Acceptorless dehydrogenative synthesis of pyrimidines from amidine and alcohols by using a carbon-supported Pt catalyst

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Abstract: We report acceptorless dehydrogenative one-pot synthesis of pyrimidine from primary alcohols secondary alcohols and amidines using a carbon-supported Pt catalyst (Pt/C). This reaction proceeds with high atom efficiency via sequencial dehydrogenation, condensation and dehydration steps where cyclization of three components undergo selective C–C and C–N bond formations. The Pt/C catalyst is reusable and the process gives good to excellent yields with wide substrate scopes for the pyrimidine synthesis (30 examples; up to 80% isolated yield).

Keywords: Pt/C catalyst, Acceptorless dehydrogenation, Pyrimidine synthesis.

1. Introduction

Pyrimidines are important structural moieties in natural products and biologically active molecules. They have wide range of applications in pharmaceutical ingredients and functional materials. Kempe and co-workers showed the first example of catalytic one-pot synthesis of pyrimidine from amidine with primary and secondary alcohols, which is more atom-efficient than conventional routes.[1,2] In all cases, however, homogeneous catalysts were utilized that generally suffer from product separation and catalyst recycling. From the viewpoint of sustainable chemistry and large-scale applications, catalyst employed for this selective hydrogenation reaction should be heterogeneous and readily recyclable. In this study, we describe a heterogeneous catalytic system for direct synthesis of pyrimidines from primary alcohols, secondary alcohols and benzamidine. The process employs a Pt-loaded carbon catalyst (Pt/C) and operates under acceptorless dehydrogenative conditions.[3]

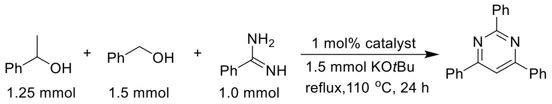
2. Experimental

The catalyst was prepared by impregnating a support with an aqueous HNO_3 solution containing $Pt(NH_3)_2(NO_3)_2$, followed by reduction with H_2 at 300 °C. For a typical reaction, the mixture of toluene (2 mL), primary alcohol (1.5 mmol), secondary alcohol (1.25 mmol) and amidine (1.0 mmol) was injected to the catalyst inside a reactor through a septum inlet, followed by adding KO*t*Bu (1.5 mmol) and by filling with N_2. Subsequently, the resulting mixture was heated at 110 °C and stirred for 24 h under N_2 atmosphere. After the reaction, the reactor was cooled to room temperature, followed by removal of the catalyst by filtration. For the studies of substrate scope, the products were isolated by column chromatography with silica gel 60 (spherical, 40-100 μm, Kanto Chemical Co. Ltd.) using 1% ether solution in pentane as eluting solvent, and the yields of the isolated products were determined. The products were identified by ^1H and ^{13}C NMR and GC-MS equipped with the same column as GC.

