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One-Pot Reductive Mono-*N*-alkylation of Aniline and Nitroarene Derivatives Using Aldehydes

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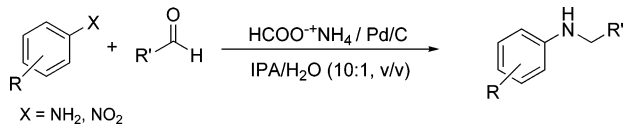


One-pot reductive mono-*N*-alkylation of aniline and nitroarene derivatives using various aldehydes by Pd/C catalyst in aqueous 2-propanol solvent with ammonium formate as in situ hydrogen donor is illustrated. The reaction proceeded smoothly and selectively with excellent yield at room temperature. Our protocol presents a facile, economical, and environmentally benign alternative for reductive amination.

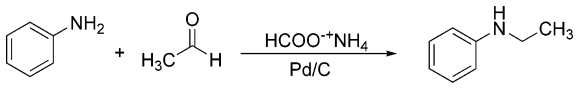
Amines and their derivatives are highly versatile building blocks for various organic substrates and are essential precursors to a variety of biologically active compounds. It has unique biological properties that make it a useful target for various therapeutic applications.[1] Amines also serve other purposes in the fields of bioorganic, industrial, and synthetic organic chemistry.[2] With this growing repertoire of applications, developing efficient methods for the synthesis of amines draws much attention.

Direct reductive amination of aldehydes and ketones is one of the most attractive methods for the synthesis of amine derivatives. This is particularly advantageous because the carbonyl compound and the amine with the appropriate reducing agent are treated in a one-pot fashion such that isolating the imine intermediate is avoided. There have been many reagents developed recently to effect reductive amination of carbonyls. These include the following: $LiClO_4$−zirconium borohydride piperazine complexes,[3] $H_3PW_{12}O_{40}$−$NaBH_4$,[4] $NaBH(OAc)_3$,[5] Ph_2SiH_2, or $PhSiH_3$ with catalytic Bu_2SnClH−pyridine *N*-oxide,[6] $Cu(PPh_3)_2BH_4$ with NH_2SO_3H,[2] thiourea with Hantzsch ester,[7,8] amino borane derivatives with $NaBH_4$,[9] triazole-derived iridium(I) carbine complexes,[10] and $[Ir(cod)_2]BF_4$.[11] These methods have some drawbacks in one way or another such as prolonged reaction time, acidic conditions, higher reaction temperature, excess amount of reagents, inert conditions, and toxic byproducts. Thus, it is necessary to develop an alternative method that employs simple and mild as well as environmentally benign conditions. In addition, there is also a growing specific interest in developing controlled synthesis of secondary amines due to its vast applications. Traditional methodologies for secondary amines are often problematic because of harsh reaction conditions, overalkylation, low chemical selectivity, and generally poor yields.[12] Recently, the use of nitrile[13,14] as alkylating agent was published as an alternative. Herein, we report an efficient, facile, mild, and environmentally benign one-pot reductive mono-*N*-alkylation of aniline and nitroarene derivatives using aldehydes by Pd/C catalyst in aqueous alcoholic solvents with ammonium formate as in situ hydrogen donor.

This investigation started from our curiosity in the reductive amination of ketone using Pd/C catalyst and formate salts.[15] We wondered if this condition worked with aldehydes but to our surprise, when we performed a test reaction using benzaldehyde, the reaction failed to proceed. Thus, we hypothesized that ammonium formate is a nonparticipant in the amination process and that it acts as an in situ hydrogen donor for heterogeneous catalytic hydrogenation. In fact, there have been numerous reports on the versatility of ammonium formate as agent in catalytic hydrogen transfer reactions.[16] Consequently, we decided to prove this hypothesis and find appropriate conditions for the reductive amination of aldehydes.

Initially, we checked for suitable solvent using aniline and acetaldehyde as our test reaction as shown in Scheme 1. We found that 2-propanol/water (10:1, v/v) would give the best yield without dialkylation product (Table 1).

SCHEME 1



Using the same test reaction and the chosen solvent system, we checked the optimum amount of catalyst (Pd/C) and ammonium formate necessary to affect reductive amination (Table 2). Various types of aldehydes were reacted with aniline using this protocol to evaluate its general applicability.

