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An efficient reduction of N-substituted carbonylimidazolides into formamides by $NaBH_4$

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ABSTRACT

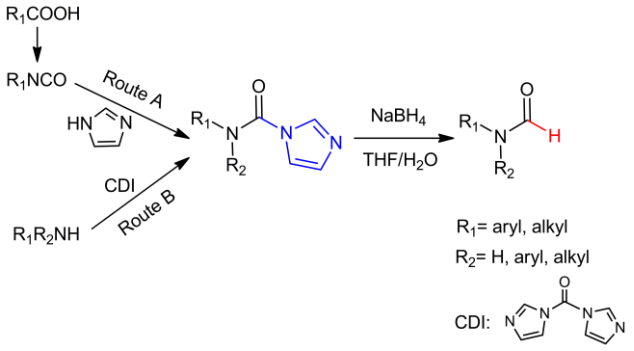
A novel, simple and versatile protocol was investigated for highly efficient synthesis of formamides through reducing N-substituted carbonylimidazolides by $NaBH_4$ under mild reaction conditions. By this method, not only carboxylic acids or isocyanates, but also amines can readily access formamides with high yields.

N-formyl derivatives serve as a valuable class of compounds having a wide range of applications in medicinal and organic chemistry. They are important pharmaceutical intermediates and some have been used as drugs.[1,2] In the field of organic chemistry, formamides are vital raw material in the synthesis of formamidines,[3] isocyanides,[4] Vilsmeier reagents[5] and fungicide.[6] Furthermore, as Lewis bases, they are excellent catalysts in allylation[7] and hydrosilylation[8] of carbonyl compounds and other transformations.[9] In addition, the formyl group is a conventional amino protecting group especially in peptide synthesis.[10]

Hence, a great deal of research has focused on the synthesis of N-formyl derivatives. In most cases, Amines were acted as starting materials, various N-formylating agents and methods were developed for the preparation of formamides.[11] Alternatively, few studies have been devoted to synthesis of formamides starting from carboxylic acids[12] or its derivative such as isocyanate[13] and carbamoyl azide[14]. These protocols had an advantage that N-protected amino acids were adaptable to the preparation of N-protected *gem*-diamines, which were particularly useful for the synthesis of retro-inverso peptides.[15]

However, synthesis of formamides from carboxylic acids often involved in converting carboxyl group into isocyanate, then reaction of it with formic acid.[12] It might be unfavorable for the raw materials of N-Boc protected amino acids or peptides because formic acid was sometimes used as N-Boc deprotection agent.[16] Direct reduction of isocyanates to formamides required a special reducing agent.[13] Although reduction of carbamoyl azide with $NaBH_4$ could also provide formamides.[14] However, carbamoyl azides had poor stability and were difficult to purify and store, which would greatly limit their application.

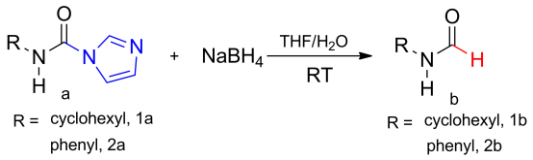
In this work, we reported a novel protocol of synthesis of various formamides in high yield by reduction of N-substituted carbonylimidazolide with $NaBH_4$ at room temperature. As important reagents, N-substituted carbonylimidazolides had good stability and played a particularly role in the preparation of ureas[17], carbamates[18] and thiocarbamates[19]. They could be conveniently prepared by treatment of isocyanates with imidazole, which made our method suitable for the synthesis of formamides from carboxylic acids because isocyanate group could be readily converted from carboxyl group. (Scheme 1, Route **A**). It was to be noted that N-substituted carbonylimidazolide could also be obtained by reaction of amines with commercially available and inexpensive N,N'-carbonyldiimidazole (CDI) (Scheme 1, Route **B**). Therefore, our method was appliable to prepare formamides from amines as well. To the best of our knowledge, there was no any report available about the preparation of formamides from both carboxylic acids or isocyanates and amines.



