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Pyrazole Synthesis Using a Titanium-Catalyzed Multicomponent Coupling Reaction and Synthesis of Withasomnine

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Abstract: The titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and amine can be used to generate tautomers of 1,3-diimines. These diimines produced *in situ* undergo cyclization with hydrazine and hydrazine derivatives in a one-pot procedure to provide pyrazoles. Seventeen examples of pyrazoles are provided using this one-pot, 4-component procedure from simple starting materials. The regioselectivity of the alkyne addition can be controlled in some cases with catalyst architecture, and regioselectivity of monosubsituted hydrazines to unsymmetrical 1,3-diimines is discussed. This multicomponent coupling strategy was applied to the synthesis of withasomnine in an efficient procedure, which gave the natural product in 24% overall yield from 4-pentyn-1-ol.

Keywords: heterocycles; hydrazines; multicomponent reactions; pyrazoles; titanium

Introduction

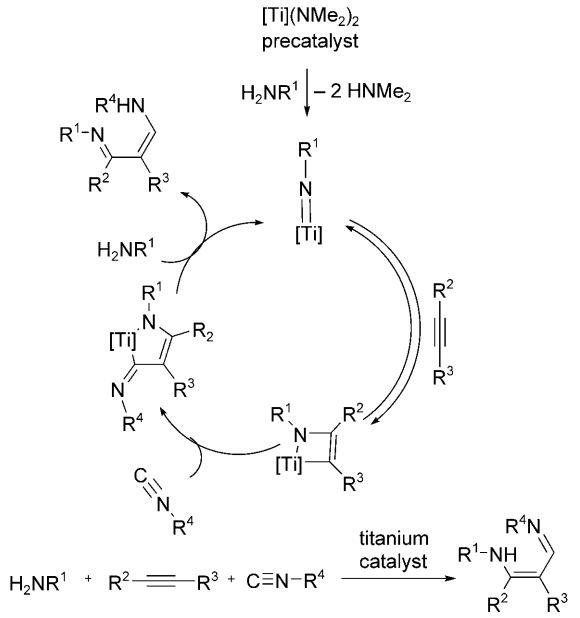
Catalyzed multicomponent coupling reactions offer the opportunity to generate important classes of molecules, such as heterocycles, in a small number of steps. The main advantages of this type of scheme are the time the researcher saves in the preparation of the compounds, the variety of compounds that can be made using these protocols by varying substituents in the starting materials, and the availability of catalyst tuning to provide regio-, stereo-, or even chemoselective control from one set of substrates.[1]

Pyrazoles and related structures are important heterocycles for their applications to pharmaceuticals such as celecoxib (Celebrex®), sildenafil (Viagra®), and rimonabant (Acomplia®); they are also one of the most common cores found in herbicides, fungicides, and insecticides.[2] Pyrazoles are also found in a few natural products such as withasomnine. Withasomnine is a popular compound in alternative medicine found in several plant species with alleged applications to a variety of ailments. It has been shown to be a mild analgesic and a central nervous system depressant.[3]

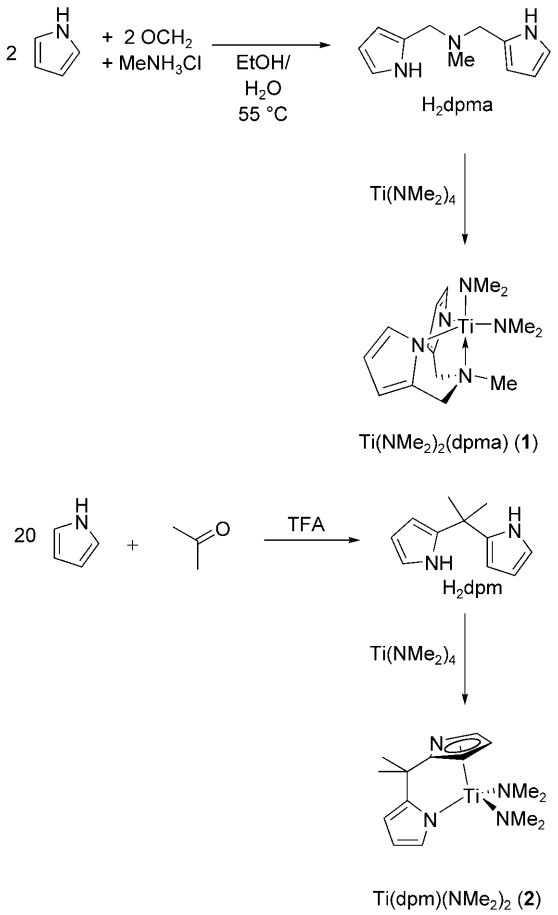
In this study, we demonstrate that a variety of different pyrazoles can be prepared in a one-pot, 4-component fashion. The methodology uses a titanium-catalyzed 3-component coupling[4] of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers.[5] Pyrazoles result from simply removing the volatiles from the multicomponent coupling reaction and treating the crude product with commercially available hydrazines.[6] Finally, we present a new, concise synthesis of the natural product withasomnine using this multicomponent coupling methodology.

Results and Discussion

The multicomponent coupling reaction utilized here is a formal alkyne iminoamination, addition of iminyl and amino groups across the triple bond.[4,7] The proposed mechanism for the reaction is shown in Scheme 1. Titanium was added as the dimethylamido-containing precatalysts, which are easily synthesized from commercially available $Ti(NMe_2)_4$.[8] The dimethylamido ligands are protolytically removed by the primary amine substrate[9] to generate titanium imido complexes that undergo [2+2]cycloaddition with alkynes.[10] The resulting azatitanacyclobutenes undergo 1,1-insertion of isonitriles to generate 5-membered metallacycles.[11] The 5-membered metallacycles are protolytically converted back to imides by primary



Scheme 1. Proposed mechanism for titanium-catalyzed iminoamination of alkynes with the overall reaction shown.



