A Base-Catalysed One-Pot Three-Component Coupling Reaction Leading to Nitrosubstituted Pyrroles

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Abstract: Tosyl isocyanide and ethyl chloroformate react with nitrostyrenes to afford nitro-substituted pyrroles in good yield when a catch-and-release protocol was employed as a purification strategy.

Key words: pyrroles, immobilized reagents, heterocycles, multicomponent

Pyrroles are one of nature's most important building blocks comprising the core scaffold of porphyrins such as haem and the chlorophylls.[1] They are also commonly encountered embedded within numerous other natural product structures generating interesting architectures such as the lamellarins and marinopyrroles.[2] In addition, many simple synthetic pyrroles display a significant range of pharmacological activities (antibacterial, antiviral, anti-inflammatory, antitumour, antioxidant and moderators associated with several neuropsychiatric diseases) as well as having found utility in the material sciences as electrical conductors.[3]

There already exists a large body of literature relating to the synthesis and modification of these important heterocyclic motifs.[4] However, we wished to attain a pyrrole unit with a unique substitution pattern (Figure 1; **1**) as a precursor to a series of 6-aminopyrrolizinone analogues **2** and a related family of 6-aminopiperazinopyrrolizine-2,6-diones **3** for application in medicinal chemistry programmes (Figure 1).

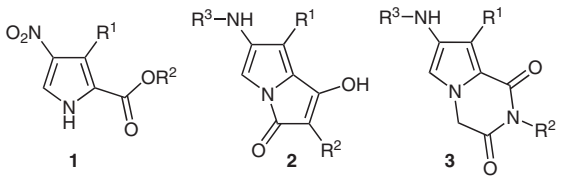
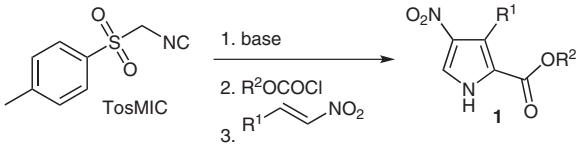


Figure 1 Core template building block (**1**) and derivatives (**2** and **3**)

Compound **1**, possessing a nitro group in the 4-position as a masked amine and requiring substituent variation at the 3-position comprised a simple, compact and yet synthetically challenging target. Using current methods it is difficult to introduce the nitro functionality at a late stage due to the intrinsic reactivity of the pyrrole and its propensity to undergo rapid polymerisation under many of the standard nitrating conditions. Furthermore, although procedures exist for C–C bond formation at the 3-position, this inevitably requires initial installation of a halogen or synthetic equivalent which is not a straightforward transformation on this particular template. However, we rationalised that a modification of the classical van Leusen[5] and Barton–Zard[6] pyrrole syntheses might allow direct access to the desired nucleus potentially as a sequential one-pot procedure (Scheme 1).



Scheme 1 Proposed synthetic scheme to pyrrole core **1**

A series of bases were screened for the initial condensation reaction between ethyl chloroformate and toluenesulfonylmethyl isocyanide (TosMIC). Weak bases such as triethylamine and Hünig's base as well as the corresponding immobilised forms proved ineffective, giving no noticeable reaction after 24 hours at ambient temperature. Employing stronger bases such as DBU and BEMP (or their polymer-supported counterparts: PS-) also gave unsatisfactory results, generating complex mixtures containing significant quantities of starting materials and unidentified by-products. We considered the problem to be one of ineffective deprotonation and the stability of the resulting intermediate under the equilibrium conditions. With this in mind we then carried out the reaction in THF at 0 °C using two equivalents of *n*-BuLi or LiHMDS. Although in both cases the starting materials were fully consumed the build up of small quantities (8–12%) of an additional adduct were also observed (later confirmed as the 4,5-disubstituted oxazole **5**; Figure 2). Reducing the temperature below –40 °C completely suppressed this side reaction giving smooth and quantitative conversion to the lithio intermediate **4** in five minutes (although for experimental convenience a temperature of –78 °C was routinely used, maintaining a five minutes incubation time). Interestingly, quenching the cold reaction mixture containing intermediate **4** with a saturated solution of sodium chloride and leaving the aqueous component to stand led to the formation of large transparent crystals of oxazole **5** (79%, Figure 2) which resulted from intramo-

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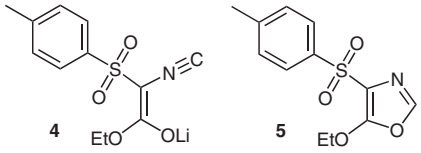


Figure 2 Lithio intermediate **4** and cyclised oxazole **5**

lecular cyclisation. This compound was shown to match the minor by-product previously detected in the condensation reactions performed at 0 °C as described above.

Using the optimised conditions for the formation of the lithio derivative **4** (2 equiv *n*-BuLi, –78 °C in THF, 5 min) a series of thirteen 10 mmol parallel reactions were set up to prepare solutions of the anion of **4**. To each reaction was added a different nitrostyrene component (1 equiv) and the reactions were allowed to warm to ambient temperature with stirring. In each case a slow reaction over a period of 2–4 days was observed to take place, generating the desired pyrrole structure **1** as the main product in good conversion according to crude ^{1}H NMR and LC-MS analysis. Attempts to accelerate the reaction through various modes of heating failed to give any improved results, leading instead to product mixtures with significantly lower purity profiles.

Isolation of the pure pyrrole products also proved challenging. A variety of aqueous quenching procedures accompanied by extensive organic extractions gave poor recovery of the products. The best work-up conditions were eventually found to be direct quenching of the reaction mixture with a saturated solution of potassium carbonate and water, followed by extraction with ethyl acetate and drying (Na_2SO_4). The organic extracts were evaporated and the crude reaction mixture loaded onto a Samplet Cartridge (Biotage FLASH EXP). Chromatographic purification using a Biotage SP4 unit employing a long gradient elution (hexane–Et_2O) gave the best separation results enabling collection of highly pure products but in only moderate final isolated yields (Figure 3).

By considering the potential acidity of the pyrrole NH proton in these systems we determined that this might be used as a handle to enable a more facile isolation. Consequently it was shown that significantly improved yields could be attained when a catch-and-release protocol[7] was employed as the purification strategy.[8] Hence, using strong immobilised bases such as the phosphazene reagent PS-BEMP[9] or the DBU equivalent PS-TBD[10] added directly to the reaction mixture (no quenching or work-up steps are required) enabled sequestering of the desired product. Over the course of approximately four hours using PS-BEMP (PS-TBD was less effective requiring 12 hours) the pyrrole was completely removed from the reaction mixture. The product was then recovered following a washing step by treatment of the resin with a solution of acetic acid (other acids including HCl in dioxane could also be used). This procedure furnished the products in much improved yields and avoided the requirement for an aqueous work-up and column chromatography (Figure 3; results in parentheses). In certain cases a small amount of a unidentified highly coloured material (red/dark orange) was also displaced from the polymeric support but could be readily removed from the sample by eluting the washings through a short plug of silica gel (pre-packed bond elute cartridges[11] were used).

