Tetrahedron 68 (2012) 807–812

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective conversion of alkynes to 4-substituted and 3,4-disubstituted isoxazoles using titanium-catalyzed multicomponent coupling reactions

Amila A. Dissanayake, Aaron L. Odom *

Michigan State University, Department of Chemistry, East Lansing, MI 48824, USA

ARTICLE INFO

Article history:
Received 29 August 2011
Received in revised form 12 November 2011
Accepted 15 November 2011
Available online 19 November 2011

Keywords:
Heterocycles
Isoxazoles
Multicomponent coupling
Titanium
Alkyne

ABSTRACT

Conditions have been developed for the regioselective synthesis of 4-substituted isoxazoles from terminal alkynes and 3,4-disubstituted isoxazoles from internal alkynes. The methodology involves a one-pot titanium-catalyzed multicomponent coupling reaction followed by simple hydroxylamine hydrochloride addition.

1. Introduction

Isoxazoles are heterocyclic frameworks of some importance in a large variety of applications including pharmaceuticals, herbicides, and pesticides.[1] Pharmaceutical examples, which are quite varied, include Leflunomide (arthritis),[2] Cloxacillin (antibiotic),[3] and NVP-AUY922 (anticancer).[4] Isoxazoles can also be converted to other compounds of potential utility in organic chemistry, e.g., *Z*-β-siloxyacrylonitriles.[5]

In previous research, we have investigated the use of a titanium-catalyzed 3-component coupling (3CC) reaction[6] for the synthesis of unsymmetrical 1,3-diimine tautomers.[7–9] The reaction involves readily-prepared titanium catalysts that couple an alkyne, isonitrile, and primary amine; in these processes, new C–C and C–N bonds are formed in a single catalytic step.

One-pot procedures are being developed that utilize these titanium-catalyzed 3CC reactions in conjunction with addition of other reagents to generate a variety of different heterocyclic frameworks, such as pyrimidines,[10] quinolines,[11] and pyrazoles.[12]

Here, we describe the use of these catalyzed 3CC reactions in conjunction with hydroxylamine addition to produce isoxazoles. Conditions for the regioselective cyclization have been developed that allow formation and ready isolation of 4-substituted and 3,4-disubstituted isoxazoles.[13]

2. Results and discussion

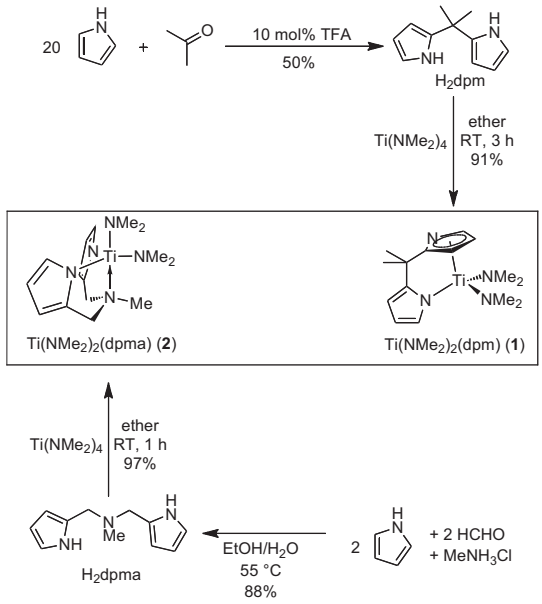
The titanium catalysts for these reactions use pyrrolyl-based ancillary ligands prepared in a single step (Scheme 1). A double Mannich reaction between methylamine hydrochloride, formaldehyde (formalin), and pyrrole generates *N*,*N*-di(methyl-α-pyrrolyl)-*N*-methylamine (H_2dpma).[14] The other ancillary commonly employed, 5,5-dimethyldipyrrolylmethane (H_2dpm), is prepared from acid-catalyzed condensation of pyrrole and acetone.[15]

Addition of the *NH*-pyrrole compounds H_2dpm and H_2dpma to commercially available $Ti(NMe_2)_4$ generates the catalysts in high yield (Scheme 1). For this work, two different catalysts were employed. For most of the reactions, the milder catalyst with the tridentate ancillary, $Ti(dpma)(NMe_2)_2$ (**2**),[16] was found to be optimal. In a few cases, more reactive $Ti(dpm)(NMe_2)_2$ (**1**)[17] gave higher conversions, especially with more sterically hindered (internal) alkynes.