Scheme 2. Synthesis of H_2dpma, H_2dpm, $Ti(NMe_2)_2$(dpma) (**1**), and $Ti(NMe_2)_2$(dpm) (**2**).

amines with concomitant release of the iminoamination products.

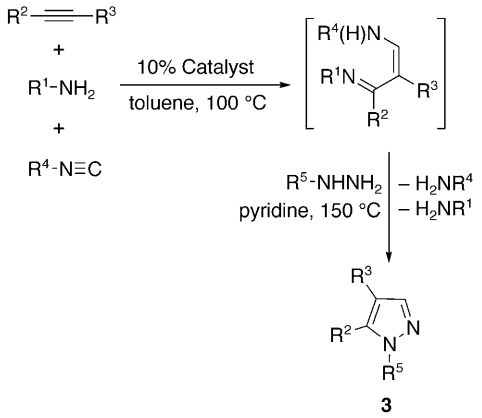
For this study, we employed two different pyrrole-based catalysts. Both catalysts use ligand architectures synthesized in a single step from pyrrole, and both ancillary ligands can be placed on titanium in near quantitative yields by reaction with commercially available $Ti(NMe_2)_4$ (Scheme 2). The first catalyst described for this 3-component coupling reaction was $Ti(NMe_2)_2$(dpma),[12] where dpma[13] = *N*,*N*-di(pyrrolyl-α-methyl)-*N*-methylamine. More recently, we have found that $Ti(NMe_2)_2$(dpm),[14] where dpm[15] = 5,5-dipyrrolylmethane, is a quite active catalyst for alkyne iminoamination.

The multicomponent coupling reaction can be facile using both terminal and internal alkynes with a variety of amines. Because the substituent on the isonitrile does not end up in the final pyrazole product, *tert*-butyl isonitrile was employed exclusively here because of its general applicability in this reaction. Ease of access is also an advantage for *t*-BuNC, which is both commercially available and readily prepared from *tert*-butylamine and chloroform in the presence of base.[16]

Barluenga and co-workers published a large series of notable papers in "1-azabutadiene" chemistry where the intermediates were obtained by reaction of saturated nitriles with Schiff bases using $AlCl_3$.[17] These 1-azabutadienes are close derivatives of the iminoamination products used here; however, the available substitution patterns are quite different. In addition, the iminoamination procedure produces these useful intermediates in a one-step, 3-component coupling procedure, and catalyst variations can be used to control regioselectivity giving different products from the same substrates. We explored the reactions of *in situ* generated iminoamination products with hydrazines in the presence of base. The reactions can be carried out with an isolated iminoamination product, or more conveniently, in a one-pot procedure generating the pyrazoles directly from alkyne, amine, isonitrile, and hydrazine (Scheme 3).

The general procedure involved the addition of amine (1 mmol), catalyst (10 mol%), alkyne (1 mmol), isonitrile (1–1.5 mmol), and 2 mL of toluene to a 40-mL pressure tube under nitrogen, which was sealed and heated at 100 °C with stirring. Once the multicomponent coupling reaction was complete as judged by GC-FID, the volatiles were removed under vacuum and 3 mL of pyridine along with hydrazine or hydrazine hydrochloride were added to the crude residue. After additional heating,[18] the product pyrazole (**3**) was purified by chromatography or crystallization.

Some applications of the methodology are shown in Table 1 and Table 2. For this initial study, we chose to



Scheme 3. One-pot synthesis of pyrazoles (**3**).

look at the multicomponent coupling product of phenylacetylene, *tert*-butyl isonitrile, and cyclohexylamine with a variety of different hydrazines, which generated pyrazoles **3a–i**. All the hydrazines attempted seemed about equally successful in the second step of the reaction, and a large variety of N-substituted and N–H pyrazoles can likely be prepared in comparable yields.

In the second stage of the study (Table 2), a selection of different internal and terminal alkynes was used with phenylhydrazine, which generated pyrazoles **3j–q**. Terminal alkynes and 1-phenylpropyne reactions could be done with the milder catalyst **1**. More difficult substrates like diphenylacetylene and 3-hexyne required **2** as catalyst, sometimes with increased catalyst loadings or longer reaction times.

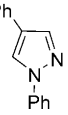
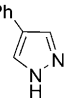
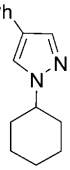
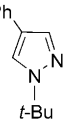
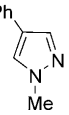
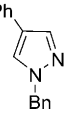
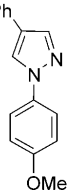
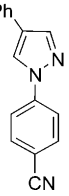
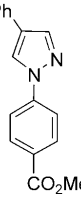
In one case (**3j**), the product was structurally characterized by X-ray diffraction to help ensure proper assignment of the regiochemistry as the 1,4,5-trisubstituted pyrazole. See the Supporting Information for details.

Not only do the two catalysts differ in their reactivity, but the regioselectivity of reactions with **1** and **2** was often different as well. In general, dipyrrolylmethane **2** favored 4-substitution in the pyrazole products when terminal alkynes were employed. The tridentate ligand **1** favored 4-substitution for aromatic groups and 3-substitution (or 5-substitution – *vide infra*) for alkyl-containing alkynes.

For example, reactions with 1-hexyne as substrate and catalysts **1** and **2** were carried out under similar conditions (Scheme 4).[19] Catalyst **1** provides 3-butylpyrazole (**3r**) as the major isomer, while catalyst **2** generates 4-butylpyrazole (**3s**) as the major product.[20]

If an alkyl- or arylhydrazine is employed with an unsymmetrical 3-component coupling product, mixtures could potentially result due to different regioisomers from the hydrazine addition [Eq. (1)]. Even so, one isomer can often be strongly favored.

