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Palladium-Catalyzed One-Pot Conversion of Aldehydes to Amides

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Abstract: The palladium-catalyzed one-pot conversion of aldehydes into primary amides in the presence of hydroxylamine hydrochloride in aqueous dimethyl sulfoxide (DMSO) at moderate temperature is described. The process is selective and free from the addition of an external chelating ligand.

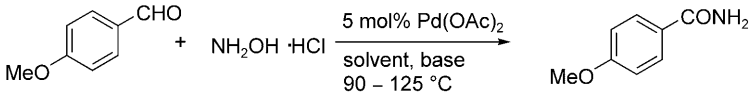
Keywords: aldehydes; homogeneous catalysis; one-pot synthesis; palladium(II) acetate; primary amides

The recent development of metal catalysis with advanced properties has accelerated progress in the organic transformations of certain functional groups into more useful moieties.[1] Among these, the one-pot interconversion of aldehydes into primary amides is one of the most important processes because of their utilities in a wide range of applications in academia and industry, especially as intermediates in organic synthesis, raw materials for plastics, detergents, lubricants and pharmaceuticals.[2] The classical methods used for this purpose, however, require stoichiometric amounts of the reagents such as CH_3SO_3H (30 equiv. with respect to substrate),[3a] CH_3SO_2Cl (1 equiv.)[3b] and ZnO (2 equiv.)[3c] with an excess of hydroxylamine (>3 equiv.). To overcome these drawbacks, attention has been recently focused on the development of catalytic systems for the transformation of aldehydes to primary amides in the presence of hydroxylamine.[4–6] $Rh(OH)_x/Al_2O_3$ has been used as a recyclable catalyst for the interconversion of aldehydes to primary amides at 160 °C in an autoclave.[4] Meanwhile $[Ir(Cp^*)Cl_2]_2$ ($Cp^* = C_5Me_5$) has also been studied for the synthesis of amides from alcohols in toluene under reflux in the presence of a hydrogen acceptor in an inert atmosphere.[5] Later, terpy-Ru$(PPh_3)Cl_2$ has been examined for conversion of aldehydes to primary amides in refluxing toluene under an inert atmosphere.[6] From an industrial standpoint, these studies are attractive because the environmental impact (E-factor) of the process can be lowered.[7] Herein, we wish to report the one-pot transformation of aldehydes with hydroxylamine hydrochloride to primary amides using $Pd(OAc)_2$ as a catalyst in aqueous dimethyl sulfoxide (DMSO) at moderate temperature.[8,9] The present protocol is simple and general for the conversion of alkyl, allyl and aryl aldehydes to the corresponding primary amides. Furthermore, the reactions are free from the addition of additives or external chelating ligands.

First, the standardization of the protocol was carried out with 4-methoxybenzaldehyde as a model substrate using $Pd(OAc)_2$ in the presence of hydroxylamine hydrochloride in different solvents and bases at various temperatures (Table 1). We were pleased to find that the reaction occurred efficiently to afford the desired 4-methoxybenzamide in 95% yield (100% conversion) when the substrate was stirred at 100 °C using 5 mol% of $Pd(OAc)_2$ in the presence of 1.2 equiv. of Cs_2CO_3 in a 3:1 mixture of DMSO and H_2O. The ratio of DMSO and water was crucial for the outcome of the reaction. Pure organic solvents, DMSO, DMF and toluene, were found to be less effective providing the amide in <30% yield. Among the bases, $NaHCO_3$, Na_2CO_3, K_2CO_3 and Cs_2CO_3, the latter provided the best results. Lowering of the reaction temperature (90 °C) or amount of the catalyst (2.5 mol%) led to the formation of the amide in <72% yield.

Next, the scope of the procedure was studied with respect to the reactions of aryl, alkyl and allyl aldehydes. Reactions of benzaldehyde and aryl aldehydes having 2-Cl, 2-OEt, 2-OMe, 2-OC_8H_{17}, 3-Br, 3-NO_2, 4-Br, 4-Cl, 4-F, 4-Me, 4-NO_2, 3,4-di-OMe and 3,4,5-tri-OMe substituents proceeded to give the respective primary amide in 65–98% yield (Table 2). Similar results were obtained with the reactions of 2-naphthal-

Table 1. The standardization of the reaction conditions.