Although the products were attained in a higher overall yield in a few cases (Figure 3) a secondary product was also identified albeit as a minor component (3–6%). In two cases chromatographic separation allowed the isolation and characterisation of the species (i.e. Figure 4). In each case the molecules had a different regioisomeric arrangement and possessed the tosylate group in exchange for the nitro functionality. The chemical structures were elucidated from extensive NMR experimentation and eventually confirmed by X-ray crystallography to be that of the general structure **6** (Figure 4). We later also confirmed that these same compounds were present in the previous reactions that were worked up using more traditional aqueous quenching and chromatography and are therefore not an artefact of the isolation method. However, because of the much lower overall recovery of material from the aqueous work-up they were originally missed. Re-examination of the original work confirmed their presence at 3–6% composition in the crude reaction mixture but they were almost undetectable following the aqueous work-up step.

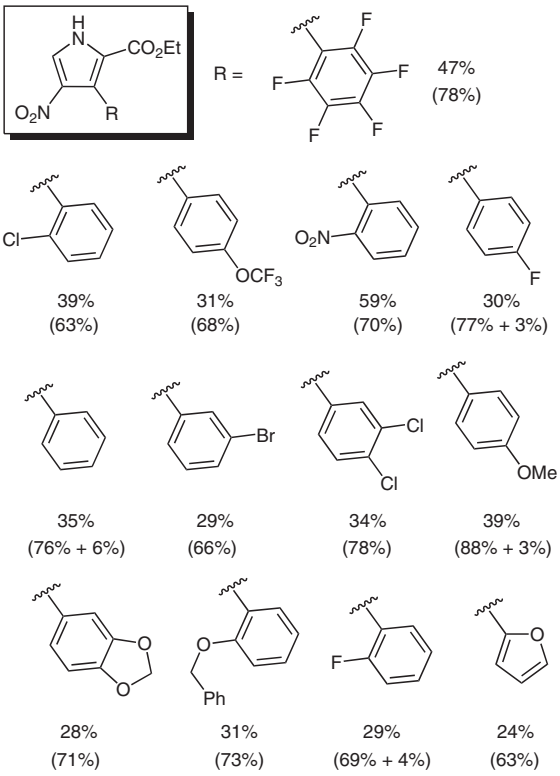


Figure 3 Pyrrole products with isolated yields following chromatographic purification; Yields in parentheses indicate the isolated material attained using the polymer-supported reagent isolation procedure. The second percentage values indicate an accompanying side-product.

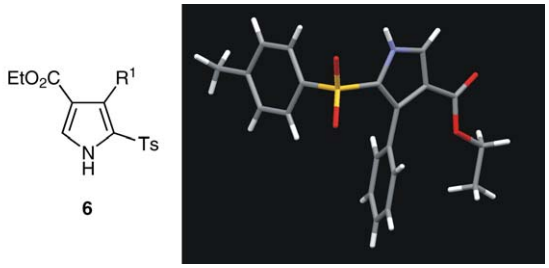


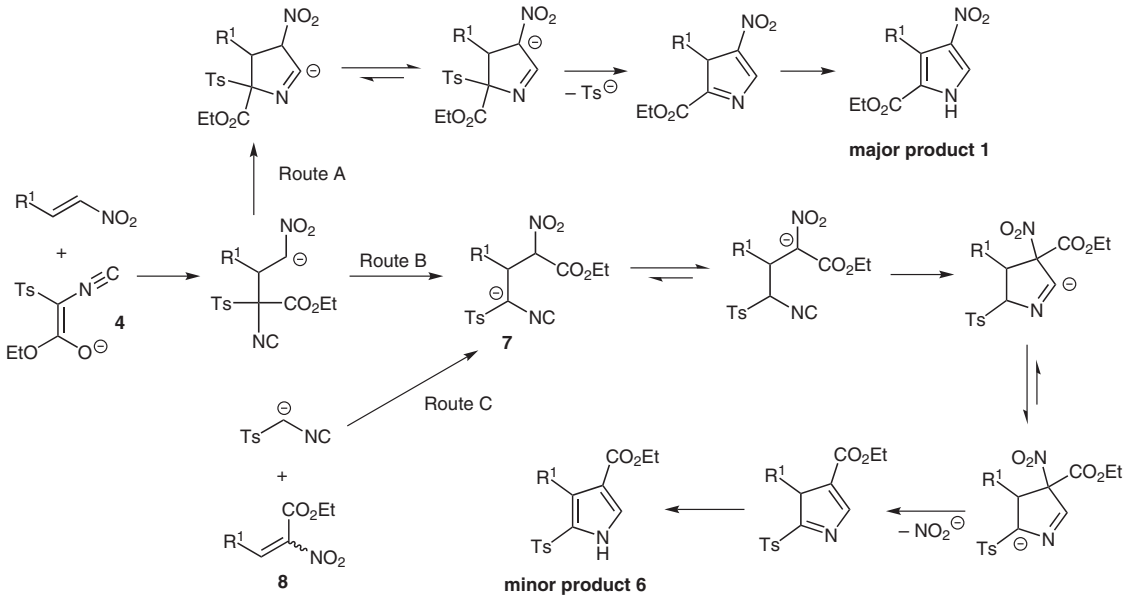
Figure 4 General rearranged structural motif and crystal structure of phenyl-substituted species

We propose that this new motif is most likely generated during the reaction through a competing pathway prior to cyclisation, thereby leading to transposition of the ethoxy carbonyl group as detailed in Scheme 2.[12] Indeed, the tosyl isocyanide would act as a reasonable leaving group following intramolecular attack of the nitroalkane into the ester functionality conducted through route B.[13] In each case the identity of the diversity group R would not be expected to change the natural selectivity of the system. It also seems unlikely that there is any reversibility in the sequence following the cyclisation (Route A) or the ester transfer (Route B). In order to help verifying this alternative pathway (Route B) we prepared the nitro alkene **8** (R = 4-methoxyphenyl) which following direct addition of TosMIC should lead to the same initial intermediate **7** (Scheme 2, Route C). We were satisfied to discover that indeed the cyclisation adduct **6** was formed and could be isolated as the sole product in 81% yield using our previously described PS-BEMP work-up protocol (X-ray analysis was obtained on the crystalline product confirming the structure).

In our future work we are interested in the possibility of favouring the alternative cyclisation pathway (route B) by changing the electronics of the ester functionality to further aid in the transfer process. Although we have already demonstrated that structures such as **6** can be attained through the alternative nitro alkene precursor **8**, these species are themselves not readily available and require care in their preparation because of the extreme accepting ability of the system. It would therefore be synthetically useful to be able to redirect the product outcome through more subtle changes in the nature of the residual ester functionality.[14] Also in a similar manner this conceptual approach could in reverse be used to potentially completely suppress the formation of **6** by reducing the propensity for addition into the ester grouping.