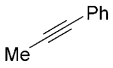
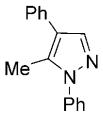
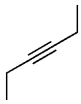
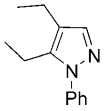
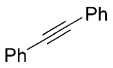
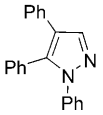
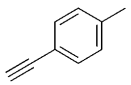
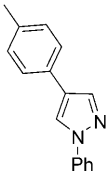
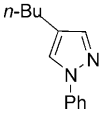
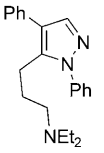
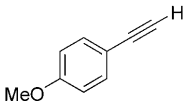
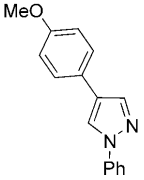
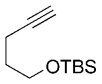
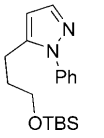
Table 1. Examples of pyrazole (**3**) syntheses using phenylacetylene and a variety of hydrazines.

Entry	Hydrazine	Product **3**	GC or NMR (Isolated) Yield[a]
a	$PhN(H)NH_2$		57 (48)
b	$NH_2NH_2{\cdot}H_2O$		51 (43)
c	$C_6H_{11}N(H)NH_2$		52 (45)
d	*t*-$BuN(H)NH_2$		68 (50)
e	$MeN(H)NH_2$		(35)
f	$BnN(H)NH_2$		45 (45)
g	4-$MeOC_6H_4$-$N(H)NH_2$		60 (45)
h	4-CNC_6H_4-$N(H)NH_2$		53 (41)
i	4-$CO_2MeC_6H_4$-$N(H)NH_2$		46 (39)

[a] 10 mol% **1** used as catalyst.

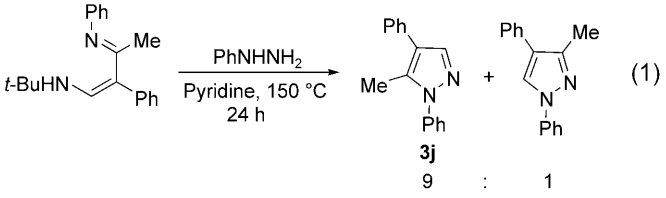
For example, the 3-component coupling product[4] derived from 1-phenylpropyne reacts with phenylhydrazine to give 1-phenyl-4-phenyl-5-methylpyrazole (**3j**) with 9:1 selectivity over the alternative isomer 1-

Table 2. Examples of pyrazole (**3**) syntheses using phenylhydrazine with other alkynes.

Entry	Alkyne	Product (**3**)	GC or NMR (Isolated) Yield
j			45 (40)[a,d]
k			39 (37)[b]
l			34 (24)[c]
m			50 (41)[a]
n			35 (28)[b]
o			(31)[b]
p			45 (38)[b]
q			44 (35)[a]

[a] 10 mol% **1**.
[b] 10 mol% **2**.
[c] 20 mol% **2**.
[d] See Eq. (1) and text for regioselectivity discussion.

phenyl-3-methyl-4-phenylpyrazole[21] [Eq. (1)]. Methods for controlling the regioselectivity further in this step are under investigation.



3j
9 : 1

(1)

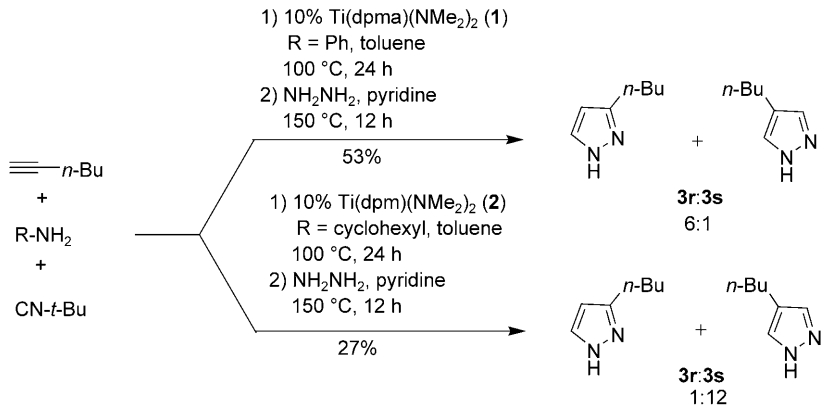
As might be expected, several of the compounds in Table 1 have been prepared previously. In general, the route here often compares favorably with previously reported syntheses in number of steps, overall yield, or both. For example, one can examine 4-phenylpyrazole (**3b**), which we prepare in 43% yield in a single step from phenylacetylene. In this case, the product precipitates from the reaction mixture and is collected by filtration and recrystallized. There are several distinct routes to the same compound.[22] For example, Vilsmeier formylation of phenylacetaldehyde diethyl acetal followed by hydrazine affords 4-phenylpyrazole in 36% yield in two steps.[23] The pyrazole was prepared in 8% yield by Suzuki coupling of 5-$B(OH)_2$-pyrazole and PhCl.[24] Kumada coupling of 1-trityl-4-bromopyrazole and PhMgBr catalyzed by $PdCl_2$(dppf) is high yielding but requires 4 steps from pyrazole.[25]

We also applied this methodology to the synthesis of the natural product withasomnine, which has been prepared using a diverse array of routes.[26] The advantages of the multicomponent coupling strategy presented here are the inexpensive and readily available reagents used in a straightforward synthesis (Scheme 5) of the natural product.