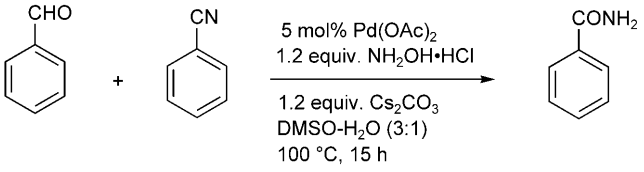
Entry	Solvent	Base	Temperature [°C]	Time [h]	Yield [%][a,b]
1	DMSO	K_2CO_3	125	12	30
2	DMF	K_2CO_3	125	12	21
3	toluene	K_2CO_3	125	12	12
4	DMSO:H_2O (9:1)	K_2CO_3	125	12	51
5	DMSO:H_2O (3:1)	K_2CO_3	125	12	90
6	DMSO:H_2O (1:1)	K_2CO_3	125	12	21
7	DMSO:H_2O (3:1)	KOH	125	10	14
8	DMSO:H_2O (3:1)	Cs_2CO_3	125	10	97
9	DMSO:H_2O (3:1)	Na_2CO_3	125	10	16
10	DMSO:H_2O (3:1)	$NaHCO_3$	125	10	14
11	DMSO:H_2O (3:1)	K_2CO_3	125	12	78[c]
12	DMSO:H_2O (3:1)	K_2CO_3	125	12	32[d]
13	DMSO:H_2O (3:1)	K_2CO_3	125	12	75[e]
14	DMSO:H_2O (3:1)	Cs_2CO_3	100	12	95
15	DMSO:H_2O (3:1)	K_2CO_3	100	12	13
16	DMSO:H_2O (3:1)	Cs_2CO_3	100	12	72[f]
17	DMSO:H_2O (3:1)	Cs_2CO_3	90	12	70
18	DMSO:H_2O (3:1)	Cs_2CO_3	100	8	14[g]

[a] To a stirred solution of *p*-methoxybenzaldehyde (0.5 mmol), $H_2NOH{\cdot}HCl$ (0.6 mmol) and base (0.6 mmol) in DMSO:H_2O (2 mL) for 5 h, $Pd(OAc)_2$ (5 mol%) was added and the reaction mixture was stirred for 5–7 h.
[b] Isolated yield.
[c] Base (1.5 equiv.) was used.
[d] $H_2NOH{\cdot}HCl$ (1 equiv.) was used.
[e] $H_2NOH{\cdot}HCl$ (1.5 equiv.) was used.
[f] $Pd(OAc)_2$ (2.5 mol%) was used.
[g] $Pd(OAc)_2$ (5 mol%) was added at the beginning.

dehyde and heteroaromatic aldehydes such as picolinaldehyde, furan-2-carbaldehyde, thiophene-2-carbaldehyde and 8-methoxyquinoline-2-carbaldehyde (Table 2). In addition, aliphatic aldehydes, acetaldehyde, *n*-hexanal, 2-propanal, and cyclohexanecarbaldehyde as well as an allyl aldehyde, cinnamaldehyde, were transformed to the corresponding primary amide in high yield (Table 3). These results suggest that the protocol is general and aryl, alkyl and allyl aldehydes can be transformed to the corresponding primary amides.

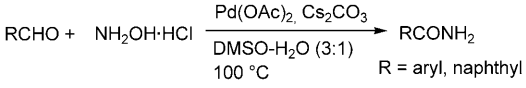
In these reactions, the aldehydes first undergo reaction with hydroxylamine hydrochloride in the presence of base to give aldoximes[10] that are transformed into amides by dehydration and hydration processes.[10h] For example, when a 1:1 mixture of benzaldehyde and benzonitrile was subjected to the optimized conditions, both the substrates were transformed into benzamide in 100% conversion and selectivity (Scheme 1). The reaction of benzaldehyde with hydroxylamine hydrochloride in the presence of molecular sieve 3 Å in dry DMSO gave a trace of amide (<5%) along with benzonitrile (30%) and phenylaldoxime (65%) (Scheme 2). Moreover, the reactions are independent with respect to air or nitrogen atmosphere. Thus, the reaction of the aldehyde with hydroxylamine can give aldoxime which can undergo reaction with $Pd(OAc)_2$ to give intermediate ***a*** (Scheme 3). The latter can transform into ***c*** *via* ***b*** to complete the catalytic cycle by dehydration and hydration processes.

