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Alkyl formates as reagents for reductive amination of carbonyl compounds

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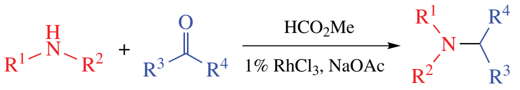
Alkyl formates in the presence of basic additives can serve as a reagent in the direct reductive amination of carbonyl compounds. The developed procedure can be applied to various aldehydes and ketones with electron donating and electron withdrawing groups.



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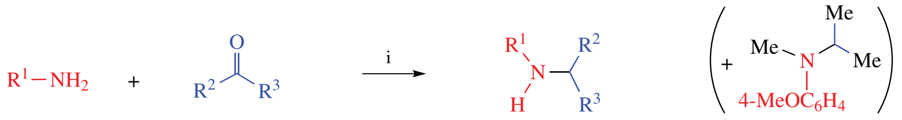
Reductive amination plays a key role in pharmaceutical and medicinal chemistry owing to its synthetic merits and ubiquitous presence of amines among biologically active compounds. Nitrogen-containing compounds play an important role in different fields of chemistry.[1–3] Various reducing agents for the reductive amination are known.[4–8] The main problem of common reducing agents is a balance between activity and selectivity. For example, one of the most selective reagents, namely, sodium triacetoxyborohydride, can reduce starting carbonyl compounds to alcohols, thus lowering the yield of the target amines.[8]

New selective and active reducing agents for the reductive amination are of a great importance for chemists. Reductive amination without an external hydrogen source was developed recently.[9,10] Carbon monoxide is typically used as an oxygen scavenger, allowing one to synthesize amines with a high functional group tolerance.[11–13] The employment of carbon monoxide is convenient and desirable for industrial scale, but it is limited in laboratories because of the necessity of cylinder with CO. A number of compounds can serve as carbon monoxide surrogates[14–16] or precursors for different processes, such as carbonylation or reduction.[14,17–19] Alkyl formates are a good example of a CO-releasing molecules[14,20–26] since they are nontoxic, cheap, readily available and non-corrosive compared with formic acid.

In this work we have developed a convenient and available procedure for the reductive amination using formates as reducing agents. Carbon monoxide can be generated from alkyl and aryl formates in the presence of a base and a metal catalyst. Various parameters influencing the reaction outcome were tested, including catalyst, temperature, solvent additives,

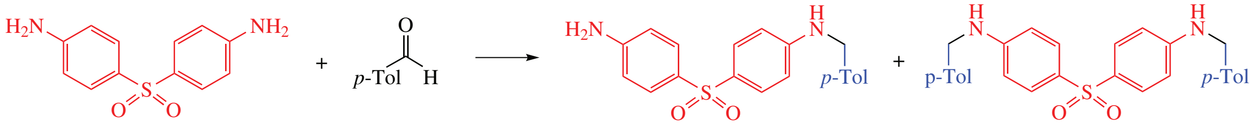


1a,**b** **2a–c** **3a–d** **3′d** (5%)

a R^1 = 4-$MeOC_6H_4$
b R^1 = 4-$EtO_2CC_6H_4$

a R^2 = 4-MeC_6H_4, R^3 = H
b R^2 = 4-ClC_6H_4, R^3 = H
c R^2 = R^3 = Me

3	R^1	R^2	R^3	Yield (%)
a	4-$MeOC_6H_4$	4-MeC_6H_4	H	67
b	4-$MeOC_6H_4$	4-ClC_6H_4	H	54
c	4-$EtO_2CC_6H_4$	4-MeC_6H_4	H	66
d	4-$MeOC_6H_4$	Me	Me	62



4 **5a** (37%) **5b** (18%)

Scheme 1 *Reagents and conditions*: i, **1** or **4**, **2** (1 equiv. or 2.2 equiv. for **4** + **2a** or 10 equiv. for **2c**), $RhCl_3$ (1 mol%), HCO_2Me (10 equiv.), NaOAc (15 equiv.), MeOH (or EtOH for **1b**), H_2O, 160 °C, 24 h.

