Communication

A Sustainable Multi-Component Pyrimidine Synthesis

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A Sustainable Multi-Component Pyrimidine Synthesis

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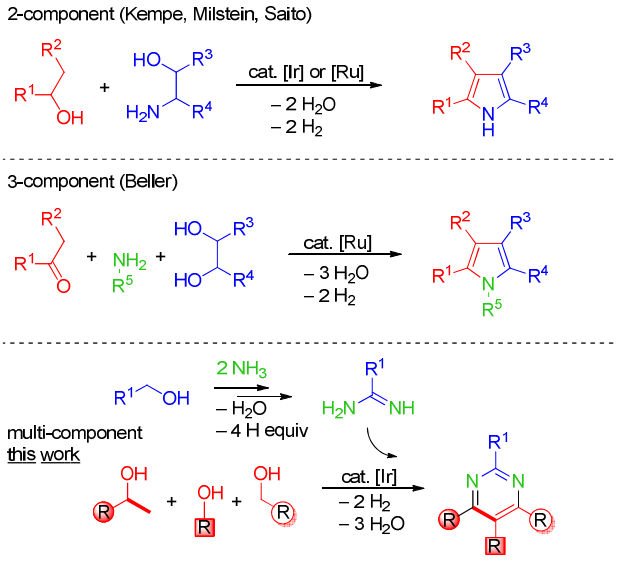
Supporting Information Placeholder

ABSTRACT: Since alcohols are accessible from indigestible biomass (lignocellulose), the development of novel preferentially catalytic reactions in which alcohols are converted into important classes of fine chemicals is a central topic of sustainable synthesis. Multi-component reactions are especially attractive in organic chemistry as they allow the synthesis of large libraries of diversely functionalized products in a short time when run in a combinatorial fashion. Herein, we report a novel, regioselective, iridium catalyzed multi-component synthesis of pyrimidines from amidines and up to three (different) alcohols. This reaction proceeds via a sequence of condensation and dehydrogenation steps which give rise to selective C-C and C-N bond formations. While the condensation steps deoxygenate the alcohol components, the dehydrogenations lead to aromatization. Two equivalents of hydrogen and water are liberated in the course of the reactions. PN_5P-Ir-pincer complexes, recently developed in our laboratory, catalyze this sustainable multi-component process most efficiently. 38 different pyrimidines were synthesized in isolated yields of up to 93%. Strong points of the new protocol are its regioselectivity and thus the immediate access to pyrimidines that are highly and unsymmetrically decorated with alkyl or aryl substituents. The combination of this novel protocol with established methods for converting alcohols to nitriles now even allows to selectively assemble pyrimidines from four alcohol building blocks and two equivalents of ammonia.

Dwindling fossil carbon resources and environmental concerns associated with their use call for alternative ways to produce fine chemicals. Out of the available biomass, lignocellulose is especially attractive since it is abundantly available[1] and food chain competition is negligible. Since lignocellulose can be catalytically processed to alcohols,[2] the development of novel catalytic reactions converting alcohols into important classes of compounds is highly desirable.[3] Aromatic N-heterocyclic compounds have a wide range of applications and also feature prominently in medicinal chemistry.[4] Recently, a sustainable 2-component synthesis of pyrroles from alcohols has been reported by the groups of Milstein, Saito and us (Scheme 1, top).[3,5,6] Diversely functionalized pyridines have been synthesized similarly.[7] In parallel, Beller and co-workers disclosed a 3-component pyrrole synthesis using the same conceptual approach (Scheme 1, middle).[8] These alcohol-to-heterocycle reactions proceed via a combination of dehydrogenation and condensation: Acceptor-less Dehydrogenative Condensation and represent a novel and sustainable approach to construct C-C and C-N multiple bonds.[9] Condensation steps deoxygenate the alcohols and dehydrogenation allows aromatization. Multi-component reactions[10] are especially attractive among the transition metal mediated or catalyzed syntheses of aromatic N-heterocycles.[11] Large libraries of diversely substituted products can be synthesized without constructing sophisticated educts. We became interested in developing a 4-component reaction in which amidines and three (different) alcohol components are selectively connected to pyrimidines (Scheme 1, bottom). Based on the already known catalytic methodology to synthesize nitriles from alcohols,[12] the selective assembly of pyrimidines just from alcohols and ammonia (Scheme 1, bottom) becomes feasible.

