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PAPER

New methodology for the N-alkylation of 2-amino-3-acylthiophenes†

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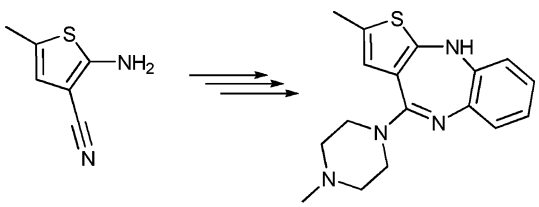
2-Amino-3-acylthiophenes are known to allosterically modulate the A_1 adenosine receptor and are also used as intermediates in the synthesis of therapeutic agents and pharmacophores such as thienoazepines and thienopyrimidines. The N-alkylation of 2-aminothiophenes has been notoriously difficult to accomplish under mild conditions and there are very few examples of N-alkylated 2-aminothiophenes in the literature, all of which use forcing conditions to effect the alkylation. Here we describe the synthesis of such compounds under mild conditions utilising 2-carbamoylamino and 2-acylamino-3-acylthiophenes with caesium carbonate, and tetrabutylammonium iodide in DMF.

Introduction

The use of 2-amino-3-acylthiophenes is prevalent in the literature, and their syntheses *via* the method communicated by Gewald[1] provides a one-pot procedure to a large variety of analogues.[2] Not only are 2-amino-3-acylthiophenes known to act as allosteric modulators of the A_1 adenosine receptor,[3–7] their derivatization to thienopyrimidines[8] and thienoazepines[9,10] has been used to produce pharmaceuticals and dyes.[2] In particular, the well known thienobenzodiazepine, Olanzapine (**2**),[9] derived from the 2-amino-5-methylthiophene-3-carbonitrile (**1**, Fig. 1), is an FDA approved antipsychotic. 2-Amino-3-acylthiophenes have also been employed as building blocks for potential therapeutic agents such as anti-inflammatory,[11] antitumor,[12] antimicrobial,[13] hypocholesterolemic,[14] epileptic[15] and antifungal[16] agents. Yet one particular chemical modification that has not been extensively explored in terms of the potential SAR of such molecules is the alkylation of the 2-amino group, which has proven to be difficult to achieve. A simple and mild method for the alkylation of the 2-amino would therefore be highly desirable. There are only a few examples of the N-alkylation of 2-amino-3-acylthiophenes in the literature and these procedures employ high pressures and temperatures,[15] or strongly basic conditions with protecting groups such as tosyl and ethyl carbamates which then require harsh conditions for their removal.[10,17–19] Herein, we report a mild and simple method for the N-alkylation of various 2-amino-3-acylthiophenes.



1 **2**

Fig. 1 The antipsychotic Olanzapine (**2**) and the thiophene **1** from which Olanzapine is derived.

Results and discussion

Our group has been actively involved in the synthesis and biological evaluation of 2-amino-3-acylthiophenes as allosteric modulators of the A_1 adenosine receptor.[3–7] In attempts to functionalize certain positions of the 2-amino-3-acylthiophenes, the 2-amino group in most cases required protection. The phthaloyl, acetyl and Boc groups are relatively easy to introduce and remove.[3,6,7] Yet these protecting groups are susceptible to cleavage under basic and acidic conditions and incorporating protecting groups that are relatively stable to these conditions is desirable. The benzyl carbamate fits this profile as it is relatively stable to basic and/or acidic conditions and is removed by hydrogenolysis. To the best of our knowledge there are only two examples in the literature that utilise this protecting group for 2-amino-3-acylthiophenes,[13,20] and in our hands these procedures failed. Carbamates are typically introduced by reaction of the appropriate amine with a chloroformate, dicarbonate, CDI, phosgene/triphosgene or activated carbonate such as succinimidyl or benzotriazyl, but these procedures have been unfruitful when applied to 2-amino-3-acylthiophene substrates in our hands.[21] Another facile method for the introduction of carbamates was realised by Butcher[22] in an attempt to N-benzylate secondary amines with benzyl chloride and potassium carbonate in DMF, isolating the expected product along with the corresponding benzyl carbamate. By substituting potassium carbonate with caesium carbonate and bubbling carbon dioxide into the mixture, Butcher was able to isolate the corresponding carbamates in very good yield. This

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† Electronic supplementary information (ESI) available: LC-MS traces of compounds **8a–g**, **11**, **24a–c**, **27a–d**, **31a–c**, **34a–c**. See DOI: 10.1039/c0ob01156h

method of N-carbamoylation of alkyl and aryl amines was further modified by Salvatore *et al.*[23] By introducing the phase transfer catalyst, tetrabutylammonium iodide (TBAI), they were able prevent direct N-alkylation and achieve chemoselective carbamate formation.[23]

In our first attempt at introducing the benzyl carbamate, ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**3**, Fig. 2), was used as an example and the conditions communicated by Salvatore *et al.* were duplicated (three equivalents each of benzyl bromide and TBAI). To our delight TLC revealed complete consumption of starting material three hours after the addition of benzyl bromide. At this stage it was assumed that the benzyl carbamate was produced, yet ^{1}H NMR of the crude product showed that the *N*-benzyl-*N*-carbamoyl derivative **4a** was the sole product isolated. This result was advantageous in two ways; firstly, the benzyl carbamate could be introduced with relative ease and secondly, N-alkylation could be accomplished under mild conditions. The serendipitous synthesis of the N-alkylated derivative **4a** was a novel outcome. There is no mention in the work communicated by Salvatore *et al.*[23] of any concomitant N-alkylation of the carbamates synthesised whether they be alkyl or aryl amines.

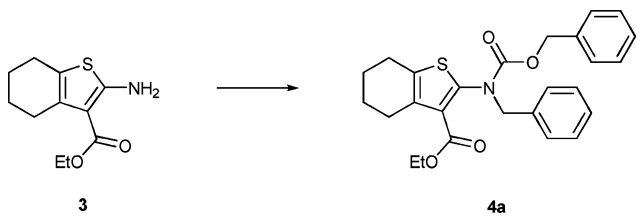
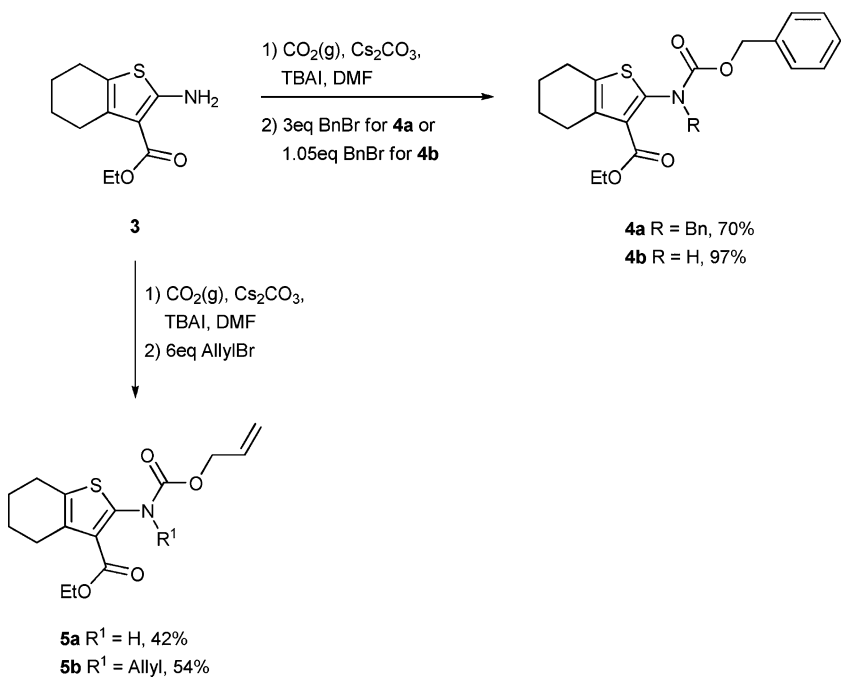


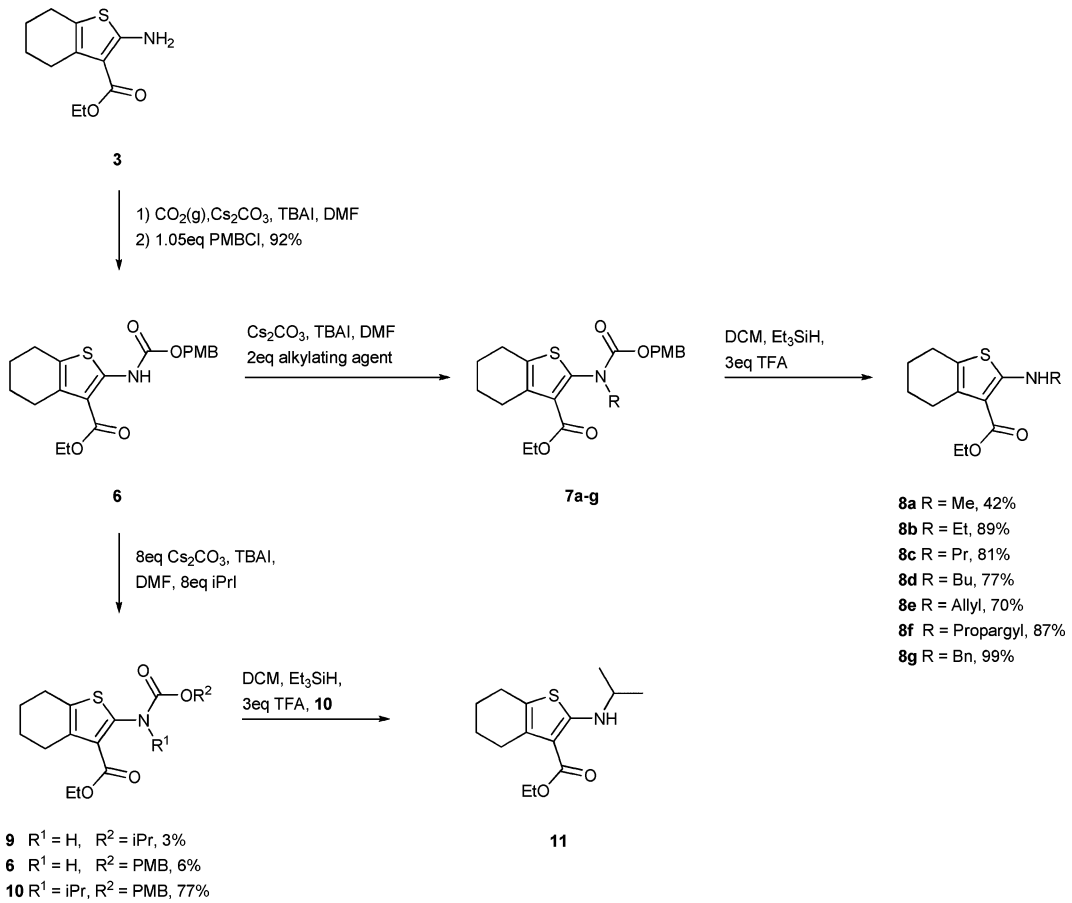
Fig. 2 N-Carbamoylation and N-alkylation of **3**.

We initially envisaged a one-pot procedure in which one equivalent of benzyl bromide was used to form the carbamate and then in the same pot excess alkyl halide is added to effect N-alkylation with various alkyl halides. Yet, under these conditions only benzyl bromide and dialkylsulfates drove the N-alkylation to completion. The incomplete alkylation was also evident in the allylation of **3** (Scheme 1). When the thiophene **3** was subjected to the one-pot synthesis of **5b** approximately 20% of **5b** was formed. By adding a further three equivalents of allyl bromide the isolated yield of **5b** was 54% after chromatography. This suggested that the one-pot procedure would only work well with the aforementioned alkylating agents. Therefore, it was far more convenient to isolate the carbamate with one equivalent of alkyl halide and then alkylate in a second step.

By reducing the amount of benzyl bromide to 1.05 equivalents, the carbamate **4b** was isolated in 97% yield. This was a promising result and at this stage it was decided to also employ a carbamate that could survive the basic conditions of the alkylations and could be removed under relatively mild conditions other than hydrogenolysis. The *p*-methoxybenzyl (PMB) carbamate was well suited since it can be removed *via* hydrogenolysis or under mildly acidic conditions.[21] This would then enable the incorporation of unsaturated and benzylic alkyl groups that would otherwise be compromised *via* hydrogenolysis if the benzyl carbamate was used. The initial synthesis of **6** began by utilising the same conditions as for the carbamate **4b**, with 1.05 equivalents of PMB-Cl instead of benzyl bromide and 3 equivalents each of caesium carbonate and TBAI (Scheme 2). It was then found that the number of equivalents of the other reagents could also be reduced without compromising the yield and repeating the synthesis with 1.05, 1.5, and 1.0 equivalents of PMB-Cl, caesium carbonate and TBAI respectively, **6** was obtained in 92% yield (Scheme 2). The carbamate **6** was then treated with 2 equivalents of caesium carbonate and half



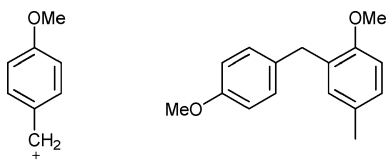
Scheme 1 Synthesis of *N*-carbamoyl and *N*-alkyl-*N*-carbamoyl derivatives of **3**.



Scheme 2 Synthesis of *N*-alkyl derivatives of **3**.

an equivalent of TBAI in DMF followed by 2 equivalents of alkylating agent at room temperature for 3–24 h providing the compounds **7a–g**. In all cases, with the exception of the isopropyl derivative **10**, alkylation was quantitative and did not require chromatography. For example **10**, 24 h reaction time effected 50% conversion to the *N*-isopropyl derivative (by ^{1}H NMR) and repeating the synthesis with eight equivalents each of isopropyl iodide and caesium carbonate provided 77% of **10**, 6% of **6** and 3% of **9** after 27 h. Although the isopropyl carbamate **9** was isolated in this reaction, albeit in very low yield, there was no sign of it in the first attempt when using only 2 equivalents each of alkylating agent and base. This was also the case with analogous N-alkylations and so no carbamoylation was observed. The ^{1}H NMR spectra of the alkylated compounds indicated the presence of *cis-trans* isomers of the carbamate at an approximate 1 : 3 ratio and this was also evident in the ^{13}C NMR.