In conclusion, we have demonstrated a new way to prepare specifically functionalised pyrroles via a one-pot three-component coupling strategy. Furthermore, we have also shown the advantage of using a polymer-assisted catch-and-release work-up and purification protocol to maximise the yields and reduce the time needed to isolate these building blocks. The origin and identity of a minor by-product has been determined which could allow access to this alternative structural motif via simple replacement of the chloroformate component. Studies to this extent are ongoing.

All solvents were distilled prior to use, petrol = petroleum ether (40–60 °C). Melting points were determined using an OptiMelt automated melting point system available from Stanford Research Systems and are calibrated against Phenacetin (mp 136 °C). ^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 or DRX-500 spectrometer with residual $CDCl_3$ as the internal reference. ^{13}C NMR spectra were also recorded in $CDCl_3$ on the same spectrometer with the central peak of the residual solvent as the internal reference using the deuterated solvent as internal deuterium lock. COSY, DEPT 135 and HMQC spectroscopic techniques were used to aid the assignment of signals in the ^{13}C NMR spectra. IR spectra were recorded on a Perkin-Elmer SpectrumOne FT-IR spectrometer neat. Letters in the parentheses refer to relative absorbency of the peak: w, weak, <40% of the main peak; m, medium, 41–74% of the main peak; s, strong, >74% of the main peak. LC/MS analysis



Scheme 2 Proposed divergent pathway leading to the synthesis of the minor product **6** and the major product **1** (R = Et)

was performed on an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an HPLC/MSD mass spectrometer. Elution was carried out using a reversed-phase gradient of MeCN–water with both solvents containing 0.1% formic acid. The gradient is described in Table 1. For HRMS a LCT Premier Micromass spectrometer was used.

Table 1 LC-MS Conditions

Time (min)	MeCN (%)	Flow rate (mL·min^{-1})
0.00	5	1
3.00	95	1
5.00	95	1
5.50	5	1
8.00	5	1

Preparation of Pyrroles; General Procedures

Procedure A: To a solution of *p*-toluenesulfonylmethyl isocyanide (1.95 g, 10 mmol, 1 equiv) dissolved in THF (75 mL) maintained at –78 °C with stirring was added a solution of *n*-BuLi (20 mmol, 2 equiv, 1.6 M in hexanes). The reaction was stirred at –78 °C for 5 min and then a solution of ethyl chloroformate (10 mmol, 1 equiv) in THF (50 mL) was added. After 10 min a solution of the appropriate nitrostyrene (10 mmol, 1 equiv) in THF (50 mL) was added and the mixture allowed to warm to ambient temperature with stirring. After 2–4 d (reaction monitored by TLC), sat. K_2CO_3 (50 mL) and H_2O (100 mL) was added and the mixture was shaken for 1 h before being separated. The aqueous layer was extracted with EtOAc (2 × 100 mL) and the organic layers were combined, and dried over Na_2SO_4. The solvents were removed in vacuo and the compounds were purified using a Biotage SP4 EXP Automated Flash Chromatography System. Compounds were pre-loaded onto 40M Samplet Cartridge as a solution in CH_2Cl_2–MeOH (1:1) and then dried under vacuum in a dessicator at 25 °C overnight. For elution gradient, described in terms of column volumes (CV), see specific compound preparations. The weak solvent was hexane and the strong solvent was Et_2O. Compounds were separated using the 40M silica column and the elution solvent was collected in fractions of 27 mL.

Procedure B: To a solution of *p*-toluenesulfonylmethyl isocyanide (1.95 g, 10 mmol, 1 equiv) dissolved in freshly distilled THF (60 mL) maintained at –78 °C with stirring was added a solution of *n*-BuLi (20 mmol, 2 equiv, 2.5 M in hexanes). The reaction was stirred at –78 °C for 5 min and then a solution of ethyl chloroformate (956 μL, 10 mmol, 1 equiv) in THF (20 mL) was added. After 10 min a solution of the appropriate nitrostyrene (10 mmol, 1 equiv) in THF (20 mL) was added and the mixture allowed to warm to ambient temperature with stirring. After 1–3 d (reaction monitored by TLC) PS-BEMP (6.8 g, 2.2 mmol/g, 15 mmol, 1.5 equiv) was added to the reaction mixture and the suspension shaken for 4 h. The immobilised PS-BEMP was filtered off and washed with THF (3 × 25 mL). Acetic acid (10 mmol) in THF (35 mL) was added to the polymer-supported base and the resulting suspension shaken for 1 h. The PS-BEMP was filtered off and the solvent was evaporated in vacuo to obtain the desired product.

Ethyl 4-Nitro-3-phenyl-1*H*-pyrrole-2-carboxylate

The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 6 CV 40% Et_2O, 5 CV 60% Et_2O to give the title compound as a light orange powder. Yield: 0.91 g, 35% (>95% purity). Using procedure B the title compound was isolated in 76% with ethyl 4-phenyl-5-tosyl-1*H*-pyrrole-3-carboxylate (6%). The latter compound was obtained as a yellow crystalline solid. Yield: 4% (purity 90%) following silica chromatography (PE–Et_2O, 12:1).

Data for Ethyl 4-Nitro-3-phenyl-1*H*-pyrrole-2-carboxylate

Mp 150.0–153.2 °C.

t_R = 4.39; *m*/*z* = 259.90 $(C_{13}H_{12}N_2O_4)^-$.

IR (neat): 3422.2 (w), 3214.9 (w), 2925.0 (w), 2199.9 (w), 1688.7 (m), 1598.0 (w), 1557.6 (w), 1503.6 (m), 1473.6 (w), 1445.9 (w), 1428.0 (w), 1372.1 (m), 1321.8 (m), 1280.4 (m), 1250.7 (m), 1226.1 (m), 1208.4 (s), 1166.6 (s), 1128.6 (s), 1094.0 (s), 1050.9 (s), 1041.5 (s), 1013.1 (s), 864.1 (w), 842.4 (w), 814.3 (m), 787.4 (m), 762.5 (m), 753.6 (m), 685.3 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.74 (s, 1 H, NH), 7.83 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.39 (d, *J* = 0.8 Hz, 1 H, 4H-phenyl), 7.38 (d, *J* = 2.6 Hz, 2 H, 3H-phenyl), 7.31 (m, 2 H, 2H-phenyl), 4.14 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.04 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.40 (C), 130.76 (C), 129.93 (CH), 129.88 (CH), 127.99 (CH), 127.49 (C), 127.27 (CH), 127.24 (CH), 126.16 (C), 122.39 (CH), 120.67 (C), 61.23 (CH_2), 13.69 (CH_3).

HRMS: *m*/*z* calcd for $C_{13}H_{11}N_2O_4$: 259.0717; found: 259.0724.

Data for Ethyl 4-Phenyl-5-tosyl-1*H*-pyrrole-3-carboxylate

t_R = 4.66; *m*/*z* = 368.79 $(C_{20}H_{18}NO_4S)^-$.

