Synthesis of [$^2\text{H}_5$]baricitinib via [$^2\text{H}_5$]ethanesulfonyl chloride

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1 | INTRODUCTION

Baricitinib (1, Figure 1), a Janus kinase (JAK) inhibitor typically used in the treatment of rheumatoid arthritis, has recently garnered interest for its potential application as an antiviral treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).$^{1-5}$ To probe the utility of baricitinib in treating COVID-19, isotope-labelled baricitinib would be beneficial for use as a mass spectrum internal standard in bioanalytical assays to quantify the concentration of the drug in biological samples, as has been shown with other drugs.$^6,7$ Although the synthesis of deuterium-labelled baricitinib, specifically [$^2\text{H}_5$]baricitinib, has been published, this was prophetic and involved the use of noxious gaseous reagents.$^8$ Thus, we were motivated to develop an alternative synthetic route to [$^2\text{H}_5$]baricitinib (2, Figure 1). Because we chose to insert the deuterium on the ethanesulfonyl component of 2, a major component of the research involved finding a suitable route to the necessary precursor: a deuterated form of ethanesulfonyl chloride. The results from this exploration are presented in this work.

2 | RESULTS AND DISCUSSION

We chose to insert the deuterium on the ethanesulfonyl component via [$^2\text{H}_5$]ethanesulfonyl chloride (3) after rationalizing that 3 could be converted to the stable intermediate 5 upon reaction with 4. Compound 5 could then be converted to the desired product 2 in a further two steps (reaction of 5 with commercially available 6 to form intermediate 7, followed by trimethylsilylthioethylmethyl [SEM] deprotection of 7 to provide 2) (Scheme 1). Our synthetic approach was derived from the original route to non-deuterated baricitinib developed by Rodgers et al.$^9,10$
The main challenge associated with this approach largely lay in the first step: the preparation and isolation of 3, as this compound is not available commercially. A preliminary literature search revealed several routes to non-deuterated ethanesulfonyl chloride. However, a prerequisite for selection of a route for the preparation of 3 was the availability of deuterated substrates. Thus, routes commencing with diethyl disulfide\(^{11-14}\) (route A), sodium ethanesulfonate\(^{15}\) (route B) and ethanesulfonic acid\(^{16}\) (route C) (Scheme 2) were not selected as none of these substrates are commercially available in the deuterated form. Route D, a prophetic route from the patent literature,\(^{8}\) involved the use of noxious gases SO\(_2\) and Cl\(_2\), so was also not attempted. Instead, we chose to explore routes E and F, which used \([\,{}^2\text{H}_5\,]\)bromoethane (8) and \([\,{}^2\text{H}_5\,]\)ethanethiol (9), respectively.

Preparation of 3 using route E is based on the procedure reported by Yang and Xu.\(^{17}\) However, as our highest yield utilizing this approach was only 31\%, we attempted the synthesis of 3 via route F, based on a procedure developed by Park et al.,\(^{18}\) commencing with \([\,{}^2\text{H}_5\,]\)ethanethiol (9).

Starting with commercial \([\,{}^2\text{H}_5\,]\)ethanethiol (9), an average yield of 46\% of 3 was obtained. However, given the very high cost of 9, we also explored the possibility of preparing it from \([\,{}^2\text{H}_5\,]\)ethanol (10) via an interchange reaction with commercially available tris(ethylthio)methane, which has previously been published for the preparation of non-labelled ethanethiol.\(^{19}\) Unfortunately, this reaction (10 → 9) only provided 9 in relatively low yield (28\%). Nevertheless, we were able to prepare sufficient of 3 using the two routes to proceed to the next step of the sequence.

Coupling of 3 with freshly prepared 4, obtained by N-Boc deprotection of tert-butyl 3(cyanomethylene)azetidine-1-carboxylate,\(^{8}\) resulted in the formation of 5 in a high yield (94\%), without the need for further purification. The following step, a nucleophilic addition reaction between compound 4 and commercially available 4-(1H-pyrazol-4-yl)-7-(2-(trimethylsilyl)ethoxy)methyl)-7\(\text{H}\)-pyrrolo[2,3-\(d\)]pyrimidine (6), based on the procedure published in the patent literature,\(^{20}\) proceeded in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at r.t., resulting in the formation of 7 in quantitative yield. SEM deprotection of 7 was attempted unsuccessfully with LiBF\(_4\)/MeCN,\(^{21,22}\) TFA/ethylene diamine\(^{23}\) and BF\(_3\)/Et\(_2\)O,\(^{24}\) before complete deprotection was achieved by reaction with a 1 M solution of tin(IV) chloride at room temperature followed by a basic workup at 0°C\(^{25}\) forming 2 in 66\% yield. This approach was employed thereon. The yield of the entire reaction sequence was a reasonable 29\%.
CONCLUSION