3. Results and discussion

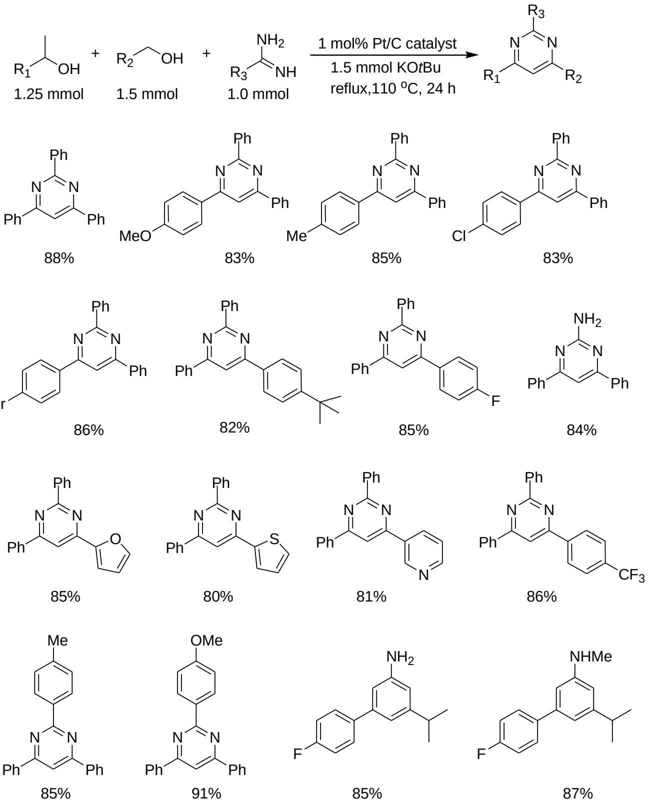
Transmission electron microscope (TEM) observations were made for Pt/C. The Pt particles are highly dispersed over the carbon support and show 4.4 nm average particle size. Results from Temperature-programmed H_2-reduction (H_2-TPR) and X-ray absorption fine structure (XAFS) showed that the deposited Pt nanoparticles are in metallic state.[4,5] The acceptorless dehydrogenation synthesis of pyrimidines was performed, as shown in Table 1. It was found that Pt/C was the most effective among various carbon-supported transition metal catalysts (Pt/C, Ir/C Ru/C, Rh/C, Pd/C, Re/C, Ni/C, Co/C and Cu/C). Pt catalysts loaded on other supports (Pt/Al_2O_3, Pt/CeO_2, Pt/ZrO_2, Pt/MgO, Pt/Nb_2O_5, Pt/TiO_2 and Pt/SiO_2) were also screened (Entry 2 – 9). The Pt/C catalyst showed the highest yield (95%) for the desired 2,3,5-trisubstituted pyrimidines within 24 h (Entry 1). In order to further optimize the reaction conditions such as the amounts of reactants, effects of bases and solvents, various control reactions were carried out using the Pt/C catalyst. The reaction with various bases showed that KO*t*Bu was more effective than other bases such as NaOH, KOH. No product was observed without KO*t*Bu, indicating that the base is indispensable for progression of the reaction. Substrate scopes for the Pt/C-catalyzed system were also explored. The developed catalytic system was effective for the reaction of various primary alcohols (benzylic and heterocyclic), secondary alcohols (aliphatic, 1-phenylethanol) and amidines, providing high yields (80-91%) of the corresponding pyrimidines (Scheme 1). Catalyst reusability was investigated under the standard condition. Pt/C could be recycled for at least four times without significant loss in activity. Moreover, this catalytic system was applicable for gram scale synthesis of pyrimidine**.**

Table 1. Catalyst screening for pyrimidine synthesis from 1-phenyl ethanol, benzylalcohol and benzamidine.^{a}



Entry	Catalyst	Yield^b (%)
1	Pt/C	95
2	Pt/Al_2O_3	65
3	Pt/CeO_2	64
4	Pt/ZrO_2	67
5	Pt/MgO	41
6	Pt/Nb_2O_5	45
7	Pt/TiO_2	55
8	Pt/SiO_2	30
9	Pt/HBEA-40	19
10	Pd/C	34
11	Rh/C	31
12	Co/C	37
13	blank	0

^{a}Reaction conditions: 1.25 mmol 1-phenyl ethanol, 1.5 mmol benzylalcohol, 1.0 mmol benzamidine, 1.5 mmol KO*t*Bu, 0.1 mol% loaded metal, 2 mL toluene, 110 °C, 24 h, N_2 atmosphere. ^{b}GC yields.



Scheme 1. Synthesis of pyrimidines using primary alcohols, secondary alcohols and amidines.

4. Conclusions

We have developed a new catalytic system one-pot synthesis of pyrimidines from primary alcohols, secondary alcohols and benzamidine by a Pt/C catalyst. This system serves as a heterogeneous and recyclable catalytic process to realize pyrimidine synthesis from alcohols and benzamidine through acceptorless dehydrogenative mechanism. Compared with previous catalytic methods with the dehydrogenation mechanism, our method has the following advantages: (1) easy catalyst/product separation, (2) catalyst recyclability, (3) two orders of magnitude higher TON and (4) wide substrate scope.

References

1. N. Deibl, K. Ament, R. Kempe, J. Am. Chem. Soc. 40 (2015) 12804.
2. N. Deibl, K. Ament, R. Kempe, Angew. Chem. Int. Ed. 56 (2017) 1663.
3. S. M. A. H. Siddiki, A. S. Touchy, C. Chaudhari, K. Kon, T. Toyao, K. Shimizu, Org. Chem. Front. 3 (2016) 846.
4. S. M. A. H. Siddiki, A. S. Touchy, K. Kon, T. Toyao, K. Shimizu, ChemCatChem 9 (2017) 2816.
5. S. M. A. H. Siddiki, A. S. Touchy, K. Kon, K. Shimizu, Chem. Eur. J. 22 (2016) 6111.