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Fatty acid amide hydrolase inhibitors. 2. Novel synthesis of sterically hindered azabenzhydryl ethers and an improved synthesis of VER-156084

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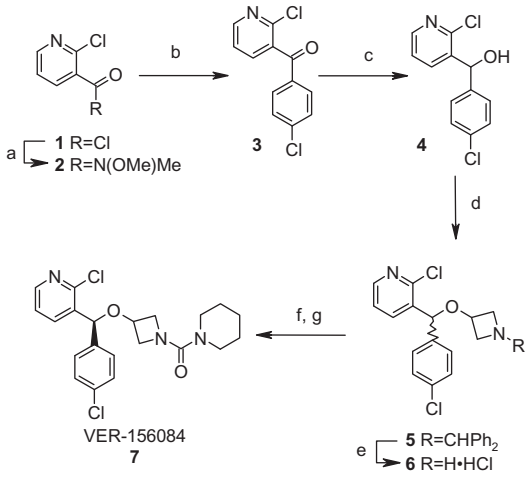
ABSTRACT

We report an improved synthesis of the fatty acid amide hydrolase (FAAH) inhibitor VER-156084. The key step is a novel, environmentally benign etherification to form an unusual, highly hindered azabenzhydryl ether. The method is applied to a variety of primary and secondary alcohols.

We have recently disclosed the discovery of VER-156084 (**7**), a potent and selective inhibitor of fatty acid amide hydrolase (FAAH).[1] Our initial synthesis of the compound was according to that previously described for our CB_1 antagonist programme (Scheme 1),[2] however, the incorporation of the benzhydryl ether portion of the molecule resulted in poor yields in the ether formation step. As part of our ongoing studies into FAAH inhibitors we required an improved route to azabenzhydryl ethers to provide analogues of VER-156084 and sufficient quantities of VER-156084 to support in vivo studies. In this Letter, we describe the results of our investigations in this area, leading to a new method for the formation of hindered azabenzhydryl ethers, which we have demonstrated to be of broad synthetic utility.

Our original route to VER-156084 involved a seven-step synthesis, in 5% overall yield (Scheme 1).[1] Whilst the three-step route to the azabenzhydrol intermediate **4** worked reasonably well (74% over three steps), a shorter route would offer operational advantages. Consequently, we investigated the addition of 4-chlorophenylmagnesium bromide to the commercially available 2-chloronicotinonitrile (**8**).[3,4] In our hands, none of the expected ketone **3** was obtained in this reaction (Scheme 2). Instead, we considered the direct formation of **4** by reaction of 2-chloronicotinaldehyde (**9**)[4] with the Grignard reagent. Surprisingly, we were unable to find any literature reports of Grignard reagent additions to **9**, although the analogous reaction of 2-chloroquinoline-3-carboxaldehyde (THF, rt 10 min, 85–95%) had been reported.[5] Reaction of **9** with 4-chlorophenylmagnesium bromide under these conditions gave **4** as a crystalline solid in 87% yield. This route proved readily amenable to the synthesis of 30 g quantities of **4**.



Scheme 1. Synthesis of VER-156084.[1] Reagents and conditions: (a) MeNHOMe·HCl, 83%; (b) 4-Cl-C_6H_4MgBr, 100%; (c) $NaBH_4$, 89%; (d) 1-Ph_2CH-azetidin-3-ol, PTSA, PhMe 35%; (e) 1-chloroethyl chloroformate then MeOH, 85%; (f) chiral HPLC; (g) triphosgene, piperidine, 50%.

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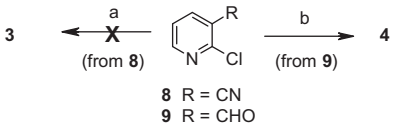


Scheme 2. Reagents and conditions: (a) 4-Cl-C_6H_4MgBr, THF, rt, 4 d, 0%; (b) 4-Cl-C_6H_4MgBr, THF, rt, 10 min; 87%.

