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An Efficient Preparation for 2-Cyano-4'-methylbiphenyl in Toluene-Tetrahydrofuran Solvents Over Transition-Metal Catalysts

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2-Cyano-4'-methyl-biphenyl, which is a key intermediate used for the preparation of anti-hypertensive drugs, was easily synthesized by the coupling of non-active *o*-chlorobenzonitrile with *p*-chlorotoluene in toluene-tetrahydrofuran mixed solvents over transition-metal catalysts. Various reaction conditions, especially catalysis of some catalysts were discussed to improve selectivity suitable for industrialization in the recycle solvent system.

Key Words: 2-Cyano-4'-methyl-biphenyl, *p*-Chlorotoluene, *o*-Chlorobenzonitrile, Synthesis.

INTRODUCTION

2-Cyano-4'-methylbiphenyl (*o*-tolylbenzonitrile, OTBN) is a key intermediate for the synthesis of anti-hypertensive drugs[1]. Some methods have been reported for the preparation of *o*-tolylbenzonitrile. As described in the literature, *o*-tolylbenzonitrile could be prepared by reacting *o*-bromobenzonitrile with *p*-tolylmagnesium bromide in presence of Pd[2-5], Ni[6,7], Mn[8,9], *etc*. transition metal catalysts in a moderate to good yield. Unfortunately, some rather expensive iodo- and bromo-substituted arenes are usually chosen for improve reactivity whereas aryl fluorides are both costly and unreactive. Thereby there arise economical disadvantages in the processes. Moreover *p*-chlorotoluene should be certainly the most attractive aryl halides for synthetic applications toward an industrial manufacture because of inexpensive and readily available in bulk quantities. The main demerit here is the exceedingly high stability of the aromatic carbon-chlorine bone whose inertness remains the major drawback on the way to wide utilization of *p*-chlorotoluene[10]. Besides tetrahydrofuran (THF) was usually used for the solvent in reactions in order to get 80 % above of product yield[11] compared with the low yield in toluene[12,13]. However, THF should be carefully treated before used and its reuse in process appear rather difficult to industrial application.

In view of the problems in the arts mentioned above, an object of the present process is to provide a method for economically, efficiently, simply and industrially preparing *o*-tolylbenzonitrile. We here report that the compound can be efficiently synthesized by the Mn(II)- or Ni(II)-catalyzed cross-coupling of *o*-chlorobenzonitrile with *p*-tolylmagnesium chloride *via p*-chlorotoluene in the mixed solvents involving

THF and toluene. Thus, this novel process for biaryl synthesis not only overcomes the substrate limitations described above, but also allows for the industrial preparation of a wide range of the choice of recycle mixed solvents.

EXPERIMENTAL

All of the starting materials were chemical purity grade or above. GC (Shimadzu GC-2014C equipped with FID detector) and HPLC (Shimadzu LC-10Avp Plus) were utilized to determine compositions of products and conversions using *n*-dodecane as internal standard.

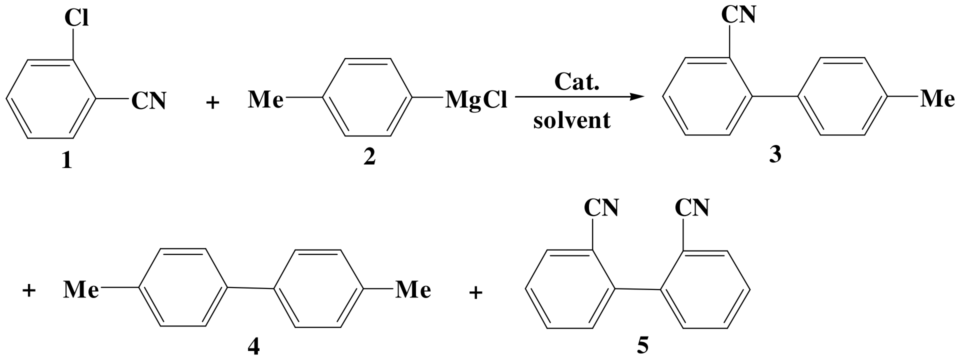
A precursor Grignard reagent used for *o*-tolylbenzonitrile was prepared by using *p*-chlorotoluene as substrate. An oven-dried three-necked round-bottomed flask equipped with a 100 mL dropping funnel and a condenser was charged with a magnetic stir bar, magnesium turnings (0.044 mol, 1.05 g) and a catalytic amounts of I_2. The flask was evacuated and backfilled with N_2 to repeated three times. Slowing stirring and heating was started to I_2 steam full of the flask, THF (5 mL) and *p*-chlorotoluene (0.0084 mol, 1.07 g) were added to the flask. Then the mixed solution toluene (20 mL) and THF (15 mL) containing *p*-chlorotoluene (0.0336 mol, 4.27 g) was added dropwise from a funnel. The solution was refluxed for the specific time until magnesium turnings disappeared. GC yield of 94.8 % *p*-tolylmagnesium chloride intermediate was obtained based on internal standard analysis.

Followed by *o*-tolylbenzonitrile preparation from the following representative procedure, *i.e.*, to a same cleaned three-necked round-bottomed flask with a magnetic stir bar was charged *o*-chlorobenzonitrile (0.042 mol, 5.78 g), manganese chloride (0.0032 mol, 0.40 g), THF (15 mL) and toluene (15 mL) to the flask. The reaction mixture was stirring for 0.5 h at room temperature. Then the solution formed was added dropwise to above prepared *p*-tolylmagnesium chloride intermediate at -5 ºC with stirring for 1 h and the stirring was maintained at -5 ºC for 3 h. The reaction was ceased by addition of dilute hydrochloric acid. The combined organic layers were washed three times by a saturated solution of sodium chloride then dried by anhydrous magnesium sulfate. The resulting organic solution was concentrated by rotary evaporation and the crude product was purified by distillation and recrystallization with petroleum ether to afford the desired product. HPLC yield of 70 % above *o*-tolylbenzonitrile was obtained based on internal standard analysis.

