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Synthesis of [$^2H_5$]baricitinib via [$^2H_5$]ethanesulfonyl chloride

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Baricitinib, typically applied as a treatment for rheumatoid arthritis, has recently attracted the attention of clinicians and researchers as a potential treatment for COVID-19. Naturally, there has been a need for the preparation of the isotope-labelled analogue of baricitinib to probe the pharmacokinetics of baricitinib in this new role. As such, we have developed a simple synthetic route to deuterated [$^2H_5$]baricitinib, facilitating its formation over four steps and in a 29% overall yield based on starting [$^2H_5$]ethanethiol (19% if we start with [$^2H_5$]bromoethane instead). A critical component of the overall process involves the synthesis of [$^2H_5$]ethanesulfonyl chloride, and we describe in detail the two routes that were explored to optimize this step.

KEYWORDS
baricitinib, COVID-19, deuteration, deuterium-labelled, isotopologue, SARS-CoV-2

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 baricitnib, specifically [$^2H_5$]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 [$^2H_5$]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 [$^2H_5$]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 trimethylsilylethoxymethyl [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 [$^2H_5$]bromoethane (**8**) and [$^2H_5$]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 [$^2H_5$]ethanethiol (**9**).

Starting with commercial [$^2H_5$]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 [$^2H_5$]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-(1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy) methyl)-7*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 $BF_3{\cdot}Et_2O$,[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 thenceforth. The yield of the entire reaction sequence was a reasonable 29%.