IR (neat): 3284.09 (w), 2984.1 (w), 2256.0 (w), 1703.6 (m), 1596.4 (w), 1541.1 (w), 1515.7 (w), 1445.3 (w), 1373.8 (m), 1318.4 (m), 1304.1 (m), 1271.8 (m), 1174.7 (m), 1141.9 (s), 1112.5 (m), 1083.0 (m), 1036.1 (m), 1018.9 (m), 985.6 (w), 909.4 (m), 813.4 (m), 763.0 (m), 728.7 (s), 697.1 (s), 663.1 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.16 (s, 1 H, NH), 7.56 (d, *J* = 3.5 Hz, 1 H, H-Pyr), 7.29 (m, 5 H, phenyl), 7.11 (m, 2 H, tosyl), 7.04 (d, *J* = 8.2 Hz, 2 H, phenyl), 4.04 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.31 (s, 3 H, CH_3), 1.03 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.45 (C), 144.19 (C), 137.95 (C), 131.35 (C), 130.63 (C), 130.46 (CH), 129.95 (CH), 129.48 (CH), 129.33 (CH), 129.27 (CH), 128.27 (CH), 127.72 (CH), 127.39 (C), 127.22 (CH), 127.22 (CH), 126.41 (CH), 117.60 (C), 59.97 (CH_2), 21.51 (CH_3), 13.90 (CH_3).

HRMS: *m*/*z* calcd for $C_{20}H_{20}NO_4S$: 370.1113; found: 370.1108.

X-ray crystal structure file reference: CCDC 714239. Formula: $C_{20}H_{19}NO_4S$. Unit cell parameters: *a* = 6.8247(2), *b* = 10.8899(3), *c* = 25.2730(7) Å; β = 91.4170(10)°. Space group: $P2_1/c$.

Ethyl 4-Nitro-3-(perfluorophenyl)-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 3 CV 25% Et_2O, 9 CV 35% Et_2O, 2CV 40% Et_2O, 2 CV 60% Et_2O to give white crystals. Yield: 1.65 g, 47% (>95% purity). General Procedure B: Yield: 2.73 g, 78%.

Mp 149–150 °C.

t_R = 4.77; *m*/*z* = 349.01 $(C_{13}H_7F_5N_2O_4)^-$.

IR (neat): 3232.6 (w), 3145.8 (w), 1685.1 (m), 1529.1 (m), 1513.6 (s), 1503.8 (s), 1448.7 (w), 14354.0 (w), 1413.4 (w), 1381.3 (m), 1363.0 (m), 1332.0 (m), 1307.5 (s), 1258.9 (m), 1220.3 (m), 1175.8 (w), 1123.4 (m), 1052.0 (m), 998.1 (s), 973.6 (w), 865.0 (w), 855.7 (w), 838.8 (m), 792.0 (s), 751.1 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.30 (br s, 1 H, NH), 7.95 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 4.26 (q, *J* = 7.4 Hz, 2 H, CH_2), 1.21 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.44 (C), 144.72 (C, dm, J_{CF} = 246.8 Hz), 141.38 (C, dm, J_{CF} = 253.8 Hz), 137.28 (C, dm, J_{CF} = 250.4 Hz), 136.35 (C), 123.31 (CH), 122.21 (C), 108.57 (C), 106.55 (C, dt, J_{CF} = 18.1, 4.1 Hz), 62.06 (CH_2), 13.66 (CH_3).

HRMS: *m/z* calcd for $C_{13}H_7F_5N_2O_4$: 350.0326; found: 350.0344.

X-ray crystal structure file reference: CCDC 714243. Formula: $C_{13}H_7F_5N_2O_4$. Unit cell parameters: a = 8.0224(1), b = 10.5196(2), c = 16.6525(3) Å; α = 88.659(1), β = 79.068(1), γ = 83.315(2)°. Space group: *P*–1.

Ethyl 3-(3-Bromophenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 6 CV 40% Et_2O, 5 CV 60% Et_2O to give an off white powder. Yield: 0.97 g, 29% (>95% purity). General Procedure B: Yield: 2.24 g, 66%.

Mp 128.5–129.5 °C.

t_R = 4.61; *m/z* = 339.74 $(C_{13}H_{11}BrN_2O_4)^-$.

IR (neat): 3276.6 (m), 3147.2 (w), 2986.6 (w), 1673.0 (s), 1600.0 (w), 1567.0 (w), 1553.0 (m), 1498.5 (s), 1472.4 (m), 1424.9 (m), 1366.2 (s), 1312.6 (s), 1312.6 (s), 1278.6 (s), 1230.7 (m), 1185.8 (s), 1146.0 (m), 1123.4 (m), 1075.3 (m), 1007.4 (m), 998.7 (m), 976.4 (w), 891.0 (w), 859.7 (m), 846.6 (w), 823.6 (m), 778.4 (m), 769.3 (s), 736.3 (s), 696.1 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.75 (s, 1 H, NH), 7.85 (d, *J* = 3.7 Hz, 1 H, H-Pyr), 7.51 (m, 1 H, 4H-phenyl), 7.48 (m, 1 H, 2H-phenyl), 7.26 (m, 1 H, 6H-phenyl), 7.25 (m, 1 H, 5H-phenyl), 4.15 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.08 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.20 (C), 133.04 (CH), 132.82 (C), 130.98 (CH), 128.00 (CH), 128.74 (CH), 124.15 (C), 122.42 (CH), 122.32 (C), 120.93 (C), 61.41 (CH_2), 13.70 (CH_3).

HRMS: *m/z* calcd for $C_{13}H_{12}BrN_2O_4$: 338.9980; found: 338.9965.

Ethyl 4-Nitro-3-[4-(trifluoromethoxy)phenyl]-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 6 CV 40% Et_2O, 5 CV 60% Et_2O to give a light orange powder. Yield: 1.07 g, 31% (>95% purity). General Procedure B: Yield: 2.34 g, 68%.

Mp 169.4–171.8 °C.

t_R = 4.73; *m/z* = 343.79 $(C_{14}H_{10}F_3N_2O_5)^-$.

IR (neat): 3254.9 (w), 1687.1 (m), 1426.3 (w), 1361.4 (w), 1319.3 (m), 1283.3 (s), 1190.8 (m), 1155.6 (m), 1012.3 (w), 854.8 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.79 (s, 1 H, NH), 7.84 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.34 (m, 2 H, phenyl), 7.23 (m, 2 H, phenyl), 4.13 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.02 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.24 (C), 149.01 (C, q, *J* = 1.6 Hz), 136.20 (C), 131.56 (CH), 129.54 (C), 124.53 (C), 122.50 (CH), 121.48 (C), 120.17 (CF_3, q, *J* = 180 Hz), 119.98 (CH) 61.45 (CH_2), 13.49 (CH_3).

HRMS: *m/z* calcd for $C_{14}H_{12}F_3N_2O_5$: 345.0698; found: 345.0767.

Ethyl 3-(3,4-Dichlorophenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 3 CV 35% Et_2O, 7 CV 40% Et_2O, 2 CV 50% Et_2O, 6 CV 60% Et_2O to give a yellow/brown powder. Yield: 1.11 g, 34% (purity >95%). General Procedure B: Yield: 2.56 g, 78%.