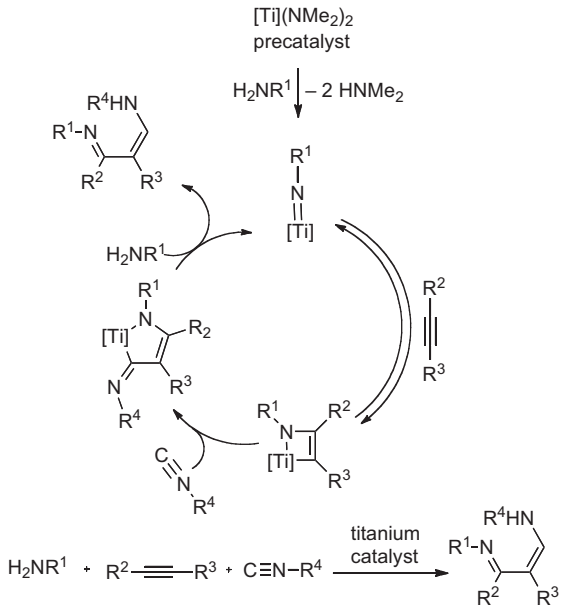
In Scheme 2 is the proposed mechanism for the 3CC,[18,6] which has been dubbed alkyne iminoamination because the overall transformation involves addition of an iminyl group and amine across the C–C triple bond.[19] The proposed pathway involves the addition of the primary amine to the titanium precatalyst forming an imido with liberation of dimethylamine. Titanium imido complexes can undergo [2+2]-cycloaddition with alkynes to produce azatitanacyclobutenes. The C–C bond in metallacycles of this type are known to 1,1-insert isonitriles to give the five-membered metallacycle. Protolysis of the Ti–C and Ti–N bonds in the metallacycle with primary amine liberates the iminoamination product from the metal and regenerates the titanium imido species.[20]

* Corresponding author. Tel.: +1 517 355 9715x171; fax: +1 517 353 1793; e-mail address: odom@chemistry.msu.edu (A.L. Odom).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.11.043



Scheme 1. Synthesis of catalysts **1** and **2**.



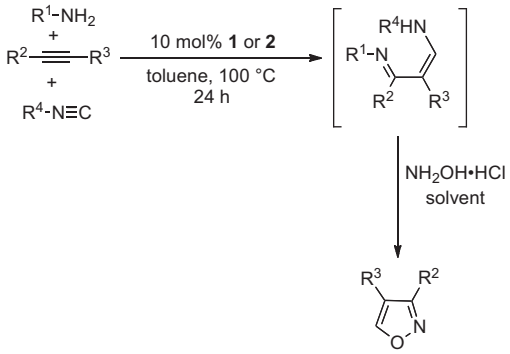
Scheme 2. Proposed catalytic cycle for alkyne iminoamination and the overall transformation (bottom).

The choice of amine is flexible, but good results were obtained when using cyclohexylamine with catalyst **2** and aniline with catalyst **1**.

The general strategy for the one-pot synthesis of isoxazoles used here is shown in Scheme 3. The 3CC reaction is commonly done at 100 °C in toluene. The products of iminoamination can be converted to isoxazoles by addition of $H_2NOH{\cdot}HCl$ and a more polar solvent.

The one-pot synthesis of 4-substituted isoxazoles was readily accomplished using the procedure in Scheme 3 where R^2=H. The added solvent for the cyclization step involving hydroxylamine hydrochloride was ethanol in this case.

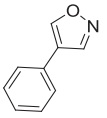
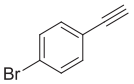
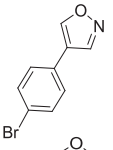
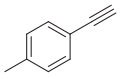
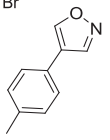
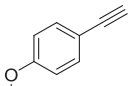
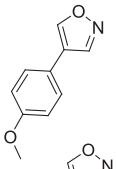
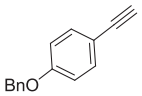
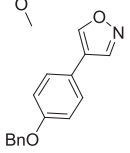
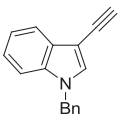
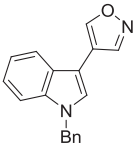
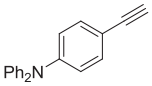
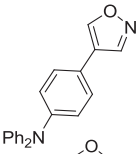
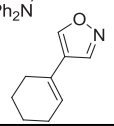
The reaction, for reasons currently unknown, was limited to vinyl-, heterocycle-, and aryl-substituted terminal alkynes. With alkyl-containing terminal alkynes, e.g., 1-hexyne, the 3-CC reaction works well; however, the addition of hydroxylamine under any conditions we investigated did not result in formation of the alkyl-



Scheme 3. General scheme for the synthesis of isoxazoles.

substituted isoxazoles. A listing of the 4-substituted isoxazoles prepared during this study is shown in Table 1.