In this paper, we report the synthesis of \([2H_5]\)baricitinib in an overall 29% yield. Our synthetic pathway was based on the route to non-deuterated baricitinib developed by Rodgers et al.\(^\text{10}\) Several routes to the important non-commercial intermediate \([2H_5]\)ethanesulfonyl chloride were considered; however, only two were explored experimentally, and we found that the route commencing from \([2H_2]\)bromoethane was slightly lower yielding (31%) compared with when the synthetic sequence commenced with \([2H_5]\)ethanethiol (46%). These synthetic routes provide an opportunity to prepare \([2H_5]\)baricitinib, circumventing the need to purchase it. \([2H_5]\)Baricitinib is significant as an internal reference standard or potentially a COVID-19 therapeutic with improved efficacy compared with the non-deuterated analogue. To evaluate the latter, metabolic profiling studies of both baricitinib and \([2H_5]\)baricitinib must be carried out.

EXPERIMENTAL

\(^1\)H NMR (400 and 500 MHz) and \(^13\)C NMR (101 and 126 MHz) spectra were recorded on Bruker AV-400 and NEO-500 instruments in CDCl\(_3\) or DMSO-\(d_6\) (as indicated). The chemical shifts are reported in \(\delta\) (ppm) relative to residual CHCl\(_3\) or DMSO, respectively, as the internal standard. High-resolution mass spectra (HRMS) were recorded on a Micromass 70-250S double focusing mass spectrometer.

4.1 Materials

All dry solvents used were purified under an argon atmosphere according to Armarego and Chai\(^\text{26}\) or purchased from commercial sources. \(N\)-Chlorosuccinimide (NCS) was recrystallized from glacial acetic acid. All commodity chemicals were purchased from commercial sources and used without further purification. \textit{tert}-Butyl 3-(cyanomethylene)azetidine-1-carboxylate was obtained from Ambeed (A124948). 4-(1H-Pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)-methyl)-7\(^H\)-pyrrolo[2,3-\(d\)]pyrimidine was obtained from Combi-Blocks (ST-0174). Tris(ethylthio)methane was obtained from TCI Chemicals (T3140). \(\text{ZnCl}_2\) (anhydrous, free-flowing, Redi-Dri\textsuperscript{TM}, reagent grade, \(\geq 98\%\)), boron trifluoride diethyl etherate (BF\(_3\)Et\(_2\)O), lithium tetrafluoroborate (LiBF\(_4\)), ethylene diamine, trifluoroacetic acid (TFA), sulfuryl chloride (SO\(_2\)Cl\(_2\)) and methyl \textit{tert}-butyl ether (MTBE) were obtained from Aldrich. Deuterated chemicals were obtained from CDN Isotopes. Trifluoroacetic acid (TFA), \(N,N\)-diisopropylethylamine (DIPEA) / Hünig’s base, DBU and anhydrous acetonitrile (MeCN) were obtained from Alfa Aesar and used without further purification.
4.2 | Experimental procedures

4.2.1 | $[^2]H_5$Ethanesulfonyl chloride (3)

Route E$^{17}$: $[^2]H_5$Bromothane (5.00 g, 48.9 mmol) and thiourea (3.33 g, 48.9 mmol) were refluxed in anhydrous ethanol (44 ml) for 1 h. After cooling the reaction mixture to r.t., the ethanol was removed in vacuo, and the residual white oil was slowly added to a stirred mixture of NCS (29.3 g, 219.3 mmol) and 2 M HCl (aq) (22 ml) in MeCN (56 ml) at 10°C, which gradually became a bright yellow solution in the process. This new reaction mixture was stirred at 10°C for a further 30 min before Et$_2$O (50 ml) was added and the organic components extracted. The organic layer was then concentrated to an orange oil, which was then dried over MgSO$_4$. The resultant residue (aromatic oil) was added and the organic components extracted. The organic layer was then concentrated to an orange oil, which was immediately used in the next step to form compound 5. Route F$^{18,19}$: A mixture of tris(ethylthio)methane (4.7 ml, 25 mmol) in anhydrous ZnCl$_2$ (102 mg, 0.75 mmol) for 48 h before freshly distilled sulfuryl chloride (4.2.2 | $[^2]H_5$Ethanesulfonyl chloride (3) was added dropwise, ensuring that a temperature of <5°C was maintained throughout. The reaction mixture was allowed to warm to room temperature before being left to stir at this temperature for 16 h. The reaction mixture was concentrated in vacuo, and the resultant residue (a red/orange oil) was diluted with DCM (100 ml) before being washed with brine (100 ml). The combined organic fractions were dried over anhydrous Na$_2$SO$_4$ before the solvent was removed in vacuo. The crude material was purified by flash chromatography over silica using hexane/ethyl acetate (60/40/20/80) as eluent, to obtain 1.94 g (94%) of 5 as a yellow oil, which forms a white amorphous solid when left to stand: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 5.38 (s, 1H), 4.72–4.62 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 155.3, 113.9, 94.6, 58.9, 58.6 (should only be 4). HRMS (ESI-TOF) m/z: [M + H]$^+$ calc'd for C$_{22}$H$_{27}$D$_5$O$_3$N$_7$SSi 507.2350; found 507.2365.