Mp 155.3–158.0 °C.

t_R = 4.74; *m/z* = 327.76 $(C_{13}H_9Cl_2N_2O_4)^-$.

IR (neat): 3258.1 (m), 3145.9 (w), 2986.5 (w), 1677.9 (s), 1562.1 (w), 1500.7 (s), 1472.0 (m), 1424.0 (m), 1382.9 (m), 1363.8 (s), 1314.1 (s), 1284.5 (s), 1230.9 (w), 1187.6 (m), 1136.2 (m), 1033.6 (m), 1021.9 (m), 1008.2 (m), 883.9 (w), 858.7 (w), 831.2 (m), 821.5 (m), 777.7 (s), 747.9 (m), 710.0 (m), 694.0 (m), 661.9 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.75 (s, 1 H, NH), 7.85 (d, *J* = 3.7 Hz, 1 H, H-Pyr), 7.47 (d, *J* = 8.3 Hz, 1 H, 4H-phenyl), 7.44 (d, *J* = 2.0 Hz, 1 H, 1H-phenyl), 7.17 (dd, *J* = 8.3, 2.0 Hz, 1 H, 5H-phenyl), 4.18 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.12 (t, *J* = 7.1, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.89 (C), 136.10 (C), 132.28 (C), 132.12 (CH), 131.59 (C), 130.68 (C), 129.57 (CH), 129.52 (CH), 123.22 (C), 122.50 (CH), 120.93 (C), 61.55 (CH_2), 13.78 (CH_3).

HRMS: *m/z* calcd for $C_{13}H_{10}Cl_2N_2O_4Na$: 350.9909; found: 350.9910.

Ethyl 4-Nitro-3-(2-nitrophenyl)-1H-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 3 CV 2% Et_2O, 2 CV 35% Et_2O, 7 CV 40% Et_2O, 4 CV 60% Et_2O to give a yellow/brown powder. Yield: 1.80 g, 59% (purity >95%). General Procedure B: Yield: 2.13 g, 70%.

Mp 151.9–153.7 °C.

t_R = 4.32; *m/z* = 304.86 $(C_{13}H_{10}N_3O_6)^-$.

IR (neat): 3252.9 (w), 1682.6 (s), 1507.9 (s), 1380.8 (m), 1350.7 (s), 1323.2 (m), 1279.0 (m), 1186.9 (m), 1115.3 (w), 1011.5 (w), 845.2 (w), 819.6 (m), 791.8 (m), 781.9 (m), 758.9 (s), 745.9 (m), 707.1 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.02 (s, 1 H, NH), 8.19 (dd, *J* = 8.2, 1.0 Hz, 1 H, 6H-phenyl), 7.88 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.65 (td, *J* = 7.5, 1.3 Hz, 1 H, 4H-phenyl), 7.58 (td, *J* = 8.2, 1.4 Hz, 1 H, 5H-phenyl), 7.36 (dd, *J* = 7.6, 1.5 Hz, 1 H, 3H-phenyl), 4.07 (q, *J* = 7.1 Hz, 2 H, CH_2), 0.97 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.74 (C), 148.43 (C), 136.1 (C), 132.70 (CH), 132.43 (CH), 129.14 (CH), 127.46 (C), 124.46 (CH), 122.67 (CH), 121.96 (C), 120.24 (C), 61.40 (CH_2), 13.54 (CH_3).

HRMS: *m/z* calcd for $C_{13}H_{12}N_3O_6$: 306.0726; found: 306.0723.

Ethyl 3-(4-Fluorophenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 6 CV 40% Et_2O, 5 CV 60% Et_2O to give a yellow/orange powder. Yield: 0.84 g, 30% (purity >95%). General Procedure B: Yield: 2.13 g, 77%.

Mp 155.4–157.2 °C.

t_R = 4.44; *m/z* = 277.85 $(C_{13}H_{10}FN_2O_4)^-$.

IR (neat): 3268.1 (w), 2985.7 (w), 1702.2 (m), 1607.2 (w), 1518.3 (s), 1420.4 (w), 1368.1 (s), 1319.2 (m), 1275.4 (s), 1220.5 (m), 1117.2 (m), 1158.0 (m), 1097.3 (w), 1019.6 (w), 841.9 (m), 809.7 (w), 783.2 (m), 731.2 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.73 (s, 1 H, NH), 7.83 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.28 (m, 2 H, phenyl), 7.07 (m, 2 H, phenyl), 4.14 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.07 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.63 (CF, d, *J* = 250 Hz), 160.24 (C), 136.27 (C), 131.80 (CH, d, *J* = 8.3 Hz), 126.53 (C, d, *J* = 3.4 Hz), 125.03 (C), 122.47 (C), 120.76 (CH), 114.57 (CH, d, *J* = 22 Hz), 61.34 (CH_2), 13.76 (CH_3).

HRMS: *m/z* calcd for $C_{13}H_{12}FN_2O_4$: 279.0781; found: 279.0769.

Ethyl 3-(2-Chlorophenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 5 CV 40% Et_2O, 6 CV 60% Et_2O to give a yellow/brown powder. Yield: 1.146 g, 39% (purity >95%). General Procedure B: Yield: 1.851 g, 63%.

Mp 158.2–160.5 °C.

t_R = 4.47; *m/z* = 293.80 $(C_{13}H_{10}ClN_2O_4)^-$.

IR (neat): 3259.8 (w), 2983.7 (w), 1704.9 (m), 1573.6 (w), 1508.4 (s), 1474.7 (w), 1423.0 (w), 1374.1 (s), 1323.2 (m), 1285.7 (s), 1255.5 (m), 1227.8 (w), 1179.8 (m), 1156.5 (w), 1114.6 (w), 1067.4 (w), 1020.1 (w), 911.1 (w), 838.8 (w), 821.5 (w), 784.0 (w), 757.8 (m), 728.7 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.93 (s, 1 H, NH), 7.86 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.44 (m, 1 H, phenyl), 7.30 (m, 3 H, phenyl), 4.13 (dq, *J* = 16.4, 7.1 Hz, 1 H, CH_2), 4.10 (dq, *J* = 16.4, 7.1 Hz, 1 H, CH_2), 0.99 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.26 (C), 136.35 (C), 133.91 (C), 131.30 (CH), 130.73 (C), 129.38 (CH), 128.92 (CH), 126.06 (CH), 122.70 (C), 122.39 (CH), 121.07 (C), 61.34 (CH_2), 13.57 (CH_3).

HRMS: *m*/*z* calcd for $C_{13}H_{12}ClN_2O_4$: 295.0486; found: 295.0478.

Ethyl 3-(1,3-Benzodioxol-4-yl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 6 CV 40% Et_2O, 5 CV 60% Et_2O to give an orange/brown solid: Yield: 0.851 g, 28% (purity >95%). General Procedure B: Yield: 2.16 g, 71%.