Scheme 1. Recently introduced syntheses of aromatic *N*-heterocycles from alcohols (top and middle) and the pyrimidine synthesis described here (bottom)

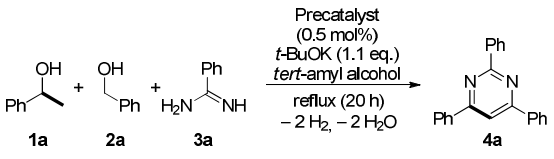


Herein, we report on a novel iridium catalyzed multi-component pyrimidine synthesis. Alcohols and one equivalent of an amidine are selectively linked via C-C and C-N bond formation steps. Two equivalents of hydrogen and water are liberated in the course of this sustainable reaction. The synthesis protocol is especially useful with regard to the formation of diversely and selectively arylated and/or alkylated pyrimidines.

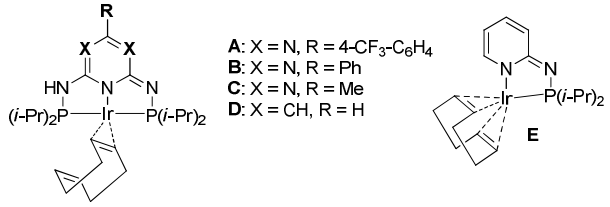
Initially, we investigated the 3-component reaction of 1-substituted ethanol derivatives with primary alcohols (Table

1, top). The two alcohols get oxidized by the Ir-catalyst with release of dihydrogen. A subsequent base-mediated aldol condensation may afford an α,β-unsaturated ketone intermediate, which in turn could react with the amidine.[4] The C-alkylation by alcohols[13] (borrowing hydrogen or hydrogen auto-transfer concept) represents a frequently used C-C bond formation strategy employing alcohols, but to date there are only a few reactions described where the unsaturated primary product is directly used as a reaction intermediate (e.g. for 1,4-addition of a nucleophile).[14] We recently extended the β-alkylation concept to methyl-N-heteroarenes.[15] The optimal conditions (solvent, base, temperature, and catalyst) for the 3-component reaction were identified by thoroughly investigating the reaction of 1-phenylethanol, benzyl alcohol, and benzamidine (Table 1). For instance, we found that the reaction should be run with KOH or *t*-BuOK as the base in *tert*-amyl alcohol under reflux [for details of the screenings *cf.* Supporting Information (SI)]. Precatalysts **A** and **B** (Table 1, entries 1, 2) gave the highest yield of 2,3,5-triphenylpyrimidine (**4a**) in the screening reaction. Based on the convenience of ^{19}F NMR spectroscopy, catalyst **A** was selected.

Table 1. Catalyst Screening[a]



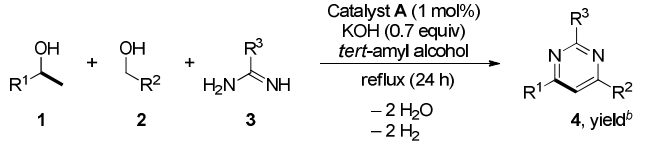
Entry	Precatalyst	Yield [%][b]
1	A	83
2	B	79
3	C	75
4	D	64
5	E	45
6	0.5 $[IrCl(COD)]_2$	43
7	0.5 $[Ir(OMe)(COD)]_2$	37

