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Titanium catalyzed one-pot multicomponent coupling reactions for direct access to substituted pyrimidines

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ABSTRACT

A titanium-catalyzed 3-component coupling reaction can be used to generate tautomers of 1,3-diimines. These diimines produced in situ undergo condensation with amidines in a one-pot procedure to provide substituted pyrimidines. Seventeen examples of pyrimidines are provided using this one-pot, 4-component procedure from simple starting materials. In some cases, catalyst architecture can be tuned to control the regioselectivity of the alkyne addition. Finally, the regioselectivity of amidine addition to unsymmetrical 1,3-diimines is discussed.

1. Introduction

The pyrimidine core is found in a wide range of natural products and bioactive molecules.[1] Recently, pyrimidyl structural motifs have appeared in a variety of synthetic pharmacophores having antibacterial,[2] antimicrobial, antifungal,[3] and antimycotic[4] activities. Even in the drug zidovudine (Retrovir®), the first drug approved for the treatment of AIDS and HIV infection, is based on the pyrimidine core.[5] Some diaminopyrimidines, such as pyrimethamine (Daraprim®) or trimethoprim (Proloprim®) are powerful antimalarial drugs.[6]

The ubiquity of the pyrimidine substructure in natural products and pharmaceuticals, has resulted in a plethora of synthetic routes to this important ring system; most of these synthetic protocols involve direct condensation of amidines or amidinium salts with 1,3-dicarbonyl compounds.[7] Cross-coupling chemistry has advanced the synthesis of various substituted pyrimidines from halogen precursors.[8] In these methods the practical disadvantage is the difficulty in synthesizing unsymmetrical pyrimidine compounds due to the multistep synthesis of the unsymmetrical diketone precursors or the appropriately substituted halo pyrimidines.

To this end, transition metal catalyzed multicomponent coupling reactions can be a suitable alternative for direct access to synthetic equivalents of unsymmetrical 1,3-dicarbonyl precursors. Herein we report a new titanium mediated one-pot multicomponent coupling followed by amidine condensation sequence for direct access to substituted pyrimidines.

2. Results and discussion

In previous multicomponent coupling research in our group, we discovered a novel titanium-catalyzed 3-component (3CC) coupling[9] of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers.[10] In this work in situ generated 1,3-diimine tautomers are reacted with a variety of amidine derivatives as a new one-pot 4-component coupling strategy for direct access to substituted pyrimidine compounds.

The multicomponent reaction utilized here is a formal addition of iminyl and amine groups across an alkyne triple bond, iminoamination.[8] The proposed catalytic cycle (Scheme 1) for the formation of the 3CC product is based on the mechanism of catalytic alkyne hydroamination.[11] It is proposed that the titanium precatalyst, bis(dimethylamido)titanium, reacts with a primary amine to generate a titanium imido species, which undergoes reversible [2+2]-cycloaddition with an alkyne to generate an azametallocyclobutene intermediate.[12] Subsequent, 1,1-insertion of isonitrile into the Ti–C bond generates a five-membered metallacycle,[13] which is then proteolytically cleaved from the metal for catalyst turnover.

For this study, two pyrrole-based titanium catalysts, Ti(dpma)$(NMe_2)_2$[14] (**1**) and Ti(dpm)$(NMe_2)_2$[15] (**2**), were employed. Both these catalysts can be synthesized in a single step in almost

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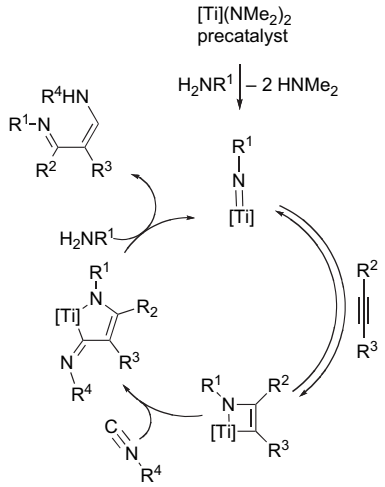
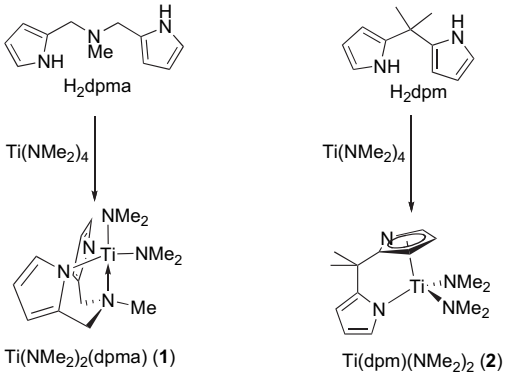
quantitative yield by reacting commercially available $Ti(NMe_2)_4$ with H_2dpma or H_2dpm (Scheme 2). The H_2dpma ligand is prepared[16] in a single step by Mannich condensation of pyrrole, formaldehyde, and methylamine hydrochloride in ethanol/water; whereas, H_2dpm is synthesized by condensation of pyrrole and acetone in the presence of trifluoroacetic acid (TFA).[17]



Scheme 1. Proposed catalytic cycle for iminoamination.



