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Efficient access to 3-alkyl-trifluoromethylbenzenes using Kumada's coupling reaction

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Abstract—3-Alkyl-trifluoromethylbenzenes are obtained in good yields by Kumada's coupling reaction between methyl or ethyl magnesium halide and 3-bromo-trifluoromethylbenzene derivatives in the presence of Ni-Xantphos catalyst.

1. Introduction

Trifluoromethyl aromatic derivatives form the most important family of fluorinated intermediates used in agrochemical, pharmaceutical and performances markets[1] such as liquids crystals. Pharmaceutical and agrochemical companies are more and more interested in trifluoromethylbenzene derivatives bearing a carbon functionalized function in addition to the CF_3 moiety, such as 3-methyl-trifluoromethylbenzene, 3-trifluoromethylbenzylalcohol and 3-trifluoromethylacetophenone. Thus, we decided to look for a safe and efficient access to central building-blocks such as 3-methyl-trifluoromethylbenzene **1**, 3-ethyl-trifluoromethylbenzene **2** and 2-chloro-5-methyl-trifluoromethylbenzene **3** (Fig. 1).

Industrial syntheses of trifluoromethylbenzenes consist in radical chlorination of the corresponding toluene derivatives followed by chlorine–fluorine exchange in anhydrous HF.[1] This chemical route is very efficient and is used at multi-tons scale, but chlorination is not enough selective on xylene derivatives[2a–c] to obtain, after fluorination, **1** or **2**.

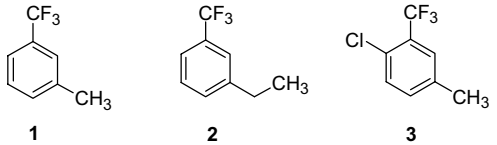

Figure 1. 3-Alkyl-trifluoromethylbenzene targets.

Other routes to alkyl-trifluoromethyltoluenes are described in the literature: they can be synthesized by radical trifluoromethylation[3] of toluenes but the low selectivity of this reaction induces difficult purification of the different isomers due to their close boiling points[4]. Electrophilic trifluoromethylation of toluene is more selective but requires reagents which are limited for scale-up: CCl_4–HF[5] co-produces large amounts of fluorochloromethane derivatives that have to be treated as CFC in accordance with the Montreal Protocol.[6a,b] Nucleophilic trifluoromethylation of bromotoluenes is possible with CF_3^- sources like trifluoroacetic acid salts[7] or Ruppert's reagent CF_3SiMe_3,[8] but a stoichiometric amount of cuprous salt must be used to obtain satisfactory yields and treatment of copper wastes is necessary. Beech's reaction[9] is an interesting route to transform trifluoromethylanilines into the corresponding benzaldehydes or acetophenones but this route involves formation of an aqueous diazonium salt of the starting aniline that is not very productive and leads to big amounts of aqueous wastes. Alkylation of Grignard derivatives of halo-trifluoromethylbenzenes seems to be an efficient access to **1**, **2** or **3**, but the formation of these Grignard reagents are known to be dangerous[10] and our experience on different aromatic Grignard reagents bearing CF_3 groups confirms this safety issue. Recent work[11] describes the synthesis of trifluoromethylbenzene Grignard reagents using a halogen–magnesium exchange reaction which leads to safer conditions. Even if thermal analyses described in this article[11] show great differences between conditions where the magnesium salt of bromo-trifluoromethylbenzene is

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directly formed and others where the Grignard of bromo-trifluoromethylbenzene is obtained via transmetalation with *i*-PrMgCl, we preferred to look for other chemical routes which minimize this potential safety problem.

We chose to study the access to **1**, **2**, **3** using Kumada's reaction:[12] coupling of methyl or ethyl magnesium salts with 3-chloro or 3-bromo-trifluoromethylbenzene in the presence of a Ni^0 catalyst with phosphines (Fig. 2).