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TABLE 1. Solvent Effect in One-Pot Reductive Amination of Acetaldehyde with Aniline[a]

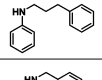
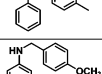
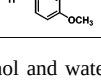
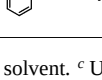
entry	solvent	reaction time (min)	yield (%) *N*-ethyl-aniline	yield (%) *N*,*N*-diethyl-aniline
1	MeOH	10	85	3
2	EtOH	10	no reaction[b]	
3	*i*-PrOH	10	no reaction[b]	
4	MeOH/H_2O[c]	10	83	
5	EtOH/H_2O[c]	10	85	
6	*i*-PrOH/H_2O[c]	10	91	

[a] Used 0.1 equiv of Pd/C and 10 equiv of ammonium formate.[15] [b] Ammonium formate does not dissolved in EtOH and *i*-PrOH. [c] 10:1, v/v.

TABLE 2. Optimization of Pd/C and Ammonium Formate Ratio

entry	solvent	Pd/C (equiv)	ammonium formate (equiv)	reaction time (min)	yield (%)
1	*i*-PrOH/H_2O (10:1, v/v)	0.1	1	120	intractable mixture
2		0.1	5	10	91
3		0.1	10	10	92
4		0.05	10	60	90
5		0.005	10	120	intractable mixture

TABLE 3. One-pot Reductive Amination of Various Aldehydes with Aniline

Entry	Aldehyde	Monoalkylated Product	Yield (%)	Entry	Aldehyde	Monoalkylated Product	Yield (%)
1			45	8[b]			97
2[a]			91	9			quant.
3			94	10[c]			quant.
4			quant.	11[c]			quant.
5			quant.	12[c]			78
6			97	13[c,d]			88
7			98	14[c,d]			86

[a] Reaction time is 10 min. [b] In methanol and water solvent. [c] Used 10 equiv of ammonium formate. [d] The reaction was carried out using premixing method ensuring the formation of imine first; otherwise, the yield would be very low (37% for entry 13 and 10% for entry 14) having several byproducts such as dialkylated amine, alcohol, and starting aniline.

The Pd/C-catalyzed reductive mono-*N*-alkylation of aniline using various aldehydes was summarized in Table 3. Equimolar amount of aldehyde and aniline was reacted at room temperature for 30 min using 0.1 equiv of Pd/C catalyst with 5 equiv of ammonium formate in 2-propanol/water (10:1, v/v) solvent system. Excellent yields of monoalkylation product were obtained except for the cases of formaldehyde (entry 1) and aromatic aldehydes (entries 12−14). They gave lower yields with either starting aniline or alcohol (reduced aldehydes) as byproduct. Aliphatic aldehydes regardless of whether they are

SCHEME 2. Presumed Mechanism

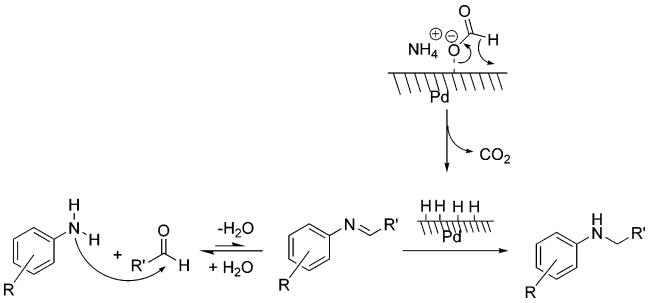
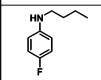
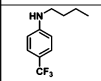


TABLE 4. One-Pot Reductive Amination of Various Aniline Derivatives with Butyraldehyde[a]

Entry	Aniline Derivative	Monoalkylated Product	Yield (%)	Entry	Aniline Derivative	Monoalkylated Product	Yield (%)
1			90	7[b]			95
2			98	8[b,c]			54
3			94	9			95
4			94	10[b,c]			80
5			92	11[b]			96
6			94				

[a] The reaction time is 60 min. [b] Used 10 equiv of ammonium formate. [c] Used 10 equiv of aldehyde.

linear (entries 2−4, 8) or α- (entry 6) or *β*-branched (entry 7) and cyclic (entries 9 and 10) reacted with the same effectiveness. On the basis of our presumed mechanism (Scheme 2), aliphatic and cyclic aldehydes gave excellent yield because the imine intermediate formed is unstable; thus, it was readily converted to product by hydrogenation. On the other hand, probably the imine intermediate formed from the reaction of aromatic aldehyde is stable, and thus, the backward reaction from the imine formed might compete with hydrogenation leading to a decreased in yield.

We further validated the reaction conditions by considering the reaction of various aniline derivatives with butyraldehyde (Table 4). Mono-*N*-alkylation of aniline derivatives bearing electron-donating groups (entries 1−6, 11) at the aromatic ring proceeded smoothly and selectively to the corresponding mono-*N*-alkylated aniline derivatives. The same observations hold with electron-withdrawing groups at the aromatic ring with some exceptions. The aniline having trifluoromethyl (entry 8) and ester (entry10) substituents gave only 54 and 80% yield having 43 and 14% starting aniline, respectively. It is noteworthy that reducible functional groups such as COOH and COOEt survived with this protocol.