Table 1
Examples of 4-aryl isoxazoles prepared[a]

Entry	Alkyne	Catalyst	Product	Isolated yield (%)
a		**2**		35[b]
b		**2**		55[b]
c		**2**		51[b]
d		**2**		48[b]
e		**2**		57[b]
f		**1**		50[c]
g		**2**		48[b]
h		**2**		60[b]

[a] Reaction conditions: cyclohexylamine or aniline (1 mmol), *tert*-butylisonitrile (1.5 mmol), alkyne (1 mmol), **1** or **2** (0.1 mmol), 2 mL toluene, 24 h, 100 °C. Then, $H_2NOH{\cdot}HCl$ (1.2 mmol) in 2 mL absolute ethanol was added, and the solution was stirred for 16 h at room temperature.

[b] Catalyst **2** and cyclohexylamine were used.

[c] Catalyst **1** and aniline were used.

The multicomponent coupling reaction is quite sensitive to the size of the alkynes. As a consequence, terminal alkynes react more readily, and the less reactive catalyst **1** can be employed.[21]

For these terminal alkynes, the regioselectivity of the 3-component coupling product is extremely good. The regioselectivity for the [2+2]-cycloaddition between the alkyne and titanium imido (Scheme 2) that goes onto product[22] favors having the aromatic group adjacent to titanium in the metallacyclobutene intermediate, which may be due to stabilization of the partial negative charge on the carbon connected to titanium by the aromatic group. The result is a single observed isomer from the multicomponent coupling reaction. From the observed isomer, the addition of hydroxylamine can only result in a single regioisomer for monosubstituted aromatic alkynes.

The only terminal alkyne not giving good regioselectivity with **2** as catalyst was 3-alkynylindole (Table 1, entry f), which gave a mixture of two regioisomers. However, the reaction with catalyst **1** did provide single observed regioisomer.

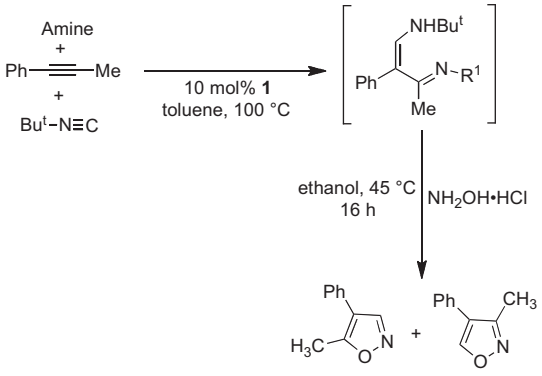
For internal alkynes, the iminoamination reaction typically gives a single product for the substrates investigated; however, regioselectivity of the hydroxylamine cyclization reaction often gave mixtures using the conditions described above for terminal alkynes.

We explored changing the amine (R^1) substituent as a method of controlling the 3,4- to 4,5-isomer ratio of isoxazole products obtained. Using 1-phenylpropyne as the test system, we investigated the effect of aniline substituents on the isomer ratio. The results of those studies are shown in Table 2. Ethanol was used as the solvent here as before, and the reactions were heated slightly as the cyclizations were somewhat slower than with terminal alkynes.

While most substitutions on the aniline ring had little consequence on the isomer ratios and there is no clear electronic effect, one of the aniline derivatives did significantly improve the regioselectivity, 3,5-dichloroaniline (Table 2, entry e).

Further optimization was undertaken through examining solvent effects on the isomer ratio. Those results are summarized in Table 3. As shown, the use of THF with 3,5-dichloroaniline as the amine substrate provided a single isomer, the 3,4-disubstituted

Table 2
Effect of R^1 on the isomer ratio in the synthesis of 4-phenyl-3-methylisoxazole