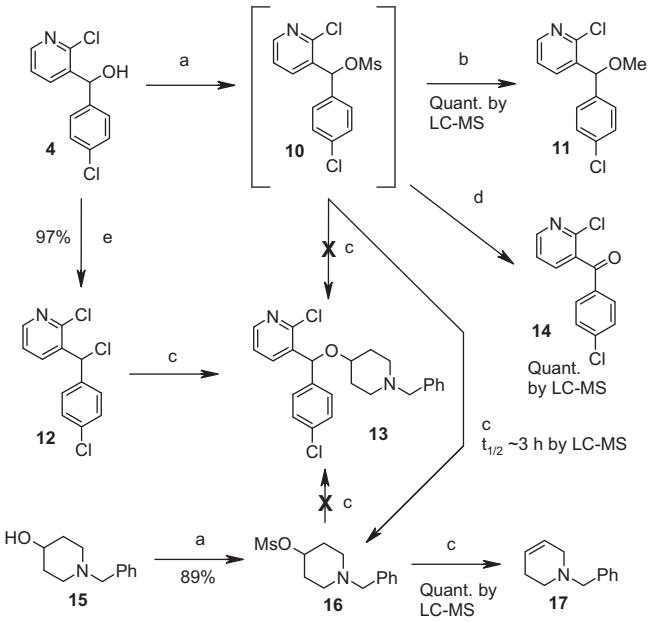
With improved access to **4**, we turned our attention to the troublesome ether formation step. Whilst the synthesis of benzhydryl ethers is well documented,[6] there are very few reports on the synthesis of azabenzhydryl ethers with hindered alcohols.[7,8] We therefore carried out a screen of conditions for the synthesis of the azabenzhydryl ether **13**, using *N*-benzylpiperidin-4-ol **15** as the nucleophilic alcohol component, as it is readily available commercially,[4] and the resulting ^{1}H NMR spectrum of the product would have fewer overlapping aromatic resonances than the benzhydryl-protected azetidine.

Our initial investigations centred on introduction of a leaving group to one component and generation of the alkoxide of the other component (Scheme 3). Thus, mesylation of **4** (MsCl, Et_3N, CH_2Cl_2 or THF) proceeded cleanly to give the highly activated mesylate **10**, which was used immediately in the following reactions. Addition of mesylate **10** to the pre-formed alkoxide of **15** failed to give any of the desired ether (Table 1). This result is surprising, as **10** reacts rapidly with DMSO at ambient temperature in a Swern-like oxidation[9] process to give the ketone **14**, and with MeOH under similar conditions to give the methyl ether **11**. Instead, heating the alkoxide of **15** with mesylate **10** in THF–DMF resulted in mesylate transfer to give **16** with $t_{1/2}$ ~3 h. Reversal of the coupling partners by synthesis of the mesylate **16** of the piperidinol component and reaction with the alkoxide of **4** also failed to result in any ether formation, in this case **16** underwent elimination to **17** on prolonged heating, even on addition of catalytic NaI.

We next turned our attention to chloride as a leaving group. Thus, chlorination of **4** ($SOCl_2$, CH_2Cl_2, cat. DMF) proceeded cleanly, the resulting chloride **12** being considerably more stable than the corresponding mesylate **10**, however, reaction with the alkoxide of **15** again failed to give any of the desired product under a variety of conditions (Table 1).

Following the failure of our attempts to form the ether by introduction of a leaving group on one of the coupling partners, we returned to the investigation of acid- or Lewis acid-catalysed conditions, in order to see if we could improve the poor-yielding conditions previously reported (Scheme 1; PTSA, PhMe, Dean–Stark, 36%).[1,2] We believe that the poor yields in this reaction compared to the corresponding benzhydryl system[2,8] to be most likely due to the competing protonation of the pyridine group under acidic conditions, disfavouring generation of the intermediate carbocation (Fig. 1).

The results of our condition screen are shown in Table 2. Lewis acids in CH_2Cl_2 gave no reaction.[10] Three equivalents of PTSA were required, but in CH_2Cl_2 the reaction was slow. Higher temperatures gave an increased conversion as determined by LC–MS, but a number of unidentified by-products began to form. Addition of 4 Å molecular sieves hindered the reaction. Changing the solvent to PhMe gave a slight improvement, but the reaction mixture underwent significant decomposition at 200 °C. MeCN, 1,4-dioxane or water were detrimental to the reaction. Changing the catalyst to the milder PPTS in PhMe gave no reaction at 120 °C, but surprisingly gave 60% conversion into the highly hindered symmetrical ether **18** at 200 °C.[11] TFA or AcOH gave no reaction or acylation of **4** at higher temperatures. However, reaction at 125 °C in neat PTSA gave clean conversion into the required ether product **13** in 90% isolated yield after 3 h.[12] Using cH_2SO_4 resulted in extremely rapid and exothermic decomposition at rt.



Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2 or THF; (b) MeOH, rt; (c) See Table 1; (d) DMSO, rt; (e) $SOCl_2$, CH_2Cl_2, cat. DMF.

Table 1
Nucleophilic displacement conditions[a]

Electrophile	Base	Solvent	*T* (°C)	Comment[b]
10	—	CH_2Cl_2	rt	NR
10	K_2CO_3	CH_2Cl_2	rt	Trace product by LC–MS
10	NaH	THF/DMF[d]	rt	NR
10	NaH	THF/DMF[d]	75	Mesylate transfer $t_{1/2}$ ~3 h
10	—	DMSO[e]	rt	Oxidation to **14**
10	—	MeOH[e]	rt	Conversion to methyl ether **11**
16	NaH	DMF	rt	NR
16	NaH	DMF	75	Elimination of OMs to give **17**
16[c]	NaH	DMF	75	Elimination of OMs to give **17**
12	—	PhMe	125	NR
12[c]	—	PhMe	125	NR
12[c]	K_2CO_3	PhMe	125	NR

[a] All reactions carried out with 1.25 equiv of nucleophilic partner with LC–MS monitoring for 3 d.
[b] NR—no reaction.
[c] Catalytic NaI added.
[d] 2.5 equiv of nucleophile.
[e] Solvent is the nucleophile—reaction complete within 5 min.