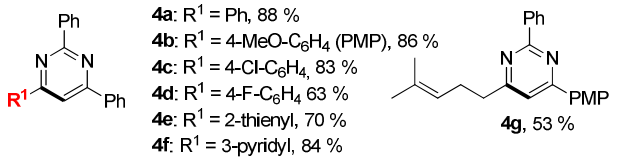


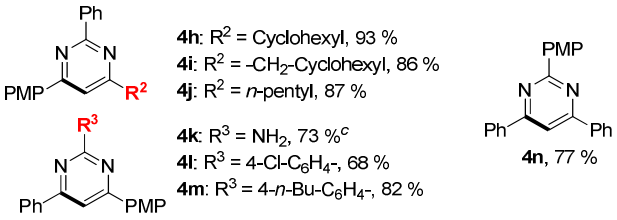
[a]Reaction conditions: 1-Phenyl ethanol (2 mmol), benzyl alcohol (2 mmol), benzamidine (1 mmol), *t*-BuOK (1.1 mmol), *tert*-amyl alcohol (3 mL), catalyst (0.005 mmol), 20 h reflux under inert atmosphere. [b]Yield was determined by GC with dodecane as internal standard. COD = 1,5-Cyclooctadiene, Me = methyl, Ph = phenyl, *i*-Pr = *iso*-propyl, Bu = butyl.

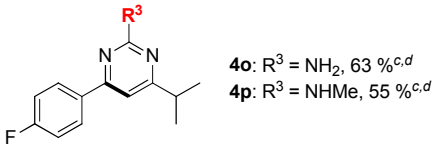
A substrate ratio of 2 equiv of each alcohol with respect to the amidine was found to give the highest yield of pyrimidine. Noticed side-reactions were self-condensation of the secondary alcohol (upon oxidation) and irreversible reduction of the conjugated C=C double bond of the unsaturated ketone. However, the amidine reacts preferably with a less-substituted α,β-unsaturated ketone compared to an unsaturated ketone which is derived from multiple alkylations. When the reaction was run with 0.5 equiv KOH (w/r to the amidine), complete conversion of the alcohols was observed for the screening reaction. A catalyst loading of 1 mol% with respect to the amidine (0.25 mol% with respect to alcohols) was chosen to allow for a broad range of alcohols. Having pinpointed these optimal conditions, we then addressed the scope of possible substrates for this 3-component reaction (Table 2, compounds **4a-p**). Variation of the secondary alcohol led to compounds **4a-g** (Table 2). Aryl chlorides, heterocycles like pyridine and thiophene, as well as olefins were tolerated. Very good isolated yield were obtained for most pyrimidine products. Compound **4g** (olefinic functional group) was isolated in lower yield since alkylation can occur on the primary and secondary carbon atom. No reduction of the double bond was observed (GC-MS analysis). The primary alcohol was then varied to introduce branched (**4h**, Cy = cyclohexyl) or linear aliphatic moieties (**4i,j**) in again very good isolated yields.

Table 2. Synthesis of tri-substituted pyrimidines via 3-component reaction[a]







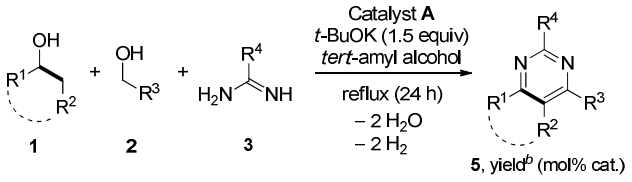


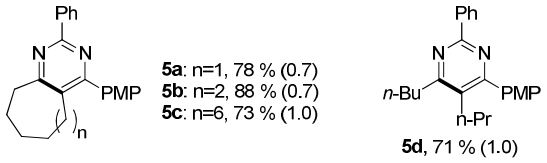
[a] Reaction conditions: Secondary alcohol (2 mmol), primary alcohol (2 mmol), amidine (1 mmol), KOH (0.7 mmol), catalyst A (0.01 mmol), *tert*-amyl alcohol (3 mL), 24 h reflux under inert atmosphere. PMP = *para*-methoxyphenyl; [b]Yields of isolated products. [c]additional 1.0 equiv KOH to trap HCl from guanidine hydrochloride. [d] 1.1 equiv of secondary alcohol.