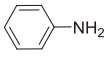
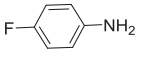
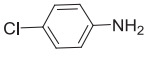
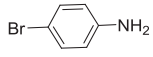
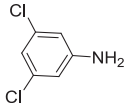
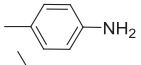
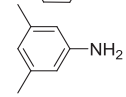
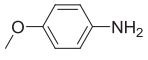
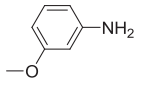
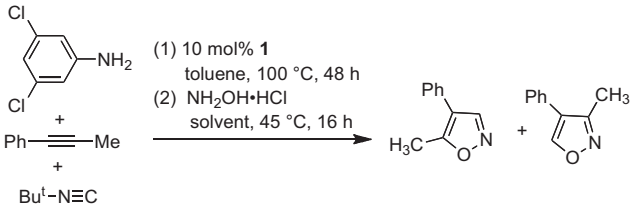
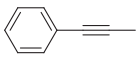
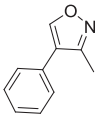
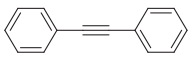
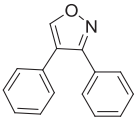
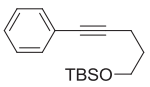
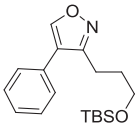
Entry	Amine	Isomer ratio
a		1.0:1.8
b		1.0:1.1
c		1.0:2.3
d		1.0:1.8
e		1.0:8.0
f		1.0:1.5
g		1.0:1.1
h		1.0:1.5
i		1.0:1.4

Table 3
Solvent effects on the isomer ratio in the synthesis of 4-phenyl-3-methylisoxazole



Entry	Solvent	Isomer ratio
a	EtOH	1.0:8.0
b	EtOAc	1.0:5.2
c	DMF	1.0:4.6
d	THF	1.0:>50
e	1,4-Dioxane	1.0:3.1
f	*N*,*N*-Dimethylacetamide	1.0:4.0
g	DMSO	1.0:5.3

Table 4
The 3,4-disubstituted isoxazoles prepared during this study[a]

Entry	Alkyne	Catalyst	Product	Isolated yield (%)
a		**1**		35
b		**1**		25
c		**1**		30

[a] Reaction conditions: 3,5-dichloroaniline (1 mmol), *tert*-butylisonitrile (1.5 mmol), alkyne (1 mmol), **1** (0.1 mmol), 2 mL toluene, 24 h, 100 °C. Then, $H_2NOH{\cdot}HCl$ (1.2 mmol) in 2 mL THF was added, and the solution was stirred for 16 h at 45 °C.

isoxazole, which was by far the best result of the seven solvents investigated.

Products derived from a few internal alkynes were isolated during the course of the study using the conditions found (Table 4). The yields are ~30% from the one-pot reaction, but the other isomer is not an observable impurity. The products were readily isolated in pure form by column chromatography.

3. Conclusions

The route described here compares favorably with other known routes to this class of compounds. For example, the product in Table 4 (entry a), 3-methyl-4-phenylisoxazole was isolated in 35% yield using the methodology described here in a two-step, one-pot procedure from commercially available 1-phenylpropyne.

This compound has been previously described in the literature. It is available from a four step synthesis starting with 3-methyl-4-phenyl-5(4*H*)-isoxazone, which doesn't appear to be commercially available, in 33% overall yield.[23] The compound is also accessible using 1,3-dipolar cycloaddition between 1-phenyl-1-trimethylsiloxyethylene and acetonitrile oxide in 54% yield where the compound was isolated by TLC.[24,25]

In summary, using a one-pot titanium-catalyzed multicomponent coupling route, it is possible to readily access a large number of 4-substituted and 3,4-disubstituted isoxazoles in a regioselective manner. The products are easily isolated in pure form after the one-pot syntheses.

4. Experimental section

4.1. General considerations

All manipulations of air sensitive compounds were carried out in an MBraun dry box under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and removing water by running through activated alumina systems purchased from Solv-Tek. ^1H and ^{13}C spectra were recorded on VXR-500 spectrometers. Melting points were measured on a Mel-Temp II apparatus with a mercury thermometer and are uncalibrated. $Ti(NMe_2)_2(dpm)$ (**1**) and $Ti(NMe_2)_2(dpma)$ (**2**) were made following the literature procedures. Alkynes were purchased either from Aldrich or from GFS chemicals and were distilled from CaO under dry nitrogen. Amines were purchased from Aldrich, dried over KOH, and distilled under dry nitrogen. *tert*-Butylisonitrile was made according to the literature procedure[26] and purified by distillation under nitrogen. Hydroxylamine hydrochloride was purchased from Columbus Chemical Industries, and neutral alumina was purchased Sigma–Aldrich Co and used as received. EtOH, CH_2Cl_2, hexanes, and EtOAc were purchased from Mallinckrodt chemicals and used as received.

