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SYNTHESES OF AMIDE-SUBSTITUTED ISOXAZOLES AND PYRAZOLES *VIA* REGIOSELECTIVE [3 + 2] CYCLOADDITIONS OF TERMINALLY UNSUBSTITUTED YNAMIDES†

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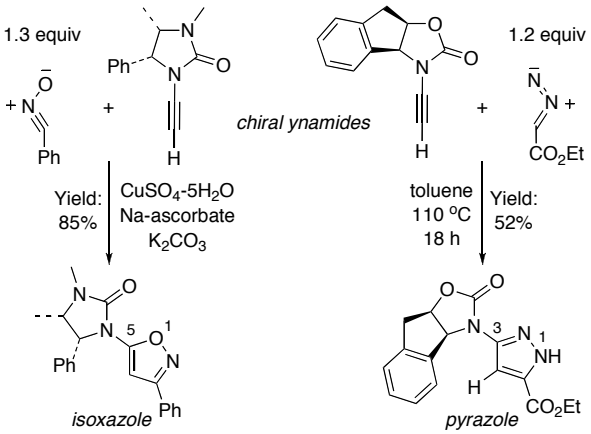
† This paper is dedicated to Professor Ekkehard Winterfeldt with the deepest respect on the special occasion of his 75th birthday.

Abstract – A series of regioselective [3 + 2] cycloadditions of terminally unsubstituted ynamides with nitrile oxides and ethyl α-diazoacetate is described here. These reactions provide an excellent synthetic entry to *de novo* 5-amide-substituted isoxazoles via a Cu(I)-catalyzed pathway and 3-amide-substituted pyrazoles via a thermally driven cycloaddition.

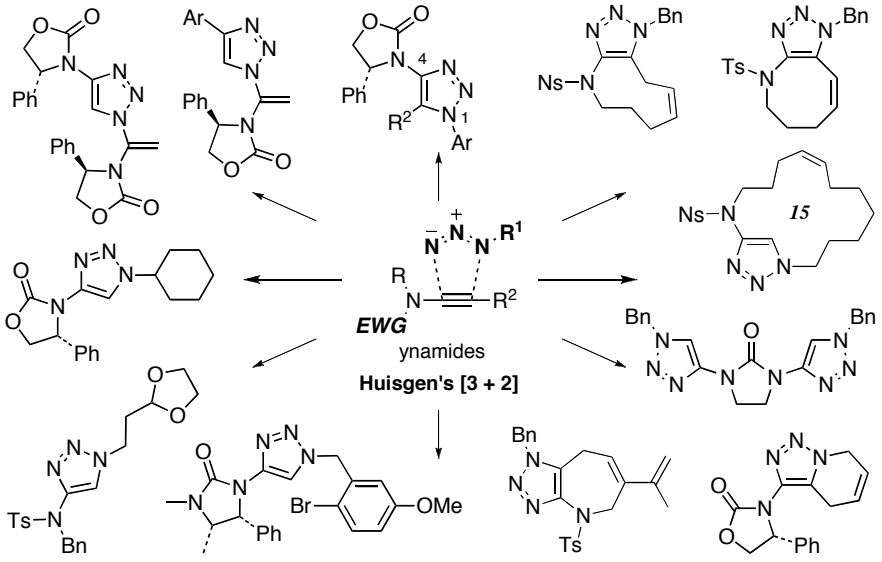


INTRODUCTION

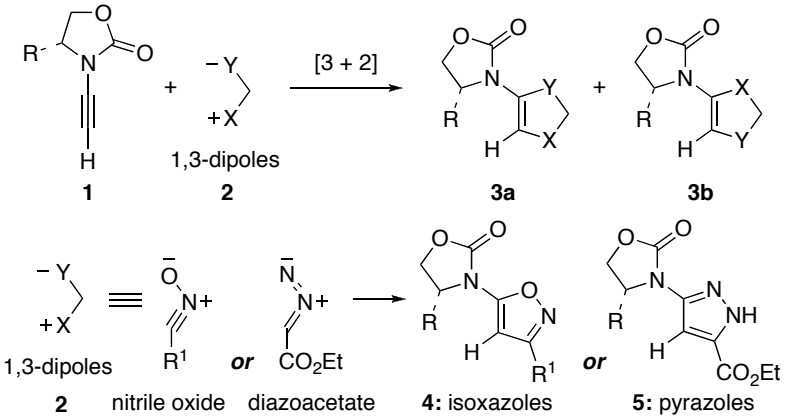
The 1,3-dipolar cycloaddition reaction[1,2] remains the most powerful synthetic method for constructing important heterocyclic pharmacophores.[3] Our interest in the chemistry of ynamides[4-6] has led us to

develop [3 + 2] cycloadditions employing ynamides for the synthesis of *de novo* amide-substituted *N*-heterocycles. Particularly, we investigated Huisgen's organic azide-[3 + 2] cycloadditions[7] of ynamides given the emerging interest in this classic transformation as being a "click" reaction with industrial relevance.[8,9] We were able to develop $CuSO_4$-$5H_2O$-catalyzed tandem azidination of aryl [or vinyl] halides-azide [3 + 2] cycloaddition,[10] an *in situ* generation of organic azides from NaN_3 and alkyl halides to broaden the synthetic scope of the cycloaddition,[11] and a triazole templated ring-closing metathesis by trapping the triazolyl copper intermediate with allyl halides[12] leading to the synthesis of a diverse array of highly substituted, fused, or bridged triazoles (**Scheme1**). With these initial successes, we continued to explore [3 + 2] cycloadditions of nitrile oxides[14-16] and α-diazoacetates[17,18] with ynamides[19-21] for syntheses of amide-substituted isoxazoles[22] and pyrazoles (**Scheme 2**). We report here details of these findings.

