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Facile preparation of thiophene C2-ethers using the Mitsunobu reaction

Craig S. Harris *, Hervé Germain, Georges Pasquet

AstraZeneca, Centre de Recherches, Z.I. la Pompelle, BP1050, 51689 Reims Cedex 2, France

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Dedicated to the memory of the late Dr. Patrice Siret whose vision and passion for modern pharmaceutical research was an inspiration for all

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ABSTRACT

The preparation of thiophene ethers generally requires forcing conditions thus limiting the choice of alkyl substituent. Herein, we report the first successful generally applicable conditions for the selective O-alkylation of 2(5*H*)-thiophenone.

During recent years, the pharmaceutical industry has been investigating new approaches to treat cancer including inhibition of cell-growth signalling pathways[1] and anti-angiogenesis[2] as well as inhibition of DNA synthesis and function.[3] We became interested in targeting thiophene ethers at C-2 having the bidentate binding bases, 2-amino-6-methylpyridine[4] and tetrahydronaphthyridine (Fig. 1).[5]

There are 2 logical possible retrosyntheses of key substructure **1**; using Ullman-style chemistry[6] from either the corresponding 2-bromo- or 2-iodothiophene precursors and the appropriate alcohol; or alkylation from commercially available 2(5*H*)-thiophenone with the appropriately functionalised side chain.[7]

The side chains were prepared by adapting existing literature. The synthesis of **4** started from commercially available 2-amino-6-picoline.[4] Boc protection followed by alkylation with iodomethane afforded **3**. Lithiation followed by carbonylation and reduction of the ethyl ester afforded **4** in acceptable overall yields. The synthesis of **7** relied upon a smooth cyclocondensation of 2-amino-3-formylpyridine with acetone in the presence of L-proline to afford the naphthyridine intermediate which was in turn reduced (Pd–C/EtOH) and N-protected with a Boc group.[5] The intermediate **6** was subjected to similar chemistry as used for the preparation of **4** to afford **7** in good overall yield (Scheme 1).

The general method to synthesise thiophene ethers at the α position is to use Ullman-style approaches.[6] However, all attempts to apply Ullman-style approaches,[7] including recent milder conditions,[8] even from aryltrifluoroborate precursors,[9] and palladium-catalysed alternatives[10] only afforded traces of product. The

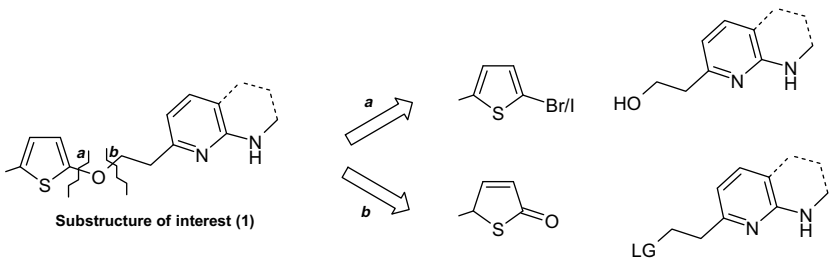

Figure 1. Synthons which could give the desired substructure.

* Corresponding author. Tel.: +33 03 26 61 5912; fax: +33 03 26 61 6842.
E-mail address: craig.harris2@astrazeneca.com (C. S. Harris).

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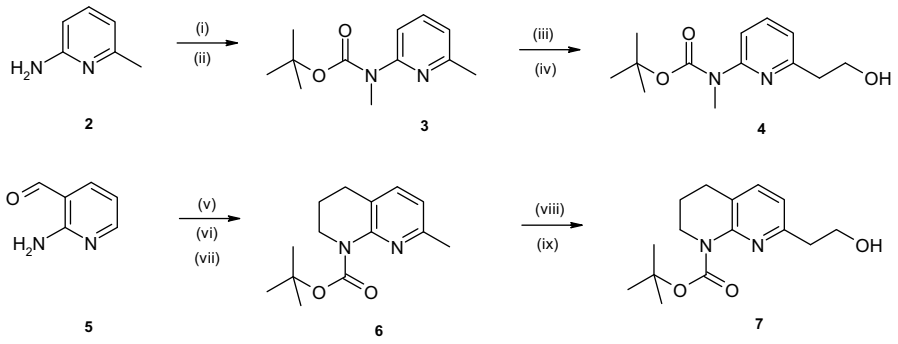
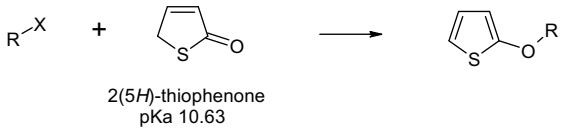