Literature[13] indicates that dppe (1,2-bis(diphenylphosphinoethane)) is an efficient ligand of $NiCl_2$ in Kumada's coupling reaction, with in situ reduction of Ni^{II}: our first trials were conducted using $NiCl_2$–dppe in THF (Table 1).

3-Chloro and 3-bromo-trifluoromethylbenzene lead to different behaviours in Kumada's coupling reaction with $NiCl_2$–dppe.

Reaction between 3-bromo-trifluoromethylbenzene and methyl magnesium chloride (entry 1) leads to total conversion of the starting materials and formation of 3-methyltrifluoromethylbenzene **1** in a fair yield (65%), accompanied by a small amount of reduced product (trifluoromethylbenzene) and large amounts of biaryls (mainly isomers of bis(trifluoromethyl)biphenyl). Reaction between 3-bromo-trifluoromethylbenzene and ethyl magnesium bromide (entry 2) leads to 3-ethyltrifluoromethylbenzene **2** in 76% yield, with low level of biaryls but high level of trifluoromethylbenzene.

On 3-chloro-trifluoromethylbenzene, the coupling reaction with MeMgCl (entry 3) is less efficient and leads to low conversion and to **1** in low yield (18%). In the presence of ethyl magnesium chloride, reduction of 3-chloro-trifluoromethylbenzene into trifluoromethylbenzene is prevailing (entry 4).

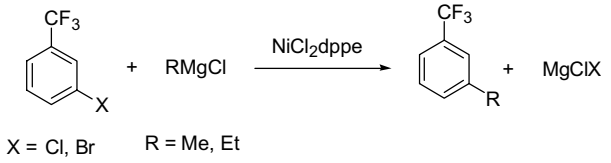


Figure 2. Kumada's coupling principle.

We confirmed this difference of reactivity between chloride and bromide trifluoromethylbenzene derivatives applying Kumada's conditions on 2,5-dichloro-trifluoromethylbenzene and 2-chloro-5-bromo-trifluoromethylbenzene (Table 2).

Conversion of 2,5-dichloro-trifluoromethylbenzene (entry 1) is very low confirming the weak reactivity of chloro-trifluoromethylbenzenes in our conditions, even if Kumada's coupling reaction is described on this substrate with another Ni–phosphine ligand in the literature.[11] Kumada's conditions applied on 2-chloro-5-bromo-trifluoromethylbenzene (entry 2) mainly lead to 2-chloro-5-methyl-trifluoromethylbenzene, with very low amounts of 2,5-dimethyl-trifluoromethylbenzene.

Considering these first results, we planned to optimize Kumada's coupling reaction between 2-chloro-5-bromo-trifluoromethylbenzene and MeMgCl in THF with the goal to reduce the amounts of biaryls by-products.

Variations of parameters, such as the nature of solvent (methyl-terbutylether, isopropyl ether, toluene instead of THF), increase of temperature (50 °C instead of 20 °C), the nature of the metal catalyst (Pd instead of Ni), do not improve the selectivity of the alkylation reaction. Thus, a study of the influence of the nickel ligand was performed. Two types of easily available phosphines were tested: mono and bidentates. Table 3 summarizes the tested phosphines and the results of coupling between 2-chloro-5-bromo-trifluoromethylbenzene and MeMgCl in THF at 20–25 °C in the presence of 0.5 mol % of catalyst.

All the results of Table 3 can be compared to the performances obtained with dppe as a ligand (entry 7). Methylation of 2-chloro-5-bromo-trifluoromethylbenzene with MeMgCl occurs even without Nickel ligand (entry 1) but gives higher amounts of biaryls than in the presence of ddpe. Electron rich monodentate phosphines (entries 3–5) lead to similar results to dppe. Triphenyl phosphine (entry 2) leads to lower performance.