reaction atmosphere and the formate structure ($HCOOBu^i$, HCOOBn, HCOOMe). The detailed optimization data is provided in the Online Supplementary Materials. As a result, the combination of methyl formate in the presence of 10 equiv. sodium acetate or sodium hydrogen carbonate and 1 mol% of rhodium(III) chloride as a catalyst at 160 °C under nitrogen atmosphere was found to be optimal. With these conditions in hands, we investigated the substrate scope (Scheme 1). Aromatic amines with both electron donating and electron withdrawing groups were benzylated in the yields around 70% (**3a** and **3c**). Electron withdrawing chlorine atom in aldehyde **2b** led to decrease in the yield of product **3b** due to elevated reduction rate of this aldehyde into 4-chlorobenzyl alcohol. Acetone **2c** could be used for the preparation of *N*-isopropylamine derivative **3d**, however, *N*-isopropyl-*N*-methyl derivative **3′d** was also formed. This fact reveals the possibility of N-methylation by methanol in the presence of the metal catalyst. Starting from diamine **4**, a mixture of mono- and dialkylation products **5a**,**b** was generated (see Scheme 1). Although yields are moderate, the developed procedure is tolerant to reducible functional groups such as sulfone. For example, aromatic chlorides can be easily reduced with molecular hydrogen,[8,27] but the chlorine atom persists under the developed conditions.

The suggested procedure was found to be suitable for N-methylation of amines by formaldehyde (Scheme 2). Anilines with electron donating groups (**1a**, **7a)** and electron withdrawing groups (**1b**, **7b)** were dimethylated in good to quantitative yields. When diphenylamine **9** was used as a substrate, along with product **10**, the comparable amount of compound **10′** was detected, whose formation can be rationalized considering the phenol-formaldehyde type condensation. However, no condensation of this type was observed for substituted anilines, which may be accounted for the inductive effect of methoxy group.

In conclusion, the new procedure for the reductive amination comprising alkyl formates as reducing agents has been developed. It does not require corrosive or complex reagents. The limitations of the method were examined and the optimal conditions were found.

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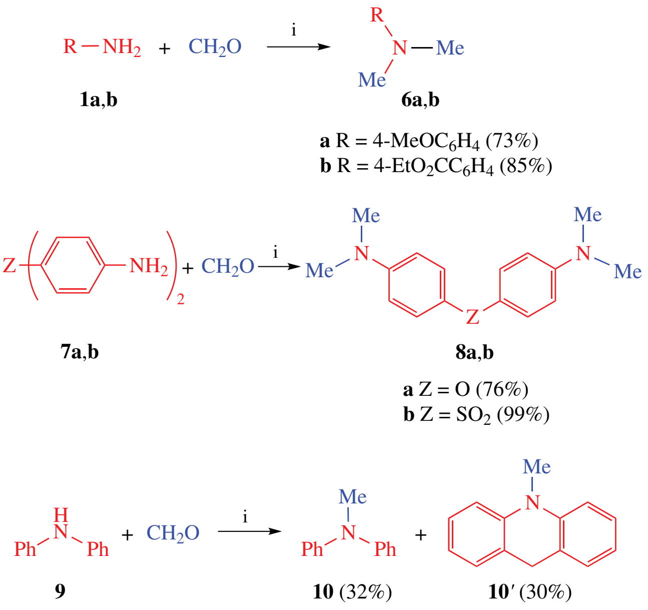

Scheme 2 *Reagents and conditions*: i, $RhCl_3$ (1 mol%), CH_2O (12–20 equiv.), HCO_2Me (10 equiv.), NaOAc (15 equiv.), MeOH (or EtOH for **1b**), H_2O, 160 °C, 24 h.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.01.037.

