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Single-step synthesis of pyrazoles using titanium catalysis†

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A simple titanium complex catalyzes the coupling of alkynes, isonitriles, and monosubstituted hydrazines to generate substituted pyrazoles in a single step.

Pyrazoles constitute a commercially important class of heterocycles found in pharmaceuticals, herbicides, fungicides, and insecticides,[1] which are accessed using a variety of different synthetic routes.[2] In previous work, our group has developed titanium-based catalysts for one-pot, two-step heterocyclic syntheses.[3] Titanium catalysts are being sought because they are inexpensive, nontoxic, and the catalysts are readily removed from the products.[4] Here, we describe a new multicomponent coupling strategy for the single-step synthesis of pyrazoles enabled by a new, robust catalyst system.

Previous research on hydrazine additions to alkynes, hydrohydrazination,[5] has focused on, for the most part, addition of 1,1-disubstituted hydrazines to alkynes. Titanium-based catalysts can accomplish this reaction, which is also a new route to indoles,[6,7] with either terminal alkynes or internal alkynes. Zinc-based compounds can also catalyze additions of hydrazines to alkynes to produce indoles, but the reaction is apparently limited to terminal alkynes.[8]

In a variant of the hydrohydrazination reaction, we showed titanium-catalysts can convert alkynes, isonitriles, and hydrazines to 1,3-iminohydrazones.[9] Unfortunately, that catalysis was limited to 1,1-disubstituted hydrazines as starting materials using previous catalysts.[10] The apparent cause of the inactivity in some of the previous systems was the removal of all the ancillary ligands by more aggressive monsubstituted hydrazines. The loss of the ancillaries likely leads to inactive bridged hydrazido complexes. This hypothesis is put forward because of the large amounts of free ligand observed under attempted catalyses.

We have discovered that 2-(2′-pyridyl)-3,5-dimethylpyrrole (Hpypyr), which is prepared[11,12] in a single step from commercially available acetylacetone and 2-aminomethylpyridine,[13] can be used to generate (Fig. 1) $Ti(NMe_2)_2(pypyr)_2$ (**1**), which efficiently catalyzes the multicomponent coupling of alkynes, isonitriles, and monosubstituted hydrazines to provide pyrazoles in a single step.

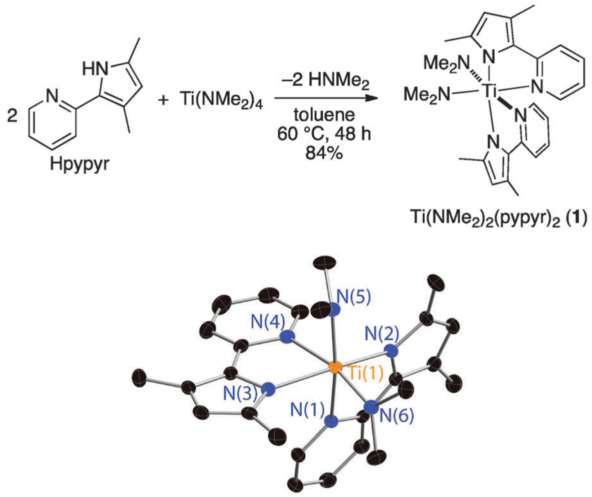

Fig. 1 Synthesis of **1** and an ORTEP diagram of the structure from X-ray diffraction.

The structure (Fig. 1) was obtained from X-ray diffraction of pseudo-octahedral **1** (see the Supplementary Information for details).‡ The more strongly donating dimethylamido ligands are *trans* to the neutral pyridine donors, placing the pyrrolyl ligands mutually *trans*. As is typical, the Ti–N(pyrrolyl) distances average 2.111(1) Å, significantly longer than the Ti–NMe_2 bonds, 1.910(2) Å. The Ti–N(pyridyl) distances average 2.260(2) Å. All these can be compared with the estimated single- and double-bond distances for Ti–N bonds according to Pyykkö's radii of 2.07 and 1.77 Å, respectively.[14]

