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ARTICLE TYPE

Highly Regioselective Nitrile Oxide Dipolar Cycloadditions with *ortho*-Nitrophenyl Alkynes.

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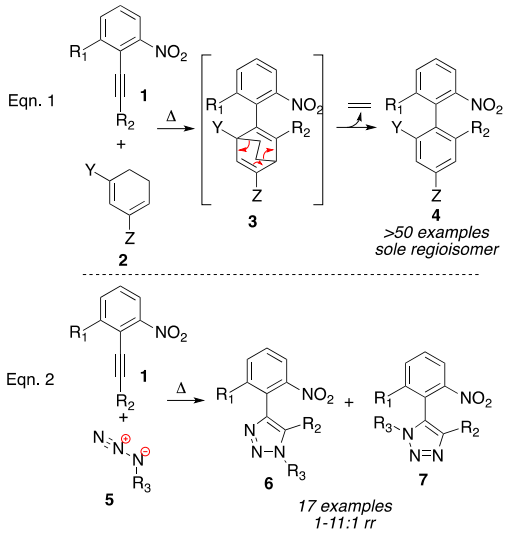
The dipolar cylcoadditions of *ortho*-nitrophenyl alkynes with aryl nitrile oxides has been demonstrated. A range of substituents are tolerated on the alkyne. These reactions proceed with excellent levels of regioselectivity. Subsequent functionalization of the isoxazole scaffold has been demonstrated.

Isoxazoles serve as a valuable class of heterocyclic structures found in natural products and medicinally relevant compounds. Pinho e Melo has written a recent detailed review of the synthesis and reactivity of isoxazoles.[1] This functional group is generally constructed via two major methods – condensation of hydroxylamine with a 1,3-dicarbonyl compound and cycloaddition of an alkyne with a nitrile oxide.[2] The cycloaddition strategy is of particular interest to our laboratory.[3,4]

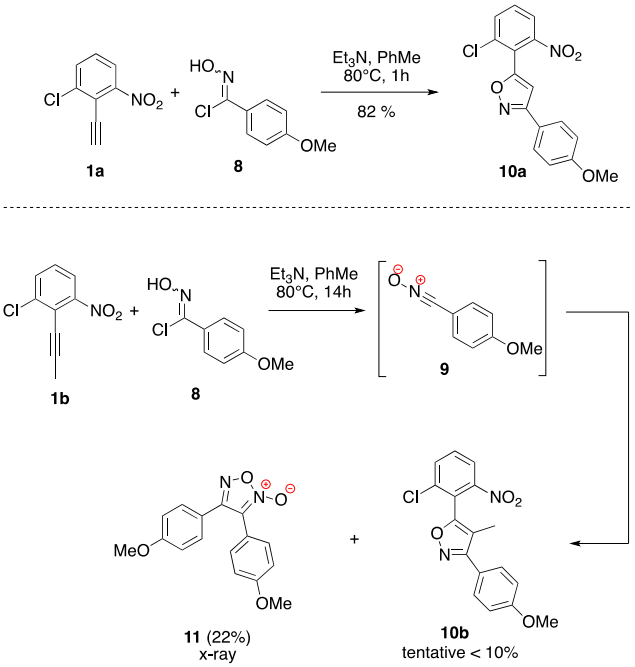
A variety of regioselective syntheses of isoxazoles using [3+2] cycloadditions have been reported. Fokin and co-workers[5] used a copper(I) catalyst to access 3,5-disubsubstituted isoxazoles regioselectively. Although a computational study suggested that the 3,5-regioisomer was strongly favoured (100:1) under thermal, uncatalyzed conditions,[6] Fokin observed a mixture of regioisomers in the absence of catalyst. Grecian and Fokin[7] optimized a ruthenium-catalyzed reaction to access the 3,5-disubstituted, 3,4-disubstituted and 3,4,5-trisubstituted isoxazoles. The regioselectivity was controlled by the complexation of the different dipoles to the ruthenium catalysts. Access to 3,4,5-trisubstituted isoxazoles could also be accomplished through a cycloaddition of an alkynyldimethylsilyl ether with an aryl or alkyl nitrile oxide.[8] This method uses the inherent bias of the dipole and dipolarophile to control regioselectivity. There are limited examples of the cycloaddition process employing haloalkynes to access 3,4,5-trisubstituted isoxazoles. Ohlemeyer and co-workers accessed 5-aryl-4-bromo-3-carboxyisoxazoles through a cycloaddition of aryl alkynes with alkyl and THP ether nitrile oxides in modest yields.[9] A separate study employed the use of an alkynyliodide in the cycloaddition reaction with nitrile oxides to provide 3,4,5-trisubstituted isoxazoles.[10] In most cases, dimerization pathways of the nitrile oxides could be avoided by *in situ* formation of the nitrile oxides. [5,8,9]

Our laboratory has demonstrated the powerful and underexploited directing ability of *ortho*-nitrophenyl-substituted alkynes to access densely functionalized biaryls through a net [4+2] cycloaddition / cycloreversion process of substituted 2-halo-6-nitrophenyl acetylenes (e.g. **1**) with cyclic dienes (e.g. **2**) as shown in Scheme 1 (Eqn. 1).[3] These transformations proved highly regioselective – routinely giving the biaryl **4** as the single regioisomer. Recently, we began to extend the scope of these reactions to include [3+2] cycloadditions. Earlier this year, we published a full account of the thermal, dipolar cycloaddition of *ortho*-nitrophenyl alkynes (e.g. **1**) with a series of azides with up to 11:1 regiomeric ratio (rr) (Scheme 1, Eqn. 2).[4] Unlike what was observed in the [4+2] series, we found that the regioselectivity of this reaction was highly dependent on the nature of the second subsitution on the alkyne (R_2) – giving low selectivity with hydrogen, alkyl or ester substitution but high selectivity with halogens (R_2 = Cl, Br). In parallel with the experimental work on these azide dipolar cycloaddditions, we computationally explored these transformations – including a detailed analysis of the dipolarophile.[4] In this Article, we extend this exploration of dipolar cycloadditions to include nitrile oxides as a highly regioselective method to access densely functionalized isoxazoles. As observed in the [4+2] series, we are aware of only a single study utilizing *ortho*-nitrophenyl alkynes in [3+2] cycloadditions to access isoxazoles.[11]



Scheme 1. Prior Work in [4+2] and [3+2] Cycloadditions with *ortho*-Nitrophenyl Alkynes.

We first selected 2-chloro-6-nitrophenyl acetylene (**1a**) and the oximyl acid chloride **8**[12] to screen for both reactivity and selectivity in the cycloaddition process (Scheme 2). To our delight, we found that clean conversion to the desired isoxazole occurred in high yield (82%) and as a single regioisomer. Unfortunately, when a more challenging substrate such as the di-substituted alkyne **1b**[4] was employed in this transformation, less than 10% of impure desired product **10b** was produced (tentatively identified by mass spectroscopy). We attributed this divergence in reactivity to competitive dimerization of the nitrile oxide.[13] Presence of nitrile oxide dimer **11** (Fig. 1) was confirmed by x-ray crystallographic analysis. We have previously observed a related reduction in reactivity for alkyl substituted alkynes (e.g. **1b**) in dipolar cycloadditions with benzyl azides.[4] Attempts to minimize this unwanted side reaction through the use of slow addition techniques proved ineffective. The reduced reactivity imparted by the addition of a methyl group on the alkyne likely increases the transition state energy for the [3+2] dipolar cycloaddition sufficiently so that the dimerization pathway is more energetically favourable.



