Research Article

Transition Metal Ions as Efficient Catalysts for Facile Ortho-Formylation of Phenols under Vilsmeier–Haack Conditions

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Aromatic compounds (phenols), when treated with Vilsmeier Haack (V-H) reagent in the presence of transition metal ions such as Cu(II), Ni(II), Co(II), Cd(II), and Zn(II) under reflux conditions, afforded corresponding ortho-formyl derivatives in good yields. Under normal conditions the metal-ion-free V-H reactions are too sluggish and resulted in poor yields. This protocol provides highly regioselective formylation under a mild and efficient condition with simple workup.

1. Introduction

One of the most fascinating developments seen in organic synthesis during the recent years is the application of transition metals for ortho functionalization of aromatic compound [1]. Ever since the application of transition metals in organic reactions is introduced, a number of chemical reactions have been reported to functionalize nonreactive aromatic C–H bond ortho to hydroxyl and other functional groups [2]. Formylation of aromatic compounds is a classical reaction in inorganic chemistry and numerous methods are available [3]. The formyl substituted phenols are important compounds in organic chemistry [4], for instance substituted salicylaldehydes (O-hydroxybenzaldehydes) are important intermediates in organic synthesis for the preparation of a variety of oxygen containing heterocyclic compounds and as a source for silane ligands [5], and only few of them are commercially available even today. Even though the synthesis of salicylaldehydes from corresponding phenols has been carried out by various methods, most of them afforded only low yields, leading to deformylation or lack in regioselectivity [6]. The Vilsmeier-Haack reaction is a mild method for the introduction of a formyl group to various aromatic and heteroaromatic compounds [7, 8]. It is also utilized in the

synthesis of a large number of heterocyclic compounds [9–11]. Some interesting cyclization reactions under Vilsmeier conditions have been reported recently [12–18]. It is seen that despite of good formylating ability of V-H reagent only sporadic reports are found on ortho-formylation of phenols using V-H reaction. One patent is reported in 1927 for synthesis of vanillin by formylation of Guaiacol with *n*-methyl formanilide-phosphoryl chloride complex [19, 20]. It is very well known that V-H reagent will produce aryl formats from phenols. In continuation of our ongoing work on V-H reactions under various modified conditions we have reported a certain V-H reaction in micellar media [21] and under ultrasonic conditions [22].

2. Results and Discussion

Recently we have found that metal ions are good promoters for a variety of organic reactions such as Hunsdiecker reaction [23] and bromination reaction [24–27]. Herewith now we report the selective formylation of phenols promoted by metal ions under V-H conditions. Nevertheless, in one of the earlier reports metal ions in conjunction with DMF/ POCl_3 have been used for one step deprotective O-formylation of

SCHEME 1

SCHEME 2

bis-O-tertiary butyl diphenyl silyl (O-TBDPS) aromatic diol [28].

Aromatic compounds (phenols) when treated with V-H reagent in the presence of metal salts such as Cu(II), Ni(II), Co(II), Cd(II), and Zn(II) in their nitrates form under reflux conditions afforded corresponding ortho-formyl derivatives (Scheme 1) in good yields (Table 1). All products were characterized by the physical data IR and ^1H -NMR and found to be satisfactory. Among various metal salts tested for proposed formylation reaction only Cu(II), Ni(II), Co(II),

Zn(II), and Cd(II) nitrates were found to be fairly soluble in CH_3CN and more effective for promoting the reaction, whereas other salts are not soluble in ACN and the reaction is sluggish. Furthermore, to optimize the reaction conditions, the reactions are carried out by using different concentrations of metal salt ranging from one millimolar (0.001 M) to centimolar solutions. Reactions underwent smoothly with very good regioselectivity (i.e., ortho-formylation) in 0.01 M metal nitrate solutions in acetonitrile medium which could be seen from the data presented in Table 1. The results

TABLE 1: Metal-ion mediated formylation of phenol with Vilsmeier–Haack reagent.

S. N	Substrate	Products ^{a,b}	(a)					
			Cu(II)		Ni(II)		Co(II)	
			Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1			10	80	10	82	10	85
2			18	70	16	75	18	70
3			10	80	10	80	12	78
4			12	78	12	80	12	75
5			16	65	18	60	16	60
6			18	72	16	78	18	75

(a) Continued.

S. N	Substrate	Products ^{a,b}	Cu(II)		Ni(II)		Co(II)	
			Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
7			16	70	16	72	16	70
8			12	78	12	75	12	75
9			10	82	10	82	10	80
10			10	70	10	65	10	65

^a All the products were characterized by usual spectral and analytical methods.^b Isolated yields.

(b)

S. N	Substrate	Products ^{a,b}	Cd(II)		Zn(II)	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1			10	78	12	75
2			16	80	16	75
3			10	80	10	78

(b) Continued.

S. N	Substrate	Products ^{a,b}	Cd(II)		Zn(II)	
			Time (h)	Yield (%)	Time (h)	Yield (%)
4			12	78	12	75
5			16	60	16	55
6			18	70	18	70
7			16	65	16	70
8			12	75	12	75
9			10	80	10	78
10			10	65	10	60

^a All the products were characterized by usual spectral and analytical methods.^b Isolated yields.

clearly indicate that the ortho-formylation of phenols can be successfully achieved by employing 0.01 M transition metal ion solution under V-H condition which is not possible in classical condition. When the present formylation reaction is carried out in the absence of the metal ion the reaction was found to be too sluggish, even after 48 hrs of reaction only 30% conversion is observed. This observation supports efficient catalytic activity of transition metal nitrates used in this study. It is presumed that the reaction is initiated by the formation of metal salt of phenols in the first step, which is assumed to be a stable species and actively involved to direct the incoming electrophile via the reaction with iminium salt (V-H reagent) to attack at ortho position and finally to give formyl derivative on basic hydrolysis. The plausible reaction path is depicted in Scheme 2.

3. Experimental Procedure

Metal salt (0.05 mol) was added to a decimolar (0.1 mol) solution of substrate (phenol) in acetonitrile and stirred for 10 minutes. To this solution Vilsmeier–Haack adduct prepared from 9.3 mL (100 mmol) POCl₃ in 9.29 mL (100 mmol) DMF at –5°C was added. The reaction mixture was refluxed. The progress of the reaction was monitored by TLC after completion of the reaction. The reaction mixture was poured into crushed ice and treated with 5% NaHCO₃ solution. This was extracted with dichloromethane. The organic layer was separated and dried over sodium sulphate. The organic layer was evaporated to get the crude product which was purified by column chromatography using silica gel (60–120 mesh) and eluted with ethyl acetate, hexane (20:80) as eluent.

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