Removing the PMB carbamate was performed under acidic conditions since it is known to be at least as acid labile as a Boc group.[21,24,25] Under the acidic conditions the *p*-methoxybenzyl cation **12** (Fig. 3) forms and is usually quenched with a cation scavenger.[25] By using the conditions of Chen *et al.*[24] and adding 1.2 equivalents of triethylsilane as the cation scavenger, the carbamate was removed within 20 min at room temperature. The deprotection reaction was quenched with bicarbonate and the crude product was chromatographed on silica gel. In all cases up to 20% of the diphenylmethane **13**[26] had co-eluted with the product, but was readily removed by recrystallization. Upon increasing the amount

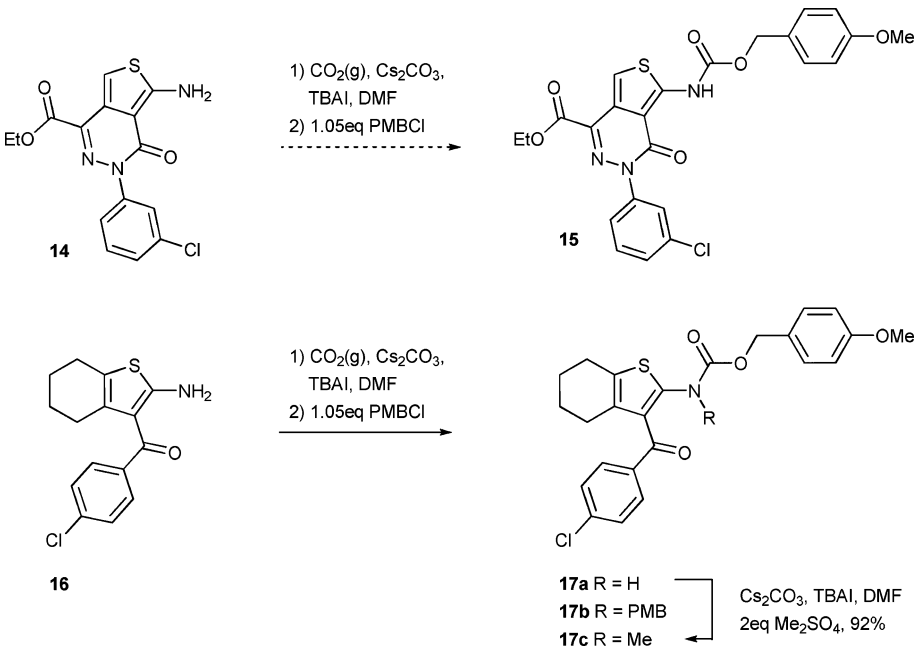


12 **13**

Fig. 3 *p*-Methoxybenzyl cation **12** and 2,4′-dimethoxy-5-methyldiphenylmethane **13**.

of triethylsilane to 2.5 equivalents, **13** was still isolated, but in dramatically reduced yield.

With the conditions for N-carbamoylation and N-alkylation optimised for thiophene **3**, the A_1 adenosine receptor antagonist **14**[27] and allosteric modulator **16**[28] were subjected to the same N-carbamoylation conditions (Scheme 3). In the case of **14**, intractable mixtures were observed after workup of the crude product. Although small amounts of product were isolated by chromatography, clean fractions could not be obtained and therefore this route was abandoned. The allosteric modulator **16** was also subjected to CO_2 mediated N-carbamoylation under the same conditions used for **14**. The desired carbamate **17a**, was isolated in 41% yield following column chromatography, along with a 1.6 : 1 mixture of starting material **16** and the *N*-alkyl derivative **17b**. The carbamate was subjected to N-methylation providing **17c** in 92% yield and although subsequent alkylations could be achieved with **17a**, this intermediate was also abandoned

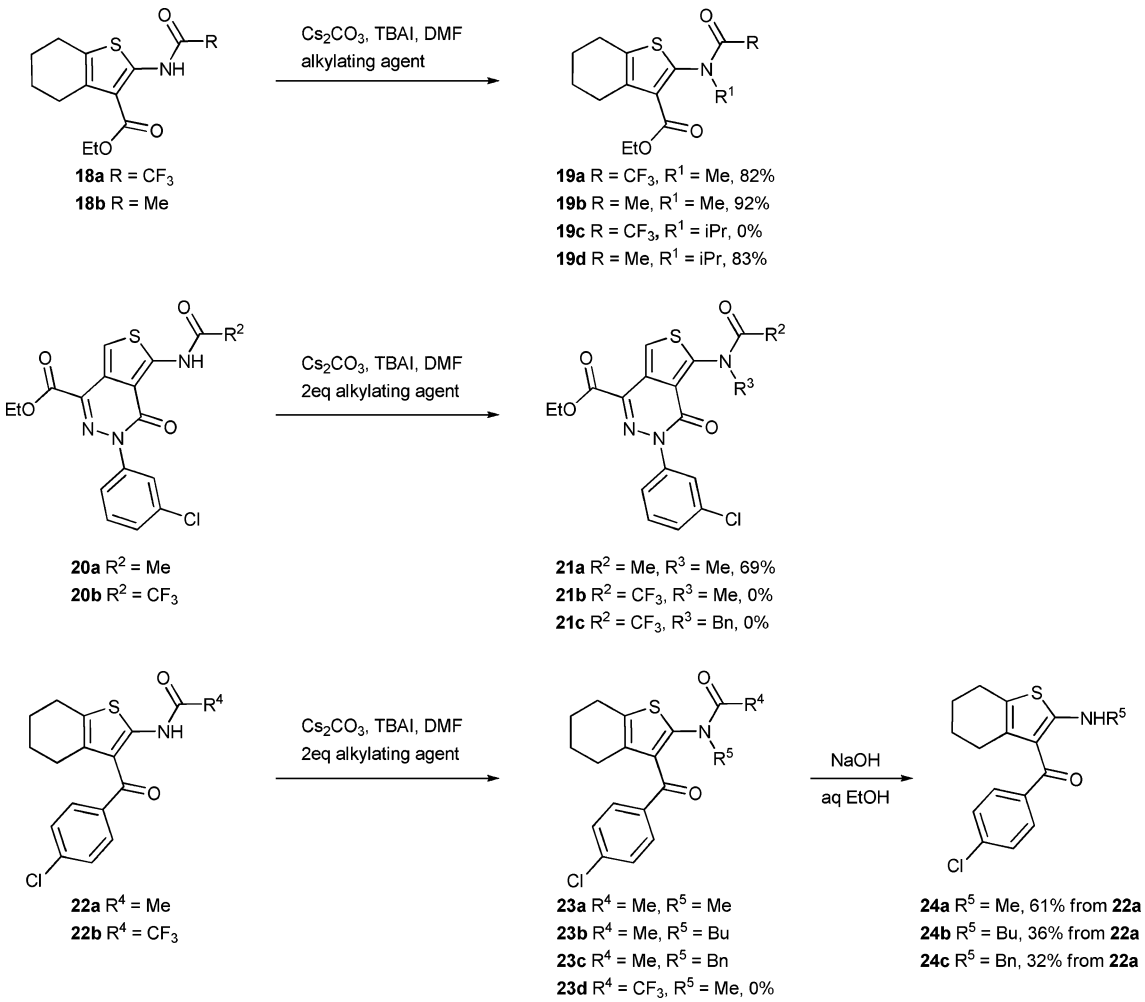


Scheme 3 N-Carbamoylation of orthosteric antagonist **14** and allosteric modulator **16**.

due to the low yields of the N-carbamoylation step. It was presumed that the highly electrophilic nature of the benzyl halide is too reactive and that once the carbamate is formed, it becomes more reactive under the basic conditions than the intermediary carbamic acid and therefore **17b** forms.

The poor yields obtained for the N-carbamoylation of **14** and **16** prompted us to investigate N-activating groups that could be suitable for the N-alkylation and subsequent mild deprotection. The trifluoroacetamide is well known for its ready introduction and mild removal with aqueous methanolic potassium carbonate,[29] and alkylation of trifluoroacetamides have also been described in the literature.[30] The trifluoroacetamide **18a** (Scheme 4) was prepared and subjected to N-methylation with dimethylsulfate under the standard conditions for 24 h. Upon workup the crude product was chromatographed and 10% of starting material **18a** was isolated followed by the desired product **19a** in 82% (90% conversion). Although this was a good result, the fact that the reaction did not go to completion was surprising compared to the N-methylation of carbamate **6**. Thus, the acetamide **18b** was available and also subjected to identical N-methylation conditions as **18a** and ^{1}H NMR revealed complete conversion to product **19b** in 92%. When both **18a** and **18b** were separately subject to N-alkylation with isopropyl iodide under identical conditions, the trifluoroacetamide **19c** did not form only returning the starting material **18a**. Yet, the acetamide **18b** reacted with isopropyl iodide to form **19d** in 83% yield (by LCMS). The lower reactivity of the trifluoroacetamide **18a** compared to the acetamide **18b** may result from the electron withdrawing trifluoromethyl group stabilising the anion formed upon deprotonation of the trifluoroacetamide. To see whether or not there was a trend with the trifluoroacetyl group, compounds **14** and **16** were both acetylated and trifluoroacetylated and subjected to N-alkylation reactions to compare with the results obtained with **18a,b** (Scheme 4). Trifluoroacetamide **20b** did not react at all with either dimethylsulfate or benzyl bromide to provide **21b** or **21c** respectively, only returning unreacted starting material. This was also the case with **22b**, only returning starting material upon attempted methylation. On the contrary, the acetamides **20a** and **22a** reacted very well in these alkylations. The N-methylation of **20a** proceeded with complete conversion to **21a** and was isolated in 69% after chromatography. Although the acetamide can be removed with hydroxide this would also compromise the ethyl ester in **21a**, therefore removal with sodium ethoxide could be used as an alternative.[31] In the case of **22a**, the acetyl group is quite convenient in that it is readily installed in high yield and it is removed with mild base hydrolysis.[6] In fact the *N*-butyl derivative did not require heating or excess 1-bromobutane to go to completion although it required 40 h reaction time. The base hydrolysis in aqueous ethanol was also advantageous in that the products precipitated during the reaction and were simply filtered to provide pure product.

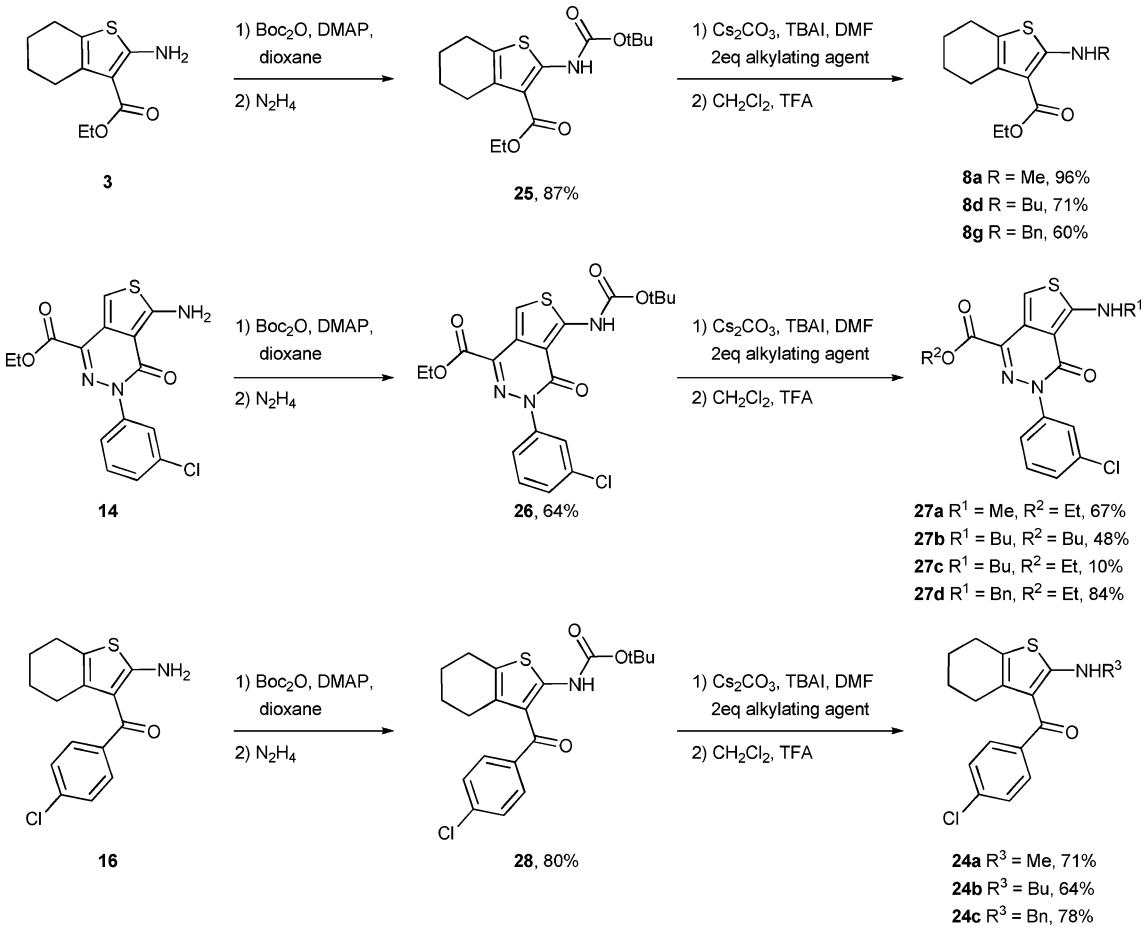
Although the PMB carbamate and the acetamide served well in the alkylations, they also have their limitations. Installing the PMB carbamate *via* the carbon dioxide mediated carbamoylation proceeded well for **3**, but not for **14** and **16**. The acetamide is easily installed and proved to be effective in the alkylation step, yet it requires basic conditions for removal, which can compromise other base sensitive groups and, in some cases, cause rearrangement of the thiophene ring.[4] Therefore, an orthogonal protecting group to the acetamide would be a complementary addition and the Boc group would serve well. It is readily installed with Boc_2O and removed with TFA. To ensure complete carbamoylation of 2-amino-3-acylthiophenes, we have found that two equivalents of Boc_2O are required for complete N-carbamoylation to isolate the bis-carbamate since one equivalent gives rise to mixtures of mono-Boc, di-Boc and starting material.[7] The bis-carbamate is highly susceptible to nucleophiles and by adding excess hydrazine one of the carbamate groups is removed as *tert*-butyl hydrazinecarboxylate and any excess Boc_2O is also converted