Scheme 2. Initial Exploration of Nitrile Oxide Dipolar Cycloadditions

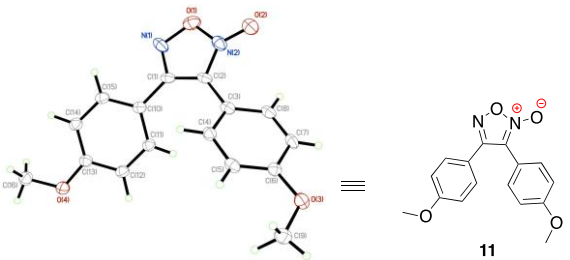


Fig. 1 . ORTEP Representation of Isolated Dimer **11.**

In order to minimize the dimerization pathway, a more sterically hindered nitrile oxide was selected. 2,4,6-Trimethyl derivative **12**[14] has been shown to minimize dimerization pathways with nitrile oxides (Table 1).[13] We screened this nitrile oxide precursor with our parent alkyne **1a** (Entry a) and again observed excellent chemical yield and regioselectivity for the isoxazole product **13a** (88% yield, sole regioisomer). Fortunately, the previously problematic alkynyl methyl isomer **1b** proved equally effective with 87% yield of the desired isoxazole **13b**. Similar high levels of regioselectivity and chemical yield were observed for a series of both mono- and di-substituted alkynes[3] (Entries c-j). We were particularly pleased to see once again that halogenated alkynes (Entries d-g) all proved highly effective in the cycloaddition process. Assignment of the regiochemistry of the reactions was confirmed by x-ray crystallographic analysis of compounds **13b, 13d** (Fig. 2), **13g** and **13h**. The high level of regioselectivity observed in Table 1 is in stark contrast to the azide series in which the R_2 substituent had a dramatic impact on the regioselective outcome of the transformation.[4]

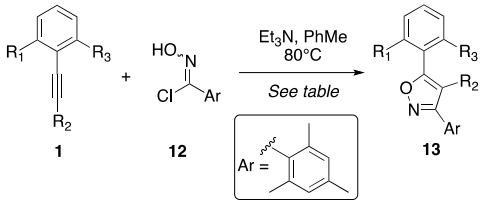


Table 1 Exploration of Scope in Nitrile Oxide / Alkyne Dipolar Cycloaddition.

Entry	R_1	R_2	R_3	% Yield[a]
a	Cl	H	NO_2	88
b	Cl	Me	NO_2	87
c	Cl	CO_2Me	NO_2	83
d	Cl	Br	NO_2	68
e	Cl	Cl	NO_2	70
f	H	Cl	NO_2	69
g	Me	Cl	NO_2	73
h	H	H	NO_2	90
i	Me	H	NO_2	92
j	Me	Me	NO_2	74

[a] Regioselectivity in each case was >20:1 as determined by crude ^{1}H NMR.

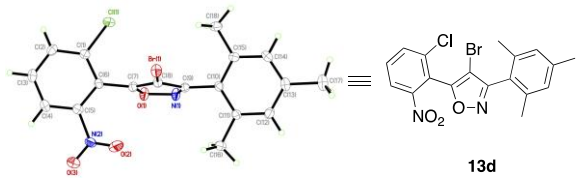
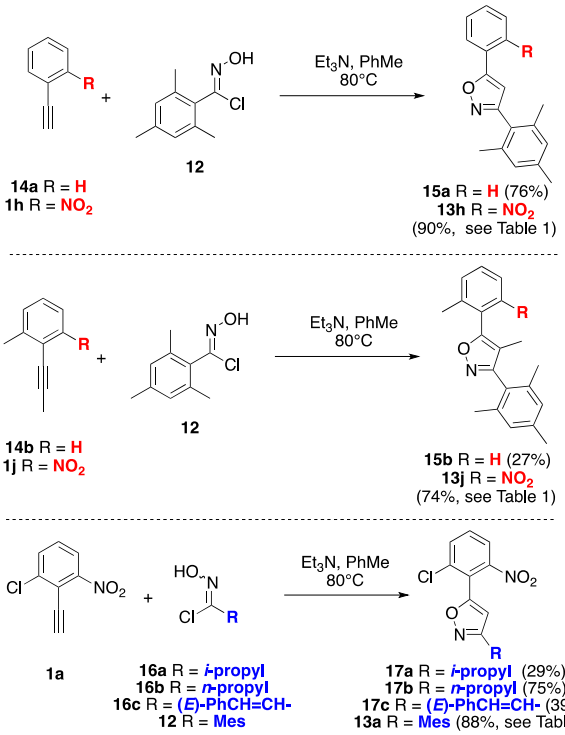


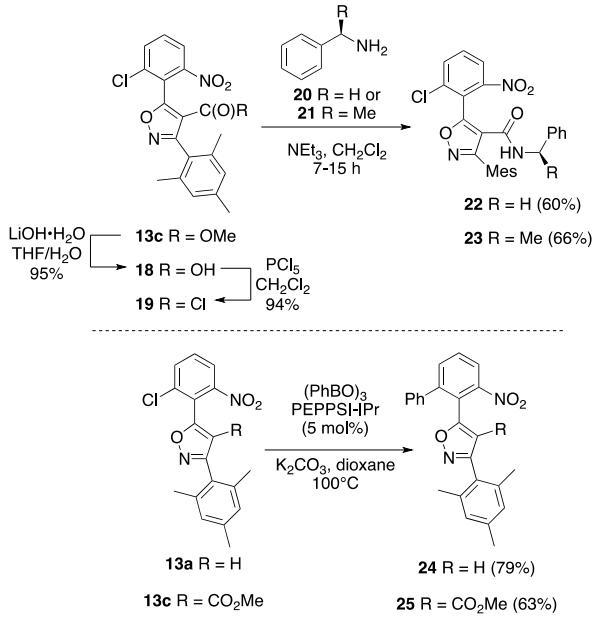
Fig. 2 . ORTEP Representations of Compound **13d** (Note: Only one position for disordered nitro moiety and chloro group are shown for clarity).

It is important to note the critical role that substituents play in the success of these dipolar cycloadditions (Scheme 3). For example, the *ortho*-nitro moiety provides a key activating role in the cycloaddition – leading to improved yields as compared to the *des*-nitro alkynes **14a** and **14b** which provided the products **15a** and **15b** in 76% and 27% yield respectively. In both cases, these yields were lower than the corresponding nitro series (90% for **13h** and 74% for **13j**) which clearly demonstrated the electronic benefits of the nitro moiety to override the steric penalty for its presence. Variation of the dipole component also led to a divergence in chemical yields. Cycloaddition of nitrile oxide percursor **16a** with alkyne **1a** provided a much lower yield (**17a**, 29%) than the less sterically hindered variant **16b** with alkyne **1a** (**17b**, 75%). The cycloaddition using nitrile oxide precursor **16c** with **1a** provided a 39% yield of the desired product **17c**. These yields are all lower than the parent mestyl series **13a** (88%, see Table 1).



Scheme 3. Important Effect of the *ortho*-Nitro Acetylene and Variation of the Nitrile Oxide

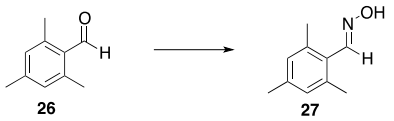
Scheme 4 illustrates that it is possible to derivatize both the halogen and the ester moieties in the isoxazole scaffold. Saponification[4] of the the methyl ester **13c** under optimized conditions provided the acid **18**. This acid could be easily converted[15] to the corresponding acid chloride **19** using PCl_5 in high yield. Subsequent coupling with benzyl amine or (+)-α-methyl benzyl amine cleanly generated the desired amide bond. Interesting, careful analysis of the ^{1}H NMR spectra of amide **23** reveals doubling of both the *ortho*-methyl moieties and the *meta*-aryl protons on the mestyl ring, which indicates that there is restricted rotation around the mesityl group on the NMR time scale. The *ortho*-chloride moiety could be cross coupled using PEPPSI-IPr[16] under our previously reported boroxine coupling conditions[3g] to provide the biaryls **24** and **25**.