The length of the carbon chain between the two phosphorus atoms of bidentate phosphines seems to have an influence:

Table 1. Kumada's coupling between MeMgCl, EtMgCl and 3-chloro or 3-bromo-trifluoromethylbenzene with $NiCl_2$–dppe[a]

Entry	CF_3Ar–X, RMgCl	CF_3Ar–X Conversion[b] (%)	CF_3Ar–R Yield[b] (%)	CF_3Ar–H Yield[b] (%)	Biaryls Yield[c] (%)
1	X = Br, R = Me	>98	65	5	17
2	X = Br, R = Et	>98	76	16	5
3	X = Cl, R = Me	30	18	2	3
4	X = Cl, R = Et	91	19	60	3

[a] $NiCl_2$dppe (from Aldrich, 190 mg, 0.36 mmol; 0.5% equiv) was suspended in THF (tetrahydrofuran, 62 g) at 20 °C. 3-bromo-trifluoromethylbenzene (16.4 g, 72.8 mmol) was added at once. Maintaining the reaction mixture between 20 and 25 °C (the coupling reaction is exothermic), methylmagnesium chloride in THF (23 wt %, 33.9 g, 104.3 mmol, 1.44 mol equiv) was slowly added in 2 h. The reaction mixture was mixed for 1 h. Quenching with aqueous hydrochloric acid (2 mol/l, 45 g) and extraction with isopropyl ether (50 g) afforded the organic phase that was analysed by GC with internal standard.

[b] GC assays.

[c] NMR and GC assays: mainly yields of isomers of bis-(trifluoromethyl)biphenyl.

Table 2. Kumada's coupling between 2,5-dichloro-trifluoromethylbenzene, 2-chloro-5-bromo-trifluoromethylbenzene and MeMgCl with $NiCl_2$–dppe in THF at 25 °C

Entry	Starting compounds	CF_3Ar–X Conversion (%)	CF_3Ar–Me[a] **3** Yield[c] (%)	CF_3Ar–H Yield[c] (%)	Biaryls Yield[d] (%)
1	2,5-Dichloro-trifluoromethylbenzene	6	3	<1	<1
2	2-Chloro-5-bromo-trifluoromethylbenzene	>98	63[b]	5	10

[a] Product: 2-chloro-5-methyl-trifluoromethylbenzene **3**.
[b] 3% of 2,5-dimethyl-trifluoromethylbenzene is detected.
[c] GC assays.
[d] GC and NMR assays of isomers of biaryls:

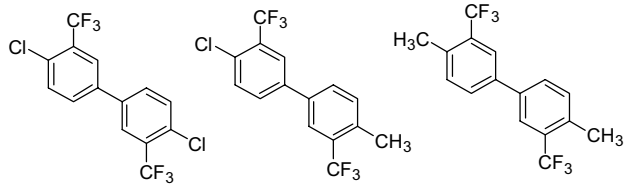
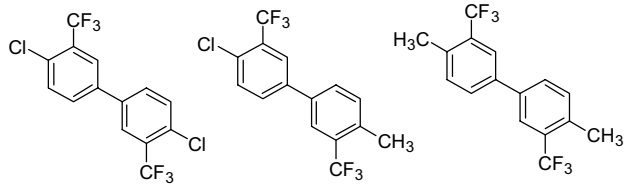


Table 3. Influence of the Nickel phosphine ligand on coupling between 2-chloro-5-bromo-trifluoromethylbenzene and MeMgCl in THF[a]

Entry	Nickel ligand	Molar ratio phosphine/Ni	CF_3Ar–Br Conversion (%)	CF_3Ar–Me **3** Yield[a] (%)	$CF_3Ar(Me)_2$ Yield[b] (%)	CF_3Ar–H Yield[b] (%)	Biaryls Yield[c] (%)
1	No phosphine	0	>98	55	<2	<2	18
2	Triphenylphosphine	2	90	52	<2	6	9
3	Triethylphosphine	2	>98	62	3	4	10
4	Tri-(*o*-tolyl)phosphine	2	>98	64	4	3	10
5	Tri-(*p*-tolyl)phosphine	2	>98	65	3	2	7
6	dppm	1	78	45	2	5	7
7	dppe	1	>98	60	3	5	10
8	dppp	1	>98	57	3	5	8
9	dppb	1	94	58	6	6	7
10	Binap	1	>98	63	<2	3	7
11	Xantphos	1	>98	81	7	<2	3

