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Dam, Johan Hygum

Published in:

Journal of Labelled Compounds and Radiopharmaceuticals

DOI:

[10.1002/jlcr.3302_2](https://doi.org/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 [¹¹C]CH₃I and Aryl Grignard

Johan H. Dam

Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark

Objectives Radiolabeling of small molecules with carbon-11 has to date been largely based on the S_N2 reaction by amines or alkoxides on [¹¹C]CH₃I or [¹¹C]CH₃OTf. 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 [¹¹C]methyl moiety.

Methods A range of transition metals *viz.* Pd, Ni, Fe and Co and ligands DPPF, DPPP, PPh₃, P(^oTol)₃, TMEDA were screened for their capability to mediate a model Kumada cross coupling between PhMgBr and [¹¹C]CH₃I in THF. The [¹¹C]CH₃I was prepared by standard gas phase reactions on the Tracerlab FXc Pro by extracting [¹¹C]CH₃I 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 N₂ for 2 minutes to discharge residual [¹¹C]CH₃I 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 [¹¹C]toluene to some extent. Of the different catalysts and ligands examined, only PdCl₂DPPF, PdCl₂(P(^oTol)₃)₂ and CoCl₂ 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 [¹¹C]CH₃I was necessary in order to obtain a high yield. Increasing the reaction time from 2 minutes to 4 minutes with PdCl₂(P(^oTol)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 [¹¹C]CH₃I with PhMgBr. Palladium with phosphine ligands, DPPF and P(^oTol)₃, was found to produce the [¹¹C]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.

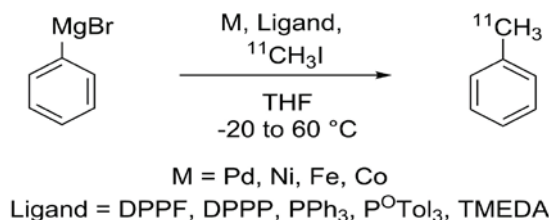


Figure 1. Model system for radiolabeling by the Kumada cross coupling