The proposed catalytic cycle for the titanium-catalyzed multicomponent coupling reaction is shown in Scheme 1. We suggest the intermediacy of titanium hydrazido(2−) **A** in the reaction. It is well known that isolable, terminal titanium hydrazido(2−) ligands can be formed using the reaction of hydrazines with bis(dimethylamido) complexes.[15] The hydrazido(2−) **A** could then undergo [2+2]-cycloaddition with the alkyne to give **B**, a reaction observed in related systems.[16,17] Isonitrile can 1,1-insert into the Ti–C bond in **B** to give the 5-membered metallacycle **C**.[16,18] Hydrazine protonolysis of metallacycle **C** would give **D**; a compound bearing a nitrogen-based acetylacetonate analogue similar to the one in **D** has been observed in 1,1-disubstituted hydrazine multicomponent coupling reactions.[16] Proton migration from the hydrazido in **D** could liberate imine **E**, which would cyclize to the pyrazole product with loss of H_2NR^4 to aromatize the heterocycle.

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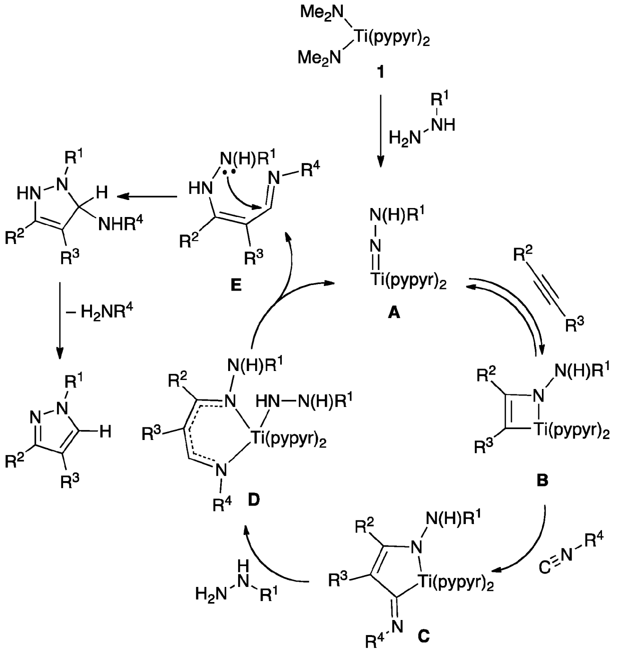
† Electronic supplementary information (ESI) available: Details for the preparation and characterization of compounds. Tables for the X-ray Diffraction Study on **1**. CCDC 845078. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15809k



Scheme 1 Proposed catalytic cycle for the synthesis of pyrazoles.

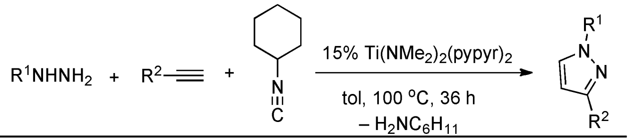
In Table 1, is a listing of the pyrazoles prepared using this multicomponent methodology during the course of this initial study.§ With catalyst **1**, only smaller alkyl- or aryl-substituted terminal alkynes are applicable.[19] In all cases, a single regioisomer was observed by GC-MS and ^{1}H NMR, and the product shown was readily isolated by chromatography.

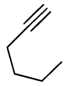
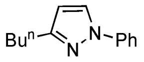
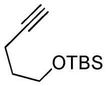
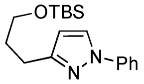
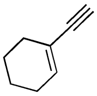
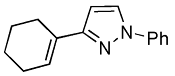
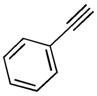
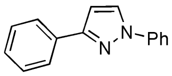
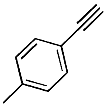
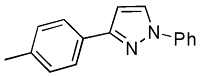
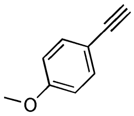
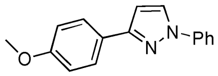
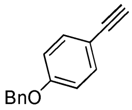
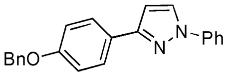
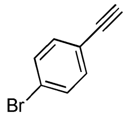
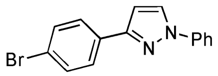
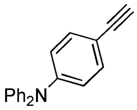
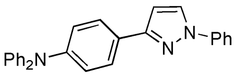
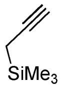
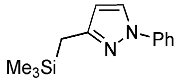
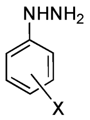
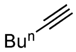
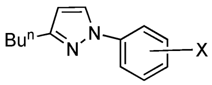
The regioselectivity of the reactions are such that a single observable isomer is generated. For the substrates examined in this study, 1,3-disubstituted pyrazoles were the products. In other words, the favored product isomer is derived from [2 + 2]-cycloaddition to place the larger group on the alkyne away from the metal center in metallacyclobutene **B** (Scheme 1) such that R^2 is the alkyne substituent and R^3 is H in these cases.