RESULTS AND DISCUSSION

In various reaction conditions *o*-tolylbenzonitrile was selectively prepared accompanying with defined amounts of other constitutions (**Scheme-I**). Some results were shown in Table-1.

Catalysts affect the synthesis in the mixed solvents system. In the presence of $MnCl_2$ (5 mol %) in THF, reaction *o*-chlorobenzonitrile with *p*-tolylmagnesium chloride at -5 ºC resulted in formation of the desired compound, *o*-tolylbenzonitrile,



Scheme-I: Formation of 2-cyano-4'-methyl-biphenyl based on the reaction of *o*-chlorobenzonitrile with *p*-tolylmagnesium chloride

TABLE-1
REACTION OF *o*-CHLOROBENZONITRILE WITH *p*-TOLYLMAGNESIUM CHLORIDE

Entry	Solvent	Catalyst (mol %)	Conversion (%)	Product composition (%)		
			1	3	4	5
1	THF	$MnCl_2$ (5 mol%)	97.7	87.2	11.1	1.6
2	THF	$MnCl_2$ (7 mol%)	97.9	81.4	10.8	7.9
3	THF	$Ni(PPh_3)_2Cl_2$ (5 mol%)	97.4	81.8	4.2	14.0
4	THF	$Ni(PPh_3)_2Cl_2$ (7 mol%)	97.6	81.3	4.1	14.5
5	THF & Toluene	$MnCl_2$ (5 mol%)	98.0	79.3	20.7	0
6*	THF & Toluene	$MnCl_2$ (5 mol%)	97.6	74.3	30.3	2.9
7	THF & Toluene	$MnCl_2$ (7 mol%)	97.4	70.7	29.3	0
8	THF & Toluene	$Ni(PPh_3)_2Cl_2$ (5 mol%)	95.7	53.9	46.1	0
9	THF & Toluene	$Ni(PPh_3)_2Cl_2$ (7 mol%)	96.2	69.6	30.4	0
10	THF & Toluene	$NiCl_2$ (5 mol%)	94.1	8.0	84.3	7.7
11	THF & Toluene	$NiCl_2$ (7 mol%)	95.4	7.1	86.4	6.5
12	THF & Toluene	$CdCl_2$ (5 mol%)	92.0	10.2	77.7	12.1
13	THF & Toluene	$CdCl_2$ (7 mol%)	93.5	9.8	79.1	11.1
14	THF & Toluene	$CuCl_2$ (5 mol%)	95.0	12.4	80.9	6.7
15	THF & Toluene	$CuCl_2$ (7 mol%)	96.2	11.5	82.6	5.9
16	THF & Toluene	$CoCl_2$ (5 mol%)	92.4	12.2	73.9	13.9
17	THF & Toluene	$CoCl_2$ (7 mol%)	94.2	11.8	76.5	11.7
18	Toluene	$MnCl_2$ (5 mol%)	96.7	36.6	58.4	5.0
19	Recovered THF	$MnCl_2$ (5 mol%)	56.9	72.3	21.0	6.7
20	Recovered THF & Toluene	$MnCl_2$ (5 mol%)	87.4	88.7	11.3	0

*The reaction was employed at -10 °C.

in 87.2 % yield by HPLC (entry 1 in Table-1) of 97.7% substrate conversion accompanied by minor amounts of two homo-coupled byproduct, 4,4'-dimethylbiphenyl (4, 11.1 %) and 2,2'-dicyanobiphenyl (5, 1.6 %). No other significant byproducts were observed by HPLC analysis. It should be noted that, with the increase of $MnCl_2$ quantity the yield of 2-cayano-4'-methylbiphenyl was slight loss in

79.4 % at the expense of 2,2'-dicyanobiphenyl as byproducts (entry 2). $Ni(PPh_3)_2Cl_2$ derived from $NiCl_2·6H_2O$ and triarylphosphine in ethanol at 70-80 ºC was also employed to the reaction. A significant yield of 2-cayno-4'-methylbiphenyl of 81.8 % was also obtained when using a catalytic amount of $Ni(PPh_3)_2Cl_2$ (5 mol %). Similarly the results weren't influenced obviously because of a increase of $Ni(PPh_3)_2Cl_2$ amount.

Although toluene is usually used solvent in organic synthesis, for the coupling reaction the yield in individual toluene was obviously inferior to that in THF (entry 18). It was noted that the combined utilization of toluene and THF could greatly improve the reaction up to a reasonable yield. The mixed solvent system is rather favoured to industrial application of the reaction, since their recycle based on a simple distillation didn't change any reaction properties (entry 20) and no 2,2'-dicyanobiphenyl was detected. Moreover regenerated THF was not of the behaviour even if a carefully regeneration, *i.e.*, a poor yield to aimed compound was observed.

Some catalysts were turned to the chloride of Cd, Co, Cu metals (entry 12-17). The results were influenced drastically. The yield of OTBN was almost reduced to 13 % to "byproduct" position. 4,4'-dimethylbiphenyl became the unexpected main product of a good selectivity in a 86.4% of high yield (entry11).

Conclusion

Therefore, a high selectivity turning to the desired product in the mixed solvents of toluene and THF can be achieved and excellent recycle of the solvents can be easily conducted in industrial preparation process.

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