In conclusion, a simple, general and practical one-pot protocol is described for interconversion of aryl, alkyl and allyl aldehdyes into primary amides using $Pd(OAc)_2$ in a DMSO and H_2O mixture under air. The reactions are selective and no by-product formation is observed.



Scheme 1. The reaction of benzaldehyde and benzonitrile in DMSO-H_2O.

Table 2. Pd-catalyzed conversion of aryl aldehydes to amides.



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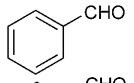
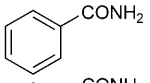
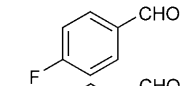
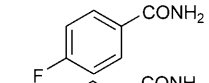
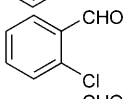
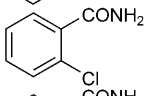
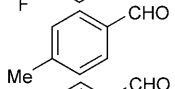
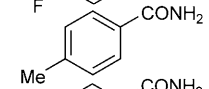
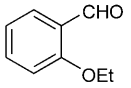
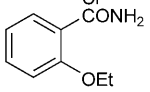
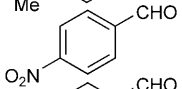
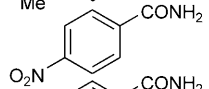
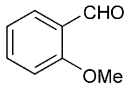
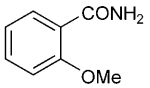
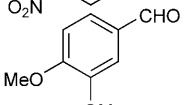
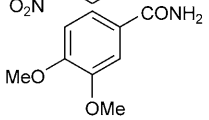
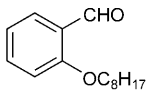
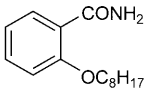
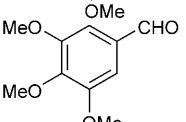
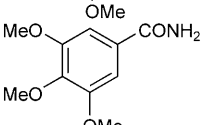
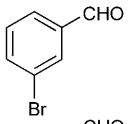
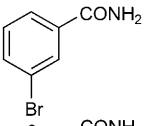
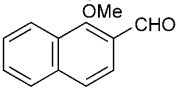
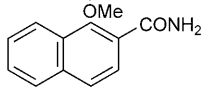
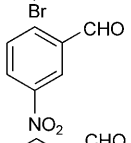
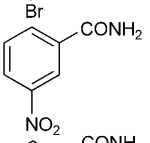
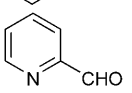
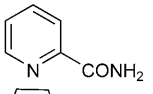
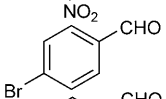
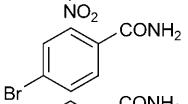
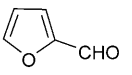
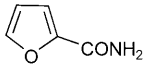
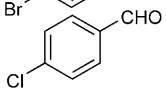
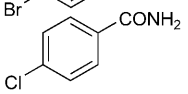
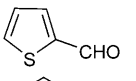
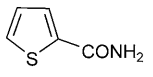
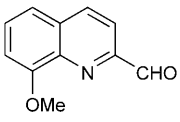
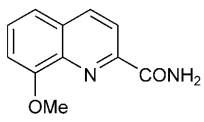
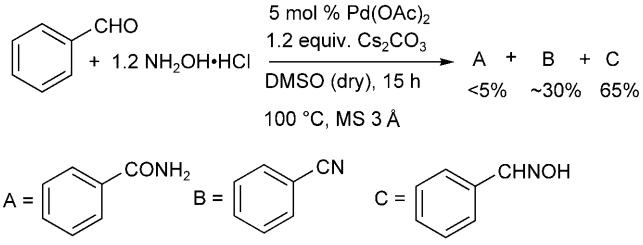
1		15		98	10		15		78
2		21		66	11		15		87
3		19		75	12		12		94
4		23		73	13		18		97
5		23		75	14		20		95
6		14		65	15		18		83
7		12		98	16		20		72
8		15		77	17		10		91
9		11		85	18		10		93
					19		16		95

[a] To a stirred solution of aldehyde (0.5 mmol), $H_2NOH{\cdot}HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) in DMSO:H_2O (3:1, 2 mL) at 100 °C for 5–7 h, $Pd(OAc)_2$ (5 mol%) was added and the reaction mixture was stirred for additional 5–19 h.