4.2.2 | $[^2]H_5$2-(1-((Ethyl)sulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)azetidin-3-ylidene)acetonitrile (5)

TFA (28 ml, 360 mmol) was added dropwise to a solution of tert-butyl 3-(cyanomethylene)azetidine-1-carboxylate (3.5 g, 18 mmol) in anhydrous DCM (250 ml), which was stirred at r.t. for 5 h before being reduced to dryness in vacuo: 2.2 g of 4, an amorphous white solid, was obtained and immediately suspended in 211 ml of anhydrous acetonitrile under an inert atmosphere at 0°C. DIPEA (11.7 ml, 67.4 mmol) was added dropwise, ensuring that a temperature of <5°C was maintained throughout. This was followed by the dropwise addition of 3 (1.8 g, 13.5 mmol), also ensuring that a temperature of <5°C was maintained throughout. The reaction mixture was allowed to warm to room temperature before being left to stir at this temperature for 16 h. The reaction mixture was concentrated in vacuo, and the resultant residue (a red/orange oil) was diluted with DCM (100 ml) before being washed with brine (100 ml). The combined organic fractions were dried over anhydrous Na$_2$SO$_4$ before the solvent was removed in vacuo. The crude material was purified by flash chromatography over silica using hexane/ethyl acetate (60/40/20/80) as eluent, to obtain 1.94 g (94%) of 5 as a yellow oil, which forms a white amorphous solid when left to stand: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 5.38 (s, 1H), 4.72–4.62 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 155.3, 113.9, 94.6, 58.9, 58.6 (should only be 4). HRMS (ESI-TOF) m/z: [M + H]$^+$ calc'd for C$_{22}$H$_{27}$D$_5$O$_3$N$_7$SSi 507.2350; found 507.2365.
4.2.4 | $[^2]H_5$Baricitinib (2)

To an ice-cold (0°C) solution of 7 (850 mg, 1.68 mmol) in anhydrous DCM (50 ml) was added a solution of SnCl$_4$ (23 ml, 1 M in DCM) over 30 min. This reaction mixture was stirred at 0°C before being left to warm to r.t. until the deprotection was complete (progress tracked using TLC). The reaction mixture was then cooled to 0°C and quenched with 4% NaOH (added until pH = 8) before being left to stir for a further 15 min. The organic fraction was then separated, washed with brine (50 ml), dried over Na$_2$SO$_4$ and filtered. Upon standing, white crystals were left to stir for a further 15 min. The organic fraction was quenched with 4% NaOH (added until pH 2) before being left to stir for a further 15 min. The organic fraction was then separated, washed with brine (50 ml), dried over Na$_2$SO$_4$ and filtered. Upon standing, white crystals precipitated from the filtrate; these were dried under ambient conditions to give 510 mg of the product (2) (81%) as a white powder: $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ ppm 12.15 (s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (d, $J$ = 9.5 Hz, 2H), 7.41 (d, $J$ = 3.5 Hz, 1H), 7.09 (d, $J$ = 3.5 Hz, 1H), 4.61 (d, $J$ = 9.5 Hz, 2H), 4.24 (d, $J$ = 9.5 Hz, 2H), 3.70 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-d$_6$) $\delta$ ppm 152.2, 150.9, 149.3, 139.9, 129.6, 126.9, 122.2, 116.6, 113.0, 99.9, 58.5, 56.0, 26.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{16}$H$_{12}$D$_5$N$_7$O$_2$S 377.15350; found 377.15510.

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**CONFLICT OF INTERESTS**

The authors report no conflicts of interest.

**DATA AVAILABILITY STATEMENT**

Data are contained within the article.

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