Scheme 1 Synthesis of formamides from both carboxylic acids or isocyanates and amines

In our initial experiment, the N-cyclohexyl and N-phenyl carbonylimidazolide were chosen to represent the N-aliphatic and N-aromatic substituted carbonylimidazolides, respectively. A common reaction condition was employed, e.g. room temperature (RT) and THF/H_2O mixed solvent system. The reaction was investigated only by regulation of the amount of $NaBH_4$. The reduction of N-cyclohexyl and N-phenyl carbonyl-imidazolide with various equivalents of $NaBH_4$ was performed as model reaction. The results were listed in Table 1.

Table 1. Model Reaction: Optimization of the amount of $NaBH_4$



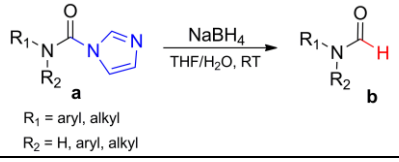
Entry	Starting material	$NaBH_4$ (equiv.)	Time[a] (min)	Yield[b] (%)
1	1a	1.0	200	90
2	2a	1.0	25	91
3	1a	2.0	86	91
4	2a	2.0	23	91
5	1a	3.0	50	90

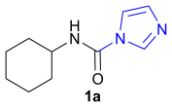
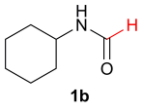
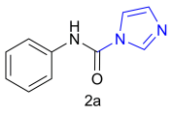
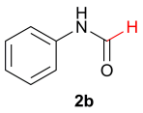
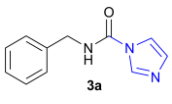
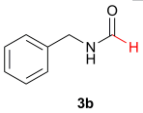
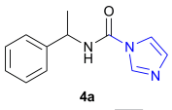
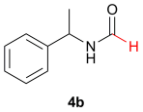
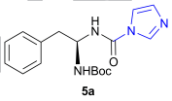
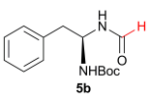
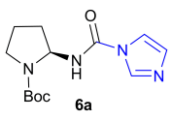
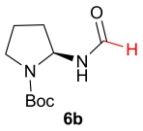
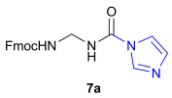
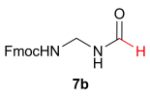
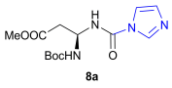
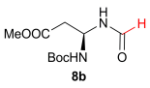
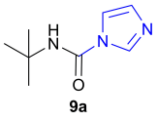
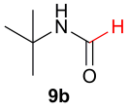
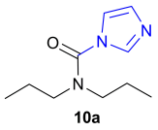
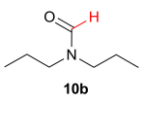
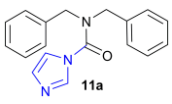
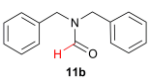
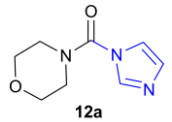
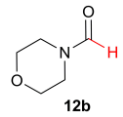
[a] Monitored by TLC. [b] Isolated yield

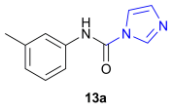
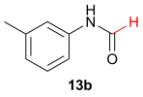
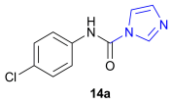
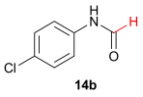
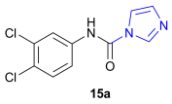
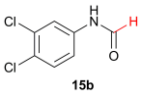
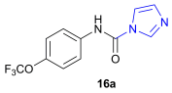
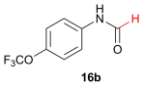
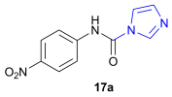
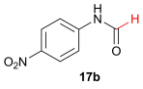
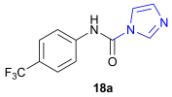
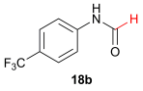
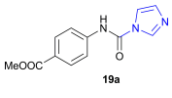
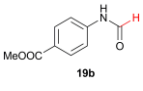
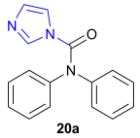
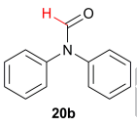
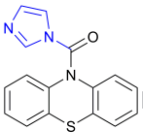
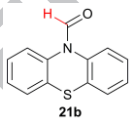
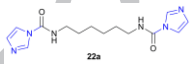
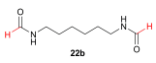
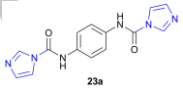
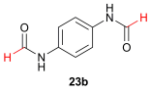
As shown in Table 1, the amount of $NaBH_4$ had a great influence on the reaction time. For N-phenyl carbonylimidazolide, it was sufficient to reduce it in about 25 minutes with 1.0 equiv of $NaBH_4$ and offered an excellent yield. The reaction efficiency cannot be significantly improved by increasing the amount of $NaBH_4$ to 2.0 equiv. However, for N-cyclohexyl counterpart, it took above three hours to carry out the reaction if only 1.0 equiv of $NaBH_4$ was used. When the amount of $NaBH_4$ was increased to 3.0 equiv, the reaction time was shortened to 50 minutes. No attempt had been made to further increase the amount of $NaBH_4$ or to adjust other parameters since these results were completely satisfactory.