Mp 185.1–187.7 °C.

t_R = 4.32; *m*/*z* = 303.87 $(C_{14}H_{12}N_2O_6)^-$.

IR (neat): 3257.0 (w), 3141.2 (w), 1669.9 (m), 1500.0 (s), 1483.8 (m), 1422.0 (m), 1359.1 (m), 1341.0 (m), 1311.3 (s), 1283.8 (s), 1244.9 (s), 1220.1 (s), 1191.5 (m), 1147.3 (m), 1103.6 (m), 1037.0 (s), 1013.1 (m), 934.8 (m), 887.09(m), 868.7 (m), 845.5 (m), 812.9 (m), 781.8 (s), 753.0 (s), 678.1 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.80 (s, 1 H, NH), 7.80 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 6.81 (m, 3 H, aryl), 5.98 (s, 2 H, CH_2), 4.17 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.13 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.22 (C), 147.43 (C), 146.94 (C), 136.31 (C), 125.76 (C), 123.96 (C), 123.73 (CH), 122.39 (CH), 120.73 (C), 110.67 (CH), 107.63 (CH), 101.11 (CH_2), 61.22(CH_2), 13.86 (CH_3).

HRMS: *m*/*z* calcd for $C_{14}H_{13}N_2O_6$: 305.0774; found: 305.0788.

Ethyl 3-[2-(Benzyloxy)phenyl]-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 5 CV 40% Et_2O, 6 CV 60% Et_2O to give an off white powder: Yield: 1.12 g, 31% (purity >95%). General Procedure B: Yield: 2.67 g, 73%.

Mp 147.8–149.5 °C.

t_R = 4.72; *m*/*z* = 365.79 $(C_{20}H_{17}N_2O_5)^-$.

IR (neat): 2981.5 (w), 1725.5 (m), 1597.8 (m), 1555.8 (m), 1492.2 (m), 1452.4 (m), 1373.1 (m), 1321.2 (m), 1291.4 (m), 1242.4 (s), 1146.3 (s), 1081.6 (m), 1017.3 (m), 912.3 (m), 858.6 (w), 812.4 (m), 753.1 (s), 735.3 (s), 697.7 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.57 (s, 1 H, NH), 7.73 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.26 (m, 7 H, phenyl and benzyl), 6.98 (m, 2 H, 3- and 5-phenyl), 4.99 (dd, *J* = 11.8, 17.3 Hz, 2 H, benzyl-CH_2), 4.11 (dq, *J* = 41.8, 7.1 Hz, 1 H, CH_2), 4.09 (dq, *J* = 41.8, 7.1 Hz, 1 H, CH_3), 1.02 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.33 (C), 156.39 (C), 136.91 (CH), 136.90 (CH), 131.55 (CH), 129.62 (CH), 128.39 (CH), 127.69 (CH), 127.17 (CH), 122.44 (C), 122.19 (CH), 120.57 (C), 120.51 (C), 120.19 (CH), 111.99 (CH), 70.36 (CH_2), 61.05 (CH_2), 13.72 (CH_3).

HRMS: *m*/*z* calcd for $C_{20}H_{19}N_2O_5$: 367.1294; found: 367.1295.

Ethyl 3-(2-Fluorophenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 5 CV 40% Et_2O, 6 CV 60% Et_2O to give an off white powder: Yield: 0.81 g, 29% (purity >95%). Using procedure B the title compound was isolated in 69% with ethyl 4-(2-fluorophenyl)-5-tosyl-1*H*-pyrrole-3-carboxylate (4%). The latter compound was obtained as a light brown solid. Yield: 2.5% (purity 90%) following silica chromoatography (PE–Et_2O, 10:1).

Data for Ethyl 3-(2-Fluorophenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

Mp 125.0–126.2 °C.

t_R = 4.38; *m*/*z* = 277.82 $(C_{13}H_{11}FN_2O_4)^-$.

IR (neat): 3243.5 (w), 3141.8 (w), 2991.3 (w), 1683.3 (s), 1581.4 (w), 1505.9 (s), 1426.5 (w), 1373.2 (s), 1360.6 (s), 1322.7 (s), 1283.0 (s), 1262.9 (m), 1234.0 (m), 1222.7 (m), 1190.0 (m), 1152.9 (w), 1102.35(w), 1014.7 (m), 906.9 (w), 867.8 (w), 829.1 (m), 812.1 (m), 783.6 (m), 749.6 (s), 690.5 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.95 (s, 1 H, NH), 7.86 (d, *J* = 3.8 Hz, 1 H, H-Pyr), 7.37 (m, 1 H, phenyl), 7.30 (m, 1 H, phenyl), 7.16 (m, 1 H, phenyl), 7.10 (m, 1 H, phenyl), 4.15 (qd, *J* = 7.1, 2.4 Hz, 2 H, CH_2), 1.05 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.26 (C), 160.10 (CF, d, *J* = 250 Hz), 135.10 (C), 132.00 (CH, d, *J* = 2.5 Hz), 130.13 (CH, d, *J* = 8.3 Hz), 123.25 (CH, d, 3.5 Hz), 122.66 (CH), 121.17 (C), 119.13 (C), 118.92 (C, d, *J* = 16 Hz), 115.03 (CH, d, *J* = 22 Hz), 61.41 (CH_2), 13.64 (CH_3).

HRMS: *m*/*z* calcd for $C_{13}H_{11}FN_2O_4$: 278.2358; found: 278.2361.

Data for Ethyl 4-(2-Fluorophenyl)-5-tosyl-1*H*-pyrrole-3-carboxylate

t_R = 4.62; no mass observed.

IR (neat): 3233.1 (w), 3130.1 (w), 2989.8 (w), 1680.6 (m), 1623.0 (w), 1594.9 (w), 1547.0 (m), 1522.5 (m), 1492.2 (w), 1472.2 (w), 1448.2 (m), 1375.9 (m), 1357.2 8(w), 1342.3 (m), 1329.7 (m), 1290.9 (m), 1256.9 (m), 1222.8 (m), 1205.6 (m), 1187.0 (s), 1143.8 (s), 1099.6 (m), 1084.7 (m), 1036.4 (m), 1018.2 (m), 993.8 (w), 939.3 (w), 873.6 (w), 844.7 (w), 811.6 (m), 757.6 (s), 705.1 (m), 675.1 (s), 656.7 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.62 (s, 1 H, NH), 7.60 (d, *J* = 3.4 Hz, 1 H, 2H-pyr), 7.30 (m, 4 H), 7.14 (m, 3 H), 6.92 (m, 1 H), 4.07 (m, 2 H, CH_2), 2.33 (s, 3 H, CH_3-Ts), 1.03 (t, *J* = 7.1 Hz, 3 H, CH_3-Et).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.96 (C), 160.09 (CF, d, *J* = 250 Hz), 144.41 (C), 137.58 (C), 132.78 (CH, d, *J* = 2.5 Hz), 130.01 (CH, d, *J* = 8.1 Hz), 129.42 (CH), 128.19 (C), 127.17 (CH), 125.79 (CH), 123.41 (C), 123.19 (CH, d, *J* = 3.5 Hz), 119.40 (C, d, *J* = 16 Hz), 118.67 (C), 114.55 (CH, d, *J* = 22 Hz), 60.01 (CH_2), 21.54 (CH_3), 13.82 (CH_3).