Scheme 1. Huisgen's Azide-[3 + 2] Cycloaddition of Ynamides



Scheme 2. Cycloadditions with Nitrile Oxide and Ethyl α-Diazoacetate



RESULTS AND DISCUSSION

1. Ynamide-[3 + 2] Cycloaddition with Nitrile Oxides

The feasibility of a [3 + 2] cycloaddition of an ynamide with a nitrile oxide was readily established. As shown in **Scheme 3**, by employing Cu(I)-catalyzed conditions specifically featuring $CuSO_4$-$5H_2O$ and Na-ascorbate as the reductant,[15] chiral ynamide **7**, substituted with Close' auxiliary,[23] reacted effectively with nitrile oxide **8**, which was generated *in situ* from α-chloro oxime **6**, to provide 3,5-disubstituted isoxazole **11** in 85% yield as a single regioisomer. The 3,5-regioselectivity found in **11** was unambiguously assigned via its X-ray structure (**Figure 1**). The regiochemical outcome observed here is related to Fokin-Sharpless' work.[15] It is likely a result of copper-acetylide formation (see **9**) en route to a copper-directed or templated cycloaddition via intermediate **A** (see the bracket), leading to the vinyl copper intermediate **10** prior to the protonation from the solvent.

Scheme 3. Cu(I)-Catalyzed [3 + 2] Cycloaddition with Nitrile Oxide

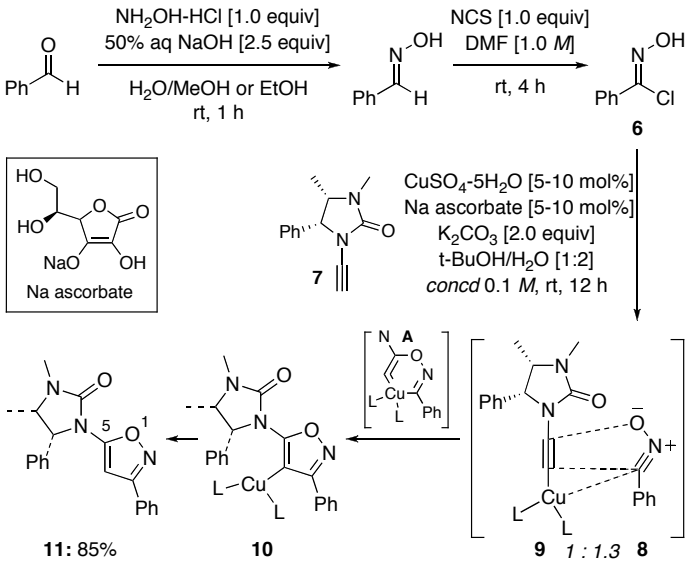
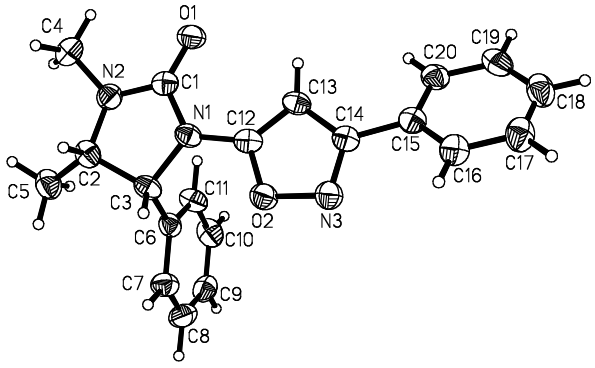
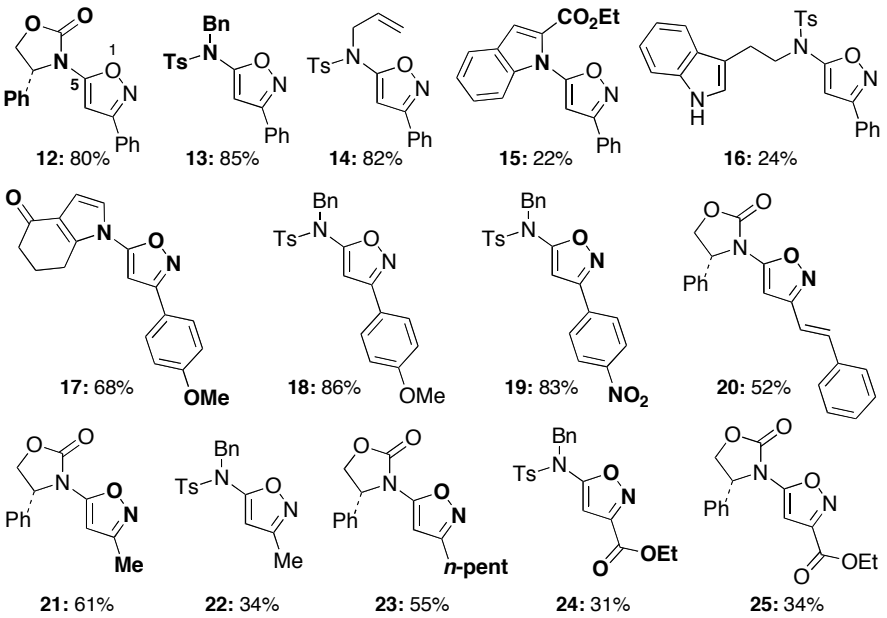


Figure 1. Single Crystal X-Ray Structure of Isoxazole **11**



The generality of Cu(I)-catalyzed [3 + 2] cycloadditions of ynamides with nitrile oxides is summarized in **Figure 2**. All these cycloadditions were highly regioselective, leading to 5-amide-substituted isoxazoles exclusively without any 4-amide-substituted isoxazoles. There are two major features showcased here. Firstly, a range of different ynamides can be utilized in this cycloaddition and they are: An Evans' auxiliary-substituted[24] ynamide (see **12** - the red portion of isoxazoles originates from the respective ynamide), *N*-Bn, *N*-allyl, and *N*-indolyl ethyl sulfonyl-substituted ynamides (see **13**, **14**, and **16**), an electron-deficient indolyl ynamine (see **15**), and a vinylogous ynamide (see **17**).