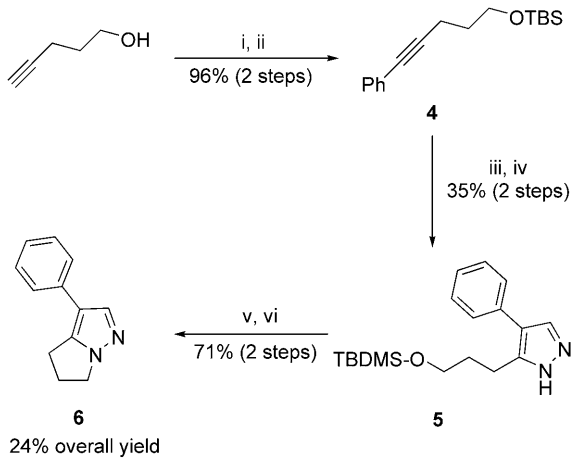
High yielding Sonogoshira coupling of iodobenzene and 4-pentyn-1-ol followed by protection of the alcohol by *tert*-butyl(dimethyl)silation provided alkyne **4**.[27] Iminoamination using 10 mol% **2**, aniline, and *tert*-butyl isonitrile followed by addition of hydrazine hydrate gave pyrazole **5** with the desired regioselectivity. The TBDMS protection was removed and converted to the alkyl bromide with BBr_3. Some of the natural product **6** was formed during the reaction with tribromoborane, and ring-closure was completed with the addition of NaOEt/HOEt to provide withasomnine in 71% yield from **5**. The overall yield was 24% from the 4-pentyn-1-ol. This is comparable in yield to the recently reported synthesis by Allin et al.,[28] which used 4-bromopyrazole as the starting material with an interesting radical cyclization to close the aliphatic ring.

Conclusions

Titanium-catalyzed 3-component coupling of primary amine, alkyne, and isonitrile followed by treatment with hydrazines provides pyrazoles in a one-pot procedure. This new procedure has significant flexibility in the types of pyrazoles that can be accessed. The yields are generally modest, but the products are readily isolated using either column chromatography or crystallization. Reactions with terminal alkynes are more facile and can be accomplished with the milder Ti(dpma)$(NMe_2)_2$ (**1**) as catalyst. The more active di-



Scheme 4. Regioselectivity of pyrazole formation using 1-hexyne as the substrate and catalyst **1** and **2**.



Scheme 5. Synthesis of withasomnine (**6**). (i) 1 mol% $Pd(PPh_3)_4$, 2 mol% CuI, 2 equiv. PhI, 10 equiv. NEt_3, THF. (ii) $ClSiMe_2(t\text{-}Bu)$, imidazole, DMF. (iii) $PhNH_2$, *t*-BuNC, 10 mol% **2**, 110 °C, 48 h, toluene. (iv) NH_2NH_2, pyridine, 150 °C, 24 h. (v) BBr_3, CH_2Cl_2, room temperature, 48 h. (vi) NaOEt, HOEt, reflux, 20 h.

pyrrolylmethane catalyst $Ti(dpm)(NMe_2)_2$ (**2**) was used for internal alkynes.

The reaction has several points to allow optimization for a specific target of interest. For example, the type of substituent on the isonitrile can potentially be varied in this reaction to improve regioselectivities or yields. The catalyst architectures themselves are also quite flexible and could be optimized for specific products. In fact, it was found that some regiochemical control is possible using simple catalysts **1** and **2** with alkyl-substituted terminal alkynes, and either 3-butyl- or 4-butylpyrazole can be synthesized from the same substrates preferentially depending on the catalyst employed (Scheme 4).

The 3-component coupling followed by hydrazine treatment strategy was also applied to the synthesis of the natural product withasomnine (**6**) from commercially available 4-pentyn-1-ol in 24% overall yield.

Experimental Section

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 purging with dry N_2, then water was removed by running through activated alumina systems purchased from Solv-Tek. Deuterated solvents were dried over purple sodium benzophenone ketyl (C_6D_6) or phosphoric anhydride ($CDCl_3$) and distilled under a nitrogen atmosphere. Deuterated toluene was degassed then dried by passing through two columns of neutral alumina. ^1H and ^{13}C NMR spectra were recorded on VXR-500 spectrometers. Melting points were measured on a Mel-Temp II apparatus with a mercury thermometer and are uncalibrated. $Ti(dpm)(NMe_2)_2$ (**2**)[14] and $Ti(dpma)(NMe_2)_2$ (**1**)[12] were made following the literature procedures. Alkynes were purchased either from Sigma–Aldrich Co. or from GFS chemicals and dried from CaO under dry nitrogen. Amines were purchased from Sigma–Aldrich Co., dried over KOH, and distilled under dry nitrogen. *tert*-Butyl isonitrile[16] was made from $CHCl_3$ and *tert*-butylamine according to the reported procedure and purified by distillation under nitrogen. Phenylhydrazine was purchased from Sigma–Aldrich Co. and distilled from KOH. Hydrazine hydrate was purchased from Spectrum Chemicals and used as received. All other hydrazines were purchased from Sigma–Aldrich Co. as hydrochloride salts and used as received. Pyridine was dried over KOH and distilled under nitrogen. The alkynes 5-(*tert*-butyldimethylsilyloxy)-1-phenylpent-1-yne and 5-phenylpent-4-yn-1-ol were made according to the literature procedures.[27] The GC yields in Table 1 are from crude reaction mixtures relative to internal octane added after reaction completion and are calibrated versus pure product/octane standards.

General Procedure for the Synthesis of Pyrazoles 3

In an N_2-filled glove box, a 40-mL pressure tube equipped with a magnetic stirbar was loaded with amine (1 mmol), catalyst (10–20 mol%), alkyne (1 mmol), isonitrile (1–1.5 mmol), and dry toluene (2 mL). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated to the appropriate temperature for the desired time with vigorous stirring. After completion of the reaction,

the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Then the tube was charged with hydrazine or hydrazine hydrochloride (1.5 mmol) in pyridine (3 mL) and heated to 150 °C for 24 h. After completion of the reaction, volatiles were removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified either by column chromatography or by crystallization from a suitable solvent.

1,4-Diphenylpyrazole (3a): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a pale yellow solid; yield: 106 mg (48%); mp 95–96 °C (Lit.[29] mp: 97 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.28–7.34 (2H, m, Ar-H), 7.42 (2H, t, *J* = 7.5 Hz, Ar-H), 7.49 (2H, t, *J* = 8 Hz, Ar-H), 7.57–7.59 (2H, m, Ar-H), 7.75–7.77 (2H, m, Ar-H), 8.03 (1H, d, *J* = 0.5 Hz, 3-C*H*-pyrazole), 8.17 (1H, d, *J* = 1 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 119.0, 123.3, 124.9, 125.7, 126.5, 126.8, 128.9, 129.4, 132.0, 138.8, 140.0; MS (EI): *m*/*z* = 220 (M^+); high resolution MS: *m*/*z* = 211.1065, calcd. for $C_{15}H_{13}N_2^+$: 221.1079.