Scheme 4 *N*-Alkylation of *N*-acyl 2-amino-3-acylthiophenes.

to *tert*-butyl hydrazinecarboxylate, which is easily removed using a short silica column. The Boc derivatives **25**, **26** and **28** (Scheme 5) were synthesised and subjected to the standard alkylation conditions. N-Methylation and N-benzylation proceeded smoothly at room temperature and the conversion of starting material was quantitative as expected for all three carbamates **25**, **26** and **28**. The other test was to see whether or not a poorly electrophilic reagent would N-alkylate these derivatives. 1-Bromobutane was chosen for this purpose and, in the case of **25**, complete alkylation was observed under the standard conditions, whereas **26** and **28** did not react to completion. After 24 h at room temperature only trace amounts of N-alkylated material were observed by TLC in the case of **26**. By adding a further two equivalents each of 1-bromobutane and caesium carbonate and then heating to 60 °C for a further 24 h the starting material had disappeared and two new compounds were observed by TLC. The NMR of the crude product revealed that the N-alkylation was complete and that a substantial amount of *trans*-esterification had occurred. This outcome is not surprising since small amounts of moisture can affect the hydrolysis of **26** at the elevated temperature and excess reagents present would esterify the carboxylate that formed. In the case of **28** up to 10% of starting material was observed by LCMS after 24 h at room temperature. By adding a further two equivalents each of 1-bromobutane and caesium carbonate and prolonging the reaction time, the amount of starting material was reduced to 1–2% and after deprotection, the crude product was readily purified by recrystallization.

Until now the focus has been the N-alkylation of 2-amino-3-acylthiophenes. We also wanted to investigate the utility of the method to see if it can be extended to anilines. There are many procedures for N-alkylating anilines and some of the more common methods utilize the reduction of Schiff bases,[19,32] amination of aryl halides,[33] or taking Boc protected anilines either in anhydrous DMF[34] or THF[35] solution and treating with NaH and an alkylating agent. Also, the alkylation of tosylamides[36] or simply alkylating the free aminoarene directly, which provides mixtures of mono and di-alkyl products that require chromatography for separation.[37] Again, some of these procedures require heating, expensive reagents and protecting groups that are difficult to remove. The commercially available vinylogous amides 2-aminobenzophenone (**29**) and 1-aminofluoren-9-one (**32**) (Scheme 6) were available and converted to the Boc derivatives **30** and **33** and subjected to the alkylation conditions as with the previous Boc compounds **25**, **26** and **28**. To our delight, the alkylations



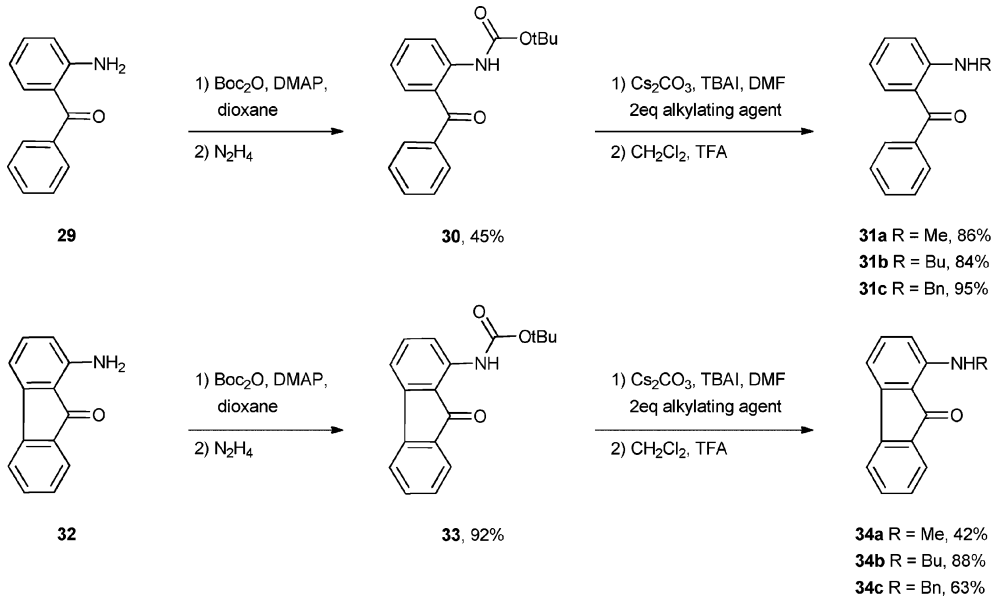
Scheme 5 N-Alkylation of *N*-Boc-2-amino-3-acylthiophenes.

proceeded smoothly and excess reagents were only required in the case of the *N*-butyl derivative **34b** (4 equivalents each of 1-bromobutane and caesium carbonate) to drive the reaction to completion without any heating.

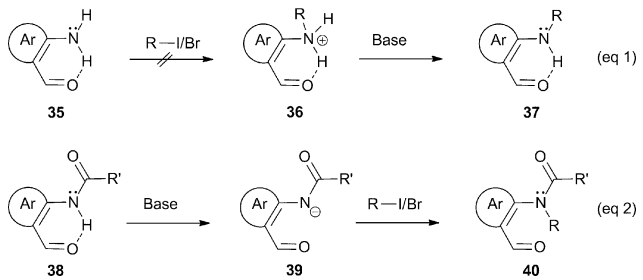
The improvements achieved here in the N-substitution of 2-aminothiophenes and anilines bearing *o*-carboxyl groups **35** is likely to reside in a change in the nature of the nucleophilic nitrogen that results from attachment of a carbonyl protecting/activating group (carbamoyl or amide). The reaction of unactivated amines **35**, performed in the presence of a weak base, would require nucleophilic attack of an electrophile (R-I/Br) by the lone-pair of electrons on the nitrogen to give the cation **36**, followed by rapid loss of a proton to give **37** (Scheme 7, eqn 1). However, the electron deficiency of the carbonyl in **35** and its strong hydrogen bonding interaction with the amine N–H, enforces a coplanar arrangement of the aryl, carbonyl and amine π-systems, diminishing the nucleophilicity of the amine electron-lone-pair, disfavouring formation of **36**. These features are clearly apparent in an X-ray crystal structure of a related (2-aminoindeno[2,1-*b*]thiophen-3-yl)(phenyl)methanone, in which a "resonance-enhanced" intramolecular hydrogen between the 2-amino and adjacent carbonyl oxygen was clearly apparent from inspection of the relevant bond distances.[6] The presence of a N-carbonyl group in **38** increases the acidity of the remaining N–H (vinylogous imide), enabling sufficient deprotonation to be achieved under weakly basic conditions so as to achieve substitution through the anionic intermediate **39**, to give **40** (Scheme 7, eqn 2).

Conclusion

The one pot N-carbamoylation and N-alkylation of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**3**) has provided a method for mild N-alkylation of what otherwise was particularly difficult to achieve. The ease in which N-alkylation takes place is exemplified by the *n*-butyl and isopropyl derivatives that would otherwise be extremely difficult to install with classical methods. Even though preliminary experiments have shown that the acetyl group is slightly enhanced in the N-alkylation, both carbamates and acetyl groups are complementary options in terms of the conditions required for their cleavage. The unreactivity of trifluoroacetamides was initially particularly interesting in that they are known to react well in such reactions, yet this was not the case for 2-amino-3-acylthiophenes. This method now provides a means to further explore the SAR of N-alkylated versions of thienoazepines and thienopyrimidines that are used as building blocks for potential therapeutic agents.



Scheme 6 *N*-Alkylation of *N*-Boc 2-aminobenzophenone **30** and 1-aminofluoren-9-one **33**.



Scheme 7 Mechanistic considerations.

Experimental

General methods

Melting points were determined with an electrothermal melting point apparatus and are uncorrected. All reagents and anhydrous DMF were purchased from Sigma-Aldrich and used without further purification. LR grade methanol, petroleum ether (40–60 °C), ethyl acetate, diethyl ether and dichloromethane were purchased from Merck and were used without further purification. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 Ultrashield Plus spectrometer at 400.13 and 100.62 MHz, respectively. Unless stated otherwise, samples were dissolved in $CDCl_3$. Thin-layer chromatography was conducted on 0.2 mm plates using Merck silica gel 60 F_{254}. Column chromatography was achieved using Merck silica gel 60 (particle size 0.063–0.200 μm, 70–230 mesh) and eluent percentages are described in volume (%v/v). High resolution mass spectra (HR-ESI) were obtained on a Waters LCT Premier XE (TOF) using electrospray ionization. Compound purity was analyzed *via* LCMS (Agilent 1200 series LC coupled directly to a photodiode array detector and an Agilent 6100 Quadrupole MS) using a Phenomenex column (Luna 5 μm C8, 50 mm × 4.60 mm ID).

Ethyl 2-(benzyl(benzyloxycarbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4a)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **3** (0.428 g, 1.9 mmol) and then purged with nitrogen. Caesium carbonate (1.86 g, 5.7 mmol) and TBAI (2.1 g, 5.7 mmol) were added followed by anhydrous DMF (10 mL). The nitrogen inlet was replaced with a carbon dioxide inlet and CO_2 (g) was bubbled through the stirred mixture at a steady rate for 1 h. Benzyl bromide (0.677 mL, 5.7 mmol) was added in one portion with continual bubbling of CO_2 (g) for 3.5 h. The CO_2 (g) inlet was removed and the mixture was diluted with ether (100 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to a resin. The resin was chromatographed on silica gel eluting with CH_2Cl_2 affording **4a** as a clear colourless resin that slowly solidified upon refrigeration (0.601 g, 70%). A small portion was recrystallized from petroleum ether. Mp 56–58 °C. ^{1}H NMR δ 7.52–7.03 (m, 10H, ArH), 5.28–5.14 (m, 2H, $ArCH_2$), 4.80 (m, 2H, $ArCH_2$), 4.33–3.81 (m, 2H, OCH_2CH_3), 2.93–2.70 (m, 2H, CH_2), 2.72–2.50 (m, 2H, CH_2), 1.98–1.61 (m, 4H, 2 × CH_2), 1.28–1.11 (m, 2H, OCH_2CH_3). ^{13}C NMR δ 162.5, 155.7, 146.0, 137.0, 136.6, 134.6, 133.6, 128.8, 128.4, 128.3, 127.8, 127.7, 127.6, 126.2, 67.6, 60.2, 55.7, 26.0, 25.0, 22.8, 22.5, 14.1. LCMS R_f (min) = 7.19. MS *m*/*z* 450.1 (M + H).

Ethyl 2-(benzyloxycarbonylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4b)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **3** (0.428 g, 1.9 mmol) and then purged with nitrogen. Caesium carbonate (1.86 g, 5.7 mmol) and TBAI (2.1 g, 5.7 mmol) were added followed by anhydrous DMF (10 mL). The nitrogen inlet was replaced with a carbon dioxide inlet and CO_2 (g) was bubbled through the stirred mixture at a steady rate for 1 h. Benzyl bromide (0.238 mL, 2.0 mmol) was added in one portion with continual bubbling of CO_2 (g) for 3.5 h. The CO_2 (g) inlet was removed and

the mixture was diluted with ether (100 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated affording **4b** as an off white solid (0.663 g, 97%) a small portion was recrystallized from MeOH. Mp 77–79 °C. ^{1}H NMR δ 10.58 (s, 1H, NH), 7.47–7.29 (m, 5H, ArH), 5.25 (s, 2H, $ArCH_2$), 4.30 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.80–2.69 (m, 2H, CH_2), 2.69–2.55 (m, 2H, CH_2), 1.86–1.70 (m, 4H, 2 × CH_2), 1.36 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.3, 153.0, 149.3, 135.7, 131.3, 128.6, 128.5, 128.4, 125.7, 110.9, 67.8, 60.4, 26.5, 24.4, 23.1, 22.9, 14.4. LCMS R_f (min) = 7.15. MS m/z 360.2 (M + H).

Ethyl 2-(((allyloxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5a) and ethyl 2-(allyl((allyloxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5b)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **3** (0.428 g, 1.9 mmol) and then purged with nitrogen. Caesium carbonate (1.86 g, 5.7 mmol) and TBAI (2.1 g, 5.7 mmol) were added followed by anhydrous DMF (10 mL). The nitrogen inlet was replaced with a carbon dioxide inlet and CO_2 (g) was bubbled through the stirred mixture at a steady rate for 1 h. Allyl bromide (0.482 mL, 5.7 mmol) was added in one portion with continual bubbling of CO_2 (g) for 3.5 h and then left to stir overnight. The next day a further aliquot of allyl bromide (0.482 mL, 5.7 mmol) was added and the mixture was stirred for a further 24 h. The mixture was diluted with ether (100 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to a resin. The resin was chromatographed on silica gel eluting with 5% ethyl acetate–petroleum ether affording **5a** as a clear colourless resin that slowly solidified upon refrigeration (0.247 g, 42%). Mp 51–53 °C. ^{1}H NMR δ 10.53 (s, 1H, NH), 5.94 (ddt, J = 17.1, 10.5, 5.7 Hz, 1H, OCH_2CHCH_2), 5.35 (ddd, J = 17.2, 2.9, 1.5 Hz, 1H, $OCHHCHCH_2$), 5.25 (ddd, J = 10.4, 2.5, 1.2 Hz, 1H, $OCHHCHCH_2$), 4.68 (dt, J = 5.7, 1.2 Hz, 2H, OCH_2CHCH_2), 4.28 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.72 (t, J = 5.1 Hz, 2H, CH_2), 2.59 (t, J = 5.1 Hz, 2H, CH_2), 1.87–1.59 (m, 4H, 2 × CH_2), 1.34 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.2, 152.8, 149.3, 132.0, 131.3, 125.6, 118.6, 110.8, 66.6, 60.4, 26.5, 24.4, 23.0, 22.8, 14.3. LCMS R_f (min) = 7.03. MS m/z 310.2 (M + H).