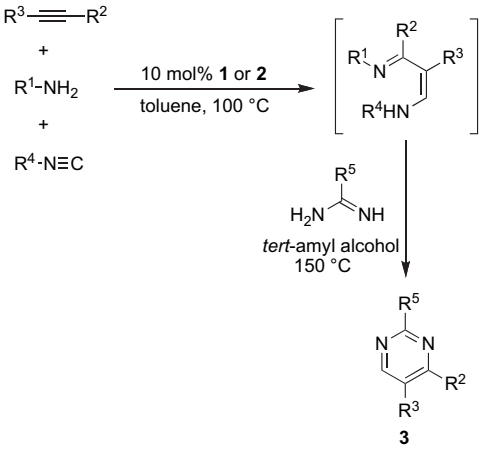
Scheme 2. Generation of titanium catalysts.

The multicomponent coupling reaction is quite effective for both terminal and internal alkynes with a variety of aliphatic and aromatic amines. Because the substituent on the isonitrile does not end up in the final pyrimidine product, *tert*-butylisonitrile was employed exclusively here due to its general applicability in this reaction. Ease of synthesis is an advantage of *t*-BuNC as well, which is readily prepared from *tert*-butylamine and chloroform in the presence of base.[18] Alternatively, the isonitrile is commercially available. Similarly in the case of the amine, we used inexpensive and readily available cyclohexylamine or aniline as these substituents are lost in the *cyclo*-condensation step of the one-pot synthesis.

Barluenga and co-workers have published many notable papers in '1-azabutadiene' chemistry where the intermediates were isolated from reactions of saturated nitriles with Schiff bases in the presence of $AlCl_3$.[19] Gupton and co-workers reported the synthesis of pyrimidines from vinylogous iminium salts, which were prepared in a few steps starting from α,β-unsaturated β-aminoketones.[20] These '1-azabutadienes' and vinylogous iminium salts 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 in some cases to control regioselectivity giving different products from the same substrates (vide infra).

Initial studies focused on the condensation reaction of the isolated 3CC product with benzamidine hydrochloride. In these reactions, the pyrimidine compounds were isolated in 60–70% yield under optimized reaction conditions. With the optimal conditions in hand, the multicomponent coupling was carried out with phenylacetylene, cyclohexylamine, and *tert*-butylisonitrile followed by one-pot condensation with benzamidine hydrochloride. The resulting 2,5-diphenylpyrimidine was isolated in 51% yield in this one-pot methodology.

The general procedure involves 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 is sealed and heated at 100 °C with stirring. Once the multicomponent coupling reaction was complete as judged by GC–FID, the volatiles were removed in vacuo and 2 mL of *tert*-amyl alcohol along with amidine or amidine hydrochloride was added to the crude residue. After additional heating,[21] the product pyrimidine (**3**) was purified by chromatography or crystallization (Scheme 3).



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

Some applications of this one-pot multicomponent coupling methodology are shown in Tables 1 and 2. Initial studies focused on the 3CC of a variety of different alkynes followed by *cyclo*-condensation with benzamidine hydrochloride to afford substituted pyrimidines. Most of the alkynes listed here formed only one 3CC product except in case of phenylacetylene (entry 3a), where ~5% of an isomer was observed. Moreover, heteroaromatic alkynes (entries 3i and 3j) as well as enynes (entry 3h) can be successfully converted to the corresponding pyrimidine compounds.

The regioselectivity of the multicomponent reaction is set by the [2+2]-cycloaddition reaction in conjunction with the relative trapping rates by isonitrile. The regioselectivity of the addition is electronically controlled when an arene is found on the alkyne triple bond through stabilization of a partial anionic charge adjacent to the metal in the azametallacyclobutene intermediate.[12b] This results in 5-(aryl)pyrimidine substitution being electronically favored for aryl substituted alkynes. For 1-hexyne, for example, it is possible to control the regioselectivity of the alkyne addition to get either 4- or 5-substitution with choice of catalyst (entries 3c and 3d).

For the second stage of the study, we chose to look at the multicomponent coupling product of phenylacetylene, *tert*-