[b] Isolated yield.

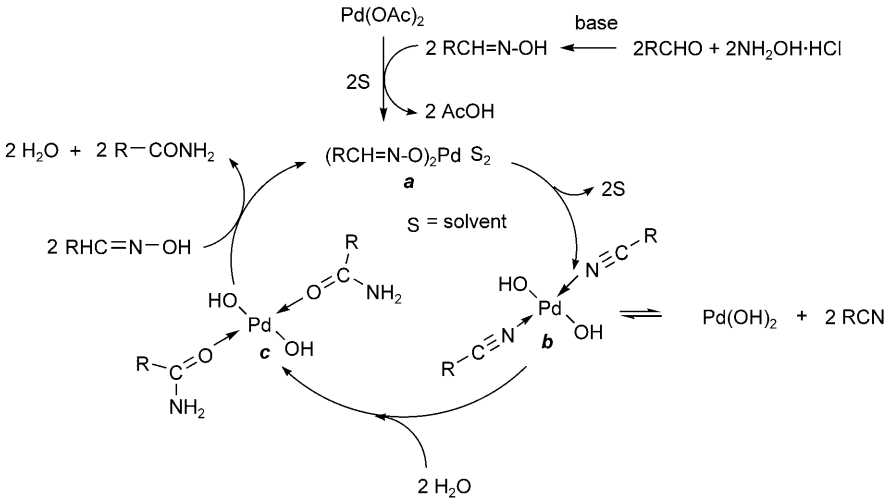


Scheme 2. The reaction in dry DMSO with molecular sieves 3 Å.

Experimental Section

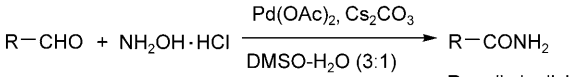
General Procedure for Pd-Catalyzed Conversion of Aldehydes to Primary Amides

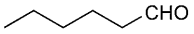
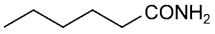
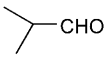
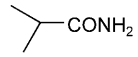
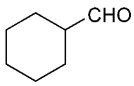
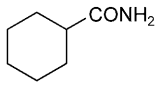
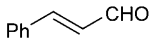
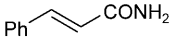
Aldehyde (0.5 mmol), $NH_2OH{\cdot}HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) were stirred at 100 °C for 5–7 h in a 3:1 mixture of DMSO-H_2O (2 mL) under air. Then, $Pd(OAc)_2$ (5 mol%) was added and the stirring continued for the appropriate time (Table 2 and Table 3). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled to room temperature and treated with water (1 mL). The resulting mixture was extracted with ethyl acetate (3×5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane. The products were characterized by NMR (^1H and ^{13}C), IR and CHN analysis.



Scheme 3. Proposed catalytic cycle.

Table 3. Pd-catalyzed conversion of alkyl and allyl aldehydes to amides.



Entry	Substrate	Time [h]	Product	Yield [%][a,b]
1	H_3C-CHO	14	$H_3C-CONH_2$	70
2		16		91
3		15		93
4		17		88
5		14		87

[a] To a stirred solution of aldehyde (0.5 mmol), $H_2NOH{\cdot}HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) in DMSO:H_2O (3:1, 2 mL) at 100 °C for 5–7 h, $Pd(OAc)_2$ (5 mol%) was added and the reaction mixture was stirred for the additional 9–10 h.

[b] Isolated yield.

Supporting Information

Characterization data and NMR (^1H and ^{13}C) spectra of all the amides are given in the Supporting Information.

Acknowledgements

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