Figure 2. Syntheses of 5-Amide-Substituted Isoxazoles



Secondly, the scope for the nitrile oxide (see the blue portion of isoxazoles) is very broad, ranging from electron-rich (see **17** and **18**) to electron-poor (see **19**) aryl-substituted nitrile oxides, a styryl-substituted nitrile oxide (see **20**), simple alkyl-substituted nitrile oxides (see **21-23**), and to electron-deficient nitrile oxide (see **24** and **25**). The yields of these cycloaddition reactions in general are very good with the exception of **24** and **25**. In addition to the medicinal significance of amide-substituted isoxazoles, The chiral amide-substituted isoxazoles prepared here should find applications as useful synthetic building blocks.[14,25]

2. Ynamide-[3 + 2] Cycloadditions with Ethyl α-Diazoacetate

With the success in achieving [3 + 2] cycloadditions with nitrile oxides, we investigated the synthesis of amide-substituted pyrazoles via [3 + 2] cycloadditions of ethyl α-diazoacetate. With Ready's beautiful work[17a] appearing recently using copper(I) iodide as the catalyst, we elected to pursue thermal version of

this cycloaddition. As shown in **Scheme 4**, by heating chiral ynamide **26** with ethyl α-diazoacetate at 110 °C for 18 h, pyrazole **28** was isolated in 43% yield as a single regioisomer. The generality of this cycloaddition should not be an issue as evident in the preparation of pyrazoles **29** in 52% yield from ynamide **27** under the same reaction conditions. However, instead of pursuing more examples, we became more interested in these new pyrazoles structurally.

Scheme 4. Cycloadditions of Ynamides with an α-Diazoacetate

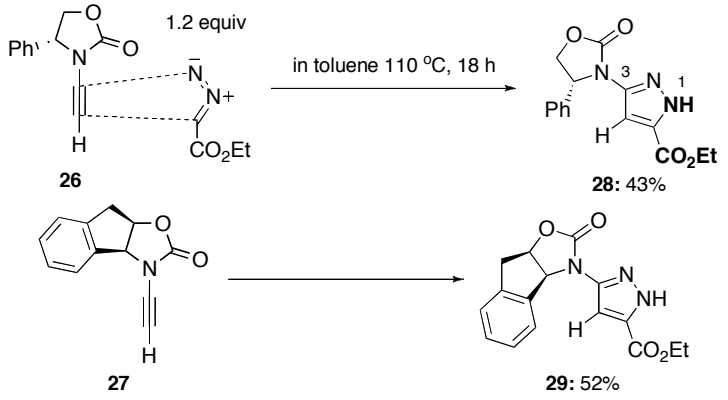
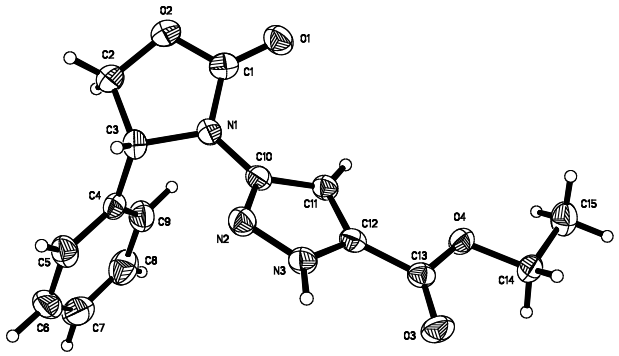


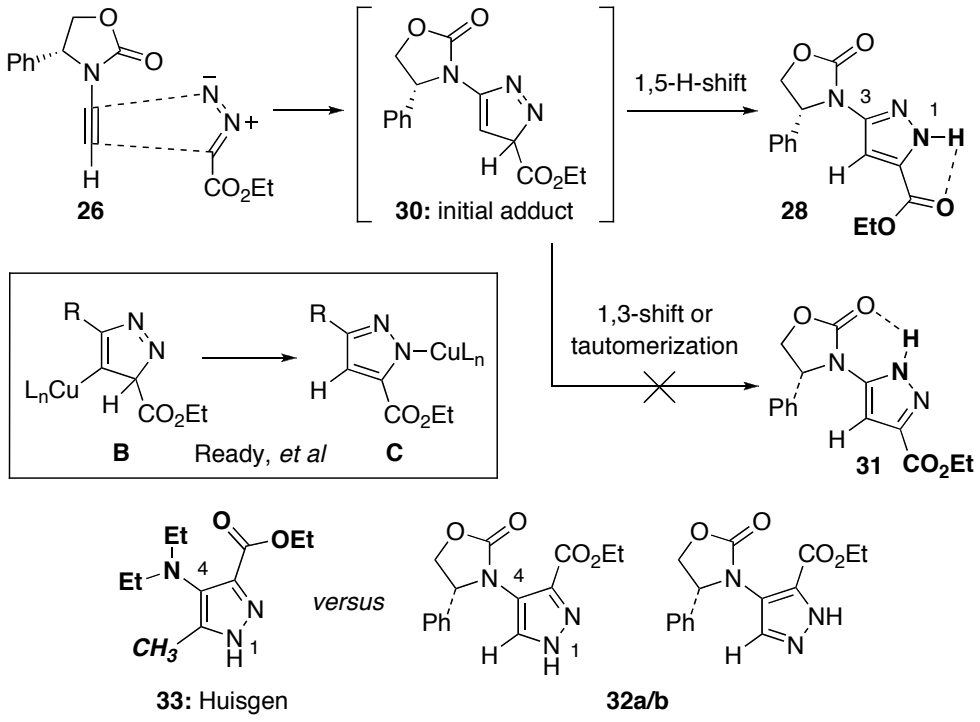
Figure 3. Single Crystal X-Ray Structure of Pyrazole **28**



