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Short Research Article

Cu(I)Br-mediated preparation of ^{14}C-labeled 3-pyridineacetate derivatives and synthesis of a novel ^{14}C-labeled PDE-IV inhibitor†

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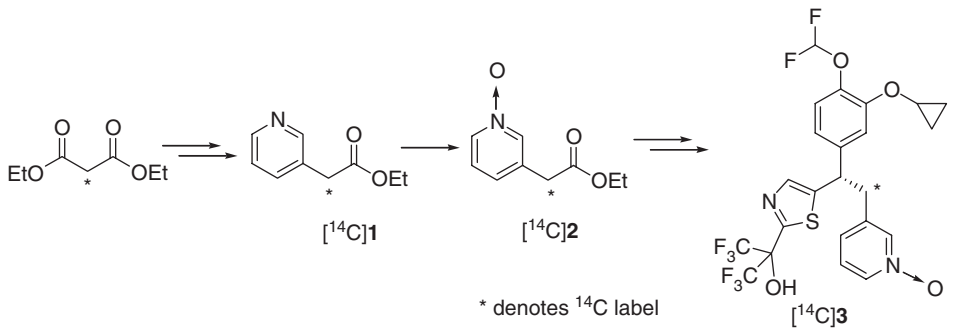
Abstract: An efficient protocol for the synthesis of ^{14}C-labeled 3-pyridineacetate (**1**) and its *N*-oxide ([^{14}C]**2**) is described. Oxidation of this pyridine ([^{14}C]**1**) to its *N*-oxide ([^{14}C]**2**) proceeded in high yield using H_2O_2 with $MeReO_3$ as a catalyst. The reaction employs readily available diethyl [2-^{14}C]malonate. This method has proven to be general in preparation of other pyridineacetate derivatives and their *N*-oxides which have been typically difficult to prepare by other means. Our development of the Cu(I)Br-coupling methodology as well as application to the synthesis of a ^{14}C-labeled phosphodiesterase-IV (PDE-IV) inhibitor, [^{14}C]**3**, are also reported. Copyright © 2007 John Wiley & Sons, Ltd.



Keywords: carbon-14 isotope labeling; Cu(I)Br-mediated reactions; 3-pyridineacetate

Introduction

At first sight pyridineacetates appear as unexciting chemical entities, but in fact they have been used in a wide spectrum of interesting and diverse chemical reactions that integrate the pyridine ring into many pharmaceuticals.[1] The 3-pyridine group and its derivative play an important role in many biological active compounds for the treatment of asthma,[2] chronic obstructive pulmonary disease,[3] rheumatoid arthritis,[4] multiple sclerosis[5] and Crohn's disease.[6] Surveying the literature we were somewhat surprised by the lack of convenient protocols for the efficient and expedient synthesis of the ^{14}C-labeled ethyl 3-pyridineacetate intermediate. We report a convenient, straightforward Cu(I)Br-mediated method that affords ^{14}C-labeled 3-pyridineacetate derivatives in good yields.

Results and discussion

Our interest in ethyl ^{14}C-labeled 3-pyridineacetate as well as other ^{14}C-labeled pyridineacetate esters stem from a series of on-going PDE-IV research projects. Critical to their use for us was their synthesis in reasonable quantities (1–100 mCi) from readily commercially available ^{14}C-labeled starting materials.

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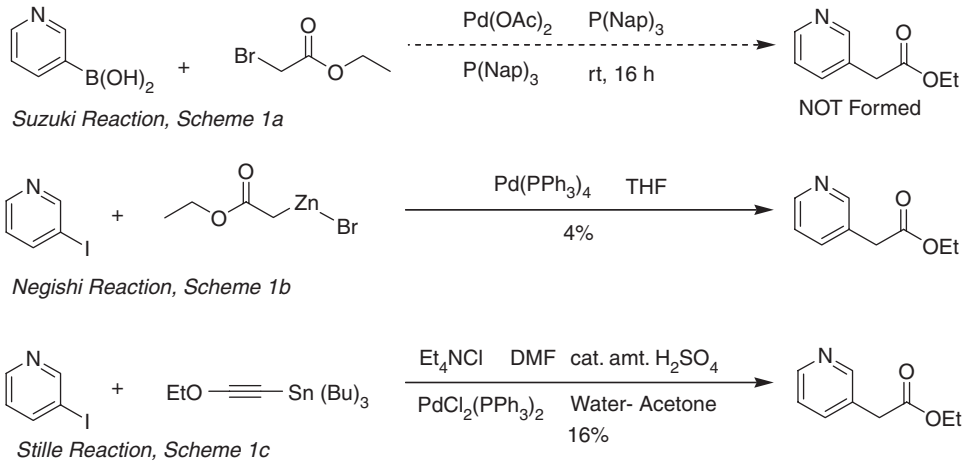