Scheme 1. Synthesis of key side chains **4** and **7**. Reagents and conditions: (i) Boc–O–Boc, THF, 60 °C, 66%; (ii) Me–I, NaH, DMSO, 82%; (iii) LDA, EtO(CO)OEt, −78 °C to rt, 4 h, 51%; (iv) $LiBH_4$, THF, −10 °C to rt, 95%; (v) L-proline, acetone, EtOH, reflux, 16 h, 74%; (vi) H_2, Pd–C, EtOH, rt, 95%; (vii) Boc–O–Boc, LiHDMS, THF, −78 °C to rt, 50%; (viii) LiHDMS, EtO(CO)OEt, −78 °C to rt, 4 h, 78% and (ix) $LiBH_4$, THF, −10 °C to rt, 75%.

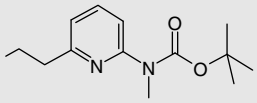
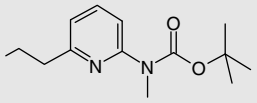
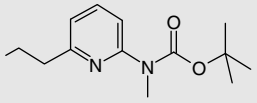
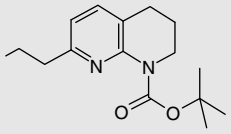
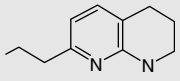
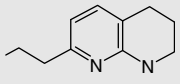
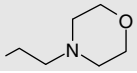


Scheme 2. Alkylation of thiophenone.

pyridine ethanol-based side chains readily eliminate at moderate to high temperatures under basic conditions to afford the corresponding vinyl pyridine side products, and we could not overcome this by modifying the conditions (ligand, temperature, copper source, etc.).

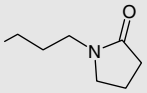
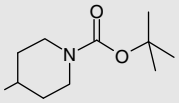
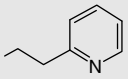
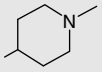
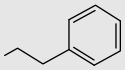
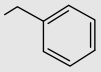
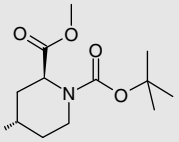
Consequently, we turned our attention to the alkylation of 2(5*H*)-thiophenone (Scheme 2). From the few relevant references

Table 1
Selected results from the Mitsunobu alkylation of 2(5*H*)-thiophenone by RX[15]

Entry	R	X	Alkylation conditions	Isolated yield (%)
1		Cl/OMs	Classical: NaH or K_2CO_3, THF or DMF, rt to 80 °C	—
2		OH	DTAD added at the end to a stirred mixture of 2(5*H*)-thiophenone, PS–TPP and alcohol at −10 °C to rt	—
3		OH	A: 2(5*H*)-thiophenone added to a suspension ofPS–TPP–O–R (preformed by adding alcohol to the PS–betaine intermediate)	49
4		OH	A	51
5		OH	A	15
6		OH	B: solution of 2(5*H*)-thiophenone and alcohol added to a stirred solution of betaine	53
7		OH	A	94
8		OH	B	83
9		OH	A	66

(*continued on next page*)

Table 1 (*continued*)

Entry	R	X	Alkylation conditions	Isolated yield (%)
10		OH	A	69
11		OH	A	66
12		OH	A	78
13		OH	B	58
14		OH	B	64
15		OH	B	49
16		OH	B	41

on this alkylation,[7,11,12] one can quickly establish that this is not generally seen as a preparatively useful way into ethers at the α-position of thiophene. All the references cited classical alkylation conditions (alkyl halides in the presence of a mineral base) with low yields and C-alkylation at C-3 posing the most serious problems. However, all attempts to apply the most appealing conditions (NaH, mesylate and THF)[7] to our case resulted only in elimination, affording, as in the Ullman trials, the vinylpyridine as the majority product. Even when the reaction was carried out with phenol, elimination dominated with little product observed confirming that classical alkylation methods were not applicable to our particular side chains.