Further elution afforded **5b** as a clear colourless resin (0.360 g, 54%). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 6.00–5.59 (m, 2H, OCH_2CHCH_2, NCH_2CHCH_2), 5.38–4.94 (m, 4H, OCH_2CHCH_2, NCH_2CHCH_2), 4.67–4.43 (m, 2H, OCH_2CHCH_2), 4.23–4.06 (m, 4H, NCH_2CHCH_2, OCH_2CH_3), 2.80–2.66 (m, 2H, CH_2), 2.66–2.53 (m, 2H, CH_2), 1.83–1.61 (m, 4H, 2 × CH_2), 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 162.4, 154.7, 145.9, 134.4, 133.1, 132.8, 132.5, 126.1, 118.0, 117.1, 66.3, 60.1, 54.5, 25.9, 24.9, 22.7, 22.4, 14.1. LCMS R_f (min) = 6.83. MS m/z 350.2 (M + H).

Ethyl 2-((((4-methoxybenzyl)oxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (6)

To a 100 mL two neck flask fitted with a nitrogen inlet was added **3** (2.14 g, 9.5 mmol) and then purged with nitrogen. Caesium carbonate (4.64 g, 14.25 mmol) and TBAI (3.51 g, 9.5 mmol) were added followed by anhydrous DMF (50 mL). The nitrogen inlet was replaced with a carbon dioxide inlet and CO_2 (g) was bubbled through the stirred mixture at a steady rate for 1 h. *p*-Methoxybenzyl chloride (1.35 mL, 9.97 mmol) was added in one portion with continual bubbling of CO_2 (g) for 3.5 h. The CO_2 (g) inlet was removed and the mixture was diluted with ether (200 mL) and then washed with water (6 × 250 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated affording **6** as an off white solid (3.41 g, 92%). A small portion was recrystallized from MeOH. Mp 91–93 °C. ^{1}H NMR δ 10.52 (s, 1H, NH), 7.44–7.27 (m, 2H, ArH), 7.01–6.73 (m, 2H, ArH), 5.17 (s, 2H, $ArCH_2$), 4.28 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 2.81–2.66 (m, 2H, CH_2), 2.67–2.53 (m, 2H, CH_2), 1.89–1.57 (m, 4H, 2 × CH_2), 1.34 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.2, 159.8, 153.0, 149.3, 131.3, 130.3, 127.7, 125.5, 114.0, 110.7, 67.7, 60.3, 55.3, 26.5, 24.4, 23.0, 22.8, 14.3. LCMS R_f (min) = 7.07. MS m/z 390.2 (M + H).

General procedure for the synthesis of N-alkylated thiophenes (8a–g)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **6** (0.195 g, 0.5 mmol) and then purged with nitrogen. Caesium carbonate (0.326 g, 1.0 mmol) and TBAI (0.092 g, 0.25 mmol) were added followed by anhydrous DMF (3 mL). The alkylating reagent (1.0 mmol) was added and the reaction was stirred at room temperature and for 3–24 h. Upon completion of the reaction (TLC), the mixture was diluted with ether (50 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the carbamates **7a–g**, which were used without further purification in the next step. The resin was taken up in CH_2Cl_2 (1 mL) and triethylsilane (0.192 mL, 1.2 mmol) was added followed by TFA (0.116 mL, 1.5 mmol) and stirred at room temperature for 15–30 min. The mixture was diluted with ether (20 mL) and quenched with saturated bicarbonate solution. The aqueous layer was removed and the organic layer was washed with water (10 mL) and then brine (5 mL), dried ($MgSO_4$), filtered and then concentrated to an oil affording the crude thiophenes **8a–g**, that was chromatographed on silica gel with 5% ethyl acetate–petroleum ether. Solids were recrystallized from petroleum ether or methanol.

Ethyl 2-((((4-methoxybenzyl)oxy)carbonyl)(methyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7a). Carbamate **6** was reacted with dimethylsulfate to obtain **7a** as an oil (0.213 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.41–7.07 (m, 2H, ArH), 6.96–6.72 (m, 2H, ArH), 5.16–4.91 (m, 2H, $ArCH_2$), 4.23–3.94 (m, 2H, OCH_2CH_3), 3.83–3.68 (m, 3H, OCH_3), 3.19 (s, 3H, NCH_3), 2.83–2.71 (m, 2H, CH_2), 2.72–2.58 (m, 2H, CH_2), 1.88–1.67 (m, 4H, 2 × CH_2), 1.23–1.11 (m, 3H, OCH_2CH_3). ^{13}C NMR (*cis* : *trans* isomers) δ 162.4, 159.4, 155.4, 148.0, 134.8, 133.1, 130.2, 129.7, 128.8, 125.9, 113.8, 113.7, 67.7, 67.3, 60.2, 55.2, 39.2, 39.1, 26.0, 25.0, 22.9, 22.5, 14.1. LCMS R_f (min) = 6.77. MS m/z 426.1 (M + Na).

Ethyl 2-(methylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8a). Yield 42% (0.05 g), obtained as a white solid after recrystallization from petroleum ether. Mp 62–64 °C. ^{1}H NMR δ 7.79–7.35 (m, 1H. NH), 4.23 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.96 (d, J = 5.2 Hz, 3H, NCH_3), 2.77–2.64 (m, 2H,

CH_2), 2.59–2.48 (m, 2H, CH_2), 1.84–1.65 (m, 4H, 2 × CH_2), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.8, 166.4, 133.3, 116.6, 102.3, 59.3, 33.4, 27.0, 24.8, 23.5, 23.0, 14.7. LCMS R_f (min) = 6.77. HR-ESI calcd for $C_{12}H_{18}NO_2S^+$ (M + H) 240.1053, found 240.1046.

Ethyl 2-(ethyl(((4-methoxybenzyl)oxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7b). Carbamate **6** was reacted with diethylsulfate to obtain **7b** as an oil (0.24 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.41–7.11 (m, 2H, ArH), 6.95–6.73 (m, 2H, ArH), 5.19–4.87 (m, 2H, $ArCH_2$), 4.22–3.92 (m, 2H, OCH_2CH_3), 3.83–3.70 (m, 3H, OCH_3), 3.71–3.53 (m, 2H, NCH_2CH_3), 2.84–2.72 (m, 2H, CH_2), 2.72–2.58 (m, 2H, CH_2), 1.92–1.68 (m, 4H, 2 × CH_2), 1.17 (m, 6H, OCH_2CH_3, NCH_2CH_3). ^{13}C NMR (*cis* : *trans* isomers) δ 162.7, 159.4, 155.1, 146.1, 134.8, 133.1, 130.2, 129.7, 128.9, 126.4, 113.9, 113.7, 69.4, 67.1, 60.2, 55.3, 47.0, 26.1, 25.1, 22.9, 22.6, 14.6, 14.1, 13.2. LCMS R_f (min) = 6.93. MS m/z 440.1 (M + Na).

Ethyl 2-(ethylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8b). Obtained as a clear colourless oil (0.113 g, 89%). ^{1}H NMR δ 7.72–7.55 (m, 1H, NH), 4.23 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.22 (qd, J = 7.2, 5.5 Hz, 2H, NCH_2CH_3), 2.80–2.63 (m, 2H, CH_2), 2.59–2.45 (m, 2H, CH_2), 1.85–1.60 (m, 4H, 2 × CH_2), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.30 (t, J = 7.2 Hz, 3H, NCH_2CH_3). ^{13}C NMR δ 166.7, 165.0, 133.0, 116.3, 102.1, 59.1, 41.9, 27.0, 24.7, 23.4, 23.0, 14.7, 14.6. LCMS R_f (min) = 7.03. HR-ESI calcd for $C_{13}H_{20}NO_2S^+$ (M + H) 254.1209, found 254.1205.

Ethyl 2-((((4-methoxybenzyl)oxy)carbonyl)(propyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7c). Carbamate **6** was reacted with 1-iodopropane to obtain **7c** as an oil (0.224 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.42–7.11 (m, 2H, ArH), 6.95–6.72 (m, 2H, ArH), 5.21–4.91 (m, 2H, $ArCH_2$), 4.23–3.90 (m, 2H, OCH_2CH_3), 3.78–3.76 (m, 3H, OCH_3), 3.57–3.48 (m, 2H, $NCH_2CH_2CH_3$), 2.82–2.71 (m, 2H, CH_2), 2.71–2.62 (m, 2H, CH_2), 1.87–1.72 (m, 4H, 2 × CH_2), 1.67–1.54 (m, 2H, $NCH_2CH_2CH_3$), 1.15 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.88 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_3$). ^{13}C NMR (100 MHz, *cis* : *trans* isomers) δ 162.6, 159.4, 155.3, 146.7, 134.8, 133.0, 130.2, 129.7, 128.9, 126.1, 113.8, 113.7, 67.6, 67.2, 60.2, 55.3, 53.8, 26.1, 25.0, 22.9, 22.6, 21.7, 21.2, 14.1, 11.2. LCMS R_f (min) = 7.17. MS m/z 454.1 (M + Na).

Ethyl 2-(propylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8c). Clear colourless oil (0.109 g, 81%). ^{1}H NMR δ 7.82–7.67 (m, 1H, NH), 4.24 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.20–3.12 (m, 2H, $NCH_2CH_2CH_3$), 2.76–2.68 (m, 2H, CH_2), 2.57–2.48 (m, 2H, CH_2), 1.90–1.57 (m, 6H, 2 × CH_2, $NCH_2CH_2CH_3$), 1.33 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.00 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_3$). ^{13}C NMR δ 166.8, 165.4, 133.0, 116.2, 102.1, 59.2, 49.2, 27.0, 24.8, 23.4, 23.0, 22.7, 14.6, 11.6. LCMS R_f (min) = 7.25. HR-ESI calcd for $C_{14}H_{22}NO_2S^+$ (M + H) 268.1366, found 268.1367.

Ethyl 2-(butyl(((4-methoxybenzyl)oxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7d). Carbamate **6** was reacted with 1-bromobutane to obtain **7d** as an oil (0.220 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.41–7.10 (m, 2H, ArH), 6.95–6.72 (m, 2H, ArH), 5.17–4.92 (m, 2H, $ArCH_2$), 4.21–3.91 (m, 2H, OCH_2CH_3), 3.83–3.69 (m, 3H, OCH_3), 3.64–3.49 (m, 2H, $NCH_2CH_2CH_2CH_3$), 2.83–2.72 (m, 2H, CH_2), 2.72–2.61 (m, 2H, CH_2), 1.89–1.70 (m, 4H, 2 × CH_2), 1.61–1.54 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.42–1.25 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.15 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.90 (t, J = 7.2 Hz, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, *cis* : *trans* isomers) δ 162.7, 159.4, 155.3, 146.6, 134.8, 133. 130.2, 129.7, 128.9, 126.1, 113.8, 113.7, 67.7, 67.2, 60.3, 60.2, 55.3, 52.0, 30.0, 26.1, 25.1, 22.9, 22.6, 20.0, 14.1, 13.9. LCMS R_f (min) = 7.29. MS m/z 468.2 (M + Na).

Ethyl 2-(butylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8d). Obtained as a clear colourless oil (0.109 g, 77%). ^{1}H NMR δ 7.79–7.63 (m, 1H, NH), 4.23 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.24–3.15 (m, 2H, $NCH_2CH_2CH_2CH_3$), 2.7–2.67 (m, 2H, CH_2), 2.56–2.47 (m, 2H, CH_2), 1.82–1.60 (m, 6H, 2 × CH_2, $NCH_2CH_2CH_2CH_3$), 1.48–1.38 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.94 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR δ 166.8, 165.3, 133.0, 116.2, 102.0, 59.1, 47.0, 31.4, 27.0, 24.7, 23.4, 23.0, 20.2, 14.6, 13.8. LCMS R_f (min) = 7.46. HR-ESI calcd for $C_{15}H_{24}NO_2S^+$ (M + H) 282.1522, found 282.1515.

Ethyl 2-(allyl(((4-methoxybenzyl)oxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7e). Carbamate **6** was reacted with allyl bromide to obtain **7e** as an oil (0.226 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.40–7.12 (m, 2H, ArH), 6.95–6.73 (m, 2H, ArH), 6.00–5.77 (m, 1H, NCH_2CHCH_2), 5.21–4.96 (m, 4H, $ArCH_2$, NCH_2CHCH_2), 4.24–3.94 (m, 4H, OCH_2CH_3, NCH_2CHCH_2), 3.84–3.70 (m, 3H, OCH_3), 2.83–2.71 (m, 2H, CH_2), 2.70–2.60 (m, 2H, CH_2), 1.87–1.70 (m, 4H, 2 × CH_2), 1.16 (t, J = 7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR (*cis* : *trans* isomers) δ 162.6, 159.4, 155.2, 146.1, 134.7, 133.4, 133.0, 130.2, 129.8, 128.8, 126.3, 118.1, 117.8, 113.7, 67.8, 67.4, 60.3, 55.3, 54.7, 30.4, 26.1, 25.1, 22.9, 22.6, 14.1. LCMS R_f (min) = 6.92. MS m/z 452.2 (M + Na).