With the optimal conditions identified, we next investigated the scope of the reaction (Table 3).[12,13] Nitrogen protection was not required, and Boc groups underwent very rapid cleavage under the reaction conditions. The reaction appeared to work well with a range of primary and secondary alcohols, although the reaction with *N*-benzhydryl azetidin-3-ol was poor. The reaction of **4** with commercially available 3-azetidinol hydrochloride in 81% yield al-

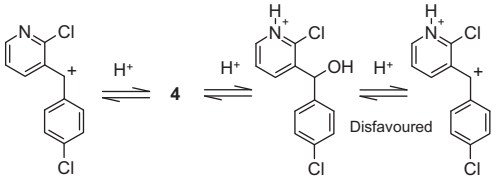
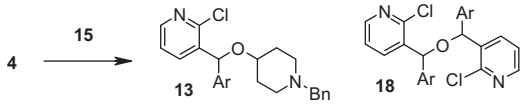


Figure 1. Competing pyridine protonation in the azabenzhydryl ether synthesis under acid catalysis disfavouring cation formation.

Table 2
Acid- and Lewis acid-catalysed conditions[a]



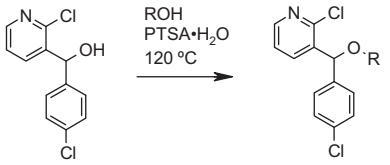
Solvent	Catalyst (equiv)	T[b] (°C)	Comment[c]
CH_2Cl_2	$FeCl_3$ (0.1)	20	NR
CH_2Cl_2	$FeCl_3$ (0.1)	120	NR
CH_2Cl_2	$Sc(OTf)_3$ (0.1)	20	NR
CH_2Cl_2	$Sc(OTf)_3$ (0.1)	120	NR
CH_2Cl_2	PTSA (0.1)	120	NR
CH_2Cl_2	PTSA (1.1)	120	NR
CH_2Cl_2	PTSA (3.0)	120	10% conversion into **13**
CH_2Cl_2	PTSA (3.0)	140	40% conversion into **13**; by-products forming
CH_2Cl_2	PTSA (3.0)[d]	120	NR
CH_2Cl_2	PTSA (3.0)[d]	140	10% conversion into **13**
PhMe	PTSA (3.0)	120	20% conversion into **13**
PhMe	PTSA (3.0)	200	All **4** consumed, many by-products
1,4-dioxane	PTSA (3.0)	120	Trace **13** formed
1,4-dioxane	PTSA (3.0)	200	40% conversion into **13**; by-products forming
MeCN	PTSA (3.0)	120	Trace **13** formed
MeCN	PTSA (3.0)	200	Decomposition
H_2O	PTSA (3.0)	120	NR
H_2O	PTSA (3.0)	200	Decomposition
PhMe	PPTS (3.0)	120	NR
PhMe	PPTS (3.0)	200	60% conversion into **18**, no **13** formed
PhMe	AcOH (3.0)	120	NR
PhMe	AcOH (3.0)	200	NR
AcOH	—	120	NR
AcOH	—	200	**4**-Ac and des-Cl-**4**
CH_2Cl_2	TFA (3.0)	120	NR
CH_2Cl_2	TFA	140	10% conversion into the trifluoroacetate of **4**
—[e]	PTSA (3.0)	125	60% conversion into **13**
—[e]	**PTSA** (3.0)	**125**[f]	90% isolated yield of **13**
H_2SO_4	—	rt	Decomposition

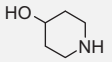
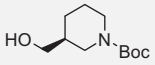
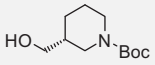
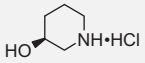
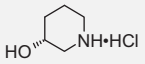
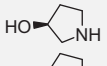
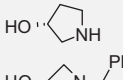
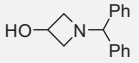
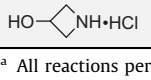
[a] All reactions carried out with a 1:1 mixture of **4** and **15** for 20 min unless otherwise indicated.
[b] Reactions heated to indicated temperature using a Biotage Synthesizer microwave.
[c] Reactions monitored by LC–MS—NR = no reaction, % conversion based on LC–MS.
[d] 4 Å molecular sieves added.
[e] Reaction performed as a melt in an open tube.
[f] Reaction run for 3 h.

lowed an improved synthesis of VER-156084 (**7**).[13] Completion of the synthesis required urea formation and resolution as described in our earlier report,[1] giving the racemic material in three steps, with an overall yield of 35%. Scale-up of the ether formation was best achieved by carrying out the reaction as a thin layer melt in a Petri dish immersed in a sandbath, under which conditions, the reaction could be run on at least 7.8 mmol scale.