There have been reports on the reduction of nitro compounds to their corresponding derivatives using ammonium formate as catalytic hydrogen transfer agent.[17] Considering this idea, we thought that by increasing the amount of ammonium formate

TABLE 5. One-Pot Reductive Amination of Various Aldehydes with Nitrobenzene[a]

Entry	Aldehyde	Monoalkylated Product	Yield (%)	Entry	Aldehyde	Monoalkylated Product	Yield (%)
1			50	7			quant.
2			90	8			98
3			90	9			95
4			quant.	10			97
5			quant.	11[b]			83
6			95				

[a] The reaction was carried out with 10 equiv of ammonium formate for 10 min. [b] Used 12 equiv of ammonium formate; reaction time: 40 min.

we could first reduce the nitro to an amino group in situ and the reaction would proceed in the same manner as mentioned above. To corroborate this hypothesis as well as further expand the applicability of our protocol, we investigated mono-*N*-alkylation of nitrobenzene with various aldehydes (Table 5). The reduction of nitrobenzene to aniline and the mono-*N*-alkylation occurred smoothly and rapidly (only 10 min), and the same observation with the aniline case mentioned above holds. However, this protocol is not applicable to aromatic aldehydes. Our test reaction using benzaldehyde did not give favorable results.

Given that the mono-*N*-alkylation of nitrobenzene proceeded smoothly, we explored the applicability of this protocol to mono-*N*-alkylation of various nitrobenzene derivatives using butyraldehyde (Table 6). Just like the case of aniline derivatives, mono-*N*-alkylation of nitroarene derivatives bearing electron-donating groups (entries 1−6, 11) at the aromatic ring proceeded smoothly and selectively to the corresponding mono-*N*-alkylated aniline derivatives. However, those having electron-withdrawing groups at the aromatic ring (entries 8−10) gave unsatisfactory results having the aniline derivative as byproduct with the exception of fluorine at the para position (entry 7). Nevertheless, it is again noteworthy that reducible functional groups such as COOH and COOEt survived with this protocol even though an excess amount of ammonium formate was used. Indeed, it is plausible to achieve mono-*N*-alkylaniline via a one-pot process without the separation of aniline intermediate.

Furthermore, we also checked the reusability of Pd/C catalyst. We filtered and washed it with water and 2-propanol and directly reused it. The yield did not change even after 10 recycles.

In summary, we have investigated and presented a valuable alternative for one-pot reductive amination. Our protocol

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TABLE 6. One-Pot Reductive Amination of Various Nitroarene Derivatives with Butyraldehyde[a]

Entry	Nitroarene Derivative	Monoalkylated Product	Yield (%)	Entry	Nitroarene Derivative	Monoalkylated Product	Yield (%)
1[b]			88	7[c]			90
2			quant.	8[b, c]			73
3			90	9			78
4[b]			99	10[b, d]			49
5			94	11[b]			98
6			quant.				

[a] The reaction was carried out with 10 equiv of ammonium formate for 60 min. [b] Used 15 equiv of ammonium formate. [c] Used 20 equiv of ammonium formate. [d] Used 10 equiv of aldehyde.

proceeds under neutral and aqueous alcoholic conditions, utilizes readily available, inexpensive, stable, and nontoxic ammonium formate as the in situ hydrogen donor, and makes use of recyclable Pd/C catalyst. Moreover, our one-pot nitro-reduction−direct reductive amination sequence is very innovative. This makes our protocol facile, economical, and environmentally benign.

Experimental Section

General Procedure. 2-Propanol (20 mL) was added to a flask containing Pd/C (0.293 g, 0.275 mmol). Ammonium formate (0.867 g, 13.75 mmol or 1.74 g, 27.5 mmol) dissolved in water (2 mL) was transferred to the same flask. The reaction mixture was stirred for 1 min to activate Pd/C. Next, primary amine or nitro compounds (2.75 mmol) and aldehyde (2.75 mmol) were added, and the reaction mixture was stirred at room temperature (10−30 min or 60 min). After completion of the reaction based on TLC monitoring, the Pd/C catalyst was filtered off on Celite and the solvent was removed by rotary evaporation. The reaction mixture was diluted with CH_2Cl_2 and washed with brine solution. The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography with an appropriate solvent system.

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Supporting Information Available: Detailed experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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