HRMS: *m*/*z* calcd for $C_{20}H_{18}FNO_4S$: 387.0941; found: 387.0955.

Ethyl 3-(4-Methoxyphenyl)-2-nitroacrylate

The title compound was prepared following the procedure of Fornicola et al.[12] for the synthesis of the corresponding methyl 3-(*p*-methoxyphenyl)-2-nitropropenoate being isolated in 82% yield (20 mmol scale) as a 1.1:1 mixture of isomers.

Isomer 1

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1 H, 1-H), 7.38 (d, *J* = 8.8 Hz, 2 H, 3H- and 5H-PhOMe), 6.91 (d, *J* = 8.8 Hz, 2 H, 2H- and 6H-PhOMe), 4.36 (q, *J* = 7.3 Hz, 2 H, CH_2-Et), 3.83 (s, 3 H, OCH_3), 1.35 (t, *J* = 7.3 Hz, 3 H, CH_3-Et).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.29 (C), 159.98 (C), 136.61 (C), 132.97 (CH), 132.55 (2 × CH), 121.75 (C), 115.31 (2 × CH), 63.16 (CH_2), 55.88 (CH_3), 14.45 (CH_3).

Isomer 2

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, 1-H), 7.48 (d, *J* = 8.8 Hz, 2 H, 3H- and 5H-PhOMe), 6.94 (d, *J* = 8.8 Hz, 2 H, 2H- and 6H-PhOMe), 4.45 (q, *J* = 7.3 Hz, 2 H, CH_2-Et), 3.86 (s, 3 H, OCH_3), 1.37 (t, *J* = 7.3 Hz, 3 H, CH_3-Et).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.66 (C), 162.14 (C), 140.16 (C), 136.94 (CH), 133.82 (CH), 121.70 (C), 115.31 (CH), 63.35 (CH_2), 55.94 (CH_3), 14.17 (CH_3).

Ethyl 4-(4-Methoxyphenyl)-5-tosyl-1*H*-pyrrole-3-carboxylate

Procedure B: To a solution of *p*-toluenesulfonylmethyl isocyanide (1.95 g, 10 mmol, 1 equiv) dissolved in freshly distilled THF (55 mL) maintained at –78 °C with stirring was added a solution of *n*-BuLi (10 mmol, 1 equiv, 1.6 M in hexanes). The reaction was stirred at –78 °C for 5 min and then a solution of the ethyl 3-(4-methoxyphenyl)-2-nitroacrylate (10 mmol, 1 equiv) in THF (15 mL) was added and the mixture allowed to warm to ambient temperature with stirring. After 36 h (reaction monitored by TLC) PS-BEMP (6.8 g, 2.2 mmol/g, 15 mmol, 1.5 equiv) was added to the reaction mixture and the suspension shaken for 4 h. The immobilised PS-BEMP was filtered off and washed with THF (3 × 25 mL). Acetic acid (10 mmol) in THF (35 mL) was added to the polymer-supported base and the resulting suspension shaken for 1 h. The PS-BEMP was filtered off and the solvent was evaporated in vacuo to obtain the desired product in 81% yield.

Mp 172.0–173.3 °C.

t_R = 4.62; *m*/*z* = 398.54 $(C_{21}H_{20}NO_5S)^-$.

IR (neat): 3261.2 (w), 2867.3 (w), 2233.9 (w), 1716.4 (m), 1530.7 (w), 1521.6 (m), 1289.7 (s), 1049.5 (m), 1009.8 (m), 985.2 (w), 693.2 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1 H, NH), 7.56 (d, *J* = 3.3 Hz, 1 H, H-Pyr), 7.29 (d, *J* = 8.4 Hz, 2 H, 3H- and 5H-PhOMe), 7.09 (m, 4 H, tosyl), 6.85 (d, *J* = 8.4 Hz, 2 H, 2H- and 6H-PhOMe), 4.10 (q, *J* = 7.1 Hz, 2 H, CH_3-Et), 3.87 (s, 3 H, OMe), 2.34 (s, 3 H, CH_3-Ts), 0.97 (t, *J* = 7.1 Hz, 3 H, CH_3-Et).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.78 (C), 159.77 (C), 144.56 (C), 138.62 (C), 132.18 (CH), 131.07 (C), 129.76 (CH), 127.78 (C), 127.62 (CH), 126.83 (CH), 123.86 (C), 118.06 (C), 113.18 (CH), 60.32 (CH_2), 55.66 (CH_3), 21.92 (CH_3), 14.47 (CH_3).

HRMS: *m*/*z* calcd for $C_{21}H_{21}NNaO_5S$: 422.1038; found: 422.1021.

X-ray crystal structure file reference: CCDC 714240. Formula: $C_{21}H_{21}NO_5S$. Unit cell parameters: *a* = 18.2420(2), *b* = 11.22880(10), *c* = 19.4059(2) Å. Space group: *Pbca*.

5-Ethoxy-4-tosyl-1,3-oxazole (5)

A solution of *n*-BuLi (20 mmol, 12.5 ml, 1.6 M in hexanes) was added to *p*-toluenesulfonylmethyl isocyanide (1.96 g, 10 mmol) dissolved in THF (100 mL) with stirring at –78 °C. To this mixture was added via a cannular ethyl chloroformate (10 mmol, 0.96 mL) dissolved in THF (75 mL). The mixture was allowed to warm to ambient temperature and quenched with a sat. K_2CO_3 solution (25 mL) and H_2O (75 mL), and extracted. The aqueous fraction was left to stand for 3 d and the oxazole product collected by filtration yielded colourless needle-shaped crystals. Yield: 1.94 g (72%).

t_R = 4.12; *m*/*z* = 268.88 $(C_{12}H_{13}NO_4S)^+$.

IR (neat): 3378.9 (m), 1618.8 (m), 1192.7 (s), 1132.6 (m), 1050.1 (m), 1015.3 (m), 814.2 (m), 693.1 (s), 665.2 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (m, 2 H, 2H-Ts), 7.33 (s, 1 H, CH), 7.31 (m, 2 H, 3H-Ts), 4.49 (q, *J* = 7.1 Hz, 2 H, CH_2-Et), 2.41 (s, 3 H, CH_3-Ts), 1.48 (t, *J* = 7.1 Hz, 3 H, CH_3-Et).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.97 (C), 144.39 (C), 140.81 (CH), 138.23 (C), 129.72 (CH), 127.64 (CH), 114.88 (C), 70.94 (CH_2), 21.61 (CH_3), 14.89 (CH_3).

HRMS: *m*/*z* calcd for $C_{12}H_{13}NO_4S$: 267.0565; found: 267.0553.