Ethyl 2-(allylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8e). Yield 70% (0.093 g), obtained as a white solid after recrystallization from methanol. Mp 40–43 °C. ^{1}H NMR δ 7.86–7.77 (m, 1H, NH), 5.95–5.85 (m, 1H, NCH_2CHCH_2), 5.35–5.27 (m, 1H, NCH_2CHCHH), 5.22–5.16 (m, 1H, NCH_2CHCHH), 4.24 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.90–3.80 (m, 2H, NCH_2CHCH_2), 2.76–2.68 (m, 2H, CH_2), 2.56–2.48 (m, 2H, CH_2), 1.81–1.69 (m, 4H, 2 × CH_2), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.7, 164.7, 133.6, 133.0, 117.0, 116.7, 102.9, 59.2, 49.5, 27.0, 24.7, 23.4, 23.0, 14.6. LCMS R_f (min) = 7.02. HR-ESI calcd for $C_{14}H_{20}NO_2S^+$ (M + H) 266.1209, found 266.1199.

Ethyl 2-((((4-methoxybenzyl)oxy)carbonyl)(prop-2-yn-1-yl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7f). Carbamate **6** was reacted with propargyl bromide to obtain **7f** as an oil (0.266 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.41–7.16 (m, 2H, ArH), 6.98–6.69 (m, 2H, ArH), 5.22–4.94 (m, 2H, $ArCH_2$), 4.47–4.29 (m, 2H, NCH_2CCH), 4.20–3.94 (m, 2H, OCH_2CH_3), 3.83–3.67 (m, 3H, OCH_3), 2.83–2.73 (m, 2H, CH_2), 2.72–2.62 (m, 2H, CH_2), 2.28 (t, J = 2.5 Hz, 1H, NCH_2CCH), 1.89–1.70 (m, 4H, 2 × CH_2), 1.15 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, *cis* : *trans* isomers) δ 162.4, 159.5, 155.0, 144.6, 134.7, 134.2, 130.2, 129.7, 128.4, 126.7, 113.7, 78.7, 73.3, 68.1, 67.7, 60.3,

55.7, 55.2, 53.5, 41.3, 41.0, 26.0, 25.1, 22.8, 22.5, 14.0. LCMS R_f (min) = 6.66. MS *m/z* 450.2 (M + Na).

Ethyl 2-(prop-2-yn-1-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (8f). Yield 87% (0.114 g) obtained as a white solid after recrystallization from petroleum ether. Mp 77–79 °C. ^{1}H NMR δ 7.77 (t, J = 5.2 Hz, 1H, NH), 4.25 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 4.00 (dd, J = 6.0, 2.5 Hz, 2H, NCH_2CCH), 2.75–2.70 (m, 2H, CH$_2$), 2.58–2.53 (m, 2H, CH$_2$), 2.27 (t, J = 2.5 Hz, 1H, NCH$_2$CCH), 1.81–1.70 (m, 4H, 2 × CH$_2$), 1.33 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR δ 166.6, 163.2, 133.3, 118.0, 104.6, 79.3, 72.1, 59.5, 36.3, 27.0, 24.8, 23.4, 23.0, 14.6. LCMS R_f (min) = 6.65. HR-ESI calcd for $C_{14}H_{18}NO_2S^+$ (M + H) 264.1053, found 264.1056.

Ethyl 2-(benzyl(((4-methoxybenzyl)oxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7g). Carbamate **6** was reacted with benzyl bromide to obtain **7g** as an oil (0.309 g). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.41–7.20 (m, 7H, ArH), 6.93–6.78 (m, 2H, ArH), 5.23–5.05 (m, 2H, ArCH$_2$), 4.89–4.65 (m, 2H, ArCH$_2$), 4.21–3.93 (m, 2H, OCH_2CH$_3$), 3.86–3.71 (m, 3H, OCH$_3$), 2.87–2.72 (m, 2H, CH$_2$), 2.68–2.53 (m, 2H, CH$_2$), 1.85–1.70 (m, 4H, 2 × CH$_2$), 1.16 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (*cis* : *trans* isomers) δ 162.5, 160.7, 159.4, 155.7, 155.1, 146.1, 137.1, 135.2, 134.6, 133.5, 129.7, 129.0, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 26.0, 24.9, 22.8, 22.5, 14.0. LCMS R_f (min) = 7.05. MS *m/z* 502.1 (M + Na).

Ethyl 2-(benzylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8g). The title compound (0.156 g, 99%) was obtained as a white solid after recrystallization from petroleum ether. Mp 90–92 °C. ^{1}H NMR δ 8.16 (t, J = 5.4 Hz, 1H, NH), 7.41–7.27 (m, 5H, ArH), 4.44 (d, J = 5.9 Hz, 2H, ArCH$_2$), 4.28 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 2.82–2.73 (m, 2H, CH$_2$), 2.58–2.51 (m, 2H, CH$_2$), 1.87–1.72 (m, 4H, 2 × CH$_2$), 1.36 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR δ 166.8, 164.7, 137.8, 133.0, 128.8, 127.6, 127.5, 116.9, 103.1, 59.3, 51.1, 27.0, 24.7, 23.4, 23.0, 14.6. LCMS R_f (min) = 7.15. HR-ESI calcd for $C_{18}H_{22}NO_2S^+$ (M + H) 316.1366, found 316.1363.

Ethyl 2-(isopropyl(((4-methoxybenzyl)oxy)carbonyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (10)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **6** (0.195 g, 0.5 mmol) and then purged with nitrogen. Caesium carbonate (0.652 g, 2.0 mmol) and TBAI (0.092 g, 0.25 mmol) were added followed by anhydrous DMF (3 mL). 2-Iodopropane (0.20 mL, 2 mmol) was added and the reaction mixture was stirred at rt for 24 h. A further aliquot of 2-iodopropane (0.20 mL, 2 mmol) and caesium carbonate (0.652 g, 2 mmol) were added and stirred a further 3 h. The mixture was diluted with ether (50 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil which was chromatographed on silica gel with 5% ethyl acetate–petroleum ether providing initially compound **9** as a white solid (0.004 g, 3%). ^{1}H NMR δ 10.42 (s, 1H, NH), 5.03 (hept, J = 6.2 Hz, 1H, OCH(CH$_3$)$_2$), 4.30 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 2.83–2.68 (m, 2H, CH$_2$), 2.68–2.53 (m, 2H, CH$_2$), 1.85–1.69 (m, 4H, 2 × CH$_2$), 1.36 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.30 (d, J = 6.3 Hz, 6H, OCH(CH_3)$_2$).

Further elution provided the starting material **6** (0.029 g, 6%) and finally **10** as a clear colourless oil (0.166 g, 77%). ^{1}H NMR (*cis* : *trans* isomers, 1 : 3) δ 7.38–7.06 (m, 2H, ArH), 6.91–6.71 (m, 2H, ArH), 5.24–4.86 (m, 2H, ArCH$_2$), 4.65–4.31 (m, 1H, NCH(CH$_3$)$_2$), 4.23–3.86 (m, 2H, OCH_2CH$_3$), 3.84–3.69 (m, 3H, OCH$_3$), 2.83–2.72 (m, 2H, CH$_2$), 2.71–2.60 (m, 2H, CH$_2$), 1.87–1.70 (m, 4H, 2 × CH$_2$), 1.27–0.97 (m, 9H, NCH(CH_3)$_2$, OCH$_2$CH_3). ^{13}C NMR (*cis* : *trans* isomers) δ 162.9, 159.3, 155.0, 142.3, 134.6, 133.4, 130.5, 129.6, 129.0, 128.2, 113.7, 66.9, 60.1, 55.2, 50.0, 26.1, 25.0, 22.9, 22.6, 14.0. LCMS R_f (min) = 7.07. MS *m/z* 454.2 (M + Na).

Ethyl 2-(isopropylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (11)

The oil **10** was taken up in CH_2Cl_2 (1 mL) and triethylsilane (0.192 mL, 1.2 mmol) was added followed by TFA (0.116 mL, 1.5 mmol) and stirred at room temperature for 15–30 min. The mixture was diluted with ether (20 mL) and quenched with saturated bicarbonate solution. The aqueous layer was removed and the organic layer was washed with water (10 mL) and then brine (5 mL), dried ($MgSO_4$), filtered and then concentrated to an oil that was chromatographed on silica gel with 5% ethyl acetate–petroleum ether providing **11** as a clear colourless oil (0.09 g, 88%). ^{1}H NMR δ 7.68 (d, J = 7.9 Hz, 1H, NH), 4.23 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 3.48 (dhept, J = 8.1, 6.4 Hz, 1H, NCH(CH$_3$)$_2$), 2.75–2.67 (m, 2H, CH$_2$), 2.56–2.48 (m, 2H, CH$_2$), 1.82–1.69 (m, 4H, 2 × CH$_2$), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.28 (d, J = 6.4 Hz, 6H, NCH(CH_3)$_2$). ^{13}C NMR δ 166.9, 164.1, 132.9, 116.3, 102.1, 59.2, 49.3, 27.1, 24.8, 23.5, 23.1, 23.0 14.7. LCMS R_f (min) = 7.30. HR-ESI calcd for $C_{14}H_{22}NO_2S^+$ (M + H) 268.1366, found 268.1363.

4-Methoxybenzyl (3-(4-chlorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamate (17a)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **16** (0.554 g, 1.9 mmol) and then purged with nitrogen. Caesium carbonate (1.86 g, 5.7 mmol) and TBAI (2.1 g, 5.7 mmol) were added followed by anhydrous DMF (10 mL). The nitrogen inlet was replaced with a carbon dioxide inlet and CO_2 (g) was bubbled through the stirred mixture at a steady rate for 2 h. *p*-Methoxybenzyl chloride (0.271 mL, 2.0 mmol) was added to the mixture in one portion with continual bubbling of CO_2 (g) for a further 3.5 h. The mixture was stirred overnight then diluted with ether (100 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to a resin. The resin was chromatographed on silica gel eluting with 10% ethyl acetate–petroleum ether affording **17a** as a clear orange resin (0.351 g, 41%). ^{1}H NMR δ 10.54 (s, 1H, NH), 7.50–7.45 (m, 2H, ArH), 7.43–7.38 (m, 2H, ArH), 7.37–7.32 (m, 2H, ArH), 6.92–6.87 (m, 2H, ArH), 5.19 (s, 2H, ArCH$_2$), 3.81 (s, 3H. OCH$_3$), 2.70–2.62 (m, 2H, CH$_2$), 1.94–1.86 (m, 2H, CH$_2$), 1.81–1.73 (m, 2H, CH$_2$), 1.58–1.49 (m, 2H, CH$_2$). ^{13}C NMR δ 192.9, 159.9, 153.3, 150.4, 139.2, 137.8, 130.4, 130.2, 129.6, 128.6, 127.6, 127.1, 120.4, 114.0, 68.0, 55.3, 27.6, 24.4, 23.0, 22.8. LCMS R_f (min) = 7.11. MS *m/z* 454.2 (M − H).

Further elution afforded a mixture of starting material **16** and **17b** in a 1.6 : 1 ratio respectively as an orange resin (0.342 g).

4-Methoxybenzyl (3-(4-chlorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)(methyl)carbamate (17c)

To a 25 mL two neck flask fitted with a nitrogen inlet was added **17a** (0.062 g, 0.14 mmol) and then purged with nitrogen. Caesium carbonate (0.089 g, 0.27 mmol) and TBAI (0.025 g, 0.068 mmol) were added followed by anhydrous DMF (0.816 mL). To the stirred mixture was added dimethylsulfate (0.026 mL, 0.27 mmol) and left to stir overnight. Upon completion of the reaction (TLC), the mixture was diluted with ether (10 mL) and then washed with water (6 × 15 mL), then brine (5 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated affording the *N*-alkylated carbamate **17c** as a resin (0.059 g, 92%). ^{1}H NMR δ 7.81–7.45 (m, 2H, ArH), 7.23–7.10 (m, 4H, ArH), 6.85 (d, J = 8.6 Hz, 2H, ArH), 4.94 (s, 2H, $ArCH_2$), 3.82 (s, 3H, OCH_3), 3.13–2.90 (m, 3H, NCH_3), 2.75–2.68 (m, 2H, CH_2), 2.53–2.30 (m, 2H, CH_2), 1.88–1.81 (m, 2H, CH_2), 1.77–1.68 (m, 2H, CH_2).

Ethyl 2-(2,2,2-trifluoroacetamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (18a)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **3** (1.0 g, 4.44 mmol) and then purged with nitrogen. To this was added CH_2Cl_2 (10 mL) followed by triethylamine (1.24 mL, 8.88 mmol) and then cooled in an ice bath. Then trifluoroacetic anhydride (0.94 mL, 6.66 mmol) was added dropwise and the mixture left to stir for 2 h. The mixture was then diluted with ethyl acetate (50 mL) and washed with water (4 × 20 mL) then brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated to a solid that was recrystallised from methanol affording **18a** as a lemon solid (1.27 g, 89%). Mp 130–132 °C. ^{1}H NMR δ 12.29 (s, 1H, NH), 4.37 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.83–2.76 (m, 2H, CH_2), 2.72–2.65 (m, 2H, CH_2), 1.87–1.75 (m, 4H, 2 × CH_2), 1.40 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.4, 153.5 (q, J = 39.1 Hz), 143.9, 132.0, 129.5, 115.8 (q, J = 287.0 Hz), 114.8, 61.3, 26.3, 24.6, 22.9, 22.7, 14.3. LCMS R_f (min) = 7.00. MS m/z 320.2 (M-H). HR-ESI calcd for $C_{13}H_{15}F_3NO_3S^+$ (M + H) 322.0719, found 322.0710.

