

Preliminary communication

Palladium catalyzed cross-coupling reaction of Grignard reagents with halobenzoic acids, halophenols and haloanilines

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Abstract

Convenient syntheses of substituted benzoic acids, phenols and anilines have been achieved by using palladium catalyzed cross-coupling reactions between Grignard reagents and aryl halides containing carboxy, hydroxy and amino groups without a protection–deprotection sequence.

Keywords: Palladium; Catalysis; Magnesium; Cross-coupling; Aryl halides

1. Introduction

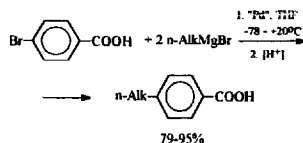
As part of a program directed towards the preparation of isotopically labelled aromatic compounds, we have investigated a new synthetic route for the selective introduction of carbon substituents into the benzene nucleus of benzoic acid, phenol and aniline. The most attractive solution to this problem would be the catalytic cross-coupling of organometallic reagents with readily available halobenzoic acids, halophenols and haloanilines. Examples of transition metal mediated coupling of reagents with free COOH, OH and NH₂ groups are restricted to the palladium catalyzed cross-coupling of hydroxy- or aminophenylmercurials with aryl iodides [1], organotin with *m*-iodobenzoic acid [2], and 2-amino-6-chloropurine [3], organoboron compounds with halobenzoic acids and halophenols [4], organozinc reagents with 3-iodo-2-aminobenzonitrile [5].

2. Results and discussion

We have found that Grignard reagents react readily with aryl halides containing carboxy, hydroxy and amine groups in the presence of Pd catalyst without the protection of functional substituents using a two- to three-fold excess of organomagnesium compound (see Table 1).

[General procedure for the Pd catalyzed coupling: a solution of 4-fluorophenylmagnesium bromide in THF (66 mmol/30 ml) was added to a stirred suspension of PdCl₂(dppf) (0.1462 g, 0.2 mmol) and 5-bromosalicylic acid (4.34 g, 20 mmol) in 20 ml of THF at –78 °C. The mixture was stirred at –78 °C for 10 min, then cooling was removed. After stirring for 3 h at 20 °C the mixture was quenched with 5% aqueous solution of hydrochloric acid and extracted with ether. The combined extracts were washed with water and dried over MgSO₄. After evaporation of the solvent the residue was recrystallized from hexane–ether to give a pure sample of 5-(4-fluorophenyl)salicylic acid, m.p. 212–214 °C [6] in 86% yield. Satisfactory spectroscopic and microanalytical data were obtained for all compounds.]

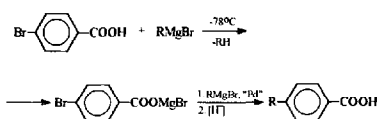
The reaction of 4-bromobenzoic acid and alkylmagnesium bromides proceeds in THF in the presence of palladium catalyst [1 mol.% of PdCl₂(dppf)] at –78/20 °C in 3.5 h to give 4-*n*-alkylbenzoic acids in high yield.



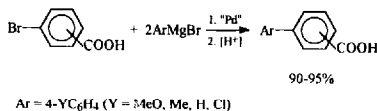
Alk = C₂H₅, C₄H₉, C₃H₇, C₇H₁₅, C₈H₁₇

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At the first step 4-bromobenzoic acid reacts with Grignard reagent to give bromomagnesium 4-bromobenzoate, which is then involved in the palladium catalyzed cross-coupling with the Grignard reagent.



nesium bromide, the yield of cross-coupling product does not exceed 40%.



The most reactive Grignard reagent studied has proved to be the arylmagnesium bromides. The reactions of 3- and 4-bromobenzoic acids with arylmagnesium bromides containing either electron-withdrawing or electron-donating groups are completed in 10–15 min at room temperature to give 3- or 4-substituted arylbenzoic acids in high yield without by-product formation. In the reaction of 2-bromobenzoic acid with phenylmag-



In the case of vinylmagnesium bromide the transfer of the vinyl group is also successful and, in the reaction with 3-iodobenzoic acid, a high isolated yield is achieved despite the longer reaction time (approximately 1 h).

