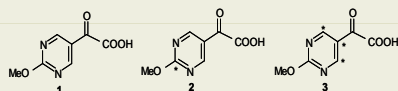


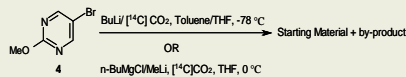
1 Introduction

Synthesis of labeled 2-methoxypyrimidine-5-carboxylic acids with [¹⁴C] label at 2-position of pyrimidine ring **2**, or at 4-, 5- and 6- positions of **3** present more challenging chemistry than the introduction of ¹⁴C on the carboxyl function of **1**.

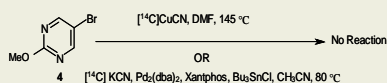


2 Results and Discussions

Attempted carbonylation of 5-bromo-2-methoxypyrimidine with [¹⁴C] CO₂ in the presence of n-butyl magnesium chloride and methyl lithium in THF at 0 °C or by metal-halogen exchange-Grignard reaction¹⁻² did not yield the desired labeled carboxylic acid.

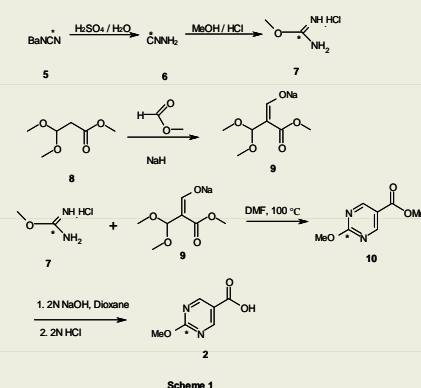


Alternatively, aromatic nitriles could be hydrolyzed to the corresponding carboxylic acids under acidic or alkaline conditions **3**. However, cyanation of **4** with [¹⁴C] CuCN under Von Braun conditions⁴⁻¹¹ did not give the corresponding nitrile derivative. Further, attempted palladium catalyzed cyanation¹² of **4**, in the presence of organotin compound resulted only in the recovery of starting material.



The synthesis of 2-methoxypyrimidine-5-carboxylic acid (**2**) with a [¹⁴C] label at 2-position of pyrimidine ring is an alternative choice. A number of synthetic methods are reported in the literature for pyrimidine 5-carboxylic acid derivatives¹³⁻¹⁶. However, a few direct approaches leading to pyrimidine ring which lacks substitution at 4- position have been reported¹⁷⁻¹⁹. Our approach to compound **2** is as depicted in **Scheme 1**.

[¹⁴C] Barium cyanamide (**5**) was converted to [¹⁴C] cyanamide (**6**) in about 75 % yield by a reaction of **5** with aqueous sulfuric acid. Compound **6** was treated with anhydrous methanol in the presence of dry hydrogen chloride gas for 3 days according to the literature method²⁰ to give [¹⁴C] O-methylisourea hydrochloride (**7**) in moderate yield.



Scheme 1

On the other hand sodium salt of **3**, 3-dimethoxy-2-methoxycarbonylpropen-1-ol (**9**)¹⁹ was synthesized by the condensation of methyl formate with methyl 3, 3-dimethoxy-propionate (**8**) using sodium hydride. The sodium salt **9** was then reacted with [¹⁴C] O-methyl-isourea hydrochloride (**7**) in dimethyl-formamide at 100 °C to give [2-¹⁴C] methyl 2-methoxypyrimidine-5-carboxylate (**10**) in 70 % yield.

The ester (**10**) was hydrolyzed by heating with 2N NaOH solution in aqueous dioxane²¹. The product was isolated after acidification of the mixture with 2N HCl in 97 % yield. The radiochemical purity of the product was found to be 98.41 % by HPLC and the specific activity was determined to be 56.39 mCi/mmol. Overall yield of [2-¹⁴C] 2-methoxypyrimidine-5-carboxylic acid (**2**) was 14 % from [¹⁴C] barium cyanamide.

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4 Summary

The employed methodology lead to a successful labeling of 2-methoxypyrimidine-5-carboxylic acid in the 2-position with ¹⁴C. This method also offers an approach to pyrimidine carboxylic acid derivatives **3** with ¹⁴C label at 4-, 5-, 6- position as well as the carboxyl function by using appropriately [¹⁴C] labeled methyl formate or methyl 3, 3-dimethoxypropionate.