Ethyl 2-acetamido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (18b)

To a 50 mL round bottom flask was added **3** (1.0 g, 4.44 mmol) and acetic anhydride (4 mL) and then refluxed for several minutes. Upon cooling a precipitate formed and while stirring saturated bicarbonate solution was slowly added until gaseous evolution ceased. The solid was filtered and washed with copious amounts of water and suction dried to afford **18b** as an off white solid (1.15 g, 97%). Mp 122–124 °C. ^{1}H NMR δ 11.26 (s, 1H, NH), 4.32 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.80–2.73 (m, 2H, CH_2), 2.67–2.60 (m, 2H, CH_2), 2.25 (s, 3H, $COCH_3$), 1.84–1.72 (m, 4H, 2 × CH_2), 1.38 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 166.7, 166.5, 147.6, 130.5, 126.5, 111.1, 60.3, 26.3, 24.3, 23.6, 22.9, 22.8, 14.2. LCMS R_f (min) = 6.43. MS m/z 268.2 (M + H). HR-ESI calcd for $C_{13}H_{18}NO_3S^+$ (M + H) 268.1002, found 268.0990.

General procedure for the synthesis of N-methylated thiophenes 19a,b

To a 50 mL two neck flask fitted with a nitrogen inlet was added **18a** or **18b** (0.5 mmol) and then purged with nitrogen. Caesium carbonate (0.326 g, 1.0 mmol) and TBAI (0.092 g, 0.25 mmol) were added followed by anhydrous DMF (3 mL). To the stirred mixture was added dimethylsulfate (0.095 mL, 1.0 mmol) and left to stir overnight. The mixture was diluted with diethyl ether (50 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the crude carbamates **19a,b**, that were chromatographed on silica gel with 5% ethyl acetate–petroleum ether.

Ethyl 2-(2,2,2-trifluoro-*N*-methylacetamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (19a). Initial fractions provided starting material **18a** (0.016 g, 10%) and further elution provided **19a** as a colorless resin (0.137 g, 82%). ^{1}H NMR δ 4.26–4.18 (m, 2H, OCH_2CH_3), 3.28 (s, 3H, NCH_3), 2.89–2.59 (m, 4H, 2 × CH_2), 1.85–1.68 (m, 4H, 2 × CH_2), 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 161.7, 157.3 (q, J = 35.8 Hz), 143.5, 135.8, 135.2, 128.1, 116.2 (q, J = 288.3 Hz), 60.8, 40.5, 26.1, 25.1, 22.7, 22.3, 14.1. LCMS R_f (min) = 6.70. MS m/z 290.1 (100%).

Ethyl 2-(*N*-methylacetamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (19b). The target compound was isolated as a colourless resin (0.129 g, 92%). ^{1}H NMR δ 4.26 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.18 (s, 3H, NCH_3), 2.82–2.76 (m, 2H, CH_2), 2.73–2.67 (m, 2H, CH_2), 1.94 (s, 3H, $COCH_3$), 1.89–1.76 (m, 4H, 2 × CH_2), 1.31 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 171.3, 162.3, 148.9, 135.1, 134.5, 127.0, 60.7, 37.8, 26.0, 25.1, 22.8, 22.4, 21.9, 14.2. LCMS R_f (min) = 6.16. MS m/z 236.1 (100%), 194.1 (25).

General procedure for the synthesis of N-isopropyl thiophenes 19c,d

To a 50 mL two neck flask fitted with a nitrogen inlet was added **18a** or **18b** (0.5 mmol) and then purged with nitrogen. Caesium carbonate (1.3 g, 4.0 mmol) and TBAI (0.092 g, 0.25 mmol) were added followed by anhydrous DMF (3 mL). 2-Iodopropane (0.40 mL, 4.0 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was diluted with ether (50 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated. Analysis of the crude product with ^{1}H NMR and LCMS showed that **19c** did not form and only starting material was returned. In the case of **19d** 83% conversion by LCMS and ^{1}H NMR.

Ethyl 5-acetamido-3-(3-chlorophenyl)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (20a)

To a 25 mL round bottom flask was added **14** (0.5 g, 1.43 mmol) and acetic anhydride (5 mL) and then refluxed for several minutes. Upon cooling a precipitate formed and while stirring methanol (5 mL) was added and the mixture chilled on ice for 30 min and then filtered and the filter cake was washed with ice cold methanol and suction dried affording **20a** as yellow needles (0.502 g, 90%).%). Mp 188–190 °C. ^{1}H NMR δ 10.98 (s, 1H, NH), 7.88 (d, J = 0.8 Hz, 1H, ArH), 7.66 (t, J = 1.8 Hz, 1H, ArH), 7.54 (ddd, J = 7.8, 2.0, 1.4 Hz, 1H, ArH), 7.43 (t, J = 7.8 Hz, 1H, ArH), 7.38 (ddd, J = 8.0, 1.9, 1.4 Hz, 1H, ArH), 4.48 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.33 (s, 3H, $COCH_3$), 1.44 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 167.5, 162.7, 159.0, 146.8, 141.3,

134.6, 134.5, 129.9, 128.4, 126.4, 126.0, 124.2, 115.4, 111.57, 62.5, 23.4, 14.4. LCMS R_f (min) = 6.23. MS *m/z* 392.1 (M + H).

Ethyl 3-(3-chlorophenyl)-4-oxo-5-(2,2,2-trifluoroacetamido)-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (20b)

To a 50 mL two neck flask fitted with a nitrogen inlet was added **14** (0.50 g, 1.43 mmol) and then purged with nitrogen. To this was added CH_2Cl_2 (10 mL) followed by triethylamine (0.398 mL, 2.86 mmol) and then cooled in an ice bath. Trifluoroacetic anhydride (0.303 mL, 2.14 mmol) was added dropwise and the mixture left to stir for 1.5 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with water (4 × 20 mL). The organic layer was dried ($MgSO_4$), filtered through a silica gel pad eluting with CH_2Cl_2 and then concentrated to a solid that was recrystallised from methanol affording **20b** as a lemon solid (0.52 g, 82%). Mp 168–170 °C. ^{1}H NMR δ 11.88 (s, 1H, NH), 8.14 (s, 1H, ArH), 7.66 (t, J = 1.8 Hz, 1H, ArH), 7.60–7.51 (m, 1H, ArH), 7.44 (t, J = 7.9 Hz, 1H, ArH), 7.40 (dt, J = 8.0, 1.6 Hz, 1H, ArH), 4.50 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 1.46 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR δ 162.4, 158.8, 154.3 (q, J = 40.3 Hz), 143.1, 140.9, 134.8, 134.3, 130.0, 128.8, 126.3, 125.7, 124.2, 118.1, 115.4 (q, J = 286.6 Hz), 114.6, 62.7, 14.4. LCMS R_f (min) = 6.70. MS *m/z* 446.0 (M + H).

Ethyl 3-(3-chlorophenyl)-5-(*N*-methylacetamido)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (21a)

To a 25 mL two neck flask fitted with a nitrogen inlet was added **20a** (0.044 g, 0.11 mmol) and then purged with nitrogen. Caesium carbonate (0.072 g, 0.22 mmol) and TBAI (0.021 g, 0.056 mmol) were added followed by anhydrous DMF (0.667 mL). To the stirred mixture was added dimethylsulfate (0.021 mL, 0.22 mmol) and left to stir at room temperature overnight. The mixture was diluted with ether (25 mL) and then washed with water (6 × 50 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to a resin which was chromatographed on silica gel with 0–30% ethyl acetate–petroleum ether affording **21a** as a pale yellow resin (0.031 g, 69%). ^{1}H NMR δ 8.57–8.40 (m, 1H, ArH), 7.70–7.59 (m, 1H, ArH), 7.59–7.47 (m, 1H, ArH), 7.44–7.33 (m, 2H, ArH), 4.49 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 3.57–3.29 (m, 3H, NCH$_3$), 2.02–1.91 (m, 3H, COCH$_3$), 1.45 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). LCMS R_f (min) = 5.95. MS *m/z* 406.1 (M + H).

***N*-(3-(4-Chlorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (22a)**

To a 50 mL round bottom flask was added **16** (1.0 g, 3.43 mmol) and acetic anhydride (5 mL) and then refluxed for several minutes. While stirring, the cooled mixture was quenched with saturated bicarbonate solution (added slowly) until gaseous evolution ceased and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and then concentrated affording **22a** as a pale yellow foam (0.90 g, 79%). ^{1}H NMR δ 11.29 (s, 1H, NH), 7.52–7.48 (m, 2H, ArH), 7.45–7.40 (m, 2H, ArH), 2.70–2.64 (m, 2H, CH$_2$), 2.26 (s, 3H, COCH$_3$), 1.96–1.88 (m, 2H, CH$_2$), 1.82–1.73 (m, 2H, CH$_2$), 1.58–1.50 (m, 2H, CH$_2$). ^{13}C NMR δ 193.6, 167.7, 148.9, 139.2, 138.0, 129.7, 129.6, 128.7, 128.1, 120.8, 27.7, 24.4, 23.9, 23.0, 22.9. LCMS R_f (min) = 6.56. MS *m/z* 334.1 (M + H).

***N*-(3-(4-Chlorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-2,2,2-trifluoroacetamide (22b)**

To a 50 mL two neck flask fitted with a nitrogen inlet was added **16** (0.70 g, 2.40 mmol) and then purged with nitrogen. To this was added CH_2Cl_2 (15 mL) followed by triethylamine (0.669 mL, 4.80 mmol) and then cooled in an ice bath. Trifluoroacetic anhydride (0.508 mL, 3.60 mmol) was added dropwise and the mixture left to stir for 1.5 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with water (4 × 20 mL). The organic layer was dried ($MgSO_4$) and then concentrated to a solid that was chromatographed on silica gel eluting with 5% ethyl acetate–petroleum ether affording **22b** as a lemon solid which was recrystallised from methanol (0.377 g, 41%). Mp 128–130 °C. ^{1}H NMR δ 12.11 (s, 1H, NH), 7.55–7.51 (m, 2H, ArH), 7.47–7.43 (m, 2H, ArH), 2.77–2.70 (m, 2H, CH$_2$), 2.04–1.97 (m, 2H, CH$_2$), 1.86–1.78 (m, 2H, CH$_2$), 1.62–1.53 (m, 2H, CH$_2$). ^{13}C NMR δ 194.0, 154.2 (q, J = 39.3 Hz), 144.7, 138.7, 138.3, 130.9, 130.8, 129.7, 128.9, 123.6, 115.6 (q, J = 287.1 Hz), 27.6, 24.5, 22.8, 22.7. LCMS R_f (min) = 6.96. MS *m/z* 388.1 (M + H).

General procedure for the synthesis of N-alkyl thiophenes 24a–c

To a 25 mL two neck flask fitted with a nitrogen inlet was added **22a** (0.167 g, 0.5 mmol) and then purged with nitrogen. Caesium carbonate (0.326 g, 1.0 mmol) and TBAI (0.092 g, 0.25 mmol) were added followed by anhydrous DMF (3.0 mL). The alkylating agent (1.0 mmol) was added and the reaction was stirred at room temperature for 24–40 h. The mixture was diluted with ether (25 mL) and then washed with water (6 × 50 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to a yellow resin. The resin was taken up in ethanol (4 mL), water (1 mL) was added, followed by NaOH (0.1 g, 2.5 mmol) and heated on an oil bath (35–40 °C) for 4 h in which time a precipitate formed. The mixture was cooled to room temperature and filtered on a Buchner funnel/flask and the filter cake washed with 2 : 1 EtOH : H_2O (5 mL) and suction dried affording the N-alkylated thiophenes **24a–c** as bright yellow solids.

(4-Chlorophenyl)(2-(methylamino)-4,5,6,7-tetrahydrobenzo[*b*]-thiophen-3-yl)methanone (24a). Dimethylsulfate was used as the alkylating agent and the target compound was isolated in 61% yield (0.093 g). Mp 149–151 °C. ^{1}H NMR δ 9.52–9.37 (m, 1H, NH), 7.37–7.33 (m, 4H, ArH), 3.05 (d, J = 5.2 Hz, 3H, NCH$_3$), 2.59–2.49 (m, 2H, CH$_2$), 1.80–1.68 (m, 4H, 2 × CH$_2$), 1.53–1.43 (m, 2H, CH$_2$). ^{13}C NMR δ 189.7, 170.1, 141.2, 135.6, 131.7, 128.8, 128.3, 118.2, 113.3, 33.4, 28.2, 25.0, 23.2, 23.0. LCMS R_f (min) = 6.90. HR-ESI calcd for $C_{16}H_{17}ClNOS^+$ (M + H) 306.0714, found 306.0709.

(2-(Butylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-chlorophenyl)methanone (24b). 1-Bromobutane was used as the alkylating agent and the target compound was isolated in 36% yield (0.062 g). Mp 109–111 °C. ^{1}H NMR δ 9.62 (t, J = 4.6 Hz, 1H, NH), 7.38–7.33 (m, 4H, ArH), 3.29 (td, J = 6.9, 5.8 Hz, 2H, NCH_2CH$_2$CH$_2$CH$_3$), 2.57–2.48 (m, 2H, CH$_2$), 1.79–1.67 (m, 6H, 2 × CH$_2$, NCH$_2$CH_2CH$_2$CH$_3$), 1.53–1.41 (m, 4H, CH$_2$, NCH$_2$CH$_2$CH_2CH$_3$), 0.96 (t, J = 7.4 Hz, 3H, NCH$_2$CH$_2$CH$_2$CH_3). ^{13}C NMR δ 189.5, 169.1, 141.3, 135.6, 131.5, 128.8, 128.3, 118.0, 113.2, 47.3, 31.1, 28.2, 25.0, 23.2, 23.0, 20.3, 13.8. LCMS R_f (min) =

7.53. HR-ESI calcd for $C_{19}H_{23}ClNOS^+$ (M + H) 348.1183, found 348.1184.

(2-(Benzylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-chlorophenyl)methanone (24c). Benzyl bromide was used as the alkylating agent and the target compound was isolated in 32% yield (0.061 g). Mp 135–137 °C. ^{1}H NMR δ 9.92–9.81 (m, 1H, NH), 7.50–7.23 (m, 9H, ArH), 4.50 (d, J = 5.7 Hz, 2H, $ArCH_2$), 2.59–2.45 (m, 2H, CH_2), 1.86–1.66 (m, 4H, 2 × CH_2), 1.54–1.42 (m, 2H, CH_2). ^{13}C NMR δ 189.9, 168.3, 141.0, 136.8, 135.7, 131.4, 2 ×128.8, 128.2, 127.8, 127.5, 118.4, 113.8, 51.2, 28.1, 24.8, 23.1, 22.9. LCMS R_f (min) = 7.27. HR-ESI calcd for $C_{22}H_{21}ClNOS^+$ (M + H) 382.1027, found 382.1017.