The cross-coupling reaction of 5-bromosalicylic acid with alkyl and aryl Grignard reagents provides a novel efficient synthesis of 5-substituted salicylic acids. In

Table 1
Synthesis of substituted benzoic acids, phenols and anilines



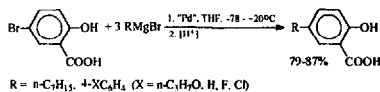
X = Br, I; Y = COOH, OH, NH₂; n = 2, 3

Y C ₆ H ₄ X	R	Time (h)	Yield ^a of Y C ₆ H ₄ X (%)
4-BrC ₆ H ₄ COOH	C ₂ H ₅	3.5	79
4-BrC ₆ H ₃ COOH	n-C ₃ H ₇	3.5	90
4-BrC ₆ H ₃ COOH	n-C ₄ H ₉	3.5	87
4-BrC ₆ H ₃ COOH	n-C ₅ H ₁₁	3.5	95
4-BrC ₆ H ₃ COOH	n-C ₇ H ₁₅	3.5	85
4-BrC ₆ H ₃ COOH	4-MeOC ₆ H ₄	10 min	92
4-BrC ₆ H ₃ COOH	4-MeOC ₆ H ₄	10 min	94
4-BrC ₆ H ₃ COOH	Ph	10 min	95
4-BrC ₆ H ₃ COOH	4-ClC ₆ H ₄	15 min	90
2-BrC ₆ H ₄ COOH	Ph	10 min	40
3-BrC ₆ H ₄ COOH	Ph	10 min	90
3-IC ₆ H ₄ COOH	CH ₂ =CH	1	70
5-Br-2-HOC ₆ H ₃ COOH	n-C ₇ R ₁₅	3	79
5-Br-2-HOC ₆ H ₃ COOH	4-n-C ₃ H ₇ OC ₆ H ₄	3	85
5-Br-2-HOC ₆ H ₃ COOH	Ph	3	87
5-Br-2-HOC ₆ H ₃ COOH	4-FC ₆ H ₄	3	86
5-Br-2-HOC ₆ H ₃ COOH	4-ClC ₆ H ₄	3	84
4-BrC ₆ H ₄ OH	n-C ₇ H ₁₅	0.5 ^b	90
4-BrC ₆ H ₃ OH	n-C ₃ H ₇ - 	0.5 ^b	94
4-BrC ₆ H ₃ OH	CH ₂ =CH	0.5 ^b	91
4-BrC ₆ R ₂ OH	4-n-C ₃ H ₇ OC ₆ H ₄	0.5 ^b	95
4-BrC ₆ H ₃ OH	Ph	0.5 ^b	95
4-BrC ₆ H ₃ OH	n-C ₄ H ₉ - 	0.5 ^b	93
4-IC ₆ H ₄ NH ₂	i-C ₃ H ₇	24 ^b	87
4-IC ₆ H ₃ NH ₂	n-C ₄ H ₉	24 ^b	90
4-IC ₆ H ₃ NH ₂	Ph	24 ^b	91

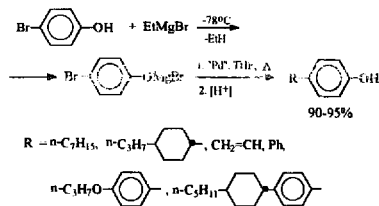
^a Isolated yields based on ArX.

^b Under reflux.

this case, an additional 2 equiv. of Grignard reagent is required to 'protect' the carboxy and hydroxy groups.

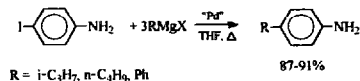


We have also shown that strongly deactivated bromomagnesium 4-bromophenolate formed from 4-BrC₆H₄OH and EtMgBr at -78°C reacts with alkyl, vinyl or arylmagnesium bromides in THF under reflux to give 4-alkyl-, 4-vinyl- and 4-arylphenols in 90–95% yield.



It was expected that some difficulties could appear in the case of 4-iodoaniline, which is poorly reactive in oxidative addition to palladium(0) complexes. However,

the reaction of 4-iodoaniline with alkyl- and arylmagnesium reagents in THF under reflux was complete in 24 h, giving good yields of 4-substituted anilines.



In summary, the reported procedure provides a convenient route to substituted benzoic acids, phenols and anilines, from readily available starting materials.

Acknowledgements

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