Scheme 1

Space considerations here do not permit a lengthy discussion on all our failed attempts. Nevertheless, the application of seemingly straightforward procedures proved problematic. For example, (a) Suzuki coupling between 3-pyridineboronic acid (or esters) and bromoacetate was fruitless (Scheme 1a)[7a]; (b) Negishi coupling employing palladium catalysts between 3-iodopyridine and organozinc reagents derived from ethyl 2-bromoacetate failed (Scheme 1b)[7b]; and (c) Stille reaction between 3-iodopyridine and a stannylacetylene afforded desired product, but the yield was very disappointing, merely 16% (Scheme 1c).[7c] The failure of these procedures forced us to search for an alternative protocol. In 1975, Bruggink and McKillop[8] reported a Cu(I)Br-mediated procedure for the coupling of ethyl acetoacetate and an aryl iodide.

It is interesting to note that although the Bruggink and McKillop methodology was reported over 30 years ago its utilization, as judged by citations, by the synthetic chemistry community has been largely nonexistent, a fact that may be attributed to the lack of understanding of its reaction mechanism compared to its counterpart of Pd-catalyzed reactions. We considered the Bruggink and McKillop process to have a number of merits, such as, the catalyst, Cu(I)Br, is cheap and readily available, the protocol is straightforward and uncomplicated with no requirement for the use of expensive ligands, and the reaction process appears to be versatile with the capacity to afford multigram quantities of products. This is in contrast to the procedures outlined in Scheme 1. For the purpose of further chemical manipulation it was important to us that the product is an acetate, not a malonate, or an acetoacete. With this in mind we attempted the synthesis of **1** (Scheme 2) using a procedure similar to that reported by Bruggink and McKillop. Stirring a mixture of ethyl malonate potassium salt, 3-iodopyridine, Cu(I)Br, $MgCl_2$ and EtOH at 100°C for 4 h afforded the desired ethyl 3-pyridineacetate in 88% yield. It is important to choose ethyl malonate potassium salt as the starting material since this will undergo *in situ* deccaboxylation to form the acetate. The role of $MgCl_2$ is to facilitate the decarboxylation; without it, longer reaction time would be needed and the yield of the desired product would be lower. When diethyl malonate is used, the product is diethyl 3-pyridinemalonate.[9] With a reliable procedure in place we probed the versatility of the procedure applying it to a range of iodopyridines to afford corresponding pyridineacetates (Scheme 2). This study confirmed that this method is robust because it works for both electron-rich and poor iodopyridines.

With this positive result in hand we conducted our 'hot' reactions (Scheme 3). By hydrolysis with 1 equiv. of KOH, diethyl [2-^{14}C]malonate was converted to ethyl [^{14}C]malonate, potassium salt, and a crystalline compound. Utilizing our modified protocol mentioned above, ethyl 2-(pyridine-3-yl)[2-^{14}C]acetate ([^{14}C]**1**) was obtained. Oxidation of [^{14}C]**1** to its *N*-oxide [^{14}C]**2** was carried out using H_2O_2 with $MeReO_3$ (MTO) as a catalyst.[10]

In an effort to develop new therapeutic agents for the treatment of asthma, Merck has been engaged in the study of phosphodiesterase-IV (PDE-IV) inhibitors. PDE-IV is a high-affinity c-AMP-selective isozyme and is found in all cell types that have been implicated in asthma pathogenesis.[11] Candidate **3** was identified as a potent, selective PDE-IV inhibitor[12] and a ^{14}C-labeled tracer was needed for drug metabolism studies. Thanks to the effort of Merck process research, a 13-step synthesis of **3** was developed, and the compound **4** is an advanced intermediate from the 9th step of that very