Last, the amidine moiety was varied. The use of guanidine (as the hydrochloride along with an additional equivalent of KOH) gave the pyrimidine **4k** and gratifyingly no *N*-alkylation of the amino function was observed under the

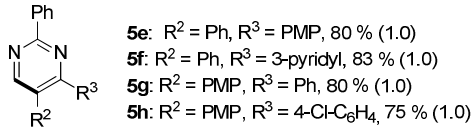
reaction conditions used. Substituents (*n*-butyl, methoxy, chloride) at the phenyl ring of benzamidine gave rise to the products **4l-n**. The application of 1-(4-fluorophenyl)-ethanol, isobutanol and guanidine or methyl guanidine hydrochloride afforded the core pyrimidines **4o** and **4p** of the drug rosuvastatin which acts as a HMG-CoA reductase inhibitor and is used to treat high cholesterol levels. In this case, the amount of secondary alcohol could be lowered to 1.1 equiv since no saturated β-alkylation product was observed. After having addressed the 2,4,6-substitution, we became interested in employing secondary alcohols carrying a substituent at the β-position. The significantly more challenging alkylation of a secondary carbon atom gives access to fully substituted pyrimidines. An optimization of the substrate ratio in the reaction between cycloheptanol, *para*-methoxybenzyl alcohol and benzamidine, which afforded pyrimidine **5b** (Table 3), indicated that the amount of primary alcohol can be lowered from 2.0 to 1.1 equivalents. When a secondary carbon atom is alkylated, reduction of the α,β-unsaturated ketone is significantly slower as the C=C bond is less accessible for the Ir catalyst. With these optimal conditions established, we prepared pyrimidines with a fused carbocycle (Table 3, **5a-c**) from cyclic alcohols and **5d** from nonan-5-ol. 2,4,5-substituted pyrimidines (**5e-h**) were obtained by employing two primary alcohols of which one contributes the C-2 fragment to the pyrimidine core. For this reaction, the use of KOH was found to be superior compared to *t*-BuOK and most of the examples were isolated in very good yields.

Table 3. Synthesis of pyrimidines via alkylation of methylene groups[a]





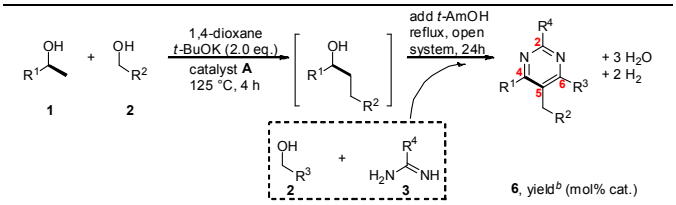
With KOH (1.5 equiv) as base for R^1 = H:

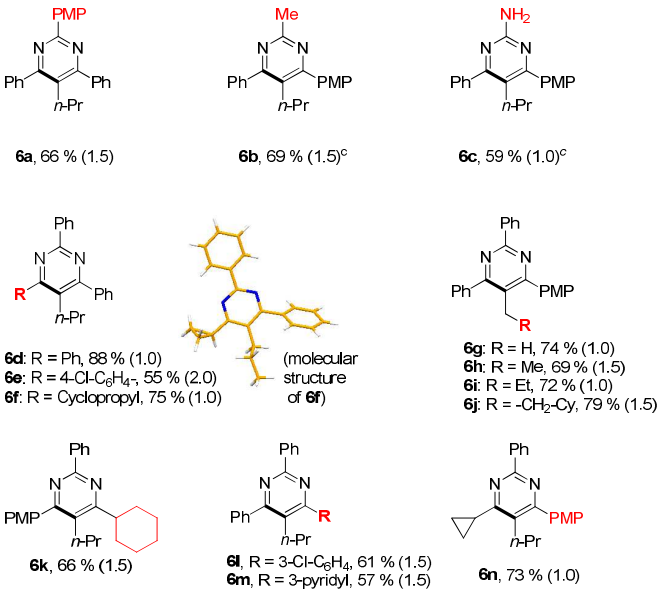


[a]Reaction conditions: Secondary alcohol (2 mmol), primary alcohol (1.1 mmol), amidine (1 mmol,), *t*-BuOK (1.5 mmol), catalyst A (0.007-0.010 mmol), *tert*-amyl alcohol (3 mL), 24 h reflux under inert atmosphere. KOH (1.5 mmol) was used for 2,4,5-substituted pyrimidines. [b]Yields of isolated products. PMP = *para*-methoxyphenyl.

