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Published in:
Journal of Labelled Compounds and Radiopharmaceuticals

DOI:
10.1002/jlcr.3302_2

Publication date:
2015

Document version
Submitted manuscript

Citation for pulished version (APA):
Dam, J. H. (2015). Transition Metal Mediated Kumada Cross Coupling of [11C]CH3I and Aryl Grignard. Journal of Labelled Compounds and Radiopharmaceuticals, 58(S1). DOI: 10.1002/jlcr.3302_2

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Transition Metal Mediated Kumada Cross Coupling of [^{11}C]CH_3I and Aryl Grignard

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Objectives Radiolabeling of small molecules with carbon-11 has to date been largely based on the S_N2 reaction by amines or alkoxides on [^{11}C]CH_3I or [^{11}C]CH_3OTf. The chemical space for labeling by cross coupling is still being developed within radiochemistry.[1] Herein, it was sought to explore the Kumada cross coupling for incorporation of the [^{11}C]methyl moiety.

Methods A range of transition metals *viz*. Pd, Ni, Fe and Co and ligands DPPF, DPPP, PPh_3, P(^{o}Tol)$_3$, TMEDA were screened for their capability to mediate a model Kumada cross coupling between PhMgBr and [^{11}C]CH_3I in THF. The [^{11}C]CH_3I was prepared by standard gas phase reactions on the Tracerlab FXc Pro by extracting [^{11}C]CH_3I from Valve 17 to an external glass vial with 0.35 mL THF, 4 µmol catalyst and 100 µmol of PhMgBr(in THF), cooled to -20 °C. The trapping was complete within 2 minutes and the vial was heated to 60 °C over 2 minutes, purged with N_2 for 2 minutes to discharge residual [^{11}C]CH_3I and quenched with 1 mL 70% ethanol. The radiochemical purity was assessed by RP-HPLC on a Zorbax C18 Stablebond.

Results As a simple model system, many different combinations of transition metals and ligands produced the [^{11}C]toluene to some extent. Of the different catalysts and ligands examined, only $PdCl_2$DPPF, $PdCl_2$(P(^{o}Tol)$_3$)$_2$ and $CoCl_2$ with DPPP produced the carbon-11 labeled toluene in the higher yields of 67.9%, 67.0% and 66.5%, d.c., respectively. For the cobalt mediated cross coupling, addition of PhMgBr after trapping of the [^{11}C]CH_3I was necessary in order to obtain a high yield. Increasing the reaction time from 2 minutes to 4 minutes with $PdCl_2$(P(^{o}Tol)$_3$)$_2$ did not increase the overall radiochemical yield. Lowering the reaction time to 1 minute reduced the radiochemical yield to 36.1% d.c.

Conclusions The Kumada cross coupling was examined for coupling of [^{11}C]CH_3I with PhMgBr. Palladium with phosphine ligands, DPPF and P(^{o}Tol)$_3$, was found to produce the [^{11}C]toluene in slightly better yields. As such, the palladium mediated Kumada cross coupling represent an attractive method for fast insertion of a metabolically more stable radiolabel into small molecules.

Acknowledgements

References [1] Pretze, M. *et al.* (2011) Molecules, 16, 1129-1165.

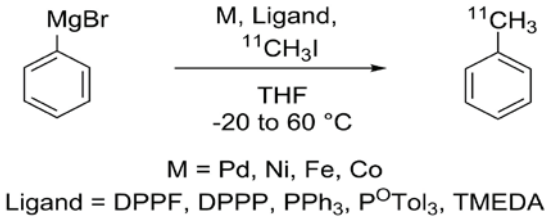

Figure 1. Model system for radiolabeling by the Kumada cross coupling