Scheme 4. Derivatization of Isoxazoles.

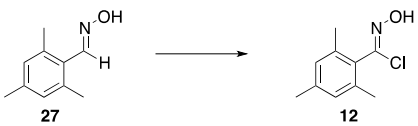
In summary, we have demonstrated a highly regioselective method for the construction of densely functionalized isoxazoles through the use of dipolar cycloaddition with *ortho*-nitrophenyl alkynes and *in situ* generated nitrile oxides. A variety of subsituents on the alkyne is tolerated. The importance of the *ortho*-nitro moeity on the alkyne and the R group on the nitrile oxide was demonstrated. The subsequent derivatization of the isoxazoles has been demonstrated. Additional applications of the cycloaddition strategy for the construction of sterically congested linkages will be reported in due course.

Experimental Section



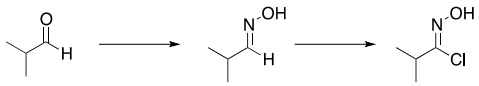
26 **27**

Oxime 27: To a stirred solution of ice (46 g) in H_2O/Ethanol (40 mL, 1:1) was added mesitylaldehyde **26** (6.0 g, 6.0 mL, 40.7 mmol), hydroxylamine hydrochloride (4.2 g, 61.0 mmol) and NaOH (17 mL, 100 mmol, 6.0 M in H_2O). After 2 h, the reaction was quenched with 1 M HCl (50 mL), extracted with Et_2O (3 X 30 mL), and washed with brine (30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by recrystallization with Et_2O and Hexanes to give known oxime **27**[14] (6.05 g, 37.1 mmol, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 6.91 (s, 2H), 2.39 (s, 6H), 2.30 (s, 3H) ppm.



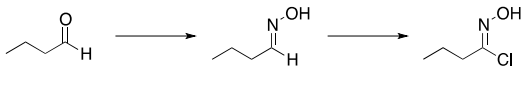
27 **12**

Oximyl Acid Chloride 12: To a stirred solution of oxime **27** (3.0 g, 18.4 mmol) in DMF (18.5 mL) at 0 °C, was added 4 portions of NCS (0.75 g X 4, 20 min apart). Upon warming to rt over 4 h, the reaction was quenched with H_2O/Ice (50 mL), extracted with Et_2O (4 X 25 mL), and washed with brine (2 X 10 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* to give known **12**[14] (3.6 g, 18.4 mmol, 99%) as a white semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 2.27 (s, 9H) ppm.



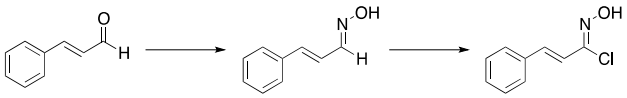
28 **29** **16a**

Oximyl Acid Chloride 16a: To a stirred solution of ice (15 g) in H_2O/Ethanol (14 mL, 1:1) was added aldehyde **28** (1.0 g, 1.3 mL, 14 mmol), hydroxylamine hydrochloride (1.5 g, 21 mmol) and NaOH (5.8 mL, 35 mmol, 6.0 M in H_2O). After 21 h, the reaction was quenched with 1 M HCl (10 mL), extracted with DCM (3 X 25 mL), and washed with brine (50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give crude oxime **29** as a yellow liquid which was used without further purification. To a stirred solution of oxime **29** (1.2 g, 14 mmol) in DMF (14 mL) at 0 °C, was added 4 portions of NCS (0.49 g X 4, 20 min apart). After 18 h at rt, the reaction was diluted with H_2O (20 mL), extracted with Et_2O (3 X 20 mL), and washed with brine (1 X 50 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* to give known **16a**[17] (1.63 g, 13.4 mmol, 96%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (bs, 1H), 2.82 (septet, J = 6.8 Hz, 1H), 1.23 (d, J = 6.8 Hz, 6H) ppm.



30 **31** **16b**

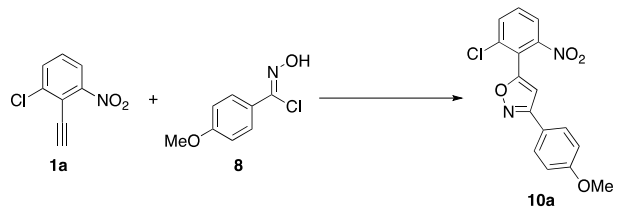
Oximyl Acid Chloride 16b: To a stirred solution of ice (15 g) in H_2O/Ethanol (14 mL, 1:1) was added aldehyde **30** (1.0 g, 1.3 mL, 14 mmol), hydroxylamine hydrochloride (1.5 g, 21 mmol) and NaOH (5.8 mL, 35 mmol, 6.0 M in H_2O). After 2.5 h, the reaction was quenched with 2 M HCl (10 mL), extracted with Et_2O (3 X 20 mL), and washed with brine (50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give crude oxime **31** as a colorless liquid which was used without further purification. To a stirred solution of oxime **31** (1.2 g, 14 mmol) in DMF (14 mL) at 0 °C, was added 4 portions of NCS (0.49 g X 4, 20 min apart). After 18.5 h at rt, the reaction was diluted with H_2O (20 mL), extracted with Et_2O (3 X 20 mL), and washed with brine (1 X 50 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* to give known **16b**[18] (1.7 g, 14 mmol, 99%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 2.50 (t, J = 7.3 Hz, 2H), 1.70 (sextet, J = 7.4 Hz, 6H), 0.98 (t, J = 7.3, 3H) ppm.



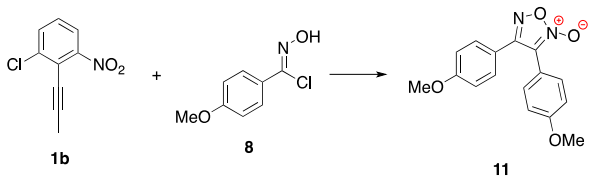
32 **33** **16c**

Oximyl Acid Chloride 16c: To a stirred solution of ice (15 g) in H_2O/Ethanol (14 mL, 1:1) was added aldehyde **32** (1.8 g, 1.8 mL, 14 mmol), hydroxylamine hydrochloride (1.5 g, 21 mmol) and NaOH (5.8 mL, 35 mmol, 6.0 M in H_2O). After

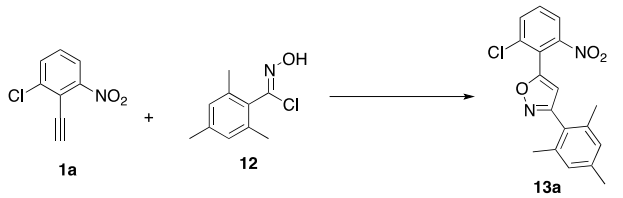
4.5 h, the reaction was quenched with 1 M HCl (12 mL), extracted with Et_2O (3 X 20 mL), and washed with brine (50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give crude oxime **33** as a yellow solid which was used without further purification. To a stirred solution of oxime **33** (2.06 g, 14 mmol) in DMF (14 mL) at 0 °C, was added 4 portions of NCS (0.49 g X 4, 20 min apart). After 11 h at rt, the reaction was diluted with H_2O (50 mL), extracted with Et_2O (2 X 40 mL), and washed with H_2O (3 X 60 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* to give known **16c**[17] (2.49 g, 13.7 mmol, 98%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (bs, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.48-7.31 (overlapping m, 4H), 6.88 (d, *J* = 15.6, 1H) ppm.