As shown in **Figure 3**, the structural assignment for pyrazole **28**, based on its single crystal X-ray structure, clearly implies that there was an unusual tautomerization. Specifically, to arrive at pyrazole **28**, the initial cycloaddition intermediate **30** had to undergo a 1,5-hydrogen shift instead of 1,3-shift or tautomerization, leading to pyrazole **30** (**Scheme 5**). From the onset, there are no obvious structural elements that would bias one or the other, and both are capable of internal hydrogen bonding (see the dotted lines). Such a shift was also observed in Ready's work[17a] in their Cu(I)-catalyzed cycloadditions. The initial copper bond cycloaddition intermediate **B** also underwent the related shift en route to the same tautomer in which the NH group is adjacent to the ethoxycarbonyl group from the original α-diazoacetate.

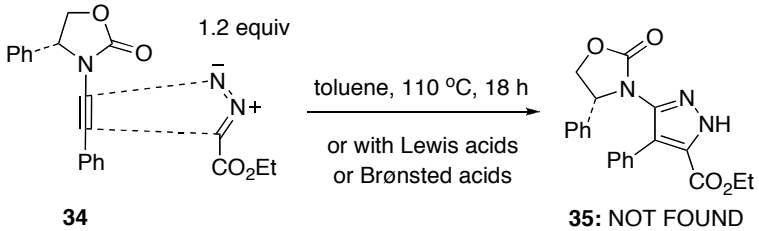
Li's elegant work[17b] in [3 + 2] cycloadditions of α-diazoacetates with alkynes using $InCl_3$ as the catalyst also revealed a similar shift of aryl and acyl groups.

Scheme 5. A Comparison of Regioselectivity

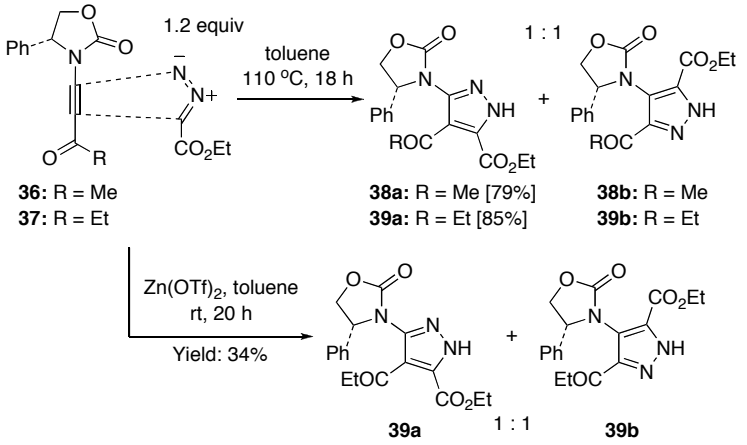


In addition to this tautomerization issue, while our regioselectivity is the same as Ready's Cu(I)-catalyzed cycloadditions, it is different from Huisgen's original work[20] using ynamines that provided pyrazole **33**. In our case, we do not see the related regioisomeric pyrazoles such as **32a/b** (the two possible tautomers) We attributed this difference to the fact that we used terminally unsubstituted ynamides, whereas Huisgen used a terminally substituted ynamine. Unfortunately, when we evaluated terminally substituted ynamides such as **34** (**Scheme 6**), we could not succeed in any of the cycloadditions using a range of conditions including Lewis and Brønsted acidic conditions.[26] This is in direct contrast to the Huisgen azide-[3 + 2] cycloaddition of ynamides in which we were able to effect the transformation for both terminally unsubstituted and substituted ynamides.[10]

Scheme 6. Cycloadditions of Terminally Substituted Ynamides



Scheme 7. [3 + 2] Cycloadditions of Push-Pull-Ynamides



Intriguingly, when we investigated cycloadditions of push-pull ynamides **36** and **37** with ethyl α-diazoacetate, we were able to isolate the respective trisubstituted pyrazoles in high yields (**Scheme 7**). In addition, we were able to use Lewis acids such as $Zn(OTf)_2$ (10 mol%) to promote the cycloaddition,[27] although the yield was lower. These cycloadditions did provide both possible regioisomers, thereby in part suggesting that terminally substituted ynamides can alter the regioselectivity, although these push-pull ynamides likely carry a different electronic profile. Like those amide-substituted isoxazoles shown in the previous section, the chiral amide-substituted pyrazoles prepared here should also find applications as useful synthetic building blocks.[14,28]

CONCLUSION

We have described here highly regioselective [3 + 2] cycloadditions of terminally unsubstituted ynamides with nitrile oxides and ethyl α-diazoacetate to synthesize 5-amide-substituted isoxazoles and 3-amide-substituted pyrazoles, respectively through Cu(I)-catalyzed and thermal conditions.