In conclusion, we have described the development of a novel ether synthesis, using molten PTSA as the catalyst. We believe this methodology to be generally applicable to the synthesis of hindered ethers resistant to conventional conditions and have demonstrated its applicability to a range of hindered nucleophilic alcohols bearing protected and free amine functionalities. Furthermore, the solvent-free, environmentally benign non-toxic nature of the reagents has significant benefits over alternative methodologies. We have demonstrated the utility of the methodology in an improved synthesis of the FAAH inhibitor VER-156084 and will discuss its wider application in the investigation of FAAH inhibitors elsewhere.

Table 3
Scope of the ether formation[a]



ROH	Time (h)	Yield (%)
15	3	90
	5.75	100% LC–MS conversion
	5	72 (Boc group lost)[b]
	5	78 (Boc group lost)[b]
	5.75	68[b]
	5.75	79[b]
	5	73[b]
	5	72[b]
	1.75	Decomp., trace product
	3.25	81

[a] All reactions performed with 1:1 **4**: ROH with 3 equiv of PTSA at 125 °C in an open tube.
[b] Product isolated as 1:1 mixture of diastereomers.

Acknowledgement

The authors thank Heather Simmonite for NMR spectroscopy (compound **13**).

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4. All reagents were purchased from the Sigma–Aldrich Chemical Company except for (*R*)- and (*S*)-1-Boc-3-hydroxymethylpiperidine (CNH Technologies Inc., Woburn, MA), 3-hydroxyazetidine hydrochloride (Atlantic SciTech Group Inc., Linden, NJ) and 1-benzhydrylazetidin-3-ol (Fluorochem Ltd, Old Glossop, Derbyshire, UK). All commercial reagents were used as supplied without further purification.
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6. See: e.g. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.
7. For a direct etherification, see: e.g. (a) De Martino, G.; La Regina, G.; Di Pasquali, A.; Ragno, R.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2005**, *48*, 4378; (b) Many alternative examples are prepared by indirect substrate-specific methods, see: e.g. Boyd, M.; Gagnon, M.; Lau, C.; Mellon, C.; Scheigetz, J. WO2004/022526, 2003; *Chem. Abstr.* **2003**, *140*, 270877.
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11. Compound **18** had been observed as a trace by-product under the original Dean–Stark conditions.[2]
12. *Typical experimental procedure*: A test-tube containing **4** (1.0 equiv), **15** (1.0 equiv) and PTSA·H_2O (3.0 equiv) was immersed in a sand-bath pre-heated to 125 °C. After 3 h, the mixture was cooled, diluted with CH_2Cl_2 (25 mL) and washed with NaOH (2.0 M in H_2O; 25 mL). The CH_2Cl_2 layer was dried by passing through a phase separator frit and evaporated to give the ether product as a pale yellow gum. All compounds showed satisfactory analytical data (LC–MS purity >95%, molecular ion and ^1H NMR) and were identical to previously published data where available. Analytical data for compound **13**: δ_H (400 MHz; MeOH-d_4) 8.28 (1H, dd, J = 4.5 and 1.8 Hz), 8.07 (1H, dd, J = 7.8 and 1.8 Hz), 7.40 (1H, dd, J = 7.8 and 4.5 Hz), 7.35 (2H, d, J = 8.8 Hz), 7.32 (2H, d, J = 8.8 Hz), 7.34–7.22 (5H, m), 5.86 (1H, s), 3.47 (2H, s), 3.46–3.40 (1H, m), 2.74–2.66 (2H, m), 2.21–2.12 (2H, m), 1.92–1.80 (2H, m) and 1.72–1.62 (2H, m); δ_C (100 MHz; MeOH-d_4) 150.3, 149.7, 140.4, 139.1, 138.4, 138.3, 134.8, 130.8, 130.2, 129.6, 129.3, 128.4, 124.7, 76.7, 74.4, 63.9, 51.7, 32.0 and 31.9; LC–MS >95%; m/z 427 ([M+H]$^+$; 100%); HRMS found [M+H]$^+$ 427.1330, calcd for $C_{24}H_{25}Cl_2N_2O$: 427.1344.
13. In order to investigate further the difference in reactivity of the *N*-benzhydryl azetidin-3-ol and unprotected 3-hydroxyazetidine, we attempted the reaction of **4** with 3-hydroxyazetidine hydrochloride under our original Dean–Stark conditions, but no product formation was observed.