4.2. General procedure for isoxazole synthesis

In an N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stir bar was loaded with amine (1 mmol), catalyst (10–20 mol %), alkyne (1 mmol), isonitrile (1.5 mmol), and 2 mL of dry toluene. While many different amines can be employed, the two amines most commonly used were cyclohexylamine (with catalyst **2**) and aniline (with catalyst **1**). For internal alkynes, the more active catalyst, **1**, was used with 3,5-dichloroaniline. The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated at the temperature listed for either 24 h (terminal alkynes) or 48 h (internal alkynes) with stirring. After completion of the reaction (checked by GC-FID), the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (1.2 mmol) and a second solvent (2 mL). The cyclization reactions were carried out at either 25 °C in ethanol (terminal alkynes) or 45 °C in THF (internal alkynes) for 16 h. After completion, volatiles were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by column chromatography as described for the individual compounds below.

4.2.1. 4-Phenylisoxazole (Table 1, entry a). The general procedure was followed. The reaction vessel was loaded with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (51 mg, 35%) as a white solid. Mp: 44–45 °C (lit.[27] mp: 44–46). ^1H NMR ($CDCl_3$, 500 MHz): 7.27–7.34 (1H, m, Ar–H), 7.39–7.42 (2H, m, Ar–H), 7.46–7.48 (2H, m, Ar–H), 8.55 (1H, s, 3-CH isoxazole), 8.66 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 121.3, 126.3, 128.0, 128.4, 129.1, 147.9, 153.3. MS(EI): *m*/*z* 145 (M^+). Elemental Analysis: found: %C, 74.85; %H, 4.52; %N, 9.71; expected: %C, 74.47; %H, 4.86; %N, 9.65.

4.2.2. 4-(4-Bromophenyl)isoxazole (Table 1, entry b). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), 1-bromo-4-ethynylbenzene (181 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9.5:0.5, which afforded the desired compound (123 mg, 55%) as a yellow solid. Mp: 111–113 °C (lit.[28] mp: 113). ^1H NMR ($CDCl_3$, 500 MHz): 7.32–7.34 (2H, d, 11 Hz, Ar–H), 7.51–7.53 (2H, d, 11 Hz, Ar–H), 8.51 (1H, s, 3-CH isoxazole), 8.65 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 120.4, 121.9, 127.4, 127.9, 132.3, 147.7, 153.5. MS(EI): *m*/*z* 224 (M^+). Elemental Analysis: found: %C, 47.93; %H, 2.59; %N, 6.34; expected: %C, 48.25; %H, 2.70; %N, 6.25.

4.2.3. 4-p-Tolylisoxazole (Table 1, entry c). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), 1-ethynyl-4-methylbenzene (116 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (81 mg, 51%) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): 2.36 (3H, s, CH_3), 7.20–7.22 (2H, d,

8 Hz, Ar–H), 7.34–7.36 (2H, d, 8 Hz, Ar–H), 8.52 (1H, s, 3-CH isoxazole), 8.62 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 21.2, 121.3, 125.5, 126.3, 129.8, 138.0, 148.0, 153.0. MS(EI): *m*/*z* 159 (M^+). Elemental Analysis: found: %C, 74.98; %H, 5.88; %N, 8.66; expected: %C, 75.45; %H, 5.70; %N, 8.80.

4.2.4. 4-(4-Methoxyphenyl)isoxazole (Table 1, entry d). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), 1-ethynyl-4-methoxybenzene (132 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (81 mg, 51%) as a yellow solid. Mp: 40–42 °C (lit.[29] mp: 40). ^1H NMR ($CDCl_3$, 500 MHz): 3.82 (3H, s, CH_3), 6.93–6.94 (2H, d, 8.5 Hz, Ar–H), 7.37–7.39 (2H, d, 8.5 Hz, Ar–H), 8.49 (1H, s, 3-CH isoxazole), 8.57 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 55.4, 114.6, 127.7, 128.4, 129.6, 148.0, 152.5, 159.5. MS(EI): *m*/*z* 175 (M^+). Elemental Analysis: found: %C, 67.98; %H, 5.33; %N, 8.13; expected: %C, 68.56, %H, 5.18, %N, 8.00.