With these optimized conditions in hand, we explored the scope of the reaction including N-alkyl carbonylimidazolides (entries 3-12, 22) and N-aryl carbonylimidazolide (entries 13-21, 23) (Table 2). All selected N-substituted carbonylimidazolides had been conveniently prepared by widely used methods. Compounds (**1a**, **9a**, **13a-16a**) were readily prepared by Route **A**,[20] Compounds (**2a-4a**, **10a-12a**, **17a-18a**) were directly synthesized by Route **B**,[21] and Compounds (**5a-8a**) were obtained by Route **A** after converting carboxylic acids to corresponding isocyanates according to the conventional methods we reported.[22] For the N-alkyl and N-aryl carbonylimidazolides, 3.0 equiv and 1.0 equiv of $NaBH_4$ was used respectively. Both N-alkyl and N-aryl carbonylimidazolides reacted smoothly and provided the corresponding formamides in good to excellent yields and for the most of cases, the reaction was completed in 25-50 minutes.[23]

Table 2. Synthesis of formamides



Entry	Substrate	Product	$NaBH_4$ (equiv.)	Yield[a] (%)
1			3.0	90
2			1.0	91
3			3.0	93
4			3.0	96
5			3.0	90
6			3.0	84
7			3.0	86
8			3.0	87
9			3.0	93
10			3.0	90
11			3.0	88
12			3.0	90

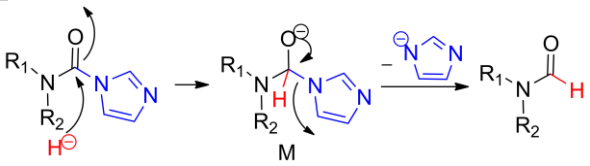
13	 13a	 13b	1.0	93
14	 14a	 14b	1.0	90
15	 15a	 15b	1.0	86
16	 16a	 16b	1.0	92
17	 17a	 17b	1.0	88
18	 18a	 18b	1.0	92
19	 19a	 19b	1.0	95
20	 20a	 20b	1.0	88
21	 21a	 21b	1.0	89
22	 22a	 22b	10.0	84 [b]
23	 23a	 23b	2.0	89

[a] Isolated yield.
[b] Reaction time: 2h.

N-Boc and N-Fmoc protected amino acids (entries **5-8**) were both adaptable to this method. Sterically hindered N-substituted carbonylimidazolides also provided the desired products with satisfied yield not only in the case of aliphatic analogues (entries **9-12**) but also for aromatic substituents (entries **20**, **21**). The substitution on the aromatic ring had no negative influence on the reaction outcome: both electron-releasing (alkyl e.g., entry **13**) and electron-withdrawing [halogen (entries **14, 15**), Trifluoromethoxy(entry **16**), nitro (entry **17**), Trifluoromethyl (entry **18**), ester (entry **19**)] functionalities were tolerated. N-heterocyclic substituted carbonylimidazolides were applicable to this reaction and all three N-heterocyclic substituted carbonylimidazolides (**6a**, **12a**, **21a**) did not compromise the efficiency of the methodology. In addition, two different characteristic methyl esters had been also tested, aliphatic ester (**8a**) and aromatic ester (**19a**) offered corresponding desired products in 87% and 95% yield respectively.