Ethyl 2-(*tert*-butoxycarbonylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (25)

To a 50 mL round bottom flask was added **3** (0.5 g, 2.22 mmol), dioxane (15 mL), Boc_2O (1.02 g, 4.67 mmol) and DMAP (0.027 g, 0.22 mmol) and the mixture was heated on an oil bath (40 °C) for 16 h with stirring. $N_2H_4{\cdot}H_2O$ (0.322 mL, 6.66 mmol) was added to the mixture and continued to stir at 40 °C for 6 h then stirred at room temperature overnight. The mixture was evaporated and then chromatographed on silica gel with 0–5% ethyl acetate–petroleum ether providing **25** as an off white solid that was recrystallised from methanol (0.628 g, 87%). Mp 110–112 °C dec. ^{1}H NMR δ 10.30 (s, 1H, NH), 4.27 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.77–2.63 (m, 2H, CH_2), 2.63–2.48 (m, 2H, CH_2), 1.83–1.61 (m, 2H, 2 × CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.33 (t, J = 7.1 Hz, 2H, OCH_2CH_3). ^{13}C NMR δ 166.4, 152.16, 149.9, 131.0, 125.1, 110.1, 81.7, 60.2, 28.2, 26.5, 24.3, 23.0, 22.9, 14.3. LCMS R_f (min) = 7.31. MS m/z 326.1 (M + H).

General procedure for the synthesis of N-alkylated thiophenes 8a,d,g from 25

To a 50 mL two neck flask fitted with a nitrogen inlet was added **25** (0.163 g, 0.5 mmol) and then purged with nitrogen. Caesium carbonate (0.326 g, 1.0 mmol) and TBAI (0.092 g, 0.25 mmol) were added followed by anhydrous DMF (3 mL). The alkylating agent (1.0 mmol) was added and the reaction was stirred at room temperature for 3–24 h. Upon completion of the reaction (TLC), the mixture was diluted with ether (50 mL) and then washed with water (6 × 150 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the carbamates, which were used without further purification in the next step. The resin was taken up in CH_2Cl_2 (1 mL) and TFA (0.5 mL) was added and stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated bicarbonate solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and then concentrated to afford the thiophenes **8a,d,g** that were chromatographed on silica gel with 5% ethyl acetate–petroleum ether. Solids were recrystallized from petroleum ether or methanol.

Ethyl 2-(methylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8a). The title compound was isolated in 96% (0.115 g) and was identical in all respects to the material **8a** *via* the general procedure described above.

Ethyl 2-(butylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8d). The title compound was isolated in 71% yield (0.10 g) and was material was identical in all respects to the material **8d** *via* the general procedure described above.

Ethyl 2-(benzylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8g). The title compound was isolated in 60% yield (0.095 g) and was identical in all respects to the material **8g** *via* the general procedure described above.

Ethyl 5-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (26)

To a 50 mL round bottom flask was added **14** (0.5 g, 1.43 mmol), dioxane (15 mL), Boc_2O (0.655 g, 3.0 mmol) and DMAP (0.018 g, 0.14 mmol) and the mixture was heated on an oil bath (40 °C) for 2 h with stirring. Then $N_2H_4{\cdot}H_2O$ (0.152 mL, 3.14 mmol) was added to the mixture and continued to stir at 40 °C for 3 h then stirred at room temperature overnight. The mixture was concentrated and then dissolved in ethyl acetate (50 mL) and washed with water (2 × 150 mL) and then brine (20 mL) dried ($MgSO_4$), filtered and then concentrated to a solid that was chromatographed on silica gel with 10% ethyl acetate–petroleum ether providing **26** as a yellow solid that was recrystallised from methanol (0.411 g, 64%). Mp 170 °C dec. ^{1}H NMR δ 10.10 (s, 1H, NH), 7.80 (d, J = 1.4 Hz, 1H, ArH), 7.66 (dd, J = 1.9, 1.4 Hz, 1H, ArH), 7.54 (ddd, J = 7.8, 2.0, 1.4 Hz, 1H, ArH), 7.41 (t, J = 7.8 Hz, 1H, ArH), 7.36 (ddd, J = 8.0, 1.9, 1.4 Hz, 1H, ArH), 4.48 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.45 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 162.7, 158.9, 152.1, 149.5, 141.4, 134.4, 134.4, 129.7, 128.1, 126.2, 125.4, 124.1, 113.8, 110.3, 83.2, 62.3, 28.2, 14.4. LCMS R_f (min) = 7.00. MS m/z 448.2 (M − H).

General procedure for the synthesis of N-alkylated thiophenes 27a,d

To a 25 mL two neck flask fitted with a nitrogen inlet was added **26** (0.150 g, 0.33 mmol) and then purged with nitrogen. Caesium carbonate (0.217 g, 0.67 mmol) and TBAI (0.062 g, 0.17 mmol) were added followed by anhydrous DMF (2 mL). The alkylating agent (0.67 mmol) was added and the reaction was stirred at room temperature for 3–24 h. Upon completion of the reaction (TLC), the mixture was diluted with ether (25 mL) and then washed with water (6 × 50 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the *N*-alkylated carbamates which were chromatographed on silica gel with 10% ethyl acetate–petroleum ether. The carbamates were taken up in CH_2Cl_2 (0.5 mL) and cooled in an ice bath and TFA (0.25 mL) was added and the mixture stirred for 3 h at 0 °C. The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated bicarbonate solution. The aqueous layer was removed and the organic layer was washed with water (10 mL) and then brine (5 mL), dried ($MgSO_4$), filtered and then concentrated to a yellow resin that slowly solidifies. The solids were recrystallised from methanol affording the thiophenes **27a,d** as bright yellow solids.

Ethyl 3-(3-chlorophenyl)-5-(methylamino)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (27a). Dimethylsulfate was used as the alkylating agent and the title compound was obtained in 67% yield (0.081 g). Mp 179–181 °C. ^{1}H NMR δ

7.65 (t, J = 1.9 Hz, 1H, ArH), 7.59–7.50 (m, 2H, ArH, NH), 7.37 (t, J = 8.0 Hz, 1H, ArH), 7.31 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H, ArH), 7.19 (d, J = 1.0 Hz, 1H, ArH), 4.44 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.06 (d, J = 5.2 Hz, 3H, NCH_3), 1.43 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 165.6, 163.12, 159.3, 141.8, 134.3, 134.2, 129.6, 127.6, 127.5, 126.1, 124.0, 104.2, 103.0, 62.1, 34.0, 14.4. LCMS R_f (min) = 6.44. HR-ESI calcd for $C_{16}H_{15}ClN_3O_3S^+$ (M + H) 364.0517, found 364.0517.

Ethyl 5-(benzylamino)-3-(3-chlorophenyl)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (27d). Benzyl bromide was used as the alkylating agent and the title compound was obtained in 84% yield (0.123 g). Mp 116–118 °C. ^{1}H NMR δ 8.01 (t, J = 5.6 Hz, 1H, NH), 7.66 (t, J = 1.9 Hz, 1H, ArH), 7.54 (ddd, J = 7.9, 2.0, 1.2 Hz, 1H, ArH), 7.41–7.28 (m, 6H, ArH), 7.18 (d, J = 1.0 Hz, 1H, ArH), 4.48–4.40 (m, 4H, $ArCH_2$, OCH_2CH_3), 1.42 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR δ 163.8, 163.0, 159.3, 141.7, 136.0, 134.3, 134.2, 129.6, 129.0, 128.3, 127.8, 127.6, 127.2, 126.1, 124.0, 104.9, 103.6, 62.1, 51.7, 14.4. LCMS R_f (min) = 6.81. HR-ESI calcd for $C_{22}H_{19}ClN_3O_3S^+$ (M + H) 440.0830, found 440.0830.

Butyl 5-(butylamino)-3-(3-chlorophenyl)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (27b) and ethyl 5-(butylamino)-3-(3-chlorophenyl)-4-oxo-3,4-dihydrothieno[3,4-*d*]pyridazine-1-carboxylate (27c)

To a 25 mL two neck flask fitted with a nitrogen inlet was added **26** (0.120 g, 0.27 mmol) and then purged with nitrogen. Caesium carbonate (0.174 g, 0.53 mmol) and TBAI (0.049 g, 0.13 mmol) were added followed by anhydrous DMF (1.6 mL). 1-Bromobutane (0.057 mL, 0.53 mmol) was added and the reaction was stirred at room temperature 24 h. Then a further portion of caesium carbonate (0.174 g, 0.53 mmol) and 1-bromobutane (0.057 mL, 0.53 mmol) were added and the mixture was heated to 60 °C for 24 h. The cooled mixture was diluted with ether (25 mL) and then washed with water (6 × 50 mL), then brine (20 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to a resin which was chromatographed on silica gel with 5% ethyl acetate–petroleum ether providing Boc protected **27b** (0.083 g). ^{1}H NMR δ 8.35 (s, 1H, ArH), 7.64 (t, J = 1.9 Hz, 1H, ArH), 7.57–7.52 (m, 1H, ArH), 7.39 (t, J = 7.9 Hz, 1H, ArH), 7.33 (ddd, J = 8.0, 1.9, 1.3 Hz, 1H, ArH), 4.42 (t, J = 6.8 Hz, 2H, $OCH_2CH_2CH_2CH_3$), 3.75 (t, J = 7.1 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.84–1.76 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.60–1.27 (m, 15H $C(CH_3)_3$, $OCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$), 0.99 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 0.89 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$).

The carbamate was taken up in CH_2Cl_2 (0.5 mL) and cooled in an ice bath and TFA (0.25 mL) was added and the mixture stirred for 3 h at 0 °C. The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated bicarbonate solution. The aqueous layer was removed and the organic layer was washed with water (10 mL) and then brine (5 mL), dried ($MgSO_4$), filtered and then concentrated to a yellow resin that slowly solidifies and was recrystallised from methanol affording **27b** as a gold coloured solid (0.055 g, 82%). Mp 92–94 °C. ^{1}H NMR δ 7.66 (t, J = 1.9 Hz, 1H, ArH), 7.60 (t, J = 5.5 Hz, 1H, NH), 7.55 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H, ArH), 7.36 (t, J = 8.0 Hz, 1H, ArH), 7.30 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H, ArH), 7.12 (d, J = 1.0 Hz, 1H, ArH), 4.37 (t, J = 6.8 Hz, 2H, $OCH_2CH_2CH_2CH_3$), 3.32–3.21 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.82–1.66 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.52–1.40 (m, 4H, $NCH_2CH_2CH_2CH_3$), 0.98 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 0.96 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR δ 164.6, 163.1, 159.4, 141.8, 134.3, 134.2, 129.6, 127.5, 127.3, 126.0, 123.9, 104.1, 102.6, 65.9, 47.8, 30.9, 30.7, 20.1, 19.3, 13.9, 13.8. LCMS R_f (min) = 7.36. HR-ESI calcd for $C_{21}H_{25}ClN_3O_3S^+$ (M + H) 434.1300, found 434.1285.

Further elution provided Boc protected **27c** (0.030 g). ^{1}H NMR δ 8.37 (s, 1H, ArH), 7.63 (t, J = 1.9 Hz, 1H, ArH), 7.55–7.51 (m, 1H, ArH), 7.39 (t, J = 7.8 Hz, 1H, ArH), 7.34 (ddd, J = 8.1, 1.9, 1.3 Hz, 1H, ArH), 4.48 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.75 (t, J = 7.1 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.60–1.28 (m, 16H, $NCH_2CH_2CH_2CH_3$, $C(CH_3)_3$, OCH_2CH_3), 0.89 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$).

The carbamate was taken up in CH_2Cl_2 (0.2 mL) and cooled in an ice bath and TFA (0.10 mL) was added and the mixture stirred for 3 h at 0 °C. The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated bicarbonate solution. The aqueous layer was removed and the organic layer was washed with water (10 mL) and then brine (5 mL), dried ($MgSO_4$), filtered and then concentrated to a yellow resin that slowly solidified and was recrystallised from methanol affording **27c** as a gold coloured solid (0.055 g, 82%). Mp 99–102 °C. ^{1}H NMR δ 7.64 (t, J = 1.9 Hz, 1H, ArH), 7.60 (t, J = 5.5 Hz, 1H, NH), 7.53 (ddd, J = 7.9, 1.9, 1.2 Hz, 1H, ArH), 7.37 (t, J = 8.0 Hz, 1H, ArH), 7.31 (ddd, J = 8.0, 1.9, 1.2 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 4.44 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.31–3.23 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.76–1.66 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.51–1.40 (m, 5H, $NCH_2CH_2CH_2CH_3$, OCH_2CH_3), 0.96 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR δ 164.7, 163.1, 159.4, 141.8, 134.3, 134.2, 129.6, 127.7, 127.3, 126.2, 124.1, 104.1, 102.7, 62.1, 47.9, 31.0, 20.2, 14.4, 13.8. LCMS R_f (min) = 7.05. HR-ESI calcd for $C_{19}H_{21}ClN_3O_3S^+$ (M + H) 406.0987, found 406.0993.

tert-Butyl 3-(4-chlorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylcarbamate (28)

To a 50 mL round bottom flask was added **16** (0.5 g, 1.71 mmol), dioxane (10 mL), Boc_2O (0.785 g, 3.6 mmol) and DMAP (0.021 g, 0.17 mmol) and the mixture was heated on an oil bath (40 °C) for 16 h with stirring. Then $N_2H_4{\cdot}H_2O$ (0.249 mL, 5.14 mmol) was added to the mixture which was stirred at 40 °C for 6 h then stirred at room temperature overnight. The mixture was concentrated and then chromatographed on silica gel with 0–5% ethyl acetate–petroleum ether providing **28** as a yellow foam (0.538 g, 80%). ^{1}H NMR δ 10.42 (s, 1H. NH), 7.55–7.45 (m, 2H, ArH), 7.44–7.32 (m, 2H, ArH), 2.69–2.59 (m, 2H, CH_2), 1.95–1.86 (m, 2H, CH_2), 1.82–1.71 (m, 2H, CH_2), 1.58–1.47 (m, 11H, $C(CH_3)_3$, CH_2). ^{13}C NMR δ 193.0, 152.5, 151.3, 139.4, 137.7, 130.0, 129.7, 128.7, 126.7, 120.0, 82.3, 28.3, 27.7, 24.4, 23.1, 23.0. LCMS R_f (min) = 7.34. MS m/z 390.1 (M – H).

