrol–EtOAc); ν_{max} 3 500 broad cm^{-1} (OH); ^1H δ (DMSO-d_6+$CDCl_3$) 7.2–8.0 (12H, m, ArH), 8.7 (disappeared on deuteration, ArOH).

Coupling of emodin (**1**) *with silver*(I)–*gelatin complex. Formation of isoskyrin* (**5a**) *:* A mixture of emodin (0.25 g) dissolved in EtOH (100 ml), 1% gelatin solution (120 ml) and $AgNO_3$ (0.17 g) was made alkaline and refluxed under N_2 for 2 h. Alcohol was distilled off and the reaction mixture was extracted with ether. The usual workup and column chromatography afforded in petrol–EtOAc eluate (5 : 1) the unconverted emodin (0.2 g). Further elution with petrol–EtOAc eluate (1 : 1) gave **5a** (0.096 g, m.p. >300°).

Formation of isoskyrin hexamethyl ether (**4b**) *:* A solution of isoskyrin (0.035 g) in dry acetone (100 ml) was refluxed with Me_2SO_4 (3 ml) over anhydrous K_2CO_3 (100 g) for 10 h. Usual workup of the reaction product gave isoskyrin hexamethyl ether (**5b**; 0.030 g), m.p. 280° (MeOH–$CHCl_3$); ^1H δ 2.30 (3H, s, ArMe), 2.42 (3H, s, ArMe), 6 78 (1H, s, H-2), 6.95 (1H, d with fine splitting, *J* 1.6 Hz, H-7), 7.03 (1H, d with fine splitting, *J* 1.6 Hz, H-7'), 7.23 (1H, d with fine splitting, *J* 1.6 Hz, H-5), 7.55 (1H, s, H-4') and 3.50 (3H, s), 3.78 (6H, s), 3.92 (6H, s), 4.02 (3H, s, aromatic methoxyls).

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