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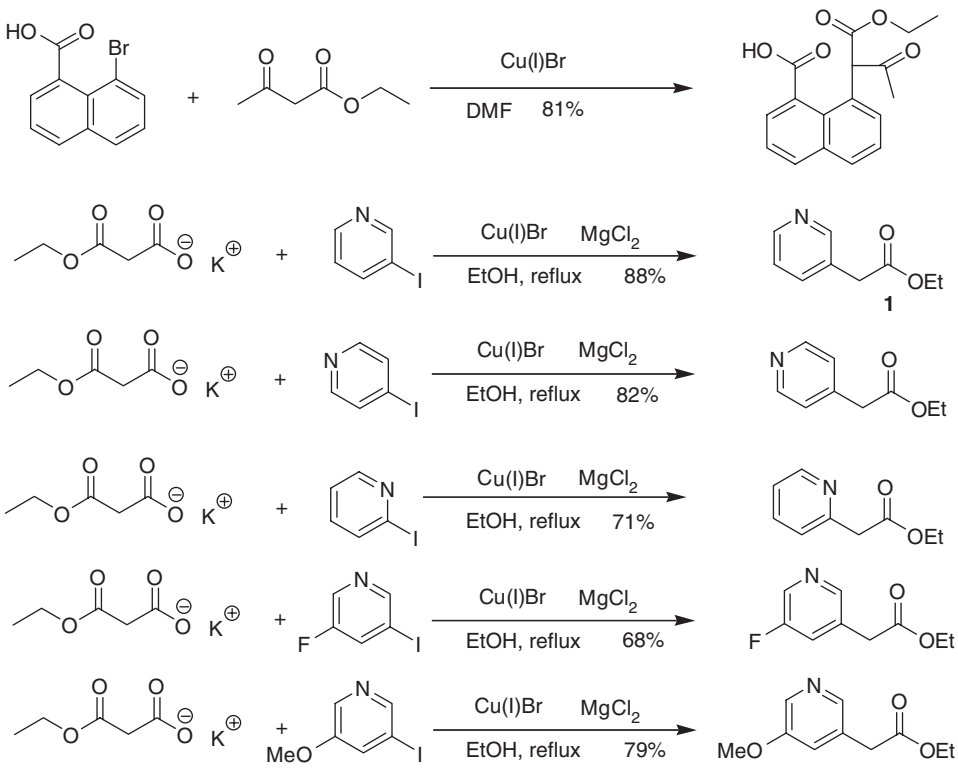
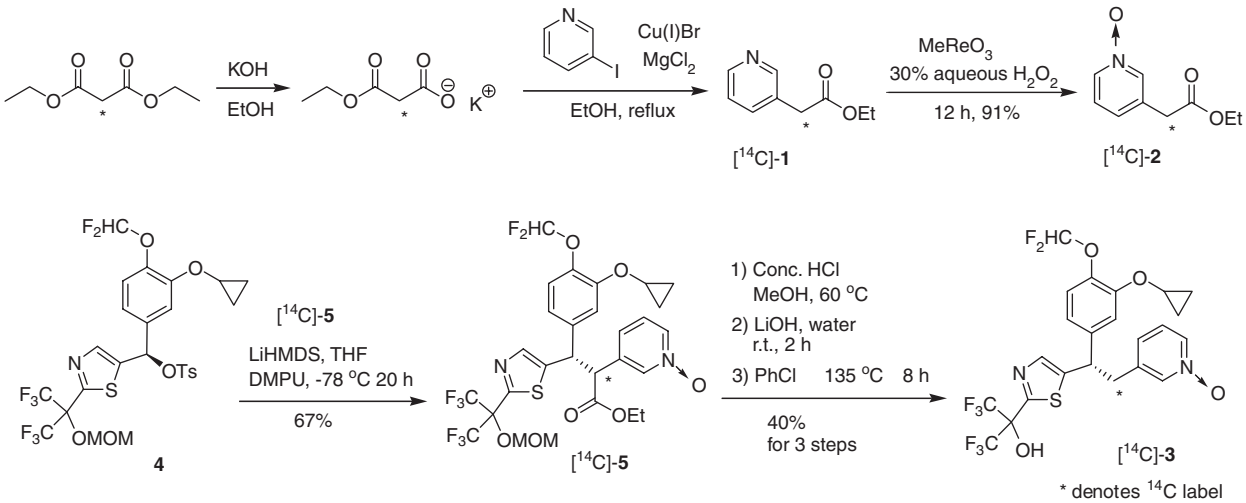


Scheme 2



Scheme 3

procedure.[13] Alkylation of compound **4** with [^{14}C]**2** gave [^{14}C]**5** in 67% (Scheme 3). The MOM protection group was removed with concentrated HCl, the ethyl ester was hydrolyzed utilizing aqueous LiOH, and the resulting acid was decaboxylated at 135°C to afford the final tracer [^{14}C]**3**. The overall yield for this one-pot, three-step reaction was 40%.

Conclusion

We have developed an efficient Cu(I)Br-mediated protocol for the synthesis of ^{14}C-labeled 3-pyridineacetate (**1**). We have also demonstrated that this procedure is general for the preparation of both electron-rich and poor pyridineacetate derivatives. Using [^{14}C]**1**, the

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synthesis of a novel PDE-IV tracer of [^{14}C]**3** has been accomplished.

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