4-Phenylpyrazole (3b): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and hydrazine hydrate (375 mg, 7.5 mmol) in dry pyridine (15 mL) was added. The mixture was heated to 150 °C for 24 h. Pyridine was removed under vacuum, and the crude product was recrystallized from methanol/ethyl acetate to afford the desired product as a white solid; yield: 310 mg (43%); mp 233–234 °C (Lit.[23] mp: 235–236 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 7.15 (1H, t, *J* = 7.5 Hz, Ar-H), 7.32 (2H, t, *J* = 7.5 Hz, Ar-H), 7.57 (2H, dd, *J* = 7.5 and 1.5 Hz, Ar-H), 7.89 (1H, br s, 3-CH pyrazole), 8.15 (1H, br s, 5-CH pyrazole), 12.90 (1H, br s, NH); ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz): δ = 121.1, 125.1, 125.3, 125.8, 128.7, 132.9, 136.1; MS (EI): *m*/*z* = 144 (M^+).

1-Cyclohexyl-4-phenylpyrazole (3c): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and cyclohexylhydrazine hydrochloride (226 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a yellow solid; yield: 102 mg (45%); mp 69–70 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22–1.30 (1H, m, cyclohexyl), 1.38–1.48 (2H, m, cyclohexyl), 1.70–1.78 (3H, m, cyclohexyl), 1.88–1.91 (2H, m, cyclohexyl), 2.17–2.2 (2H, m, cyclohexyl), 4.08–4.14 (1H, m, 1-cyclohexyl), 7.17–7.20 (1H, m, Ar-H), 7.31–7.34 (2H, m, Ar-H), 7.44–7.46 (2H, m, Ar-H), 7.64 (1H, d, *J* = 0.5 Hz, 3-C*H*-pyrazole), 7.75 (1H, d, *J* = 0.5 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 25.4, 33.6, 61.4, 122.3, 123.5, 125.4, 126.2, 128.8, 132.9, 136.0. Two of the resonances, assigned as being due to the 3- and 4-carbons of the cyclohexyl, are coincident in the ^{13}C NMR spectrum at 25.39 ppm. MS (EI): *m*/*z* = 226 (M^+); high resolution MS: *m*/*z* = 227.1552, calcd. for $C_{15}H_{19}N_2^+$: 227.1548.

1-*tert*-Butyl-4-phenylpyrazole (3d): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and *tert*-butylhydrazine hydrochloride (187 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a yellow liquid; yield: 100 mg (50%) ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.61 (9H, s, CH_3), 7.18 (1H, tt, *J* = 7.5 and 1 Hz, 4-*H*-Ph), 7.33 (2H, t, *J* = 8 Hz, Ar-H), 7.46–7.48 (2H, m, Ar-H), 7.74 (1H, d, *J* = 1 Hz, 3-C*H*-pyrazole), 7.78 (1H, s, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 29.8, 58.5, 122.2, 122.6, 125.4, 126.1, 128.8, 133.0, 136.1; MS (EI): *m*/*z* = 200 (M^+); high resolution MS: *m*/*z* = 201.1393, calcd. for $C_{13}H_{17}N_2^+$: 201.1392.

1-Methyl-4-phenylpyrazole (3e): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (323 mg, 1 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and methylhydrazine (345 mg, 7.5 mmol) in dry pyridine (15 mL) was added. The mixture was heated to 140 °C for 24 h. After completion of the reaction, pyridine was removed under reduced pressure and crude product was dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by column chromatography using 20% ethyl acetate/hexanes on neutral alumina; yield: 280 mg (35%); mp 98–99 °C (Lit.[30] mp: 100–101 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.92 (3H, s, CH_3), 7.20 (1H, tt, *J* = 7.5 and 1 Hz, Ar-H), 7.34 (2H, t, *J* = 8 Hz, Ar-H), 7.44–7.46 (2H, m, Ar-H), 7.58 (1H, s, 3-C*H*-pyrazole), 7.74 (1H, d, *J* = 0.5 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 39.1, 123.2, 125.5, 126.3, 126.8, 128.8, 132.6, 136.7; MS (EI): *m*/*z* = 158 (M^+); high resolution MS: *m*/*z* = 159.0909, calcd. for $C_{10}H_{11}N_2^+$: 159.0922.

1-Benzyl-4-phenylpyrazole (3f): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and benzylhydrazine (183 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was 15% ethyl acetate/hexanes, which afforded the desired compound as a white solid; yield: 105 mg

(45%); mp 92–94 °C (Lit.[31] mp: 95–96 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.35 (2H, s, N-CH_2), 7.25 (1H, t, J = 7.5 Hz, Ar-H), 7.27–7.29 (2H, d, J = 8 Hz, Ar-H), 7.35–7.40 (5H, m, Ar-H), 7.50 (2H, dd, J = 8.5 and 1 Hz, Ar-H), 7.64 (1H, s, 3-C*H*-pyrazole), 7.85 (1H, s, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 56.2, 123.6, 125.5, 126.5, 126.4, 127.8, 128.2, 128.8, 128.9, 132.5, 136.4, 137.0; MS (EI): m/z = 234 (M^+); high resolution MS: m/z = 235.1238, calcd. for $C_{16}H_{15}N_2^+$: 235.1235.

