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Copper-mediated reaction of 2-halopyridines with ethyl bromodifluoroacetate

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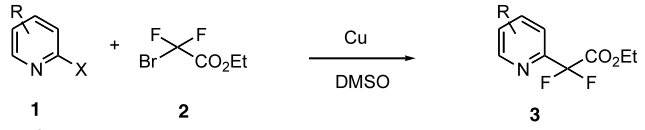
Abstract—A facile process for the preparation of substituted ethyl 2′-pyridyldifluoroacetates **3** is described starting from readily available ethyl bromodifluoroacetate **2** and substituted 2-bromo or 2-chloropyridines **1**. This process features a copper-mediated cross-coupling reaction in DMSO and is the first to utilise pyridylbromides or chlorides with ethyl bromodifluoroacetate **2** in this reaction. © 2002 Published by Elsevier Science Ltd.

As part of our program to develop novel thrombin inhibitors we required a facile route to substituted 2′-pyridyldifluoroacetates. Potential routes that were investigated involved the difluorination of α-ketoesters with either diethylaminosulphur-trifluoride (DAST)[1] or Deoxo-Fluor,[2] or the electrophilic fluorination of ethyl pyridylacetates.[3] These routes involved the use of highly toxic reagents or commercially unavailable starting materials and as a result had limited utility.

We wish to report a facile synthesis of substituted 2′-pyridyldifluoroacetates **3** involving a copper-mediated cross-coupling reaction of readily available pyridyl halides **1** with ethyl bromodifluoroacetate **2**.



1 X= Cl, Br **2** **3**

Scheme 1.

The copper-mediated coupling of methyl iododifluoroacetate with 2-bromopyridine giving the required difluoropyridyl methyl ester has been described in the literature by Kobayashi.[4] However, the starting ester is expensive and not available in bulk quantities. It was reported that coupling reactions of the related methyl bromodifluoroacetate were less successful, higher temperatures being required and poorer yields obtained. Kobayashi also described the reaction of (methyl difluoroacetate) copper reagent with bromobenzene in DMSO to give methyl phenyldifluoroacetate in 79% yield.[5]

The literature also described the preparation of aryldifluoroacetates using a copper complex from ethyl bromodifluoroacetate. Aryl iodides were reacted with the copper complex to give 53–66% yields of the aryldifluoroacetates. An attempt at using bromobenzene resulted in the recovery of unreacted starting material.[6]

Ethyl bromodifluoroacetate **2** has been used in Reformatsky reactions to prepare α,α-difluoromethylene-functionalised compounds.[7] In situ preparation of this zinc reagent and attempted palladium-catalysed coupling reaction with 2-bromo or 2-iodopyridine failed to give the required pyridyldifluoroacetate **3** in contrast to the reported reaction using ethyl bromoacetate.[8]

Here we demonstrate that good yields of substituted 2′-pyridyldifluoroacetates **3** can be obtained directly from the reaction of commercially available ethyl bromodifluoroacetate **2** and substituted 2-halopyridines **1**.

We discovered that stirring the readily available ethyl bromodifluoroacetate **2** with 2-bromopyridine (**1**, X= Br) and copper bronze[9] in DMSO at 50°C gave the

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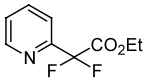
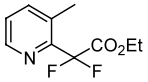
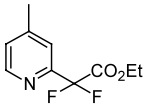
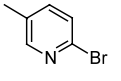
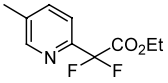
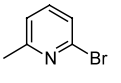
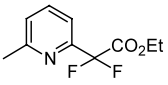
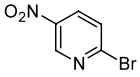
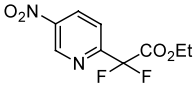
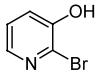
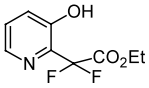
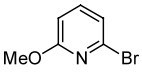
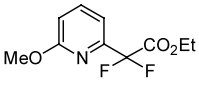
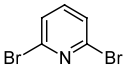
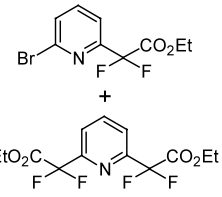
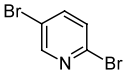
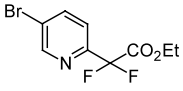
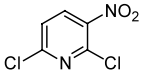
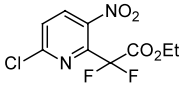
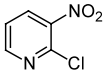
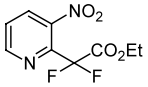
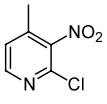
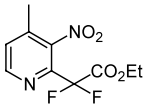
required ethyl (2′-pyridyl)-2,2-difluoroacetate **3** in 82% yield. The reaction was complete within 2 hours.