General procedure for the synthesis of N-alkylated thiophenes 24a–c from 28

To a 50 mL two neck flask fitted with a nitrogen inlet was added **25** (0.098 g, 0.25 mmol) and then purged with nitrogen. Caesium carbonate (0.163 g, 0.5 mmol) and TBAI (0.046 g, 0.125 mmol)

were added followed by anhydrous DMF (1.5 mL). The alkylating reagent (0.5 mmol) was added and the reaction was stirred at room temperature for 3–24 h. In the case of **24b** a further aliquot of 1-bromobutane (0.054 mL, 0.5 mmol) and caesium carbonate (0.163 g, 0.5 mmol) were added and stirred a further 16 h. Upon completion of the reaction (TLC), the mixture was diluted with ether (25 mL) and then washed with water (6 × 75 mL), then brine (10 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the carbamates, which were used without further purification in the next step. The resin was taken up in CH_2Cl_2 (0.5 mL) and TFA (0.25 mL) was added and stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated bicarbonate solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and then concentrated to afford the thiophenes **24a–c**, that were recrystallized from methanol.

(4-Chlorophenyl)(2-(methylamino)-4,5,6,7-tetrahydrobenzo[*b*]-thiophen-3-yl)methanone (24a). The title compound was obtained in 71% yield (0.054 g) and was identical in all respects to the material **24a** *via* the general procedure described above.

(2-(Butylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-chlorophenyl)methanone (24b). The title compound was obtained in 64% yield (0.056 g) and was identical in all respects to the material **24b** *via* the general procedure described above.

(2-(Benzylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-chlorophenyl)methanone (24c). The title compound was obtained in 78% yield (0.075 g) and was identical in all respects to the material **24c** *via* the general procedure described above.

***tert*-Butyl 2-benzoylphenylcarbamate (30).** To a 50 mL round bottom flask was added **29** (0.438 g, 2.22 mmol), and Boc_2O (1.02 g, 4.67 mmol) and DMAP (0.027 g, 0.22 mmol) and the mixture was heated on an oil bath (65–70 °C) for 2 h with stirring. Then EtOH (0.5 mL) was added followed by $N_2H_4 \cdot H_2O$ (0.322 mL, 6.66 mmol) was added to the mixture and continued to stir at 65–70 °C for 2 h then stirred at room temperature overnight. The mixture was concentrated and then chromatographed on silica gel with 0–5% ethyl acetate–petroleum ether providing **30** as an off white solid (0.297 g, 45%). Mp 100–102 °C dec. ^{1}H NMR δ 10.06 (s, 1H, NH), 8.41 (d, J = 8.0 Hz, 1H, ArH), 7.71–7.65 (m, 2H, ArH), 7.59–7.42 (m, 5H, ArH), 6.98 (ddd, J = 8.0, 7.3, 1.1 Hz, 1H, ArH), 1.51 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ 199.4, 153.09, 141.5, 138.9, 134.2, 133.6, 132.4, 130.0, 128.3, 122.8, 120.8, 120.0, 80.6, 28.4. LCMS R_f (min) = 6.67. MS m/z 198.2 (100%), 102.2 (75).

General procedure for the synthesis of N-alkylated 2-aminobenzophenones 31a–c

To a 50 mL two neck flask fitted with a nitrogen inlet was added **30** (0.050 g, 0.17 mmol) and then purged with nitrogen. Caesium carbonate (0.110 g, 0.34 mmol) and TBAI (0.031 g, 0.084 mmol) were added followed by anhydrous DMF (1.0 mL). The alkylating reagent (0.34 mmol) was added and the reaction was stirred at room temperature for 3–24 h. Upon completion of the reaction (TLC), the mixture was diluted with ether (20 mL) and then washed with water (6 × 50 mL), then brine (10 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the carbamates, which were used without further purification in the next step. The resin was taken up in CH_2Cl_2 (0.5 mL) and TFA (0.25 mL) was added and stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated bicarbonate solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and then concentrated to afford the crude benzophenones that were chromatographed on silica gel with 0–5% ethyl acetate–petroleum ether providing **31a–c**.

(2-(Methylamino)phenyl)(phenyl)methanone (31a). The title compound was obtained as a yellow solid in 86% yield (0.031 g). Mp 48–50 °C. ^{1}H NMR δ 8.67–8.45 (m, 1H, NH), 7.64–7.58 (m, 2H, ArH), 7.54–7.39 (m, 5H, ArH), 6.77 (d, J = 8.1 Hz, 1H, ArH), 6.55 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H, ArH), 2.98 (d, J = 5.1 Hz, 3H, NCH_3). ^{13}C NMR δ 199.4, 152.8, 140.7, 135.6, 135.1, 130.7, 129.0, 128.1, 117.38, 113.7, 111.2, 29.5. LCMS R_f (min) = 6.28. HR-ESI calcd for $C_{14}H_{14}NO^+$ (M + H) 212.1070, found 212.1064.

(2-(Butylamino)phenyl)(phenyl)methanone (31b). The title compound was obtained as a viscous yellow oil in 84% yield (0.036 g). ^{1}H NMR δ 8.72–8.54 (m, 1H, NH), 7.70–7.56 (m, 2H, ArH), 7.55–7.28 (m, 5H, ArH), 6.78 (d, J = 8.4 Hz, 1H, ArH), 6.51 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H, ArH), 3.27 (td, J = 7.0, 5.2 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.79–1.66 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.58–1.45 (m, 2H, $NCH_2CH_2CH_2CH_3$), 0.99 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR δ 199.4, 152.2, 140.8, 135.7, 135.1, 130.8, 129.1, 128.1, 117.0, 113.5, 111.6, 42.6, 31.3, 20.5, 14.0. LCMS R_f (min) = 6.92. HR-ESI calcd for $C_{17}H_{20}NO^+$ (M + H) 254.1539, found 254.1545.

(2-(Benzylamino)phenyl)(phenyl)methanone (31c). The title compound was obtained as a viscous yellow oil in 95% yield (0.046 g). ^{1}H NMR δ 9.09–8.68 (m, 1H, NH), 7.59–7.49 (m, 2H, ArH), 7.46–7.40 (m, 2H, ArH), 7.40–7.33 (m, 2H, ArH), 7.33–7.14 (m, 6H, ArH), 6.65 (d, J = 8.5 Hz, 1H, ArH), 6.47 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H, ArH), 4.42 (d, J = 5.6 Hz, 2H, $ArCH_2$). ^{13}C NMR δ 199.6, 151.7, 140.6, 138.7, 135.6, 135.1, 130.9, 129.2, 128.8, 128.2, 127.4, 127.3, 117.7, 114.3, 112.2, 47.1. LCMS R_f (min) = 6.71. HR-ESI calcd for $C_{20}H_{18}NO^+$ (M + H) 288.1383, found 288.1373.

tert-Butyl 9-oxo-9*H*-fluoren-1-ylcarbamate (33)

To a 50 mL round bottom flask was added **32** (0.433 g, 2.22 mmol), Boc_2O (1.02 g, 4.67 mmol) and DMAP (0.027 g, 0.22 mmol) and the mixture was heated on an oil bath (65–70 °C) for 3 h with stirring. Then EtOH (0.5 mL) was added followed by $N_2H_4 \cdot H_2O$ (0.322 mL, 6.66 mmol) was added to the mixture and continued to stir at 65–70 °C for 2 h then stirred at room temperature overnight. The mixture was concentrated and then chromatographed on silica gel with 0–5% ethyl acetate–petroleum ether providing **33** as a yellow resin that solidified upon refrigeration (0.60 g, 92%). Mp 66–68 °C dec. ^{1}H NMR δ 9.34 (s, 1H, NH), 8.12 (d, J = 8.5 Hz, 1H, ArH), 7.64–7.59 (m, 1H, ArH), 7.52–7.39 (m, 3H, ArH), 7.29 (td, J = 7.2, 1.5 Hz, 1H, ArH), 7.11 (dd, J = 7.2, 0.7 Hz, 1H, ArH), 1.55 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ 195.1, 152.6, 143.9, 143.7, 140.0, 136.6, 134.5, 134.1, 129.0, 123.9, 120.5, 118.8, 117.5,

114.0, 81.1, 28.3. LCMS R_f (min) = 6.86. MS *m/z* 196.1 (100%), 102.3 (20).

General procedure for the synthesis of N-alkylated 1-aminofluoren-9-one 34a–c

To a 50 mL two neck flask fitted with a nitrogen inlet was added **33** (0.050 g, 0.17 mmol) and then purged with nitrogen. Caesium carbonate (0.110 g, 0.34 mmol) and TBAI (0.031 g, 0.084 mmol) were added followed by anhydrous DMF (1.0 mL). The alkylating reagent (0.34 mmol) was added and the reaction was stirred at room temperature for 3–24 h. In the case of **34b** a further aliquot of 1-bromobutane (0.037 mL, 0.34 mmol) and caesium carbonate (0.110 g, 0.34 mmol) were added and stirred a further 16 h. Upon completion of the reaction (TLC), the mixture was diluted with ether (20 mL) and then washed with water (6 × 50 mL), then brine (10 mL). The ethereal layer was dried ($MgSO_4$), filtered and then concentrated to an oil affording the carbamates, which were used without further purification in the next step. The resin was taken up in CH_2Cl_2 (0.5 mL) and TFA (0.25 mL) was added and stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated bicarbonate solution. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and then concentrated to afford the crude fluorenones that were chromatographed on silica gel with 0–5% ethyl acetate–petroleum ether providing **34a–c**.

1-(Methylamino)-9*H*-fluoren-9-one (34a). The title compound was obtained as a yellow solid after recrystallization from methanol in 42% yield (0.015 g). Mp 125–127 °C. ^{1}H NMR δ 7.60–7.54 (m, 1H, ArH), 7.47–7.42 (m, 1H, ArH), 7.39 (td, J = 7.4, 1.1 Hz, 1H, ArH), 7.32–7.26 (m, 1H, ArH), 7.26–7.21 (m, 1H, ArH), 7.04–6.90 (m, 1H, NH), 6.76 (dd, J = 7.0, 0.5 Hz, 1H, ArH), 6.53 (d, J = 8.5 Hz, 1H, ArH), 2.97 (d, J = 5.2 Hz, 3H, NCH_3). ^{13}C NMR δ 195.0, 149.5, 144.8, 143.3, 136.9, 135.4, 133.3, 128.7, 123.1, 120.4, 114.2, 112.3, 108.5, 29.2. LCMS R_f (min) = 6.18. HR-ESI calcd for $C_{14}H_{12}NO^+$ (M + H) 210.0913, found 210.0919.

1-(Butylamino)-9*H*-fluoren-9-one (34b). The title compound was obtained as a viscous orange oil in 88% yield (0.037 g). ^{1}H NMR δ 7.63–7.50 (m, 1H, ArH), 7.48–7.40 (m, 1H, ArH), 7.37 (td, J = 7.4, 1.1 Hz, 1H, ArH), 7.30–7.17 (m, 2H, ArH), 7.14–7.00 (m, 1H, NH), 6.73 (dd, J = 7.0, 0.5 Hz, 1H, ArH), 6.52 (d, J = 8.5 Hz, 1H, ArH), 3.25 (td, J = 7.0, 5.8 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.71–1.58 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.53–1.38 (m, 2H, $NCH_2CH_2CH_2CH_3$), 0.97 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR δ 194.8, 148.8, 144.8, 143.2, 136.7, 135.4, 133.2, 128.6, 122.9, 120.3, 113.9, 112.7, 108.3, 42.2, 31.6, 20.2, 13.9. LCMS R_f (min) = 6.80. HR-ESI calcd for $C_{17}H_{18}NO^+$ (M + H) 252.1383, found 252.1377.

1-(Benzylamino)-9*H*-fluoren-9-one (34c). The title compound was obtained as a yellow solid after recrystallization from petroleum ether in 63% yield (0.030 g). Mp 114–115 °C. ^{1}H NMR δ 7.63–7.58 (m, 1H, ArH), 7.52 (t, J = 4.6 Hz, 1H, NH), 7.49–7.45 (m, 1H, ArH), 7.42 (td, J = 7.4, 1.1 Hz, 1H, ArH), 7.38–7.26 (m, 6H, ArH), 7.25–7.19 (m, 1H, ArH), 6.80 (dd, J = 7.1, 0.5 Hz, 1H, ArH), 6.51 (d, J = 8.5 Hz, 1H, ArH), 4.54 (d, J = 6.1 Hz, 2H, $ArCH_2$). ^{13}C NMR δ 195.1, 148.6, 144.9, 143.4, 138.7, 136.9, 135.4, 133.5, 128.9, 128.8, 127.5, 127.1, 123.2, 120.5, 114.6, 113.2, 109.0, 46.6. LCMS R_f (min) = 6.76. HR-ESI calcd for $C_{20}H_{16}NO^+$ (M + H) 286.1226, found 286.1231.

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