1-(4-Methoxyphenyl)-4-phenylpyrazole (3g): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and 4-methoxyphenylhydrazine hydrochloride (261 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was 15% ethyl acetate/hexanes, which afforded the desired compound as a white solid; yield: 110 mg (44%); mp 124–125 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.87 (3H, s, OMe), 7.0–7.02 (2H, m, Ar-H), 7.28 (1H, tt, J = 7.5 and 1 Hz, Ar-H), 7.41 (2H, t, J = 8 Hz, Ar-H), 7.57 (2H, dd, J = 8 and 1 Hz, Ar-H), 7.64–7.66 (2H, m, Ar-H), 7.98 (1H, d, J = 0.5 Hz, 3-C*H*-pyrazole), 8.08 (1H, d, J = 0.5 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 55.5, 114.5, 120.7, 123.4, 124.5, 125.6, 126.7, 128.9, 132.2, 133.9, 138.3, 158.3; MS (EI): m/z = 250 (M^+); high resolution MS: m/z = 251-1169, calcd. for $C_{16}H_{15}N_2O^+$: 251.1184.

1-(4-Cyanophenyl)-4-phenylpyrazole (3h): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and 4-cyanophenylhydrazine hydrochloride (255 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 4:1, which afforded the desired compound as a white solid; yield: 100 mg (41%); mp 166–167 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.27–7.31 (1H, m, Ar-*H*), 7.40 (2H, t, J = 8 Hz, Ar-*H*), 7.53–7.54 (2H, m, Ar-*H*), 7.74–7.76 (2H, m, Ar-*H*), 7.85–7.87 (2H, m, Ar-*H*), 8.02 (1H, s, 3-C*H* pyrazole), 8.18 (1H, d, J = 0.5 Hz, 5-C*H* pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 109.6, 118.3, 118.7, 123.0, 125.8, 126.2, 127.4, 129.0, 131.2, 133.6, 140.2, 142.8; MS (EI): m/z = 245 (M^+); high resolution MS: m/z = 246.1040, calcd. for $C_{16}H_{12}N_3^+$: 246.1031.

1-(4-Methylcarboxylphenyl)-4-phenylpyrazole (3i): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and methyl 4-hydrazinylbenzoate hydrochloride (303 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 4:1, which afforded the desired compound as a white solid; yield: 108 mg (39%); mp 179–180 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.92 (3H, s, OCH_3), 7.26–7.29 (1H, m, Ar-*H*), 7.39 (2H, t, J = 8 Hz, Ar-*H*), 7.53–7.55 (2H, m, Ar-*H*), 7.80–7.82 (2H, m, Ar-*H*), 8.13–8.15 (2H, m, Ar-*H*), 8.01 (1H, s, 3-C*H* pyrazole), 8.21 (1H, d, J = 0.5 Hz, 5-C*H* pyrazole); ^{13}C{^{1}H] NMR ($CDCl_3$, 125 MHz): δ = 52.2, 118.1, 123.2, 125.7, 125.8, 127.2, 127.9, 129.0, 131.2, 131.6, 139.7, 143.1, 166.3; MS (EI): m/z = 278 (M^+); high resolution MS: m/z = 279.1131, calcd. for $C_{17}H_{15}N_2O_2^+$: 279.1134.

1,4-Diphenyl-5-methylpyrazole (3j): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (136 μL, 1.2 mmol), aniline (92 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 48 h at 100 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was 10–15% ethyl acetate/hexanes, which afforded the desired compound as a pale yellow solid; yield: 95 mg (40%); mp 150–152 °C (Lit.[32] mp: 159–160 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.42 (3H, s, Me), 7.28 (1H, tt, J = 7 and 2 Hz, Ar-H), 7.37–7.44 (5H, m, Ar-H), 7.49 (4H, d, J = 4.5 Hz, Ar-H), 7.77 (1H, s, 3-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 12.0, 122.0, 125.1, 126.4, 127.8, 127.8, 128.7, 129.1, 133.5, 135.3, 139.2, 139.9; MS (EI): m/z = 234 (M^+).

4,5-Diethyl-1-phenylpyrazole (3k): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), aniline (92 mg, 1 mmol), 3-hexyne (82 mg, 1 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 30.8 mg, 0.1 mmol) in toluene (2 mL) and was heated for 48 h at 110 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a yellow-red liquid; yield: 74 mg (37%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (3H, t, J = 7.5 Hz, 4-CH_2CH_3), 1.23 (3H, t, J = 7.5 Hz, 5-CH_2CH_3), 2.47 (2H, q, J = 7.5 Hz, 4-CH_2CH_3), 2.64 (2H, q, J = 7.5 Hz, 5-CH_2CH_3) 7.34–7.45 (5H, m, Ar-H), 7.46 (1H, s, 3-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 13.8, 15.2, 17.1, 17.6, 121.0, 125.3, 127.6, 129.0, 139.2, 140.4, 140.9; MS (EI): m/z = 200 (M^+); high resolution MS: m/z = 201.1395, calcd. for $C_{13}H_{17}N_2^+$: 201.1392.

1,4,5-Triphenylpyrazole (3l): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), aniline (92 mg, 1 mmol), diphenylacetylene (174 mg, 1 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 61.6 mg, 0.2 mmol) in toluene (2 mL) and was heated for 48 h at 140 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a pale pink solid; yield: 71 mg (24%); mp 202–203 °C (Lit.[33] mp: 197–198 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.16–7.35 (15H, m, Ar-H), 7.94 (1H, s, 3-CH pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 122.4, 125.1, 126.4, 127.2, 128.0, 128.4, 128.4, 128.6, 128.7, 130.2, 130.4, 132.8, 139.2, 139.7, 139.9; MS (EI): m/z = 296

(M^+); high resolution MS: $m/z = 297.1388$, calcd. for $C_{21}H_{17}N_2^+$: 297.1392.