The pK_a of 2(5*H*)-thiophenone was measured at 10.63,[13] suggesting it could be a suitable substrate for milder, more tolerant Mitsunobu alkylation conditions,[14] well documented for favouring substitution over elimination. However, to our knowledge there is no reference identifying the Mitsunobu reaction as a suitable answer to this particular problem, although the process is generally used for alkylations with **4** and **7** of phenolic substrates.[4,5] After a significant amount of process development, we managed to successfully apply Mitsunobu conditions to this sensitive alkylation. The mode of addition of the Mitsunobu reagents was absolutely critical. If the di-*tert*-butylazodicarboxylate (DTAD) was not pre-reacted with triphenylphosphine (TPP) to form the betaine intermediate before 2(5*H*)-thiophenone was introduced, the reaction failed resulting in electrophilic substitution at C-3 by DTAD. The best conditions for readily eliminable side chains involved adding a solution of the alcohol and 2(5*H*)-thiophenone in dichloromethane to a stirred solution of the betaine (pre-formed by adding DTAD to TPP at −10 °C over a period of 5 min) at −10 °C (acetone/ice).

With the conditions optimised, we decided to apply these to a broader range of alcohols. Table 1 shows the results obtained from a selection of alcohols. As mentioned previously, attempts to alkylate the 2(5*H*)-thiophenone with the mesylate or chloride of **4** afforded the vinylpyridine by-product and traces of product (entry 1). The mode of addition of the Mitsunobu reagents had a critical bearing on the actual yields (entry 2 vs entry 3), whereby the DTAD needed to be consumed before adding the reactive 2(5*H*)-thiophenone (alkylation conditions A). Moreover, in the case of tetrahydronaphthyridine with no *N*-Boc protection, it was essential to add the alcohol and 2(5*H*)-thiophenone at the same time to the betaine intermediate in order to reduce elimination and maximise yields (entry 5 vs entry 6, alkylation conditions B). Alcohols containing basic functionality (e.g., entries 9 and 13), secondary alcohols (e.g., entries 8, 11, 13, and 16), alcohols serving as protecting groups (e.g., entry 15) and elimination-prone chiral alcohols (e.g., entry 16) can all be transformed in acceptable to excellent overall yields with this process. During the course of the alkylation, *C3*-alkylation is occasionally observed by LCMS but at unsignificant levels (<5%).

In conclusion, we have discovered a new application of the Mitsunobu reaction that allows access to acceptable yields of a diverse set of thiophene ethers at C-2 otherwise difficult to attain using existing methodology.

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12. Gronowitz, S. *Heterocyclic Compounds: Thiophene and its Derivatives Part III*; John Wiley and Sons, 1986; pp 73–80 and references cited therein.
13. The pK_a of 2(5*H*)-thiophenone was determined by multi-wavelength spectrophotometry on a Sirius GlpKa, sweeping the pH from 2.5 to 11.5 and returning to 2.5. The analyte, composed of 2 mg of substrate, was dissolved in 200 μl of DMSO; 7.5 μl of this solution was diluted with 250 μl of a buffer solution containing 0.2 g of KH_2PO_4 dissolved in 100 ml of water.
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15. *Typical procedure A*: To a stirred solution/suspension of triphenylphosphine/polymer-supported triphenylphosphine (3 equiv, 1.6 mmol/g) was added di-*tert*-butyl azodicarboxylate (DTAD, 3 equiv) in dichloromethane (5 ml/ 100 mg of input thiophenone) at −10 °C. The solution was stirred for 10 min at −10 °C and a solution of the alcohol (3 equiv) in dichloromethane (1 ml) was added. The resulting suspension was slowly agitated for 20 min and 2(5*H*)-thiophenone (1 equiv)* in dichloromethane (1 ml) was added dropwise to the mixture over a period of time so that the internal temperature did not rise above 0 °C. After the addition was complete, the solution/suspension was stirred at room temperature for 1 hour, filtered if necessary, concentrated to dryness and the residue was generally purified by flash chromatography on silica gel eluting with gradient of pentane/dichloromethane (100:0) to dichloromethane/MeOH (90:10) to afford the title compounds generally as oils. For non-polar ethers (e.g., entry 7), the reduced DTAD could be eliminated by trituration with pentane prior to purification. *Procedure B involved the simultaneous addition of the alcohol (3 equiv) and 2(5*H*)-thiophenone (1 equiv) in dichloromethane (1 ml) to a stirred suspension of the betaine at −10 °C.