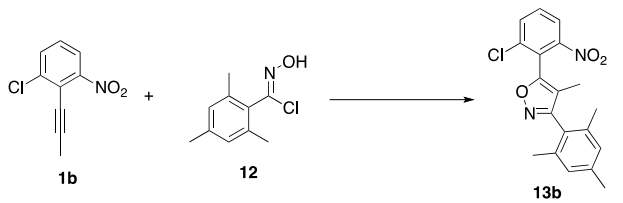
Isoxazole 10a: To a pressure vessel containing **1a**[3c] (63.2 mg, 348 µmol) was added dry PhMe (600 µL), NEt_3 (109 mg, 150 µL, 1.08 mmol) and **8**[2,12] (208.5 mg, 1.123 mmol) sequentially, and heated to 80 °C. Immediately after addition of **8**, a white solid formed along with a mild exotherm. After 1 h, the reaction was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 10-25% EtOAc / Hexanes to give **10** (101.4 mg, 306.6 µmol, 82%) as a yellow solid. Mp 82-84 °C; IR (neat) 3087, 2839, 1612, 1534, 1434, 1255, 1029, 809, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.82 (m, 3H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.02 (m, 2H), 6.82 (s, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 162.2, 161.2, 150.4, 136.2, 134.3, 131.6, 128.4, 123.0, 122.2, 121.0, 114.4, 104.0, 55.4 ppm; HRMS (ES+) calcd. for $C_{16}H_{12}N_2O_4Cl$ (M+H) 331.0486, found 331.0476.



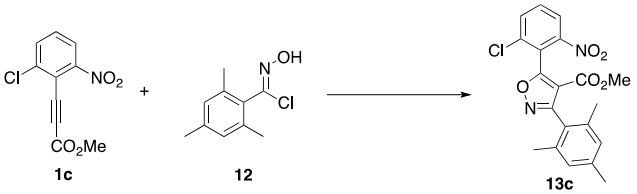
Dimer 11: To a stirred solution of **1b**[4] (19.4 mg, 99 µmol) and **8**[2,12] (184 mg, 990 µmol) in PhMe (500 µL) at 80 °C was added NEt_3 (800 µL, 1.19 mmol, 1.50 M in PhMe) via syringe pump over 5 hours. After 14 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-50 % EtOAc / Hexanes to give undesired dimer **11** (64.6 mg, 216 µmol, 22%) as a yellow solid. Mp 105-107 °C; IR (neat) 2938, 2840, 1611, 1591, 1574, 1520, 1450, 1258, 1179, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 4H), 6.97 (m, 4H), m, 3H), 3.88 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 161.1, 155.9, 130.2, 129.8, 199.0, 114.9, 114.5, 55.4 ppm; HRMS (EI+) calcd. for $C_{16}H_{14}N_2O_4$ (M+) 298.0953, found 298.0952.



Isoxazole 13a: To a stirred solution of **1a**[3c] (63.8 mg, 351 µmol) and NEt_3 (500 µL, 363 mg, 3.59 mmol) in PhMe (700 µL) at 80 °C was added **12**[14] (15.4 mL, 3.846 mmol, 250 mM in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 2-8% EtOAc / Hexanes gave pure **13a** (105.9 mg, 309.0 µmol, 88%) as a yellow oil. IR (thin film) 1750, 1613, 1536, 1464, 1439, 1382, 1353, 906, 882, 808, 757, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.00 (s, 2H), 6.49 (s, 1H), 2.36 (s, 3H), 2.25 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 162.2, 150.2, 139.1, 137.3, 136.3, 134.4, 131.7, 128.4, 125.5, 123.1, 122.4, 107.6, 21.8, 20.2 ppm; HRMS (EI+) calcd. for $C_{18}H_{15}N_2O_3Cl$ (M+) 342.0771, found 342.0759.).

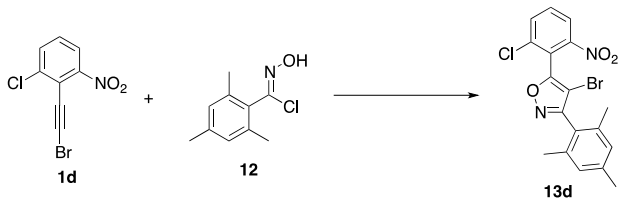


Isoxazole 13b: To a stirred solution of **1b**[4] (41.4 mg, 212 µmol) and **12**[14] (446.3 mg, 2.258 mmol) in PhMe (1.00 mL) at 80 °C was added NEt_3 (1.72 mL, 2.58 mmol, 1.50 M in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 5-15 % EtOAc / Hexanes to give impure **13b** as a yellow oil. The impure oil was triturated and recrystallized from hexanes / methanol to give pure **13b** (65.6 mg, 184 µmol, 87%) as a pale yellow solid. Mp 151-153 °C; IR (thin film) 1609, 1535, 1456, 1437, 1348, 901, 852, 808, 759, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.68 (t, *J* = 8.2 Hz, 1H), 7.00 (s, 2H), 2.37 (s, 3H), 2.18 (s, 6H), 1.75 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 159.0, 150.3, 139.0, 137.5, 137.0, 134.5, 131.8, 128.3, 124.8, 123.3, 122.8, 114.8, 21.2, 19.7, 7.1 ppm; HRMS (EI+) calcd. for $C_{19}H_{17}N_2O_3Cl$ (M+) 356.0928, found 356.0926.

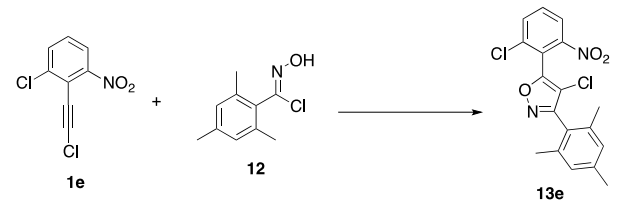


Isoxazole 13c: To a stirred solution of **1c**[3c] (50 mg, 208 µmol) and **12**[14] (411 mg, 2.08 mmol) in PhMe (1.5 mL) at 80 °C,

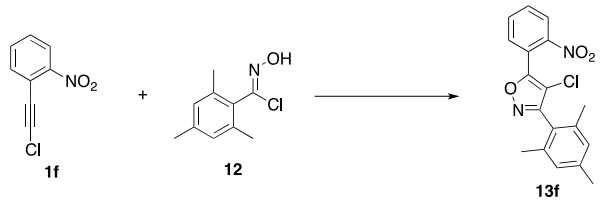
was added NEt_3 (1.7 mL, 2.55 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 14 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 10-20% EtOAc/Hexanes to give impure **13c** as a yellow solid. Repurification via trituration with hexanes gave impure **13c** as a pale yellow solid. Repurification via flash chromatography over silica gel, eluting 20-40% EtOAc/Hexanes gave impure **13c**. Repurification via trituration with hexanes and EtOAc gave **13c** (69.5 mg, 173 µmol, 83%) as a white solid. Mp 177-178 °C; IR (neat) 1730, 1534, 1456, 1400, 1348, 1310, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 0.8, 8.3 Hz, 1H), 7.89 (dd, *J* = 0.8, 8.1 Hz, 1H), 7.75 (t, *J* = 8.2 Hz, 1H), 6.98 (s, 2H), 3.51 (s, 3H), 2.37 (s, 3H), 2.81 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 162.0, 160.7, 149.2, 139.1, 136.6, 134.9, 132.2, 128.1, 124.2, 123.4, 123.0, 111.9, 51.9, 21.3, 19.9 ppm; HRMS (EI+) calcd. for $C_{20}H_{17}N_2O_5Cl$ (M+) 400.0826, found 400.0838.