4.2.5. 4-(4-(Benzyloxy)phenyl)isoxazole (Table 1, entry e). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), 1-(benzyloxy)-4-ethynylbenzene (208 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the pressure tube was cooled to room temperature. Then the same tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9.5:0.5, which afforded the desired compound (143 mg, 57%) as a light brown solid. Mp: 110–112 °C. ^1H NMR ($CDCl_3$, 500 MHz): 5.09 (2H, s, CH_2), 7.00–7.01 (2H, d, 6.5 Hz, Ar–H), 7.32–7.34 (1H, d, 6.5 Hz, Ar–H), 7.37–7.44 (6H, m, Ar–H) 8.45 (1H, s, 3-CH isoxazole), 8.57 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 70.1, 115.5, 121.0, 121.2, 127.4, 127.7, 128.1, 128.6, 136.6, 148.0, 152.6, 158.6. MS(EI): *m*/*z* 251 (M^+). Elemental Analysis: found: %C, 76.12; %H, 5.01; %N, 5.72; expected: %C, 76.48; %H, 5.21; %N, 5.57.

4.2.6. 4-(1-Benzyl-1H-indol-3-yl)isoxazole (Table 1, entry f). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), aniline (93 mg, 1 mmol), 1-benzyl-3-ethynyl-1*H*-indole (231 mg, 1 mmol) and **1** (30.8 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 8:2, which afforded the desired compound (137 mg, 50%) as a light brown solid. Mp: 128–130 °C. ^1H NMR ($CDCl_3$, 500 MHz): 5.28 (2H, s, CH_2) 7.08–7.10 (2H, d, 7 Hz, Ar–H), 7.14–7.29 (8H, m, Ar–H), 7.63–7.65 (2H, d, 9.5 Hz, Ar–H) 8.49 (1H, s, 3-CH isoxazole), 8.65 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 50.2, 100.2, 119.4, 120.5, 122.7, 125.9, 126.9, 127.9, 128.9, 136.8, 148.8, 152.1. MS(EI): *m*/*z* 274 (M^+). Elemental Analysis: found: %C, 78.64; %H, 5.22; %N, 10.32; expected: %C, 78.81; %H, 5.14; %N, 10.21.

4.2.7. 4-(Isoxazol-4-yl)-N,N-diphenylaniline (Table 1, entry g). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), 4-ethynyl-*N*,*N*-diphenylaniline (269 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9.5:0.5, which afforded the desired compound (143 mg, 48%) as a white solid. Mp: 144–146 °C. ^1H NMR ($CDCl_3$, 500 MHz) 6.97–6.99 (2H, t, 7 Hz, Ar–H), 7.02–7.05 (6H, m, Ar–H), 7.18–7.22 (4H, m, Ar–H), 7.25–7.27 (2H. d, 9 Hz, Ar–H) 8.44 (1H, s, 3-CH isoxazole), 8.54 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 121.1, 122.1, 123.3, 123.7, 124.6, 127.2, 129.4, 147.4, 147.8, 147.9, 152.7. MS(EI): *m*/*z* 312 (M^+). Elemental Analysis: found: %C, 80.82; %H, 5.24; %N, 8.82; expected: %C, 80.75; %H, 5.16; %N, 8.97.

4.2.8. 4-(Cyclohex-1-enyl)isoxazole (Table 1, entry h). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), cyclohexylamine (95 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and **2** (32.4 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. After completion of the reaction the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL) and stirred at room temperature for 16 h. After completion of the reaction, solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9.5:0.5, which afforded the desired compound (143 mg, 57%) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): 1.60–1.64 (2H, m, CH_2), 1.68–1.73 (2H, m, CH_2), 2.12–2.15 (2H, m, CH_2), 2.20–2.23 (2H, m, CH_2), 6.02–6.04 (1H, m, C*H*), 8.24 (1H, s, 3-CH isoxazole), 8.33 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.0, 22.3, 25.2, 27.3, 122.9, 125.2, 125.3, 146.8, 151.4. MS(EI): *m*/*z* 149 (M^+). Elemental Analysis: found: %C, 72.33; %H, 7.29; %N, 9.24; expected: %C, 72.46; %H, 7.43; %N, 9.39.

4.2.9. 3-Methyl-4-phenylisoxazole (Table 4, entry a). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), 3,5-dichloroaniline (162 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and **1** (30.8 mg, 0.1 mmol) in toluene (2 mL) with heating for 48 h at 100 °C. The pressure tube was cooled to room temperature. The reaction tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and tetrahydrofuran (2 mL) then stirred at 45 °C for 16 h. Solvents were removed in vacuo, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (55 mg, 35%) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): 2.56 (3H, s, CH_3), 7.32–7.34 (1H, d, Ar–H), 7.35–7.37 (2H, m, Ar–H), 7.40–7.44 (2H, m, Ar–H), 8.34 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR

($CDCl_3$, 125 MHz): 31.0, 126.0, 126.7, 127.4, 127.9, 129.1, 130.1, 150.2. MS(EI): *m*/*z* 159 (M^+). Elemental Analysis: found: %C, 75.28; %H, 5.59; %N, 8.92; expected: %C, 75.45; %H, 5.70; %N, 8.80.