1-Phenyl-4-(*p*-tolyl)pyrazole (3m): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), *p*-tolylacetylene (116 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a pale yellow solid; yield: 96 mg (41%); mp 120–121 °C (Lit.[34] mp: 127–128 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.36 (3H, s, CH_3), 7.20 (2H, d, J = 8 Hz, Ar-H), 7.28 (1H, tt, J = 7.5 and 1 Hz, 4-*H*-Ph), 7.43–7.47 (4H, m, Ar-H), 7.71–7.73 (2H, m, Ar-H), 7.97 (1H, d, J = 0.5 Hz, 3-C*H*-pyrazole), 8.11 (1H, d, J = 0.5 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 21.1, 118.9, 123.0, 124.9, 125.6, 126.4, 129.1, 129.4, 129.6, 136.5, 138.7, 140.1; MS (EI): $m/z = 234$ (M^+); high resolution MS: m/z = 235.1242, calcd. for $C_{16}H_{15}N_2^+$: 235.1235.

1-Phenyl-4-butylpyrazole (3n): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), 1-hexyne (82 mg, 1 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 30.8 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a yellow-red liquid; yield: 56 mg (28%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.96 (3H, t, J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.39–1.46 (2H, m, $CH_2CH_2CH_2CH_3$), 1.58–1.65 (2H, m, $CH_2CH_2CH_2CH_3$), 2.55 (2H, t, J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 7.26 (1H, tt, J = 7.5 and 1 Hz, Ar-H), 7.44 (2H, tt, J = 7.5 and 0.5 Hz, Ar-H), 7.56 (1H, s, 3-C*H*-pyrazole), 7.67–7.69 (2H, m, Ar-H), 7.72 (1H, d, J = 1 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 13.8, 22.3, 23.8, 32.9, 118.7, 124.0, 124.6, 125.9, 129.3, 140.3, 140.9; MS (EI): $m/z = 200$ (M^+).

1,4-Diphenyl-5-(3-*N*,*N*-diethylamino-*n*-propyl)pyrazole (3o): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (85 μL, 0.75 mmol), aniline (46 μL, 0.5 mmol), *N*,*N*-diethyl-5-phenylpent-4-yn-1-amine (107.5 mg, 0.5 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 15.4 mg, 0.05 mmol) in toluene (1 mL) and was heated for 48 h at 110 °C. Volatiles were removed, and phenylhydrazine (81 mg, 0.75 mmol) in dry pyridine (1.5 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate:triethylamine 74:25:1, which afforded the compound as a red liquid; yield: 52 mg (31%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.87 (6H, t, J = 7 Hz, CH_2CH_3), 1.48–1.54 (2H, m, $CH_2CH_2CH_2NEt_2$), 2.24 (2H, t, J = 7 Hz, $CH_2CH_2CH_2NEt_2$), 2.31 (4H, q, J = 7 Hz, CH_2CH_3), 2.87 (2H, t, J = 8 Hz, $CH_2CH_2CH_2NEt_2$), 7.29–7.33 (1H, m, Ar-*H*), 7.43–7.48 (5H, m, Ar-*H*), 7.49–7.51 (4H, m, Ar-*H*), 7.76 (1H, s, 3-C*H* pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 11.4, 22.6, 26.1, 46.5, 52.1, 121.5, 125.8, 126.4, 127.9, 128.1, 128.6, 129.0, 133.7, 139.4, 139.9, 140.1; MS (EI): $m/z = 333$ (M^+); high resolution MS: m/z = 334.2291, calcd. for $C_{22}H_{28}N_3^+$: 334.2283.

1-Phenyl-4-(4-methoxyphenyl)pyrazole (3p): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), cyclohexylamine (99 mg, 1 mmol), 4-methoxyphenylacetylene (132 mg, 1 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 30.8 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound as a white solid; yield: 94 mg (38%); mp 136–138 °C (Lit.[35] mp: 138–140 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.82 (3H, s, OCH_3), 6.92–6.94 (2H, m, Ar-*H*), 7.26–7.29 (1H, m, Ar-*H*), 7.43–7.47 (4H, m, Ar-*H*), 7.70–7.72 (2H, m, Ar-*H*), 7.92 (1H, s, 3-C*H* pyrazole), 8.06 (1H, d, J = 1 Hz, 5-C*H* pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 55.2, 114.3, 118.9, 122.6, 124.56, 124.58, 126.3, 126.8, 129.3, 138.4, 139.9, 158.6; MS (EI): $m/z = 250$ (M^+); high resolution MS: m/z = 251.1185, calcd. for $C_{16}H_{15}N_2O^+$: 251.1184.

1-Phenyl-5-[3-(*tert*-butyldimethylsiloxy)propyl]pyrazole (3q): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (171 μL, 1.5 mmol), aniline (93 mg, 1 mmol), *tert*-butyldimethyl(pent-4-ynyloxy)silane (198 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and phenylhydrazine (162 mg, 1.5 mmol) in dry pyridine (3 mL) was added. The mixture was heated to 150 °C for 24 h which afforded two isomer in 6.6:1 ratio. Purification of the major isomer was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the major isomer as a yellow-red liquid; yield: (110 mg (35%). ^{1}H NMR ($CDCl_3$, 500 MHz): Major isomer: δ = 0.015 (6H, s, Si-CH_3), 0.86 (9H, s, Si-CMe_2CH_3), 1.79–1.84 (2H, m, $CH_2CH_2CH_2$OTBS), 2.77 (2H, t, J = 7.5 Hz, $CH_2CH_2CH_2$OTBS), 3.62 (2H, t, J = 6 Hz, $CH_2CH_2CH_2$OTBS), 6.23 (1H, d, J = 2 Hz, 4-C*H* pyrazole), 7.37–7.40 (1H, m, Ar-*H*), 7.44–7.48 (4H, m, Ar-*H*), 7.60 (1H, d, J = 1.5 Hz, 3-C*H* pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = −5.4, 18.1, 22.5, 25.8, 31.8, 61.8, 105.3, 125.2, 127.6, 128.9, 139.7, 139.9, 143.1; MS (EI): $m/z = 317$ (M^+ + H); high resolution MS: $m/z = 317.2055$, calcd. for $C_{18}H_{29}N_2OSi^+$: 317.2049.