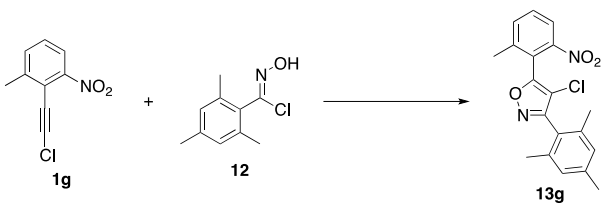
Isoxazole 13d: To a stirred solution of **1d**[4] (42.8 mg, 164 µmol) and **12**[14] (353.8 mg, 1.790 mmol) in PhMe (1.00 mL) at 80 °C was added NEt_3 (1.43 mL, 2.15 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 2-10 % EtOAc / Hexanes to give impure **13d** as a yellow solid. The impure solid was recrystalized from methanol to give pure **13d** (46.8 mg, 111 µmol, 68%) as a light brown oil. IR (thin film) 1527, 1356, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 8.2 Hz, 1H), 7.02 (s, 2H), 2.38 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 161.7, 149.6, 139.8, 138.0, 137.3, 135.0, 132.6, 128.4, 128.3, 123.6, 121.4, 97.3, 21.3, 19.7 ppm; HRMS (EI+) calcd. for $C_{18}H_{14}N_2O_3ClBr$ (M+) 419.9876, found 419.9880.



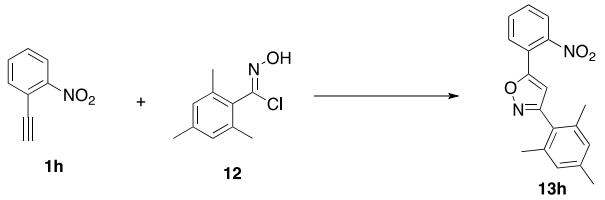
Isoxazole 13e: To a stirred solution of **1e**[4] (41.1 mg, 190 µmol) and **12**[14] (386.8 mg, 1.957 mmol) in PhMe (1.00 mL) at 80 °C was added NEt_3 (1.67 mL, 2.51 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 10-30 % EtOAc / Hexanes to give impure **13e** as a yellow solid. The impure solid was recrystallized from methanol to give pure **13e** (50.2 mg, 133 µmol, 70%) as a light brown oil. IR (thin film) 1528, 1353 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.74 (t, *J* = 8.2 Hz, 1H), 7.02 (s, 2H), 2.38 (s, 3H), 2.23 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 159.4, 149.7, 139.8, 137.9, 137.4, 134.9, 132.6, 128.4, 123.6, 122.6, 120.9 111.2, 21.2, 19.7 ppm; HRMS (EI+) calcd. for $C_{18}H_{14}N_2O_3Cl_2$ (M+) 376.0382, found 376.0400.



Isoxazole 13f: To a stirred solution of **1f**[4] (50 mg, 276 µmol) and **12**[14] (545 mg, 2.76 mmol) in PhMe (1.5 mL) at 80 °C, was added NEt_3 (2.2 mL, 3.30 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 16.5 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 5-10% EtOAc/Hexanes to give impure **C** as a yellow oil. Purification via flash chromatography over silica gel, eluting 10% EtOAc/Hexanes gave impure **13f** as a yellow oil. Repurification via flash chromatography over silica gel, eluting 20% Et_2O/Pentane gave **13f** (66 mg, 0.193 mmol, 69%) as a beige solid. Mp 89-92 °C; IR (neat) 1534, 1351, 1129, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.76-7.86 (m, 3H), 7.01 (s, 2H), 2.37 (s, 3H), 2.21 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.5, 148.2, 139.8, 137.8, 133.4, 131.8, 131.6, 128.4, 125.3, 122.7, 121.0, 109.6, 21.3, 19.8 ppm; HRMS (EI+) calcd. for $C_{18}H_{15}N_2O_3Cl$ (M+) 342.0771, found 342.0772.

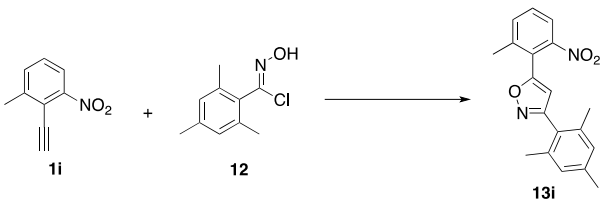


Isoxazole 13g: To a stirred solution of **1g**[4] (240.9 mg, 1.231 mmol) and **12**[14] (2.369 g, 11.98 mmol) in PhMe (6.10 mL) at 80 °C was added NEt_3 (10.1 mL, 15.1 mmol, 1.50 M in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 10-30 % EtOAc / Hexanes to give impure **13g** as a yellow solid. The impure solid was recrystallized from methanol to give pure **13g** (346.8 mg, 977.5 µmol, 73%) as a yellow solid. Mp 178-180 °C; **IR** (thin film) 1538, 1455, 1384, 1339, 912, 880, 854, 803, 748, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.70 (d, *J* = 5.7 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 2.23 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 161.4, 149.0, 141.5, 139.8, 135.5, 131.5, 128.4, 122.8, 122.8, 120.4, 110.0, 21.3, 19.7, 19.5 ppm; HRMS (EI+) calcd. for $C_{19}H_{17}N_2O_3Cl$(M+) 356.0928, found 356.0913.



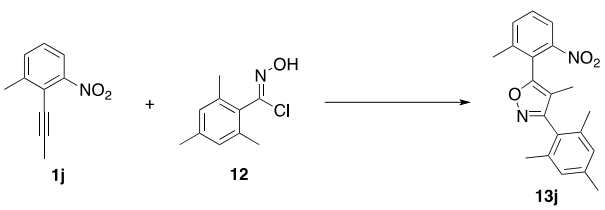
1h 12 13h

Isoxazole 13h: To a stirred solution of **1h** (50 mg, 340 µmol) and **12**[14] (672 mg, 3.40 mmol) in PhMe (1.5 mL) at 80 °C, was added NEt_3 (2.7 mL, 4.05 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 11.5 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 10% EtOAc/Hexanes to give impure **13h** as a yellow solid. Repurification via flash chromatography over silica gel, eluting 20% EtOAc/Hexanes gave impure **13h**. Repurification via trituration with hexanes gave **13h** (94.4 mg, 0.306 mmol, 90%) as a white solid. Mp 122-123 °C; IR (neat) 1534, 1353 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (td, *J* = 1.2, 8.1 Hz, 2H), 7.75 (td, *J* = 1.2, 7.6 Hz, 1H), 7.66 (td, *J* = 1.3, 7.7 Hz, 1H), 6.98 (s, 2H), 6.46 (s, 1H), 2.35 (s, 3H), 2.12 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.7, 148.2, 139.1, 137.3, 132.6, 131.0, 130.4, 128.4, 125.5, 124.4, 121.8, 105.4, 21.2, 20.3 ppm; HRMS (EI+) calcd. for $C_{18}H_{16}N_2O_3$ (M+) 308.1161, found 308.1162.