4.2.10. 3,4-Diphenylisoxazole (Table 4, entry b). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), 3,5-dichloroaniline (162 mg, 1 mmol), diphenylacetylene (178 mg, 1 mmol), and **1** (30.8 mg, 0.1 mmol) in toluene (2 mL) with heating for 48 h at 100 °C. The pressure tube was cooled to room temperature. Then, the reaction tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and THF (2 mL) then stirred at 45 °C for 16 h. Solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (55 mg, 25%) as a yellow solid. Mp: 90–92 °C (lit.[30] mp: 91 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): 7.35–7.40 (8H, m, Ar–H), 7.61–7.62 (1H, m, Ar–H), 7.62–7.64 (1H, m, Ar–H), 8.35 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 116.2, 127.2, 127.6, 128.0, 128.3, 128.6, 128.7, 129.0, 130.0, 131.6, 151.9, 164.0. MS(EI): *m*/*z* 221 (M^+). Elemental Analysis: found: %C, 81.29; %H, 5.13; %N, 6.42; expected: %C, 81.43; %H, 5.01; %N, 6.33.

4.2.11. 3-(3-(tert-Butyldimethylsilyloxy)propyl)-4-phenylisoxazole (Table 4, entry c). The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (171 μL, 1.5 mmol), 3,5-dichloroaniline (162 mg, 1 mmol), *tert*-butyldimethyl(5-phenylpent-4-ynyloxy)silane (274 mg, 1 mmol), and **1** (30.8 mg, 0.1 mmol) in toluene (2 mL) with heating for 48 h at 100 °C. The pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and THF (2 mL) then stirred at 45 °C for 16 h. Solvents were removed in vacuo, and the crude product was dissolved in CH_2Cl_2 (20 mL) then washed with water (50 mL). Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 19:1, which afforded the desired compound (95 mg, 30%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.059 (6H, s, Si–CH_3), 0.85 (9H, s, Si–CMe_2CH_3), 1.94–1.98 (2H, m, $CH_2CH_2CH_2$OTBS), 2.99–3.02 (2H, m, $CH_2CH_2CH_2$OTBS), 3.64–3.66 (2H, m, $CH_2CH_2CH_2$OTBS), 7.31–7.32 (1H, m, Ar–H), 7.32–7.42 (4H, m, Ar–H), 8.33 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 1.0, 22.4, 25.9, 30.6, 35.7, 61.7, 127.4, 127.6, 128.2, 128.9, 131.5, 150.3, 167.8. Elemental Analysis: found: %C, 67.94; %H, 8.42; %N, 4.52; expected: %C, 68.09; %H, 8.57; %N, 4.41.

Acknowledgements

The authors thank the National Science Foundation (CHE-1012537) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.043.