X-ray crystal structure file reference: CCDC 714241. Formula: $C_{12}H_{13}NO_4S$. Unit cell parameters: *a* = 11.8439(3), *b* = 7.5647(2), *c* = 13.9630(4) Å; β = 101.1900(10)°. Space group: $P2_1/n$.

Ethyl 3-(Furan-2-yl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 2 CV 25% Et_2O, 5 CV 35% Et_2O, 6 CV 40% Et_2O, 7 CV 60% Et_2O to give a brown solid. Yield: 0.60 g, 24% (purity >95%). General Procedure B: Yield: 1.57 g, 63%.

t_R = 4.16; *m*/*z* = 249.95 $(C_{11}H_9N_2O_5)^-$.

IR (neat): 3238.4 (w), 1675.7 (s), 15.43.6 (w), 15.04 (s), 1426.7 (w), 1365.1 (m), 1359.2 (m), 1318.2 (s), 1278.8 (s), 1197.5 (m), 113.82 (m), 1010.1 (m), 1001.1 (s), 903.1 (w), 816.7 (m), 780.4 (m), 736.8 (m), 727.7 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1 H, NH), 7.82 (d, *J* = 3.8 Hz, 1 H, 2H-pyr), 6.65 (d, *J* = 3.2 Hz, 1 H, furyl), 6.53 (dd, *J* = 3.2, 1 Hz, 1 H, furyl), 4.38 (q, *J* = 7.3 Hz, 2 H, CH_2-Et), 1.21 (t, *J* = 7.3 Hz, 3 H, CH_3-Et).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.22 (C), 142.85 (CH), 142.34 (C), 122.72 (CH), 121.72 (C), 114.80 (C), 112.44 (CH), 110.99 (CH), 61.70 (CH_2), 13.99 (CH_3).

HRMS: *m*/*z* calcd for $C_{11}H_{11}N_2O_5$: 251.0668; found: 251.0661.

Ethyl 3-(4-Methoxyphenyl)-4-nitro-1*H*-pyrrole-2-carboxylate

General Procedure A: The Biotage separation used the elution 1 CV 25% Et_2O, 7 CV 35% Et_2O, 5 CV 40% Et_2O, 6 CV 60% Et_2O to give a light orange solid. Yield: 1.13 g, 39% (purity >95%). General Procedure B: Yield: 2.55 g (88%) with ethyl 4-methoxy-5-tosylpyrrole-3-carboxylate (3%).

Mp 152.0–153.5 °C.

t_R = 4.38; *m*/*z* = 289.08 $(C_{14}H_{14}N_2O_5)^-$.

IR (neat): 3265.7 (m), 3234.3 (m), 3147.0 (w), 1667.8 (s), 1610.8 (w), 1518.8 (s), 1497.8 (s), 1467.2 (m), 1424.2 (m), 1359.0 (s), 1317.9 (m), 1281.0 (s), 1253.0 (s), 1208.8 (m), 1176.9 (s), 1109.7 (m), 1032.3 (m), 1009.4 (m), 863.2 (w), 847.9 (m), 830.4 (m), 822.4 (m), 781.4 (s), 753.7 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.15 (br s, 1 H, NH), 7.85 (d, *J* = 3.7 Hz, 1 H, H-Pyr), 7.26 (d, *J* = 8.8 Hz, 2 H, PhOMe), 6.92 (d, *J* = 8.8 Hz, 2 H, PhOMe), 4.15 (q, *J* = 7.3 Hz, 2 H, CH_2), 3.86 (s, 3 H, OMe), 1.08 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.14 (C), 159.87 (C), 136.61 (C), 131.76 (2 × CH), 126.66 (C), 123.34 (C), 123.16 (CH), 120.89 (C), 113.42 (2 × CH), 61.71 (CH_2), 55.65 (CH_3), 14.23 (CH_3).

HRMS: *m*/*z* calcd for $C_{14}H_{14}N_2O_5$: 290.0903; found: 290.0916.

X-ray crystal structure file reference: CCDC 714242. Formula: $C_{14}H_{14}N_2O_5$. Unit cell parameters: *a* = 10.7326(3), *b* = 11.4430(3), *c* = 12.8689(4) Å; α = 81.253(2), β = 74.532(2), γ = 64.739(2)°. Space group: $P\bar{1}$.

Ethyl 5-Tosylpyrrole-1*H*-3-carboxylate

General Procedure A: The Biotage separation used the elution 3 CV 25% Et_2O, 4 CV 35% Et_2O, 4 CV 40% Et_2O, 8 CV 60% Et_2O to give a white crystalline solid. Yield: 0.211 g, 7% (purity >90%).

t_R = 4.29; *m*/*z* = 294.71 $(C_{14}H_{16}NO_4S)^-$.

IR (neat): 3272.12 (m), 3142.07 (w), 2982.76 (w), 1687.44 (s), 1593.65 (w), 1552.28 (m), 1479.51 (w), 1437.97 (m), 1413.29 (m), 1387.88 (s), 1369.05 (w), 1337.42 (m), 1312.02 (s), 1302.43 (s), 1288.77 (m), 1256.65 (s), 1201.62 (s), 1140.13 (s), 1120.66 (m), 1092.66 (s), 1072.95 (m), 1022.58 (m), 966.34 (m), 950.79 (m), 913.19 (w), 875.41 (w), 842.77 (m), 832.01 (w), 814.49 (m), 776.34 (s), 733.98 (w), 704.97 (m), 676.99 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.30 (s, 1 H, 1H-pyr), 7.77 (m, 2 H, tosyl), 7.50 (q, *J* = 1.7 Hz, 1 H, 5H-pyr), 7.24 (d, *J* = 8.3 Hz, 2 H, tosyl), 7.09 (m, 1 H, 3H-pyr), 4.27 (q, *J* = 7.1 Hz, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.53 (C), 143.77 (C), 139.73 (C), 129.76 (CH), 127.26 (C), 126.98 (CH), 125.53 (CH), 124.84 (C), 114.02 (CH), 61.26 (CH_2), 21.49 (CH_3), 14.22 (CH_3).

X-ray crystal structure file reference: CCDC 714244. Formula: $C_{29}H_{31}Cl_3N_2O_8S_2$ (two molecules per unit with one molecule of $CHCl_3$). Unit cell parameters: *a* = 10.4955(2), *b* = 12.0180(3), *c* = 14.0496(4) Å; α = 79.975(1), β = 76.909(1), γ = 79.572(1)°. Space group: $P\bar{1}$.

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(10) PS-TBD refers to 1,5,7-triazabicyclo[4.4.0]dec-5-ene–polystyrene cross-linked with 2% DVB, loading 1.33 mmol/g. Commercially available from Biotage Cat. No. 800422.
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(14) The reaction between the lithio enolate **4** and ethyl acrylate gave only a mixture of products from which only 7% of a rearrangement product (ethyl 5-tosylpyrrole-1*H*-3-carboxylate) could be isolated. ^{1}H NMR and X-ray analysis was used to confirm the structure.