3-Butylpyrazole (3r): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (565 μL, 5 mmol), aniline (456 μL, 5 mmol), 1-hexyne (575 μL, 5 mmol), and $Ti(NMe_2)_2$(dpma) (**1**, 162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and hydrazine hydrate (375 mg, 7.5 mmol) in dry pyridine (15 mL) was added. The mixture was heated to 150 °C for 12 h. Purification was accomplished by Kugelrohr distillation, which afforded the desired compound as a mixture of two isomers in a 6:1 ratio as a pale yellow liquid; yield: 328 mg, (53%). Data for the major isomer: ^{1}H NMR[36] ($CDCl_3$, 500 MHz): δ = 0.91 (3H, t, J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.34–1.38 (2H, m, $CH_2CH_2CH_2CH_3$), 1.59–1.65 (2H, m, $CH_2CH_2CH_2CH_3$), 2.66 (2H, t, J = 8.0 Hz, $CH_2CH_2CH_2CH_3$), 6.06 (1H, d, J = 2 Hz, 4-C*H*-pyrazole), 7.47 (1H, d, J = 2 Hz, 5-C*H*-pyrazole); ^{13}C{^{1}H} NMR

($CDCl_3$, 125 MHz): δ = 13.8, 22.3, 26.4, 31.5, 103.4, 121.3; MS (EI): m/z = 124 (M^+).

4-Butylpyrazole (3s): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (850 μL, 7.5 mmol), cyclohexylamine (570 μL, 5 mmol), 1-hexyne (575 μL, 5 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 154 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed, and hydrazine hydrate (375 mg, 7.5 mmol) in dry pyridine (15 mL) was added. The mixture was heated to 150 °C for 12 h. Purification was accomplished by Kugelrohr distillation, which afforded the desired compound as a pale yellow liquid;[23] yield: 167 mg (27%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.90 (3H, t, J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.30–1.37 (2H, m, $CH_2CH_2CH_2CH_3$), 1.50–1.56 (2H, m, $CH_2CH_2CH_2CH_3$), 2.47 (2H, t, J = 7.0 Hz, $CH_2CH_2CH_2CH_3$), 7.37 (2H, s, C*H*-pyrazole), 9.43 (1H, br s, N*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 13.8, 22.3, 23.6, 33.1, 121.4, 132.6; MS (EI): m/z = 124 (M^+).

Withasomnine(6) Synthesis

5-[3-(*tert*-Butyldimethylsilyloxy)propyl]-4-phenyl-1*H*-pyrazole (5): A reaction using the general conditions was carried out with *tert*-butyl isonitrile (1.29 mL, 7.5 mmol), aniline (465 mg, 5 mmol), 5-(*tert*-butyldimethylsilyloxy)-1-phenylpent-1-yne[23] (1.37 g, 5 mmol), and $Ti(NMe_2)_2$(dpm) (**2**, 154 mg, 0.5 mmol) in toluene (5 mL) and was heated for 48 h at 110 °C. Volatiles were removed, and hydrazine hydrate (375 mg, 7.5 mmol) in pyridine (15 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was initially hexanes:ethyl acetate 1:1 followed by 5% methanol in ethyl acetate, which afforded the desired compound as a viscous dark red oil; yield: 552 mg (35%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.055 (6H, s, Si-C*H*$_3$), 0.89 (9H, s, Si-CC*H*$_3$), 1.85–1.91 (2H, m, $CH_2CH_2CH_2OTBDMS$), 2.91 (2H, t, J = 7.5 Hz, $CH_2CH_2CH_2OTBDMS$), 3.69 (2H, t, J = 6 Hz, $CH_2CH_2CH_2OTBDMS$), 7.23–7.26 (2H, m, Ar-H, NH), 7.36–7.39 (4H, m, Ar-H), 7.64 (1H, s, 3-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = −5.4, 18.3, 22.2, 25.9, 31.4, 62.6, 119.6, 126.2, 127.7, 128.2, 128.6, 131.5, 133.6; MS (EI): m/z = 316 (M^+); high resolution MS: m/z = 317.2041, calcd. for $C_{18}H_{29}N_2OSi^+$: 317.2049.

Withasomnine (6): Under nitrogen **5** (140 mg, 0.443 mmol) in 5 mL CH_2Cl_2 was treated with BBr_3 (1.1 mL, 1 M soln in CH_2Cl_2, 1.1 mmol). The reaction mixture was stirred at room temperature for 48 h and then quenched with saturated $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, and concentrated under rotary evaporation. The crude product was dissolved in absolute EtOH (10 mL) and treated with sodium ethoxide (240 mg, 3.53 mmol). The mixture was heated to reflux for 20 h and then cooled to room temperature. The volatiles were removed under rotary evaporation. The crude mixture was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated under rotary evaporation. The product was purified by column chromatography on alumina using ethyl acetate:hexanes 1:1 with gradient to methanol:ethyl acetate 1:4 to obtain withasomnine; yield: 58 mg (71%); mp 113–115 °C (Lit.[3d] mp: 117–118 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.64–2.70 (2H, m, N-$CH_2CH_2CH_2$), 3.08 (2H, t, J = 7.5 Hz, N-$CH_2CH_2CH_2$), 4.16 (2H, t, J = 7.5 Hz, N-$CH_2CH_2CH_2$), 7.16 (1H, tt, J = 7 and 1 Hz, Ar-H), 7.33 (2H, d, J = 7.5 Hz, Ar-H), 7.42–7.44 (2H, m, Ar-H), 7.79 (1H, s, 3-C*H*-pyrazole); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 23.8, 26.4, 47.6, 115.3, 125.0, 125.6, 128.8, 133.4, 140.9, 142.6; MS (EI): m/z = 184 (M^+).

Supporting Information

Tabular data for the X-ray diffraction experiment on **3j**. CCDC 734720 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. ^{1}H and ^{13}C NMR spectra for the pyrazoles **3**. GC FID traces for the pyrazole products with the exception of *NH*-pyrazoles, **3o**, and withasomnine, which did not pass through our GC column. MS EI fragmentation pattern for withasomnine (**6**).

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