EXPERIMENTAL

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual $CHCl_3$ in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm

polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported. X-Ray analyses were performed at the X-Ray facility in University of Minnesota.

General Procedure for [3 + 2] Cycloadditions of Ynamides with Nitrile Oxides.

To a vial equipped with 1.0 equiv of terminal ynamide, 0.1 equiv of $CuSO_4$-$5H_2O$, 0.2 equiv of Na-ascorbate and 2.0 equiv of K_2CO_3 in *t*-BuOH/H_2O (1:1) solution was added 1.30 equiv of the respective α-chloro oxime. After the mixture was stirred for 12 h, and TLC showed that the starting ynamide was all consumed, the reaction mixture was poured into dilute aq NH_4Cl, and then extracted by EtOAc (3 x equal volume). The combined organic layers were washed with sat aq NaCl and dried over Na_2SO_4. Removal of solvent under reduced pressure gave crude isoxazole, which was purified via silica gel column flash chromatography with EtOAc/hexane as gradient eluent.

Characterizations of New Isoxazoles.

Isoxazole 11 [Yield: 85%]. R_f = 0.53 [50% EtOAc in hexanes]; mp 196-198 ºC; $[\alpha]_D^{20}$ -31.3 (*c* 4.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, 3 H, *J* = 6.5 Hz), 2.90 (s, 3 H), 4.08 (qd, 1 H, *J* = 6.5, 8.5 Hz), 5.41 (d, 1 H, *J* = 8.5 Hz), 6.68 (s, 1 H), 7.24 (d, 2 H, *J* = 6.5 Hz), 7.31-7.38 (m, 3 H), 7.42-7.46 (m, 3 H), 7.78-7.82 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 28.8, 55.9, 61.1, 84.6, 126.9, 127.5, 128.9, 129.0, 129.1, 129.6, 130.2, 135.8, 155.7, 162.4, 163.6; IR (film) cm^{-1} 2975w, 1717s, 1601s, 1581m, 1481w, 1446s, 1421s, 1303m, 1263s, 1120m, 1078m, 1010m; mass spectrum (MALDI): m/e (% relative intensity) 334.2 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{20}H_{20}N_3O_2$ 334.1550, found 334.1540.

Isoxazole 12 [Yield: 80%]. R_f = 0.52 [33% EtOAc in hexanes]; mp 169-171 ºC; $[\alpha]_D^{20}$ -63.3 (*c* 1.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (dd, 1 H, *J* = 4.4, 8.8 Hz), 4.84 (dd, 1 H, *J* = 8.8, 8.8 Hz), 5.53 (dd, 1 H, *J* = 4.4, 8.8 Hz), 6.65 (s, 1 H), 7.34-7.42 (m, 8 H), 7.72-7.75 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3, 71.3, 86.9, 126.4, 126.9, 129.0, 129.1, 129.6, 129.7, 130.5, 138.0, 153.2, 160.4, 163.8; IR (film) cm^{-1} 2852w, 1684s, 1542s, 1514m, 1415m, 1358m, 1229s, 1137s, 1101m, 1063m, 1041m; mass spectrum (MALDI): m/e (% relative intensity) 307.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{18}H_{15}N_2O_3$ 307.1077, found 307.1070.

Isoxazole 13 [Yield: 85%]. R_f = 0.67 [33% EtOAc in hexanes]; mp 157-159 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 5.00 (s, 2 H), 6.51 (s, 1 H), 7.30-7.38 (m, 5 H), 7.44-7.50 (m, 5 H), 7.73 (d, 2 H, *J*

= 8.0 Hz), 7.77-7.81 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 52.6, 93.3, 126.9, 127.6, 128.5, 128.8, 129.0, 129.1, 129.2, 130.3, 130.6, 135.2, 135.5, 145.2, 162.6, 163.9; IR (film) cm^{-1} 2924w, 1701m, 1596s, 1575s, 1495w, 1470m, 1456w, 1412m, 1360s, 1341m, 1291m, 1167s, 1085m, 1044m; mass spectrum (MALDI): m/e (% relative intensity) 405.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{23}H_{20}N_2O_3SNa$ 427.1087, found 427.1093.

Isoxazole 14 [Yield: 82%]. R_f = 0.36 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 4.38 (d, 2 H, *J* = 6.0 Hz), 5.21 (dd, 1 H, *J* = 1.0, 10.0 Hz), 5.32 (dd, 1 H, *J* = 1.0, 18.0 Hz), 5.81-5.90 (m, 1 H), 6.50 (s, 1 H), 7.29 (d, 2 H, *J* = 8.0 Hz), 7.43-7.46 (m, 3 H), 7.71 (d, 2 H, *J* = 8.0 Hz), 7.76-7.78 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 51.6, 92.7, 120.1, 126.9, 127.7, 129.1, 129.2, 130.3, 130.6, 131.8, 135.5, 145.2, 162.8, 164.0; IR (film) cm^{-1} 2361(m), 1597(s), 1576(s), 1475(w), 1445(w), 1408(m), 1362(s), 1166(s), 1089(m), 1049(m); mass spectrum (APCI): m/e (% relative intensity) 355.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_3SNa$ 377.0930, found 377.0942.