Other sources of copper (active Raney type or copper beads (40, 100 and 200 μm)) were successfully used in this reaction. Copper bronze gave shorter reaction times and higher yields. During the extractive work-up the heterogeneous reaction was buffered with potassium dihydrogen phosphate (pH 4.5) to prevent hydrolysis of the sensitive ester group.[10]

The reaction was also successfully carried out using DMF as the solvent, giving the required pyridylacetate **3** in an almost identical yield. However in DMF the

Table 1. Pyridyldifluoroacetates **3** prepared via Scheme 1

Entry	Pyridine 1	Product 3[a]	Isolated Yield %
1			82 81[b]
2			75
3			66
4			70
5			85
6			66
7			53
8			50
9			80[c]
10			53
11			71
12			65
13			38

[a] Products were characterised by ^{1}H, ^{13}C , ^{19}F NMR and either high resolution mass spectrometry or elemental analysis.

[b] Reaction carried out in DMF gave a similar yield of the pyridylacetate

[c] A 1:1 mixture of the mono and dialkylated pyridines was formed.

reaction was slower, requiring 8 hours for complete consumption of starting material.

We decided to explore the generality of this reaction by using a variety of bromo and chloro substituted pyridines (**1**, X = Cl, Br). The results are sumarised in Table 1.

2-Bromopyridine and alkyl bromopyridines (entries 1–5) gave good yields of the 2′-pyridyldifluoroacetates **3**. Electron-withdrawing groups on the pyridine ring, e.g. 5-nitro-2-bromopyridine (entry 6) also gave a good yield of the acetate. 3-Hydroxy-2-bromopyridine (entry 7) gave a moderate yield of the acetate. Electron-donating groups at the 6-position as in 6-methoxy-2-bromopyridine (entry 8) also gave a moderate yield of the 6-methoxyacetate.

2,6-Dibromopyridine (entry 9), not surprisingly, gave a mixture of mono and disubstituted pyridylacetates in good yield, whereas 2,5-dibromopyridine (entry 10) selectively gave 5-bromo-2′-pyridyldifluoroacetate. 3-Bromopyridine, 5-bromo-2-nitropyridine and 3,5-dibromopyridine did not react at all under these conditions.

Activated 2-chloropyridines (**1**, X = Cl) were also substrates for this reaction. A nitro group at the 3-position was required to activate the 2-chloropyridine, whereas a nitro group in the 5-position did not activate the 2-position sufficiently. 2-Chloro-3-nitropyridine (entry 12) gave a good yield of the 3-nitropyridyldifluoroacetate. 2,6-Dichloro-3-nitropyridine (entry 11) gave a single product selectively alkylated at the 2-position (the 3-nitro group activating the 2-position but not the 6-position). This was also supported by the fact that 2,6-dichloropyridine and 2-chloro-5-nitropyridine did not react whereas 2-chloro-3-nitropyridine gave the 3-nitropyridyldifluoroester in good yield (entry 12).

The mechanism of these reactions is unclear.[5,6] For complete reaction 2.1 equivalents of copper were required, one equivalent giving only a 50% conversion of 2-bromopyridine to the pyridyldifluoroacetate.

In conclusion, we have demonstrated the copper-mediated cross-coupling reaction of ethyl bromodifluoroacetate **2** with substituted 2-bromopyridines (**1**, X = Br) in DMSO to give moderate to good yields of substituted 2′-pyridyl-2,2-difluoroacetates **3**. 2-Chloro-3-nitropyridines are also reactive under these conditions.

Acknowledgements

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9. Flakes of copper 1 μ thick with a very high surface area.
10. Typical procedure: Copper bronze (0.9 g; 14.2 mmol) was added to a solution of ethyl bromodifluoroacetate (1.35 g; 6.7 mmol) and 2-bromopyridine (1.0 g; 6.3 mmol) in DMSO (5 mL). The mixture was heated to 50°C and stirred at this temperature for 2 hours. The reaction mixture was cooled to 20°C and diluted with isopropyl acetate (10 mL). A solution of potassium dihydrogen phosphate (1.27 M; 15 mL) was added and the mixture stirred for 30 minutes before filtering. The copper salts were washed with isopropyl acetate (10 mL). The filtrate layers were separated and the organic layer washed with water (2×10 mL). The organic layer was evaporated to an orange oil, which was purified on silica gel with 4:1 hexane:methyl *tert*-butyl ether as eluant. Ethyl 2-(2′-pyridyl)-2,2-difluoroacetate (1.05 g) was obtained as a colourless oil in 82% yield. ^{1}H NMR (CD_2Cl_2): δ ppm 1.19 (t, J = 7.2 Hz, 3H), 4.25 (q, J = 7.2 Hz, 2H), 7.39 (tddd, J = 0.8, 1.3, 4.8, 7.6 Hz, 1H), 7.65 (td, J = 1.3, 7.9 Hz, 1H), 7.82 (tddd, J = 0.3, 1.8, 7.6, 7.9 Hz, 1H), 8.58 (tdd, J = 0.7, 1.5, 4.8 Hz, 1H). ^{13}C NMR (CD_2Cl_2): δ ppm 13.6, 63.1, 111.6, 120.6, 125.9, 138.3, 149.3, 151.3, 163.1. ^{19}F NMR (CD_2Cl_2): δ ppm −105.8. MS/HRMS: calcd for $C_9H_{10}F_2NO_2$ ($M+H^+$) 202.0680, found 202.0674.