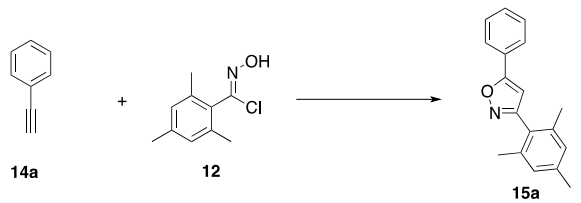
1i 12 13i

Isoxazole 13i: To a stirred solution of **1i**[4] (47.2 mg, 293 µmol) and **12**[14] (519.9 mg, 2.630 mmol) in PhMe (1.50 mL) at 80 °C was added NEt_3 (2.40 mL, 3.60 mmol, 1.50 M in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and was purified via flash chromatography over silica gel, eluting with 10-25 % EtOAc / Hexanes to give impure **13i** as a solid. The impure solid was recrystalized from Hexanes / methanol to give pure **13i** (87.1 mg, 269 µmol, 92%) as a pale yellow oil. IR (thin film) 1613, 1528, 1457, 1381, 1354, 906, 855, 832, 802, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.63 (d, *J* = 6.5 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 6.99 (s, 2H), 6.29 (s, 1H), 2.40 (s, 3H), 2.36 (s, 3H), 2.24 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 162.3, 149.6, 140.8, 139.0, 137.2, 134.9, 130.8, 128.4, 125.7, 122.3, 122.1, 106.1, 21.2, 20.2, 20.0 ppm; HRMS (EI+) calcd. for $C_{19}H_{18}N_2O_3$ (M+) 322.1317, found 322.1304.



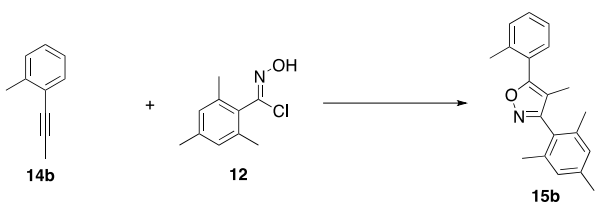
1j 12 13j

Isoxazole 13j: To a stirred solution of **1j**[4] (80.9 mg, 462 µmol) and **12**[14] (845.6 mg, 4.278 mmol) in PhMe (2.30 mL) at 80 °C was added NEt_3 (3.70 mL, 5.55 mmol, 1.50 M in PhMe) via syringe pump over 5 hours. After 10 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 2-10 % EtOAc / Hexanes to give impure **13j** as a yellow solid. The impure solid was recrystalized from methanol to give pure **13j** (115.7 mg, 349.3 µmol, 74%) as a light brown solid. Mp 133-135 °C; IR (thin film) 1643, 1613, 1533, 1457, 1347, 914, 853, 804, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.00 (s, 2H), 2.36 (s, 3H), 2.33 (s, 3H), 2.18 (s, 6H), 1.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 161.3, 149.6, 141.4, 138.9, 137.3, 135.0, 130.7, 128.2, 125.0, 122.5, 122.3, 113.4, 21.2, 19.7, 19.6, 6.9 ppm; HRMS (EI+) calcd. for $C_{20}H_{20}N_2O_3$ (M+) 336.1470, found 336.1462.



14a 12 15a

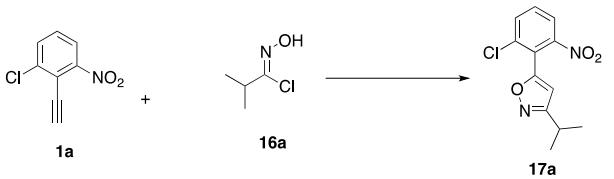
Isoxazole 15a: To a stirred solution of **14a** (50 µL, 455 µmol) and **12**[14] (900 mg, 4.55 mmol) in PhMe (3.0 mL) at 80 °C was added NEt_3 (3.6 mL, 5.46 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 20 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-10 % EtOAc / Hexanes to give impure **15a** as a yellow solid. The impure solid was recrystallized from EtOAc/Hex to give known **15a**[10] (89.4 mg, 340 µmol, 75%) as a white solid. ^1H NMR (700 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.1 Hz, 2H), 7.53 (t, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.1 Hz, 1H), 6.99 (s, 2H), 6.50 (s, 1H), 2.36 (s, 3H), 2.22 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 162.7, 138.8, 137.2, 130.1, 129.0, 128.4, 127.6, 126.2, 125.9, 100.9, 21.1, 20.2 ppm.



14b 12 15b

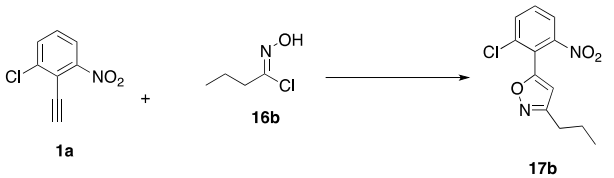
Isoxazole 15b: To a stirred solution of **14b**[19] (50.0 mg, 384 µmol) and **12**[14] (759 mg, 3.84 mmol) in PhMe (1.5 mL) at 80 °C was added NEt_3 (3.1 mL, 4.61 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 15 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-20 % EtOAc / Hexanes to give impure **15b**. Repurification via trituration with Hexanes and EtOAc gave **15b** (29.9 mg, 103 µmol, 27%) as a white solid. Mp 96-99 °C; IR (neat) 2923, 1614, 1450, 1145, 1006, 898, 852, 766, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (overlapping m, 4H), 6.99 (s, 2H), 2.41 (s, 3H), 2.37 (s, 3H), 2.16 (s, 6H), 1.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 163.4, 138.7, 137.8, 137.3, 130.8, 129.8, 129.6, 128.2, 128.0, 125.7, 111.4, 21.2, 20.1, 19.8, 7.6 ppm. HRMS (ES+) calcd. for $C_{20}H_{22}NO$

(M+H) 292.1701, found 292.1689.



1a 16a 17a

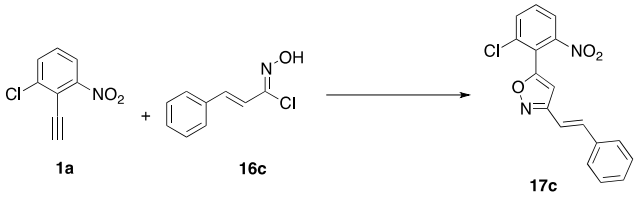
Isoxazole 17a: To a stirred solution of **1a**[3c] (69.7 mg, 384 µmol) and **16a**[17] (467 mg, 3.84 mmol) in PhMe (1.5 mL) at 80 °C was added NEt_3 (3.1 mL, 4.61 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 15 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-30 % EtOAc / Hexanes to give impure **17a**. Repurification via flash chromatography over silica gel, eluting with 0-10 % EtOAc / Hexanes gave **17a** (29.5 mg, 111 µmol, 29%‡) as a yellow oil. IR (neat) 3089, 2970, 1537, 1352, 1124, 950, 883, 759, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.60 (t, *J* = 8.2 Hz, 1H), 6.42 (s, 1H), 3.16 (septet, *J* = 7.1 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 161.5, 150.4, 136.0, 134.2, 131.4, 122.9, 122.4, 104.4, 26.7, 21.6 ppm. HRMS (EI+) calcd. for $C_{12}H_{11}N_2O_3Cl$ (M+) 266.0458, found 266.0462.



1a 16b 17b

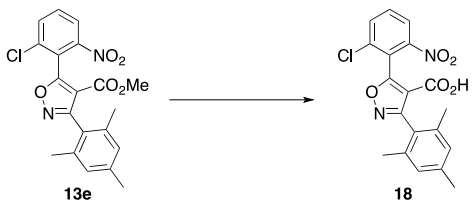
Isoxazole 17b: To a stirred solution of **1a**[3c] (69.7 mg, 384 µmol) and **16b**[18] (467 mg, 3.84 mmol) in PhMe (1.5 mL) at 80 °C was added NEt_3 (3.1 mL, 4.61 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 15 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-30 % EtOAc / Hexanes to give impure **17b**. Repurification via flash chromatography over silica gel, eluting with 0-10 % EtOAc / Hexanes gave **17b** (76.8 mg, 288 µmol, 75%) as a yellow oil. IR (neat) 3090, 2964, 2875, 1538, 1417, 1354, 1125, 950, 883, 808, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 8.1 Hz, 1H), 6.40 (s, 1H), 2.75 (t, *J* = 7.3 Hz, 2H), 1.77 (sextet, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.6, 150.3, 136.0, 134.2, 131.5, 122.9, 122.4, 105.8, 28.0, 21.5, 13.6 ppm. HRMS (EI+) calcd. for $C_{12}H_{11}N_2O_3Cl$ (M+) 266.0458, found 266.0469.