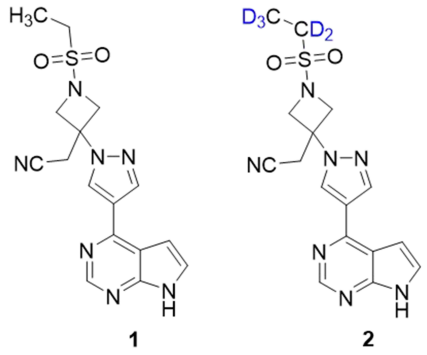
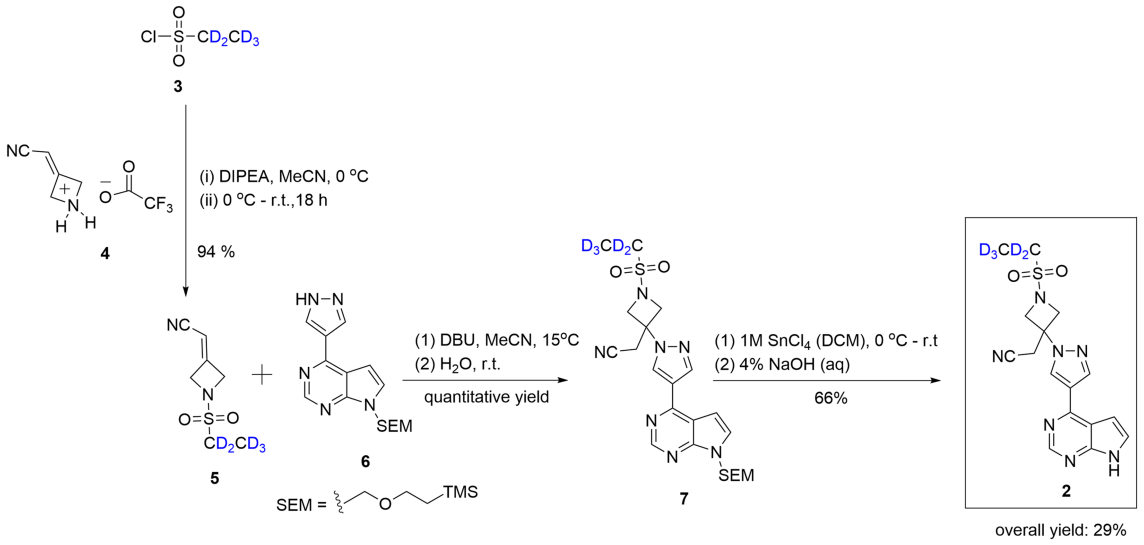
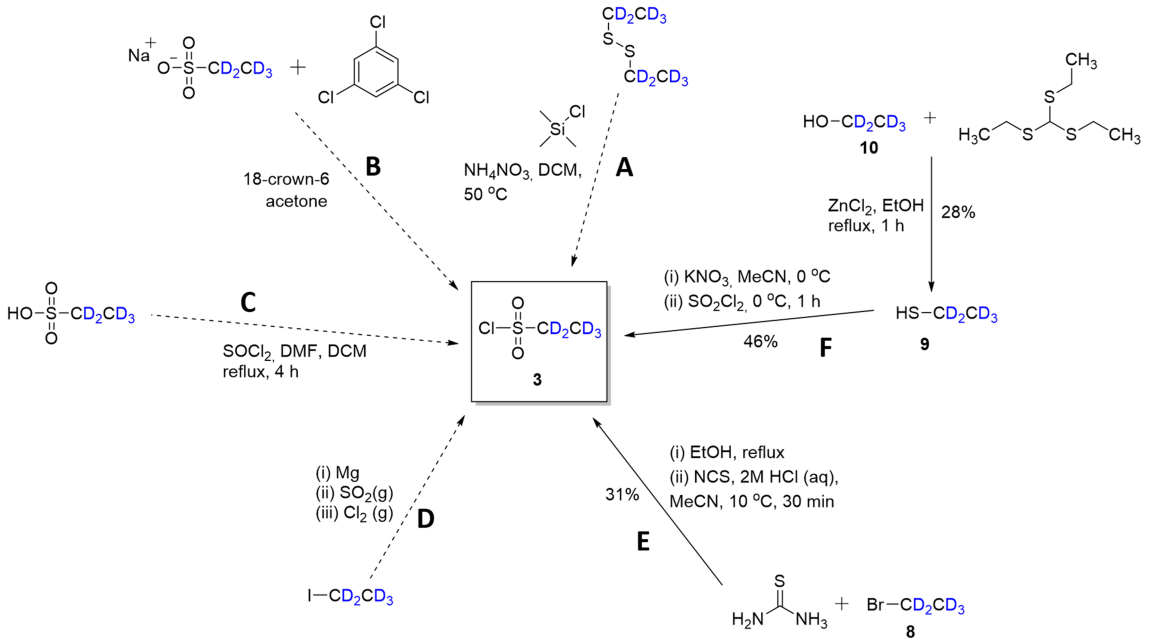


FIGURE 1 Chemical structures of baricitinib (**1**) and [$^2H_5$] baricitinib (**2**)



SCHEME 1 Synthetic route to [$^2H_5$]baricitinib (**2**) commencing from [$^2H_5$]ethanesulfonylchloride (**3**)



SCHEME 2 Various routes (**A**–**F**) to intermediate **3**

3 | 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.[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 [$^2H_5$]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.

4 | 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 δ (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[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. *tert*-Butyl 3-(cyanomethylene)azetidine-1-carboxylate was obtained from Ambeed (A124948). 4-(1*H*-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). $ZnCl_2$ (anhydrous, free-flowing, Redi-Dri™, reagent grade, ≥98%), boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$), lithium tetrafluoroborate ($LiBF_4$), ethylene diamine, trifluoroacetic acid (TFA), sulfuryl chloride (SO_2Cl_2) and methyl *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 | [$^2H_5$]Ethanesulfonyl chloride (**3**)

