

Letter

β -Cyclodextrin mediated regioselective photo-Reimer–Tiemann reaction of phenols

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Abstract

In the presence of β -cyclodextrin and its derivatives, the photo-Reimer–Tiemann reaction of phenols with chloroform proceeded smoothly with high selectivity for the formation of 4-hydroxy benzaldehydes. © 1998 Elsevier Science B.V.

Keywords: Photo-Reimer–Tiemann reaction; Cyclodextrins; Regioselective; Phenols

β -Cyclodextrin (BCD), a macrocyclic compound consisting of 7 units of α -1,4-linkaged D-glucopyranose, has attracted much attention because of the ability of forming inclusion complexes with a variety of organic compounds [1]. The inclusion complex formation is stereo and regiospecific and it depends on the size and polarity of the guest molecule and are water soluble [2]. This property of BCD is responsible for changes in the reactivity and selectivity of organic reactions. Thus, when BCD is used as a reaction vessel, we might expect that the guest (substrate) molecule will find a fixed definite orientation inside the BCD cavity and thus exposes only certain selective position/group for attack by the reagent, leading to selectivity in organic reactions. The regioselective control of reactions by BCD has been observed for the chlorination of anisole [3], formylation of phenols [4], hydroxymethylation of phenols [5] and so on. As high as 100% selectivity has been

reported in Reimer–Tiemann formylation by use of BCD [4].

On irradiation, electron rich aromatic compounds such as phenol, are known to eject an electron to form the corresponding radical cations or radicals. If the electron ejected cleaves chloroform [6] at the C–Cl bond then the resultant dichloromethyl radical must easily couple with the aromatic radical cation to result in the formation of aromatic substitution products.

The present communication reports the results of such hitherto unreported regioselective photo-Reimer–Tiemann reactions of phenols mediated by β -cyclodextrin, 2,6-di-O-methyl-BCD (DMBCD) and hydroxy propyl-BCD (HP-BCD). The results obtained are summarised in Table 1.

Phenol is a typical compound to eject an electron by irradiation. When an aqueous methanolic solution of phenol (1) and chloroform was irradiated, 4-hydroxy benzaldehyde

Table 1
Photo-Reimer–Tiemann reaction of phenols with chloroform

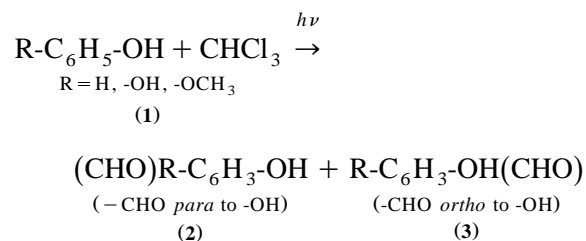
Substrate		Ratio of 2/3 (yield of aldehydes), % Selectivity of 2			
Solvent	Base	Control	BCD	DM-BCD	HP-BCD
Phenol	—	0.6 (28), 37.5	2.0 (39), 66.6	0.9 (38), 47.3	4.3 (90), 81
CH ₃ OH	Et ₂ NH	1.0 (56), 50.0	2.2 (71), 68.7	1.3 (67), 56.5	8.1 (92), 89
CH ₃ CN	Et ₂ NH	2.0 (62), 66.6	4.7 (74), 82.4	3.9 (68), 79.6	99.9 (94), 100
CH ₃ OH	K ₂ CO ₃	1.7 (31), 62.9	3.0 (61), 75.0	2.7 (53), 72.9	13.3 (92), 93
CH ₃ OH	KOH	0.9 (11), 47.3	2.8 (29), 73.6	2.4 (28), 70.6	10.1 (91), 91
Pyrocatechol ^a	—	6.9 (36), 87.3	21 (79), 95.5	17 (80), 94.4	99.9 (96), 100
Resorcinol ^a	—	3.9 (52), 79.6	14 (84), 93.3	13 (71), 92.8	99.9 (98), 100
Guaiacol ^a	—	4.4 (39), 81.5	9 (90), 90.0	10 (83), 90.9	49.0 (94), 98

^aWithout any base in CH₃OH.

(2) and salicylaldehyde (3) were mainly isolated. The yield of the photo products in the absence of any base is similar to those in the usual Reimer–Tiemann reaction [7]. The addition of a large excess of diethylamine for the removal of liberated hydrogen chloride improved significantly the yield of the products, where as more strong bases like potassium hydroxide reduced the yield. The proton is an effective quencher for a solvated electron [8]. The results are in good agreement with those expected from the calculated electron-spin densities in the phenoxy radicals derived from phenol [9].

The effects of BCD on this reaction were found in two respects. Firstly, the yield of the reaction (aldehyde formation) was enhanced along with the acceleration of the reaction rate. Secondly, the position of formylation was altered i.e. the ratio of 2/3 (*para/ortho* attack) was increased. The presence of BCD showed an enhanced yield of 74% (minimum 29%) with 82.4% selectivity (minimum 66.6) for the formation of 4-hydroxy benzaldehyde against a yield of 62% (minimum 11%) with 66.6% selectivity (minimum 37.5%) for the same compound in the uncatalysed reaction. In the reaction catalysed by DMBCD, a maximum yield of 68% (minimum 28%) with 79.6% selectivity (minimum 47.3%) was observed. The presence of HP-BCD showed a remarkable variation

compared to the uncatalysed reaction. In all the reactions studied, HP-BCD showed a yield higher than 90% and selectivity beyond 81% for the formation of 2. Exceptionally, in one case it showed 100% selectivity and registered a yield as high as 94%.



Since dihydroxy benzene is sensitive to air, especially in an alkaline solution, the Reimer–Tiemann reaction is not applicable to these compounds. However, the photo Reimer–Tiemann reaction is expected to take place, because it does not necessarily need a base. The anticipated results were as given in Table 1. Here also, the presence of BCD and DM-BCD showed higher selectivity for the formation of a *para* product (-CHO *para* to -OH) and showed a similar trend. However, the use of HP-BCD played a key role in enhancing the yield to a maximum of 98% and with cent percent selectivity.

Thus, a significant increase in *para* selectivity was observed with BCD and its derivatives. This selectivity can be explained as follows, as

has been proposed for other similar systems [4,5]. The phenolate molecule approaches the chloroform accommodated inside the cavity of BCD, from the side involving the *para*-carbon atom, since the cavity favours this apolar side of the phenolate more than the polar side involving the phenoxide oxygen atom. As a result, the coupling of dichloromethyl radical takes place preferentially at the *para*-carbon atom of the phenol radical. Reactions at the *ortho*-carbon atoms are also sterically inhibited. The high selectivity observed with HP-BCD may be due to the tightness in the position of the substrate and reagent due to strong physical bonding and steric hinderance.

In a typical experiment, a solution of phenol (5 mM), cyclodextrins (equimolar) and chloroform (55 mM) in 10 ml of 50% aqueous organic solvent in the presence of a base (100 mM) was irradiated with a 10 W low pressure mercury lamp under nitrogen for 2 h. In the case of

dihydroxy phenols, it was irradiated with a 200 W high pressure lamp for 6 h in the absence of base. After acidification, the products and unreacted substrate were extracted in dichloromethane and analysed by GLC using a 20 M 2 ft 10% carbowax column and quantified by separating on preparative TLC.

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