Isoxazole 15 [Yield: 22%]. R_f = 0.38 [15% EtOAc in hexanes]; mp 87-89 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3 H, *J* = 7.2 Hz), 4.32 (q, 2 H, *J* = 7.2 Hz), 6.70 (s, 1 H), 7.26-7.31 (m, 1 H), 7.35-7.43 (m, 2 H), 7.48-7.54 (m, 4 H), 7.74 (d, 1 H, *J* = 7.2 Hz), 7.88-7.90 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 61.5, 97.2, 111.6, 114.6, 123.0, 123.1, 127.0, 127.1, 127.2, 129.2, 129.3, 129.6, 130.6, 139.8, 160.6, 161.2, 163.9; IR (film) cm^{-1} 2361m, 1711s, 1632s, 1611w, 1582m, 1470m, 1264m, 1212m, 1180m, 1147m, 1032m; mass spectrum (APCI): m/e (% relative intensity) 333.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{20}H_{17}N_2O_3$ 333.1239, found 333.1238.

Isoxazole 16 [Yield: 24%]. R_f = 0.53 [50% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.14-3.18 (m, 2H), 4.00-4.04 (m, 2H), 6.11 (s, 1H), 7.01 (d, 1H, *J* = 2.4 Hz), 7.13 (td, 1H, *J* = 7.2, 1.2 Hz), 7.17 (td, 1H, *J* = 7.8, 1.6 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.43-7.46 (m, 3H), 7.67 (d, 3H, *J* = 8.4Hz), 7.76-7.78 (m, 2H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 25.8, 49.9, 92.5, 111.5, 111.8, 119.0, 19.9, 122.4, 122.8, 126.9, 127.5, 129.1, 129.2, 130.3, 130.6, 135.5, 136.5, 145.1, 163.0, 164.1 [missing 1 carbon due to overlap]; IR (film) cm^{-1} 3411w, 3057w, 2923w, 2854w, 2361w, 1774w, 1597m, 1567m, 1406m, 1165s; mass spectrum (APCI): m/e (% relative intensity) 458.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{26}H_{23}N_3O_3SNa$ 480.1352, found 480.1373.

Isoxazole 17 [Yield: 68%]. R_f = 0.19 [50% EtOAc in hexanes]; mp 150-156 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (quintet, 2H, *J* = 6.3 Hz), 2.56 (dd, 2H, *J* = 7.4, 5.7 Hz), 3.08 (t, 2H, *J* = 6.2 Hz), 3.88 (s, 3H), 6.31 (s, 1H), 6.75 (d, 1H, *J* = 3.4 Hz), 7.01 (dd, 2H, *J* = 8.9, 2.1 Hz), 7.07 (d, 1H, *J* = 3.4 Hz), 7.76 (d, 2H, *J* = 8.9, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 23.7, 37.8, 55.7, 89.1, 108.9, 114.8, 121.0,

121.5, 123.9, 128.5, 143.1, 161.4, 161.8, 163.7, 194.5; IR (film) cm^{-1} 2925m, 1738w, 1663s, 1615s, 1554m, 1531m, 1505w, 1478w, 1448m, 1434s, 1408m, 1351w, 1279s, 1256s, 1173m, 1151w, 1116w, 1101m, 1023m; mass spectrum (APCI): m/e (% relative intensity) 309.2 (100) $(M + H)^+$, 150.2 (10), 136.2 (30); HRMS (MALDI) calcd for $C_{18}H_{17}N_2O_3$ 309.1239, found 309.1247.

Isoxazole 18 [Yield: 86%]. R_f = 0.23 [25% EtOAc in hexanes]; mp 148-153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.83 (s, 3H), 4.91 (s, 2H), 6.38 (s, 1H), 6.93 (ddd, 2H, *J* = 9.6, 2.8, 2.8Hz), 7.26-7.32 (m, 5H), 7.39 (dd, 2H, *J* = 8.4, 2.0Hz), 7.64-7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 52.5, 55.6, 93.1, 114.5, 121.5, 127.6, 128.3, 128.4, 128.7, 128.9, 130.2, 135.2, 135.5, 145.1, 161.4, 162.3, 163.5; IR (film) cm^{-1} 3670w, 3055w, 2981m, 2887w, 2361w, 2341w, 1701w, 1597m, 1168s; mass spectrum (APCI): m/e (% relative intensity) 435.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{24}H_{23}N_2O_4S$ 435.1373, found 435.1391.

Isoxazole 19 [Yield: 83%]. R_f = 0.65 [50% EtOAc in hexanes]; mp 153-155 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.95 (s, 2H), 6.50 (s, 1H), 7.25 – 7.33 (m, 5H), 7.39 (ddd, 2H, *J* = 8.4, 2.0, 2.0 Hz), 7.67 (ddd, 2H, *J* = 8.4, 2.0, 2.0 Hz), 7.91 (ddd, 2H, *J* = 8.8, 2.0, 2.0 Hz) 8.29 (ddd, 2H, *J* = 8.8, 2.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 52.5, 92.8, 124.4, 127.5, 127.7, 128.5, 128.6, 129.0, 130.3, 134.9, 135.0, 135.3, 145.4, 149.0, 162.1, 163.6; IR (film) cm^{-1} 3652w, 3063w, 2981w, 2360w, 2341w, 1585m, 1496m, 1342s, 1168s; mass spectrum (APCI): m/e (% relative intensity) 450.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{23}H_{19}N_3O_5SNa$ 472.0938, found 472.0950.