References and notes

1. (a) Grünanger, P.; Vita-Finzi, P. Isoxazoles In *The Chemistry of Heterocyclic Compounds*; John Wiley: New York, NY, 1991; (b) Wakefield, B. J. *Sci. Synth.* **2001**, *11*, 229; (c) Zhou, Y.; Chen, Y.; Miao, W.; Qu, J. *J. Heterocycl. Chem.* **2010**, *47*, 1310.
2. For a recent review see Behrens, F.; Koehm, M.; Burkhardt, H. *Curr. Opin. Rheumatol.* **2011**, *23*, 282.
3. For a recent study see Peter-Getzlaff, S.; Polsfuss, S.; Poledica, M.; Hombach, M.; Giger, J.; Gottger, E. C.; Zbinden, R.; Bloemberg, G. V. *J. Clin. Microbiol.* **2011**, *49*, 2924.
4. Brough, Paul A.; Aherne, Wynne; Barril, Xavier; Borgognoni, Jenifer; Boxall, Kathy; Cansfield, Julie E.; Cheung, Kwai-Ming J.; Collins, Ian; Davies, Nicholas G. M.; Drysdale, Martin J.; Dymock, Brian; Eccles, Suzanne A.; Finch, Harry; Fink, Alexandra; Hayes, Angela; Howes, Robert; Hubbard, Roderick E.; James, Karen; Jordan, Allan M.; Lockie, Andrea; Martins, Vanessa; Massey, Andrew; Matthews, Thomas P.; McDonald, Edward; Northfield, Christopher J.; Pearl, Laurence H.; Prodromou, Chrisostomos; Ray, Stuart; Raynaud, Florence I.; Roughley, Stephen D.; Sharp, Swee Y.; Surgenor, Allan; Walmsley, D. Lee; Webb, Paul; Wood, Mike; Workman, Paul; Wright, Lisa *J. Med. Chem.* **2008**, *51*, 196.
5. Gonzales, B.; Gonzales, A. M.; Pulido, F. J. *Synth. Commun.* **1995**, *25*, 1005.
6. Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880.
7. For a review on azadienes in synthesis see Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.
8. Calvo, L. M.; Gonzalez-Nogal, A. M.; Gonzalez-Ortega, A.; Sañudo, M. C. *Tetrahedron Lett.* **2001**, *42*, 8981.
9. For reviews on the extensive work of Barluenga and co-workers on applications of 1,3-diimines to organic synthesis see (a) Barluenga, J.; Tomás, M. *Adv. Heterocycl. Chem.* **1993**, *57*, 1; (b) Barluenga, J. *Bull. Soc. Chim. Belg.* **1988**, *97*, 545.
10. Majumder, S.; Odom, A. L. *Tetrahedron* **2010**, *66*, 3152.
11. Majumder, S.; Gipson, K. R.; Odom, A. L. *Org. Lett.* **2009**, *11*, 4720.
12. Majumder, S.; Gipson, K. R.; Staples, R. J.; Odom, A. L. *Adv. Synth. Catal.* **2009**, *351*, 2013.
13. For related chemistry on isoxazole synthesis from 1,3-diimines see Barluenga, J.; Jardon, J.; Rubio, V.; Gotor, V. *J. Org. Chem.* **1983**, *48*, 1379 The conditions in this paper for isoxazole formation, which involve heating pyridine solutions of hydroxylamine with 1,3-diimines followed by an H_2SO_4 quench, where not successful with the somewhat different 1,3-diimines available using the titanium-catalyzed multicomponent coupling chemistry discussed here.
14. Li, Y.; Turnas, A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2002**, *41*, 6298.
15. Littler, B. J.; Miller, M. A.; Hung, C. H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391.
16. Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2001**, *40*, 1987.
17. Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chem. Commun.* **2003**, 586.
18. Vujkovic, N.; Fillol, J. L.; Ward, B. D.; Wadepohl, H.; Mountford, P.; Gade, L. H. *Organometallics* **2008**, *27*, 2518.
19. Odom, A. L. *Dalton Trans.* **2005**, 225.
20. For discussions of mechanism in related titanium-catalyzed multicomponent couplings see Banerjee, S.; Odom, A. L. *Organometallics* **2006**, *25*, 3099.
21. One possible side reaction is the oligomerization of the alkyne, which has been observed in some titanium catalysts, although not directly reported for **1** or **2**. We typically employ the milder dpma-based catalyst **2** for terminal alkynes Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, 3767.
22. The product ratio may not be directly related to the ratio of [2+2]-cycloaddition products due to a Curtin–Hammett equilibrium in the system. See (a) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753 However see; (b) Tillack, A.; Khedkar, V.; Jiao, H.; Beller, M. *Eur. J. Org. Chem.* **2005**, 5001 For discussions of Curtin–Hammett kinetics see; (c) Follett, A. D.; McNeill, K. *J. Am. Chem. Soc.* **2005**, *127*, 844; (d) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
23. Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synth. Commun.* **1993**, *23*, 685.
24. (a) Hosomi, A.; Shoji, H.; Sakurai, H. *Chem. Lett.* **1985**, 1049 Caution, nitrile oxides are unstable and sometimes explosive. For a review see; (b) Belen'Kii, L. I. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; John Wiley: 2008.
25. For an alternative synthesis involving reduction of the 5-chloroisoxazole see Ponticelli, F.; Tedeschi, P. *Synthesis* **1985**, 792.
26. Gokel, G. W.; Widera, R. P.; Weber, W. P. *Org. Synth.* **1976**, *55*, 96.
27. Olofson, R. A.; Landesberg, J. M.; Berry, R. O.; Leaver, D.; Robertson, W. A. H.; McKinnon, D. M. *Tetrahedron* **1966**, *22*, 2119.
28. De Munno, A.; Bertini, V.; Lucchesini, F. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1121.
29. Bravo, P. *Gazz. Chim. Ital.* **1972**, *102*, 395.
30. Kohler, E. P.; Davis, A. R. *J. Am. Chem. Soc.* **1930**, *52*, 4520.