For all of the reactions cyclohexylisonitrile was used. In screening isonitriles, we used the coupling between phenylacetylene, phenylhydrazine, and CNR^4 catalyzed by **1**. The isonitriles investigated had R^4 = *tert*-butyl, 2,6-dimethylphenyl, cyclohexyl, and n-butyl. While cyclohexylisonitrile gave relatively clean reactivity, reactions employing 2,6-dimethylphenylisonitrile and n-butylisonitrile resulted in a myriad of unidentified products. On the other hand, the reaction with *tert*-butylisonitrile was relatively clean but did not proceed with as good conversion as the slightly smaller cyclohexyl derivative.

The synthetic route presented here can be compared with other syntheses for the same compounds in the literature. As an example, one could consider alternative routes to 1,3-diphenylpyrazole. There are a large number of routes previously published to this simple compound, most involving multistep procedures.[20] Perhaps the most straightforward route involves addition of phenylhydrazine to phenylpropynone in HCl/MeOH with microwave heating,[21] which gives a 76% yield of the 1,3-diphenylpyrazole along with a 15% yield of the 1,5-derivative. As shown, this route presented here involves titanium-catalyzed coupling of commercially available compounds under thermal conditions and gave 48% isolated yield of a single regioisomer.

Table 1 Pyrazoles prepared using multicomponent couplings with **1**§



Hydrazine	Alkyne	Product	Isolated yield
PhNHNH$_2$			66%
PhNHNH$_2$			71%
PhNHNH$_2$			55%
PhNHNH$_2$			48%
PhNHNH$_2$			46%
PhNHNH$_2$			60%
PhNHNH$_2$			49%
PhNHNH$_2$			60%
PhNHNH$_2$			47%
PhNHNH$_2$			75%
			X = 4-Br 52% X = 4-I 62% X = 4-Me 57% X = 4-OMe 70% X = 3,5-Cl$_2$ 45%

In conclusion, the use of 2-(2′-pyridyl)pyrrolyls as ancillaries on titanium allows 3-component coupling of monosubstituted hydrazines with alkynes and isonitriles to produce pyrazoles in a single step. Improvements in catalyst design to increase the substrate scope and reduce heating times are currently being sought in different derivatives of this successful framework.

Notes and references

‡ *Crystal data* for **1**: $C_{26}H_{34}N_6Ti$, M = 478.49, monoclinic, a = 10.7933(11) Å, b = 14.4889(14) Å, c = 15.8761(16) Å, β = 97.072(1)°, U = 2463.9(4) Å^3, space group $P2_1/c$, Z = 4, μ(Mo-Kα) = 0.606 mm^{-1}, θ range 1.90 to 25.36°, 4497 independent reflections (R_{int} = 0.0333), GoF = 1.040, $wR(F^2)$ = 0.0875, R_1 = 0.033.

§ *General Procedure for Catalyses*: A pressure tube with a threaded top was loaded with a stir bar, toluene (2 mL), cyclohexylisonitrile (1.5 mmol), hydrazine (1 mmol), alkyne (1 mmol), and **1** (15 mol%, 72 mg). The tube was fitted with a Teflon cap, removed from the dry box, and heated at 100 °C for 36 h. The compounds were purified by column chromatography on neutral alumina.

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