Reduction of 22a and 23a, bearing two N-substituted carbonylimidazolide functionalities, became elusive under the standard conditions. For **22a**, it took 36 minutes to compete the reaction when 2.0 equiv of $NaBH_4$ was used. For **23a**, however, if the amount of $NaBH_4$ was 6.0 equiv, the reaction cannot yet be completed over 4 hours. By increasing the amount of $NaBH_4$ to 10.0 equiv, the reaction time was shortened to 120 minutes.

It is known that the general urea functionality was not susceptible to reducing agent $NaBH_4$ because of the poor electrophilic character of the amide carbonyl group. However, the urea functionality on the N-substituted carbonyl-imidazolides had displayed excellent reactivity. Two key factors could contribute to it. First, by the formation of acylimidazoles, the electron-withdrawing effect of imidazole made the carbonyl carbon more electrophilic to increase its reactivity to nucleophilic attack. Second, as a sufficiently good leaving group[24], the dissociation of the imidazole anion provided the significant driving force. Like the common reaction of N-substituted carbonylimidazolides with nucleophiles such as amines, thiols and alcohols, the dissociation of imidazole anion was also conducive to the reaction.[17-19]



Scheme 2 The possible reaction mechanism

The possible reaction mechanism was shown in Scheme 2. Initially, as an excellent nucleophile, hydrogen anion (H^-) provided by $NaBH_4$ attacked carbonyl carbon atom on urea functionality to form alkoxide intermediate **M**. Subsequently, accompanying by the dissociation of imidazole anion, the unstable alkoxide intermediate converted to carbonyl again and formed the target formamide, which constituted a good amide conjugation system and was stable enough for mild reducing agent $NaBH_4$. The requirement of a less amount of $NaBH_4$ for N-aromatic substituted carbonylimidazolides was closely related to not only the increased electrophilic of N-aromatic substituted carbonylimidazolides by the electron-withdrawing effect of aryl group, but also the easy formation of stronger conjugation system of the resulting N-aromatic formamide products. Different from N-substituted carbonylimidazolides, the carboxylic acid imidazolides were readily reduced into primary alcohols by $NaBH_4$,[25] because the formed intermediate aldehyde was highly reactive and tended to be further reduced by $NaBH_4$ after the carbonyl carbon was attacked by H^- ion and the imidazole anion was removed. When a stronger reducing agent such as $LiAlH_4$ was used, formamides would be over-reduced into N-methylamines.[26]

In summary, we have developed a more versatile method than the previously reported for the preparation of formamides. By our method, not only carboxylic acids or isocyanates, but also amines can readily access formamides. In addition, our method is economical and no expensive catalyst or special reagent is employed. Moreover, the reaction is simple, mild, fast and shows good applicability.