‡ This product contains a small (<10% impurity) which is inseparable.



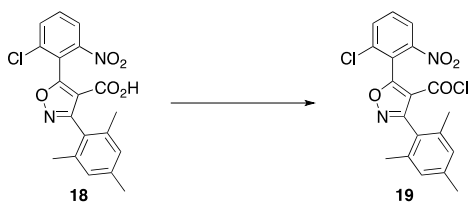
1a 16c 17c

Isoxazole 17c: To a stirred solution of **1a**[3c] (69.7 mg, 384 µmol) and **16c**[17] (697 mg, 3.84 mmol) in PhMe (1.5 mL) at 80 °C was added NEt_3 (3.1 mL, 4.61 mmol, 1.5 M in PhMe) via syringe pump over 5 hours. After 14 h, the crude mixture was cooled to rt, filtered, concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-20 % EtOAc / Hexanes to give impure **17c**. Repurification via trituration with Hexanes and EtOAc gave **17c** (49.4mg, 151 µmol, 39%‡) as a yellow solid. Mp 117-120°C; IR (neat) 1535, 1425, 1353, 965, 884, 755, 737, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.44-7.33 (overlapping multiplets, 3H), 7.27, 7.20 (ABq, *J* = 16.5 Hz, 2H), 6.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.9, 150.4, 136.6, 136.3, 135.7, 134.3, 131.7, 129.1, 128.9, 127.1, 123.0, 122.1, 155.6, 103.3 ppm. HRMS (ES+) calcd. for $C_{17}H_{12}N_2O_3Cl$ (M+H) 327.0536, found 327.0543.



13e 18

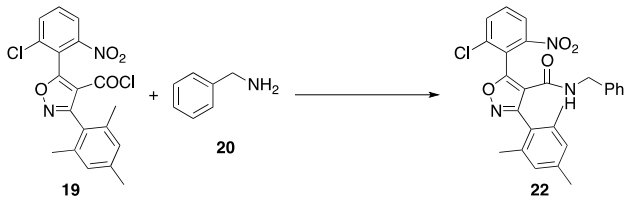
Carboxylic Acid 18: To a stirred solution of **13e** (100 mg, 249 µmol) stirring in THF/H_2O (2:1, 0.2 M, 1.2 mL) was added $LiOH•H_2O$ (36.2 mg, 863 µmol). After 5 days the reaction mixture was quenched with 6 M HCl (1.5 mL) and the aqueous layer extracted with EtOAc (3 x 10 mL ea.). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield **18** as a beige solid (91.9 mg, 238 µmol, 95%). Mp 195-197 °C; IR (neat) 2919, 1691, 1536, 1348, 1139, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.4 Hz, 1H), 6.98 (s, 2H), 2.36 (s, 3H), 2.18 (s, 6H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.7, 162.9, 161.9, 148.8, 139.3, 137.4, 137.1, 136.6, 135.1, 132.4, 128.3, 128.1, 123.9, 123.6, 122.8, 111.2, 21.3, 19.9 ppm; HRMS (ES+) calcd. for $C_{19}H_{16}ClN_2O_5$ (M+H) 387.0762, found 387.0748.



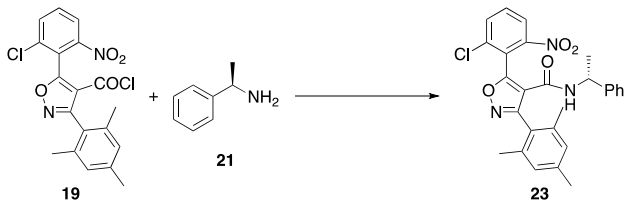
18 19

Acid Chloride 19: To a stirred solution of **18** (10 mg, 25.8 µmol) in CH_2Cl_2 (100 µL) was added PCl_5 (6.4 mg, 30.7 µmol). After 2 h at reflux the crude mixture was cooled to rt

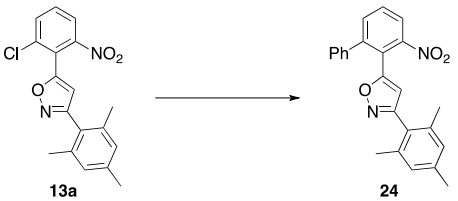
and concentrated *in vacuo* to give **19** as a beige solid (9.8 mg, 24.2 µmol, 94%). Crude materials were used without further purification. Mp 132-136 °C; IR (neat) 2925, 1733, 1536, 1315, 1124, 737 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.82 (t, *J* = 8.4 Hz, 1H), 7.02 (m, 2H), 2.83 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.8, 161.6, 157.9, 148.5, 139.9, 137.4, 137.1, 136.6, 135.5, 133.0, 128.5, 128.4, 123.9, 123.0, 122.4, 116.5, 21.1, 19.9 ppm; HRMS (EI+) calcd. for $C_{19}H_{14}Cl_2N_2O_4$ (M+) 404.0331, found 404.0330.



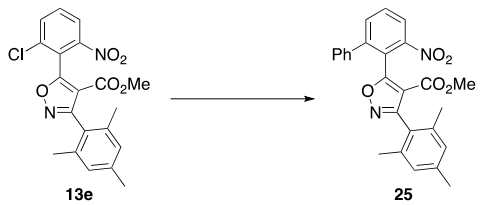
Amide 22: To a stirred solution of **19** (14.5 mg, 35.8 µmol) in CH_2Cl_2 (360 µL) was added NEt_3 (7.2 mg, 10 µL, 71.6 µmol) and benzylamine **20** (7.8 mg, 8 µL, 73.2 µmmol) at rt. After 15 h the crude materials were concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting 0-40% EtOAc/Hexanes to give **22** as a beige solid (10.2 mg, 21.4 µmol, 60%). Mp 139-141 °C; IR (neat) 3400, 2922, 1666, 1531, 1350, 1150, 738 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.23 (m, 3H), 6.93 (s, 2H), 6.86 (m, 2H), 5.52 (s, 1H), 4.25 (d, *J* = 4.6 Hz, 1H), 4.18 (d, *J* = 4.1 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 6H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.2, 159.2, 159.1, 149.2, 140.7, 138.0, 137.3, 136.8, 136.6, 134.8, 131.9, 129.2, 129.0, 128.5, 127.5, 127.2, 123.6, 123.4, 123.3, 113.6, 43.2, 21.2, 19.7 ppm; HRMS (ES+) calcd. for $C_{26}H_{23}ClN_3O_4$ (M+H) 476.1377, found 476.1358.