[a] The procedure described below Table 1 was used for this screening of ligands.
[b] GC assays.
[c] GC and NMR assays of isomers of biaryls:



- dppm (bis-diphenylphosphinomethane) has a too short carbon chain and leads to the lowest methylation rate (entry 6).
- dppp (bis-diphenylphosphinopropane, entry 8) and dppb (bis-diphenylphosphinobutane, entry 9) give similar coupling results to dppe.

Binap (entry 10) also leads to similar results to dppe. The best result is obtained with Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, entry 11): the coupling product 2-chloro-5-methyl-trifluoromethylbenzene **3** is obtained in 81% yield, together with 7% yield of 2,5-dimethyl-trifluoromethylbenzene and very low amounts of reduction and biaryls by-products.

The same conditions with $NiCl_2$/Xantphos (0.5% molar equivalent) applied to 2-chloro-5-bromo-trifluoromethylbenzene and EtMgCl also lead efficiently to the coupling product (2-chloro-5-ethyl-trifluoromethylbenzene) in 75% yield. 3-Methyl-trifluoromethylbenzene **1** is obtained in 76% yield from 3-bromo-trifluoromethylbenzene and MeMgCl in the presence of $NiCl_2$/Xantphos.

In any of these cases, purification of products is easy: after quench of the reaction with aqueous hydrochloric acid and extraction with isopropyl ether, fractional distillation leads to the trifluoromethyltoluene derivatives with high purity (>98%), biaryls by-products remain in the boiler.

We scaled-up these Kumada's coupling procedure from 25 ml to 2 l reactors.

On the safety issue, we report above that Grignard derivatives of trifluoromethylbenzene are hazardous. In Kumada's coupling reaction, there is always a risk of transmetalation between MeMgCl (or EtMgCl) and halogenated aromatic substrates. This transmetalation

reaction on 3-bromo or 3-chloro trifluoromethylbenzene can lead to hazardous conditions. A way to estimate the level of transmetalation is to quantify the rate of reduced product (which can come from hydrolysis of the Grignard derivative of trifluoromethylbenzene during work-up) and the level of biaryl compounds. In our conditions using Xantphos as the Nickel ligand, the level of these by-products is very low and thus we think that transmetalation reaction is limited.

To explore the thermal behaviour and potential hazard of this Kumada's coupling reaction, we performed thermal analysis:

- DSC analysis of a mixture of MeMgCl, 2-chloro-5-bromo-trifluoromethylbenzene in the presence of Ni–dppe (0.5 mol %) in THF shows an exothermy which begins at 25 °C and strongly increases above 70 °C with a maximum at 100 °C.
- Measurement of the enthalpy of this coupling reaction in a Mettler Calorimeter (79 kcal/mol of 2-chloro-5-bromo-trifluoromethylbenzene) shows that, at 20–25 °C, the exothermy begins as soon as the MeMgCl solution is added and the coupling reaction is instantaneous. That is the safety criteria of this coupling reaction: it is necessary that the Grignard reagent is consumed as soon as possible to avoid any accumulation and risk of transmetalation. Even if in our case we did not detect any safety issue, we recommend in any coupling reaction of this type on trifluoromethylbenzene derivatives, to analyze the thermal behaviour of the medium by DSC and calorimeter analysis.

2. Conclusion

Addition of methylmagnesium chloride or ethyl magnesium chloride in THF (1.5 mol equiv) to a solution of 3-bromo-trifluoromethylbenzene or derivatives in the presence of $NiCl_2$/Xantphos (1/1; 0.5 mol %) at 20–25 °C affords the corresponding 3-methyl and 3-ethyltrifluoromethylbenzene in 81% and 75% yield, respectively. These two compounds are versatile intermediates whose derivatizations by bromination or oxidation of benzylic positions are in progress.

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