Isoxazole 20 [Yield: 52%]. R_f = 0.08 [25% EtOAc in hexanes]; mp 100-104 ºC; $[\alpha]_D^{20}$ -19.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (dd, 1H, *J* = 8.8, 4.4Hz), 4.87 (t, 1H, *J* = 8.8Hz), 5.52 (dd, 1H, *J* = 8.8, 4.8Hz), 6.57 (s, 1H), 6.94 (d, 1H, *J* = 16.8Hz), 7.15 (d, 1H, *J* = 20.4Hz), 7.26-7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3, 71.3, 85.9, 115.9, 126.4, 127.1, 127.3, 129.1, 129.3, 129.6, 135.9, 137.0, 138.0, 153.2, 159.8, 163.3; IR (film) cm^{-1} 3035w, 2251w, 2155w, 1774s, 1604m, 1472m, 1453s, 1397m, 1205m; mass spectrum (APCI): m/e (% relative intensity) 333.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{20}H_{16}N_2O_3$ 332.1161, found 332.1150.

Isoxazole 21 [Yield: 61%]. R_f = 0.38 [50% EtOAc in hexanes]; mp 127-130 ºC; $[\alpha]_D^{20}$ -74.5 (*c* 1.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 4.37 (dd, 1H, *J* = 4.4, 8.8 Hz), 4.84 (t, 1H, *J* = 8.8 Hz), 5.48 (dd, 1H, *J* = 4.4, 8.8 Hz), 6.14 (s, 1H), 7.31-7.40 (m, 5H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 59.2, 71.2, 89.6, 126.4, 129.5, 129.6, 138.1, 153.2, 159.7, 161.7; IR (film) cm^{-1} 3529w, 3162w, 2362w, 1768s, 1607m, 1482m, 1504m, 1378s, 1207s; mass spectrum (APCI): m/e (% relative intensity) 245.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{13}H_{12}N_2O_3Na$ 267.0740, found 267.0742.

Isoxazole 22 [Yield: 34%]. R_f = 0.31 [25% EtOAc in hexanes]; mp 149-151 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.42 (s, 3H), 4.86 (s, 2H), 5.92 (s, 1H) 7.25 – 7.30 (m, 5H), 7.34 (dd, 2H, *J* = 8.0, 2.0Hz), 7.62 (ddd, 2H, *J* = 8.4, 2.0, 2.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 21.9, 52.4, 96.0, 127.6, 128.3, 128.6, 128.8, 130.2, 135.3, 135.5, 145.0, 161.8, 161.9; IR (film) cm^{-1} 3666w, 3132w, 3053w, 2361w, 1598m, 1373s, 1263m, 1164s; mass spectrum (APCI): m/e (% relative intensity) 343.1 (100) (M + H)$^+$; HRMS (MALDI) calcd for $C_{18}H_{18}N_2O_3SNa$ 365.0930, found 365.0933.

Isoxazole 23 [Yield: 55%]. R_f = 0.30 [25% EtOAc in hexanes]; $[\alpha]_D^{20}$ -58.1 (*c* 2.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ0.85-0.90 (m, 3H), 1.25-1.32 (m, 4H), 1.59-1.63 (m, 2H), 2.54 (t, 2H, *J* = 7.2 Hz), 4.36 (dd, 1H, *J* = 8.8, 4.4Hz), 4.86 (t, 1H, *J* = 8.8Hz), 5.48 (dd, 1H, *J* = 8.8, 4.4Hz), 6.16 (s, 1H), 7.32-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.5, 26.6, 27.8, 31.5, 59.2, 71.2, 88.4, 126.4, 129.5, 129.6, 138.2, 153.2, 159.6, 166.0; IR (neat) cm^{-1} 3159w, 2957w, 2930w, 2860w, 2360w, 2341w, 1774s, 1606s, 1497m, 1364s; mass spectrum (APCI): m/e (% relative intensity) 301.2 (100) (M + H)$^+$; HRMS (MALDI) calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366, found 323.1372.

Isoxazole 24 [Yield: 31%]. R_f = 0.59 [50% EtOAc in hexanes]; mp 71-74 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, 3H, *J* = 7.2 Hz), 2.43 (s, 3H), 4. 39 (q, 2H, *J* = 7.2 Hz), 4.91 (s, 2H), 6.48 (s, 1H), 7.27-7.34 (m, 7H) 7.63 (ddd, 2H, *J* = 8.4, 2.0, 2.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.9, 52.6, 62.5, 95.4, 127.6, 128.6, 128.7, 129.0, 130.3, 134.7, 135.1, 145.5, 157.8, 159.7, 163.8; IR (film) cm^{-1} 3657w, 3157w, 2980m, 2886w, 2361w, 1733m, 1585m, 1496m, 1253m, 1187s; mass spectrum (APCI): m/e (% relative intensity) 401.1 (100) (M + H)$^+$; HRMS (MALDI) calcd for $C_{20}H_{20}N_2O_5SNa$ 423.0985, found 423.1000.

Isoxazole 25 [Yield: 34%]. R_f = 0.12 [25% EtOAc in hexanes]; mp 69-78 ºC; $[\alpha]_D^{20}$ -70.2 (*c* 2.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J* = 6.0Hz), 4.38 (dq, 2H, *J* = 6.0, 1.6Hz), 4.43 (dd, 1H, *J* = 7.2, 3.6Hz), 4.90 (t, 1H, *J* = 7.2Hz), 5.54 (dd, 1H, *J* = 6.8, 3.6Hz), 6.68 (s, 1H), 7.33-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 57.7, 63.1, 70.7, 89.5, 126.3, 129.2, 129.5, 137.4, 152.8, 157.7, 159.7, 161.5; IR (film) cm^{-1} 2985w, 2360w, 2340w, 1782s, 1737m, 1604m, 1480m, 1397m, 1366w; mass spectrum (APCI): m/e (% relative intensity) 303.1 (100) (M + H)$^+$; HRMS (MALDI) calcd for $C_{15}H_{14}N_2O_5Na$ 325.0795, found 325.0798.