Route **E**[17]: [$^2H_5$]Bromoethane (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_2O (50 ml) was added and the organic components extracted. The organic layer was then concentrated to an orange oil, which was rapidly passed through a silica plug (eluent: hexanes → 1:4 [EtOAc:hexanes] → 2:3 EtOAc:hexanes; co-spot with commercially available non-deuterated ethanesulfonyl chloride: $R_f = 0.75$ in 2:3 EtOAc:hexanes; for visualization: stain by spraying TLC plate with a 10% solution of NaI in acetone[27]), enabling the isolation of **3** as a pale-yellow liquid (1.82 g, 31%), 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 [$^2H_5$]ethanol (5 g, 100 mmol) was refluxed with anhydrous $ZnCl_2$ (102 mg, 0.75 mmol) for 48 h before [$^2H_5$]ethanethiol (**9**) (1.88 g, 28%) was distilled off (oil bath set to 50°C); Ar balloon was attached to condenser to ensure reasonably constant internal pressure of ~1 bar. In order to contain the stench of the [$^2H_5$]ethanethiol, the flask containing the distillate must instantly be capped and transferred to the refrigerator for storage under Ar (or used immediately in the next step). [$^2H_5$]Ethanethiol (2 g, 29.8 mmol) was added to anhydrous MeCN (100 ml) under Ar at 0°C before freshly distilled sulfuryl chloride (SO_2Cl_2) (6 ml, 74.5 mmol) and anhydrous KNO_3 (7.53 g, 74.5 mmol) were rapidly added, and the reaction mixture was stirred for 1 h at 0°C. The mixture was then quenched by the dropwise addition of saturated $NaHCO_3$ (aq) (added until pH = 8) after which the organic component was extracted with Et_2O (3 × 40 ml), washed with brine (50 ml) and dried over anhydrous $MgSO_4$. Filtration followed by concentration of the filtrate *in vacuo* resulted in the isolation of 1.86 g of **3** (46%) as a pale-yellow liquid, taken immediately through to the next step.

4.2.2 | [$^2H_5$]2-(1-((Ethyl)sulfonyl)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_2SO_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*: $[M + H]^+$ calcd for $C_7H_5D_5N_2O_2S$: 192.08411; found 192.08496.

4.2.3 | [$^2H_5$]2-(1-((Ethyl)sulfonyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl) azetidin-3-yl)acetonitrile (**7**)

To a suspension of **5** (0.5 g, 2.61 mmol) and 4-(1*H*-pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)-methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (6.87 mg, 2.18 mmol) in anhydrous acetonitrile (6.83 ml) was added DBU (0.39 ml, 2.61 mmol) dropwise while keeping the temperature between 15°C and 25°C. After the addition of DBU, the reaction mixture was stirred for 30 min at r.t. until a precipitate formed. The reaction mixture was then allowed to stir for a further 16 h before being quenched with distilled water (10 ml) and stirred for a further 30 min at r.t. prior to filtering. The solid residue (**7**) was washed with water (50 ml) followed by MTBE (50 ml) and left to dry under ambient conditions before being collected (0.96 g, quantitative yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.88 (s, 1H), 8.48 (s, 1H), 8.37 (s, 1H), 7.44 (d, $J = 4$ Hz, 1H), 6.81 (d, $J = 3.5$ Hz, 1H), 5.70 (s, 2H), 4.66 (d, $J = 9.5$ Hz, 2H), 4.28 (d, $J = 9.5$ Hz, 2H), 3.57 (t, $J = 8$ Hz, $J = 8.25$ Hz, 2H), 3.43 (s, 2H), 0.94 (t, $J = 8.5$ Hz, $J = 8.25$ Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 152.3, 151.8, 150.1, 140.8, 128.8, 128.1, 123.4, 115.0, 114.4, 100.6, 72.8, 66.6, 58.9, 56.1, 27.7, 17.7, 1.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{27}D_5O_3N_7SSi$ 507.23504; found 507.23650.

4.2.4 | [$^2H_5$]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_2SO_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) δ ppm 12.15 (s, 1H), 8.94 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (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) δ 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 $C_{16}H_{12}D_5N_7O_2S$ 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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