Amide 23: To a stirred solution of **19** (4.8 mg, 11.8 µmol) in CH_2Cl_2 (120 µL) was added NEt_3 (2.4 mg, 3.3 µL, 23.6 µmol) and (R)-(+)-α-methyl benzylamine **21** (2.8 mg, 3 µL, 23.6 µmmol) at rt. After 7 h the crude materials were concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting 0-30% EtOAc/Hexanes to give **23** as a beige solid (3.8 mg, 7.75 µmol, 66%). Mp 51-53 °C; IR (neat) 3388, 2924, 1667, 1534, 1351, 757, 699 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.85 (dd, *J* = 7.6, 14.8 Hz, 1H), 7.68 (t, *J* = 8.2 Hz, 1H), 7.22 (m, 3H), 7.13 (s, 1H of rotamer), 7.10 (s, 1H of rotamer), 6.96 (s, 1H of rotamer), 6.94 (s, 1H of rotamer), 6.80 (m, 2H), 5.65 (bs, 1H), 4.89 (s, 1H), 2.39 (s, 3H), 2.28 (s, 3H of a rotamer), 2.26 (s, 3H of a rotamer), 2.09 (s, 3H), 1.16 (m, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.0, 159.1, 158.3, 149.2, 142.4, 142.2, 140.8, 138.3, 138.1, 137.7, 137.4, 136.6, 134.8, 131.8, 129.4, 129.2, 128.9, 128.5, 127.3, 125.4, 123.6, 123.4, 113.7, 48.6, 22.2, 21.3, 19.8, 19.7 ppm; HRMS (ES+) calcd. for $C_{27}H_{25}ClN_3O_4$ (M+H) 490.1534, found 490.1524.



Isoxazole 24: To a pressure vessel containing **13a** (83.4 mg, 243 µmol) and dioxane (1.00 mL), was sequentially added PEPPSI-IPr (16.8 mg, 24.7 µmol), $(PhBO)_3$ (124.3 mg, 340 µmol), K_2CO_3 (127.6 mg, 923 µmol). The solution was sealed under Ar and heated to 80 °C. After 48 h, the reaction was cooled to rt, and filtered through a Celite pad with CH_2Cl_2 (40 mL). The elutant was concentrated *in vacuo*, and purified via flash chromatography over silica gel, eluting with 0-15% EtOAc / hexanes to give **24** (74.1 mg, 19.3 µmol, 79%) as a pale yellow solid. Mp 168-170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 2.1, 7.3 Hz, 1H), 7.76 (m, 2H), 7.35 (m, 3H), 7.24 (m, 2H), 6.92 (s, 2H), 5.85 (s, 1H), 2.32 (s, 3H), 2.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.0, 149.5, 145.3, 138.8, 138.4, 137.3, 134.6, 130.9, 128.9, 128.4, 128.21, 128.20, 125.7, 123.6, 121.7, 107.0, 21.1, 20.0 ppm; HRMS (EI+) calcd. for $C_{24}H_{20}N_2O_3$ (M+) 384.1474, found 384.1465.



Isoxazole 25: To a seal tube containing **13e** (50 mg, 125 µmol) was added sequentially K_2CO_3 (52 mg, 374 µmol), $(PhBO)_3$ (117 mg, 374 µmol), and PEPPSI-IPr (3.8 mg, 5.6 µmol). The vessel was evacuated and backfilled with argon 3 times. Dioxane was added and the reaction was let stir at 100 °C. After 15 h, the crude material was cooled to rt, filtered through Celite and concentrated *in vacuo*. Purification via flash chromatography over silica gel, eluting 5-20% EtOAc/Hexanes gave **25** as a yellow solid (37.4 mg, 84.5 µmol, 63%). mp 175-178 °C; IR (neat) 2953, 1732, 1534, 1123, 737, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (t, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 4.8 Hz, 2H), 7.32 (m, 3H), 7.21 (m, 2H), 6.92 (s, 1H), 6.86 (s, 1H), 3.41 (s, 3H), 2.31 (s, 3H), 2.13 (s, 3H) 1.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 161.8, 160.6, 148.3, 145.6, 138.8, 137.9, 137.1, 136.9, 135.1, 131.3, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 124.4, 123.9, 122.1, 111.7, 51.6, 21.2, 19.8, 19.7 ppm; HRMS (EI+) calcd. for $C_{26}H_{22}N_2O_5$ (M+) 442.1529, found 442.1531.

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra, for all new compounds and X-ray data for **13b, 13d** (Fig. 1), **13g** and **13h** are provided. See DOI: 10.1039/b000000x/

REFERENCES

1. T. M. V. D. Pinho e Melo, *Curr. Org. Chem.*, 2005, **9**, 925-958.
2. (a) H. Pellisier, *Tetrahedron*, 2007, **63**, 3235-3285. (b) V. Nair and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247-12275. (c) M. Pineiro, and T. M. V. D. Pinto e Melo, *Eur. J. Org. Chem*. 2009, 5287-5307.
3. (a) B. O. Ashburn and R. G. Carter, *Angew. Chem. Int. Ed.*, 2006, **45**, 6737-6741. (b) M. R. Naffziger, B. O. Ashburn, J. R. Perkins and R. G. Carter, *J. Org. Chem.*, 2007, **72**, 9857-9865. (c) B. O. Ashburn, R. G. Carter and L. N. Zakharov, *J. Am. Chem. Soc.*, 2007, **129**, 9109-9116. (d) B. O. Ashburn and R. G. Carter, *J. Org. Chem.*, 2007, **72**, 10220-10223. (e) B. O. Ashburn and R. G. Carter, *Org. Biomol. Chem.*, 2008, **6**, 255-257. (f) Ashburn, B. O; Rathbone, L. K.; Camp, E. H; Carter, R. G. *Tetrahedron*, 2008, **64**, 856-865. (g) J. R. Perkins, and R. G. Carter, *J. Am. Chem. Soc.*, 2008, **130**, 3290-3291. (h) B. O. Ashburn and R. G. Carter, *J. Org. Chem*., 2008, **73**, 7305-09.
4. M. L. McIntosh, R. C. Johnston, O. Pattwong, B. O. Ashburn, M. R. Naffziger, P H.-Y. Cheong and R. G. Carter, *J. Org. Chem.*, 2012, **77**, 1101-1112.
5 T. V. Hansen, P. Wu and V. V. Fokin, *J. Org. Chem.*, 2005, **70**, 7761-7764.
6 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovstev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Amer. Chem. Soc*., 2005, **127**, 210-216.
7 S. Grecian and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2008, **47**, 8285-8287.
8 S. E. Denmark and J. M. Kallemeyn, *J. Org. Chem.*, 2005, **70**, 2839-2842.
9 J. J. Letourneau, C. Riveillo and M. H. J. Ohlmeyer, *Tetrahedron Lett.*, 2007, **48**, 1739-1743.
10 J. A. Crossley and D. L. Browne, *J. Org. Chem.*, 2010, **75**, 5414-5416.
11. (a) D. A. Patrick, S. A. Bakunov, S. M. Bakunova, E. V. K. S. Kumar, R. J. Lombardy, S. K. Jones, A. S. Bridges, O. Zhirnov, J. E. Hall, T. Wenzler, R. Brun and R. R. Tidwell *J. Med. Chem*., 2007, **50**, 2468-2485. (b) R. R. Tidwell, S. Bakunova, S. Bakunova, D. A. Patrick. *Eur. Pat. Appl.* (2006), EP 1719767 A1 20061108.
12. M. C. Pirrung, L. N. Tumey, C. R. H. Raetz, J. E. Jackman, K. Snehalatha, A. L. McClerren, C. A. Fierke, S. L. Gantt and K. M. Rusche, *J. Med. Chem.*, 2002, **45**, 4359-4370.
13. F. De Sarlo, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1951-1953.
14. K.-C. Liu, B. R. Shelton and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916-3918.
15. Rajinder, S.; Hui, L. *PCT Int. Appl.* (2005), 2005033103.
16. M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien and C. Valente, *Eur. J. Chem.*, 2006, **12**, 4749-4755.
17 Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180-1183.
18 Bourbeau, M. P.; Rider, J. T. *Org. Lett.* **2006**, *8*, 3679-3680.
19 Mesnard, D.; Bernadou, F.; Migniac, L. *J. Chem. Res. (S)*, **1981**, *9*, 270-271.