Based on the efficient and selective alkylation of a secondary carbon atoms (synthesis of **5a-h**, Table 3), a consecutive 4-component reaction becomes feasible. In the first step, the "secondary carbon atom" is formed by selective β-alkylation of the methyl group of 1-substituted ethanol derivatives (Table 4, top, left). Addition of a third alcohol and the amidine building block can give rise to fully substituted pyrimidines. Since this synthesis features four starting materials and four catalyst operations (three oxidations, one reduction) suitable reaction conditions had to be found. The reaction between 1-phenylethanol, 1-propanol and the later addition of benzamidine and benzyl alcohol was chosen as the model reaction. We found that the β-alkylation reaction proceeds within less than four hours if 1,4-dioxane and *t*-BuOK were used as solvent and base, respectively.

Table 4. Synthesis of tetra-substituted pyrimidines by a consecutive 4-component reaction[a]





[a]Reaction conditions: Secondary alcohol (2 mmol), primary alcohol (2.2 mmol), *t*-BuOK (2.0 mmol), catalyst **A** (0.01-0.02 mmol), 1,4-dioxane (1-2 mL), 4 h at 125 °C (oil bath). Then addition of remaining starting materials: primary alcohol (1.1 mmol), amidine (1.0 mmol) in *tert*-amyl alcohol (2 mL), 24 h reflux under inert atmosphere. [b] Yields of isolated products. PMP = *para*-methoxyphenyl, Cy = cyclohexyl. [c] Corresponding amidine or guanidine hydrochloride (respectively) along with 1 additional equiv of *t*-BuOK was used.

The optimal ratio for the β-alkylation reaction was 1 equiv of secondary alcohol and 1.1 equiv of primary alcohol. The complete conversion of the secondary alcohol is important, because its reaction with the later added third alcohol component would lead to 5-unsubstituted pyrimidines and thus to a

product mixture. It should be noted, that the β-alkylation reaction can either be run in a pressurized tube or in an open system (reflux condenser). In no case, a product with a C=C bond was observed (GC-MS monitoring). Next, the addition of a solution of benzamidine and benzyl alcohol was investigated and *tert*-amyl alcohol (2 mL/mmol amidine) turned out to be optimal as the solvent. A base screening indicated, that *t*-BuOK is most efficient, as is catalyst **A** in 1-2 mol% loading. With these reaction conditions in hand, we started exploring the substrate scope of the consecutive 4-component reaction (Table 4). First, the "N-C-N" substituent was varied. Aryl (**6a**), alkyl (**6b**) and an amino function (**6c**, from guanidine) can be introduced in this position. Second, the substituent at the 4-position was varied by employing different 1-substituted ethanol derivatives which, in addition to this substituent, contribute two carbon atoms to the pyrimidine ring (for numbering, see Table 4, top right). Aromatic (**6d,e**) as well as aliphatic substituents (**6f**) were tolerated. Third, different primary alcohols were used in the first reaction as a source of the respective residues at the 5-position (**6g-j**). Notably, the use of methanol gave rise to a primary quasi-benzylic functional group at the pyrimidine in 5-position which is interesting for further functionalization reactions. Fourth, the remaining substituent at C-6, which is introduced with the primary alcohol added last, was varied. Aliphatic (Cy = cyclohexyl, **6k**) and (hetero)aromatic (**6l-n**) substituents can be introduced. Based on the examples listed in Table 4, and the modular synthesis concept of the consecutive 4-component reaction, a virtual library of more than 300 compounds (5x4x4x4-doublings) has been created.

In summary, we introduced a novel sustainable multicomponent pyrimidine synthesis. Alcohols and amidines can be assembled in 3- or consecutive 4-component reactions. The selective C-C and C-N bond formations proceed with the liberation of two equivalents of dihydrogen (acceptor-less dehydrogenation) and the elimination of water (condensation). Unsymmetrically and fully substituted pyrimidines are accessible. The synthesis protocol is especially useful in forming selectively alkylated and/or arylated pyrimidines. The synthesis of 4-(4-fluorophenyl)-6-isopropylpyrimidin-2-amine underlines the applicability of the novel reactions to the synthesis of important pharmaceuticals. The Ir catalyst used and the optimized reaction conditions allow the presence of a wide range of typical organic functional groups.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interests.

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