General Procedure for [3 + 2] Cycloadditions of Ynamides with α-Diazo-Acetate.

To a solution of ynamide **26** (50.0 mg, 0.27 mmol) in toluene (2.0 mL) was added ethyl α-diazoacetate (0.037 mL, 0.32 mmol). The reaction was heated to 110 ºC in a sealed vial and stirred for 18 h. The solvent was then removed under reduced pressure and the resulting oil was purified via silica gel column

flash chromatography (gradient eluent: 30-50% EtOAc in hexanes) to afford the pyrazole **28** (35.0 mg, 43%) as a white solid.

Characterizations of New Pyrazoles.

Pyrazole 28 [Yield: 43%]. R_f = 0.29 [40% EtOAc in hexanes]; mp 147-149 ºC; $[\alpha]_D^{20}$ -89.0 (*c* 6.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3 H, *J* = 7.2 Hz), 4.25 (dd, 1 H, *J* = 4.8, 8.8 Hz), 4.31 (q, 2 H, *J* = 7.2 Hz), 4.76 (dd, 1 H, *J* = 8.8, 8.8 H), 5.53 (dd, 1 H, *J* = 4.8, 8.8 Hz), 7.10 (brs, 1 H), 7.24-7.33 (m, 5 H), 11.57 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 59.1, 61.5, 70.7, 99.0, 125.9, 128.5, 129.0, 135.3, 138.7, 146.5, 155.1, 159.5; IR (film) cm^{-1} 1764s, 1725s, 1511m, 1120w, 1156w; mass spectrum (APCI): m/e (% relative intensity) 302.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{15}H_{15}N_3O_4Na$ 324.0955, found 324.0959.

Pyrazole 29 [Yield: 52%]. R_f = 0.49 [40% EtOAc in hexanes]; mp 165-167 ºC; $[\alpha]_D^{20}$ 283 (*c* 2.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, 3 H, *J* = 7.2 Hz), 3.40 (d, 2 H, *J* = 3.6 Hz), 4.39 (q, 2 H, *J* = 7.2 Hz), 5.39-5.44 (m, 1 H), 5.99 (d, 1 H, *J* = 7.6 Hz), 7.15 (dd, 1 H, *J* = 7.6, 7.6 Hz), 7.22 (s, 1 H), 7.25-7.33 (m, 2 H), 7.63 (d, 1 H, *J* = 7.6 Hz), 10.26 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 38.5, 62.0, 64.4, 78.9, 99.2, 125.6, 126.9, 127.9, 129.9, 135.4, 139.0, 140.3, 147.6, 154.5, 159.9; IR (film) cm^{-1} 1721s, 1509m, 1420w, 1173m, 1152m; mass spectrum (APCI): m/e (% relative intensity) 314.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{16}H_{15}N_3O_4Na$ 336.0955, found 336.0961.

Pyrazole 38a/b [Yield: 79%]. R_f = 0.18 [40% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) **38a**: δ 1.43 (t, 3 H, *J* = 7.5 Hz), 2.53 (s, 3 H), 4.34-4.46 (m, 3 H), 4.88 (dd, 1 H, *J* = 8.5, 9.0 Hz), 5.81 (dd, 1 H, *J* = 8.5, 9.0 Hz), 7.24-7.40 (m, 5 H), 11.40 (brs, 1 H); **38b**: δ 1.36 (t, 3 H, *J* = 7.5 Hz), 2.55 (brs, 3 H), 4.26 (dd, 1 H, *J* = 7.5, 8.5 Hz), 4.34-4.46 (m, 2 H), 4.83 (dd, 1 H, *J* = 8.5, 9.0 Hz), 5.59 (dd, 1 H, *J* = 7.5, 8.5 Hz), 7.24-7.40 (m, 5 H), 11.40 (brs, 1 H); IR (film) cm^{-1} 1723m, 1687s, 1465m, 1395m; mass spectrum (APCI): m/e (% relative intensity) 344.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{17}H_{17}N_3O_5Na$ 366.1060, found 366.1063.

Pyrazole 39a/b [Yield: 85%]. R_f = 0.20 [40% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) **39a**: δ 1.14 (t, 3 H, *J* = 7.0 Hz), 1.41 (t, 3 H, *J* = 7.5 Hz), 2.95 (q, 2 H, *J* = 7.0 Hz); 4.30-4.44 (m, 3 H), 4.87 (dd, 1 H, *J* = 8.5, 9.0 Hz), 5.81 (dd, 1 H, *J* = 8.5, 8.5 Hz), 7.22-7.42 (m, 5 H), 11.50 (brs, 1 H); **39b**: δ 1.14 (t, 3 H, *J* = 7.0 Hz), 1.33 (t, 3 H, *J* = 7.0 Hz), 3.01 (q, 1 H, *J* = 7.0 Hz), 3.05 (q, 1 H, *J* = 7.0 Hz), 4.23 (dd, 1 H, *J* = 8.0, 8.5 Hz), 4.30-4.44 (m, 2 H), 4.81 (dd, 1 H, *J* = 8.5, 9.0 Hz), 5.59 (dd, 1 H, *J* = 8.0, 9.0 Hz), 7.22-7.42 (m, 5 H), 11.50 (brs, 1 H); IR (film) cm^{-1} 1725m, 1688s, 1459m, 1399m; mass spectrum (APCI): m/e (% relative intensity) 358.1 (100) $(M + H)^+$; HRMS (MALDI) calcd for $C_{17}H_{17}N_3O_5Na$

380.1217, found 380.1217.

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