Acknowledgments

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23. **General procedure for the synthesis of formamides (b) from N- substituted carbonylimidazolides (a)**
To a solution of compound **a** 1.0mmol in THF (8 mL) at room temperature, $NaBH_4$ (3.0mmol for N-aliphatic substituted carbonylimidazolides and 1.0mmol for N-aromatic substituted carbonylimidazolides) in 1 mL H_2O was added with vigorous stirring. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was cooled with ice water, 1 M HCl was added carefully till pH=2-3. The solution was extracted with dichloromethane (3×20 mL) and the organic layers were combined. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crudes were purified by silica gel column chromatography.
(6b) yield 84% of white solid; Rf = 0.6 (CH_2Cl_2/MeOH, 9:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) (*trans/cis*= 35/65) δ 8.31 (d, *J* = 10.8 Hz, 1H, *trans*), 8.20 – 7.98 (m, 1H, *cis*), 7.24 (br s, 1H, *cis*), 6.51 (br s, 1H, *trans*), 5.76 – 5.40 (m, 1H, *trans*), 5.34 – 5.06 (m, 1H, *cis*), 3.53 – 3.16 (m, 2H, *trans*, 2H, *cis*), 2.41 – 1.73 (m, 4H, *trans*, 4H, *cis*), 1.43 (s, 9H, *trans*), 1.40 (s, 9H, *cis*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.85, 165.07, 154.12, 153.61, 80.84, 80.30, 65.72, 45.62, 33.47, 32.30, 28.38, 23.07, 22.23. ESI-MS, *m/z* calcd. for $C_{10}H_{18}N_2O_3Na^+$ $[M+Na]^+$ 237.132; found 237.105.
(8b) yield 87% of white solid; Rf = 0.65 (CH_2Cl_2/MeOH, 9:1, v/v);^{1}H NMR (400 MHz, $CDCl_3$) (*trans/cis*= 30/70) δ 8.26 (d, *J* = 11.7 Hz, 1H, *trans*), 8.09 (s, 1H, *cis*), 6.94 (br s, 1H, *cis*), 6.78 (br s, 1H, *trans*), 5.86 (br s, 1H, *cis*), 5.78 (br d, *J* = 8.7 Hz, 1H, *trans*), 5.65 (s, 1H, *cis*), 5.40 (s, 1H, *trans*), 3.72 (s, 3H, *trans*), 3.69 (s, 3H, *cis*), 2.91 (s, 2H, *cis*), 2.81 (s, 2H, *trans*), 1.41 (s, 9H, *trans*, 9H, *cis*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.26, 164.42, 160.58, 154.69, 80.47, 53.96, 52.35, 52.06, 39.47, 38.51, 28.29. ESI-MS, *m/z* calcd. for $C_{10}H_{18}N_2O_5Na^+$ $[M+Na]^+$ 269.122; found 269.094.
(21b) yield 89% of pale green solid; Rf = 0.5 (PE/EtOAc, 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.34 (ddd, *J* = 18.3, 15.0, 8.4 Hz, 5H), 7.25 – 7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.09, 137.39, 135.20, 130.93, 129.46, 127.79, 127.72, 127.54, 127.17, 127.08, 125.66, 121.91. ESI-MS, *m/z* calcd. for $C_{13}H_{10}NOS$ $[M+H]^+$ 228.040; found 228.031.
(22b) 10.0mmol $NaBH_4$ was used; yield 89% of white solid; Rf = 0.35 (CH_2Cl_2/MeOH, 10:1, v/v); ^{1}H NMR (400 MHz, DMSO-d_6) (*trans/cis*= 85/15) δ 7.97 (s, 2H, *trans*), 7.91 (d, *J* = 11.9 Hz, 2H, *cis*), 3.05 (q, *J* = 6.4 Hz, 4H, *trans*, 4H, *cis*), 1.47 – 1.31 (m, 4H, *trans*, 4H, *cis*), 1.28 – 1.18 (m, 4H, *trans*, 4H, *cis*). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.93, 161.34, 41.21, 37.44, 31.29, 29.40, 26.45, 25.97. ESI-MS, *m/z* calcd. for $C_8H_{17}N_2O_2$ $[M+H]^+$ 173.121; found 173.117.
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Supplementary Material

Characterization data of compounds including NMR and MS spectra are available as supplementary material.

Graphical Abstract

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An efficient reduction of N-substituted carbonylimidazolides into formamides by $NaBH_4$

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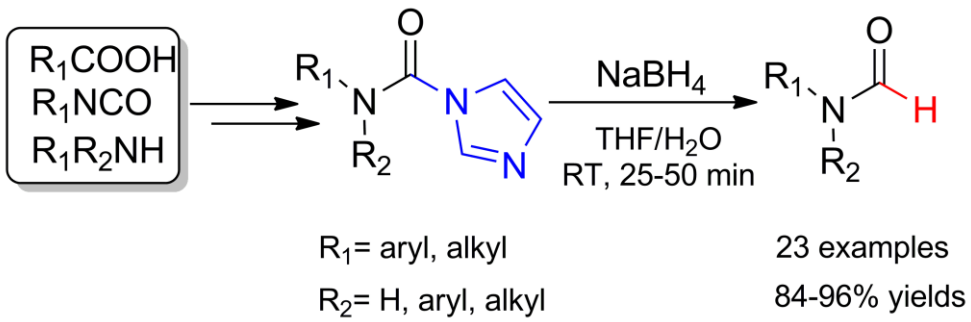
Zhiyong Chen , Yiming Cao, Zeyu Tian , Xuan Zhou , Wenjin Xu , Jia Yang , Hanbing Teng *



R_1= aryl, alkyl

R_2= H, aryl, alkyl

23 examples

84-96% yields

Carboxylic acids, isocyanates and amines are all easy to access formamides by this method.
The method is economical and no expensive catalyst or special reagent is employed.
The reaction is simple, mild, fast and shows good applicability.