References

1 A. N. Vereshchagin, K. A. Karpenko, M. N. Elinson, E. O. Dorofeeva, A. S. Goloveshkin and M. P. Egorov, *Mendeleev Commun.*, 2018, **28**, 384.
2 K. P. Trainov, R. F. Salikov, Yu. N. Luponosov, P. S. Savchenko, A. L. Mannanov, S. A. Ponomarenko, D. N. Platonov and Yu. V. Tomilov, *Mendeleev Commun.*, 2019, **29**, 304.
3 V. V. Baranov, Ya. A. Barsegyan, N. G. Kolotyrkina and A. N. Kravchenko, *Mendeleev Commun*., 2019, **29**, 323.
4 K. N. Gusak, Zh. V. Ignatovich and E. V. Koroleva, *Russ. Chem. Rev.*, 2015, **84**, 288.
5 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.
6 T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753.
7 R. P. Tripathi, S. S. Verma, J. Pandey and V. K. Tiwari, *Curr. Org. Chem.*, 2008, **12**, 1093.
8 E. Podyacheva, O. I. Afanasyev, A. A. Tsygankov, M. Makarova and D. Chusov, *Synthesis*, 2019, **51**, 2667.
9 D. Chusov and B. List, *Angew. Chem., Int. Ed.*, 2014, **53**, 5199.
10 N. V. Shvydkiy, E. A. Trifonova, A. M. Shved, Y. V. Nelyubina, D. Chusov, D. S. Perekalin and A. R. Kudinov, *Organometallics*, 2016, **35**, 3025.
11 A. A. Tsygankov, M. Makarova and D. Chusov, *Mendeleev Commun.*, 2018, **28**, 113.
12 J. W. Park and Y. K. Chung, *ACS Catal.*, 2015, **5**, 4846.
13 O. I. Afanasyev, A. A. Tsygankov, D. L. Usanov, D. S. Perekalin, N. V. Shvydkiy, V. I. Maleev, A. R. Kudinov and D. Chusov, *ACS Catal.*, 2016, **6**, 2043.
14 D. Formenti, F. Ferretti and F. Ragaini, *ChemCatChem*, 2018, **10**, 148.
15 S. N. Gockel and K. L. Hull, *Org. Lett.*, 2015, **17**, 3236.
16 P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 6061.
17 N. Jana, F. Zhou and T. G. Driver, *J. Am. Chem. Soc.*, 2015, **137**, 6738.
18 O. I. Afanasyev, D. L. Usanov and D. Chusov, *Org. Biomol. Chem.*, 2017, **15**, 10164.
19 O. I. Afanasyev, A. Zarochintsev, T. Petrushina, A. Cherkasova, G. Denisov, I. Cherkashchenko, O. Chusova, O. Jinho, C. Man-Seog, D. L. Usanov, S. E. Semenov and D. Chusov, *Eur. J. Org. Chem.*, 2019, 32.
20 H. Li, H. Neumann, M. Beller and X.-F. Wu, *Angew. Chem., Int. Ed.*, 2014, **53**, 3183.
21 Y. Katafuchi, T. Fujihara, T. Iwai, J. Terao and Y. Tsuji, *Adv. Synth. Catal.*, 2011, **353**, 475.
22 S. P. Chavan and B. M. Bhanage, *Eur. J. Org. Chem.*, 2015, 2405.
23 W. Chang, J. Li, W. Ren and Y. Shi, *Org. Biomol. Chem.*, 2016, **14**, 3047.
24 H. Konishi, H. Nagase and K. Manabe, *Chem. Commun.*, 2015, **51**, 1854.
25 T. Ueda, H. Konishi and K. Manabe, *Org. Lett.*, 2012, **14**, 3100.
26 T. Fujihara, T. Hosoki, Y. Katafuchi, T. Iwai, J. Terao and Y. Tsuji, *Chem. Commun.*, 2012, **48**, 8012.
27 S. K. Aavula, A. Chikkulapalli, N. Hanumanthappa, I. Jyothi, C. H. V. Kumar and S. G. Manjunatha, *Tetrahedron Lett.*, 2013, **54**, 5690.

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