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# New approach for induction of alkyl moiety to aliphatic amines by $NaBH(OAc)_3$ with carboxylic acid

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ABSTRACT

We had found the novel *N*-alkylation method, which utilizes carboxylic acids as alkyl sources with sodium triacetoxyborohydride [$NaBH(OAc)_3$]. Our methodology had been revealed to have some advantages over the reported similar procedures. Through the further investigation about our method, it was disclosed that acetonitrile was the suitable solvent and *N*-alkylation for aliphatic amines were also smoothly proceeded. On the way of the research, we discovered that 4-hydroxybutyl moiety was induced to aniline by use of old THF containing peroxidic materials.



## Introduction

Now so many nitrogen-containing compounds are found in the industrial, medical, and material world. In particular for the pharmaceuticals, they receive a lot of attention as Njardarson and coworkers reported that 59% of unique small drugs contain a nitrogen heterocycle from the analysis for U.S. approved drugs in their review article on the sub-structures of medicines including nitrogen [1]. Furthermore, it leaves no room for doubt that alkaloids, natural *N*-containing products, are useful as drug seeds showing various bioactivity as ever [2]. Unfortunately, although the *N*-containing compounds undoubtedly play the important role in many life area, the universal methodology for *N*-alkylation aren't found, yet. In that sense, the novel approach to *N*-alkylation must be continued to be researched and will be great help to construct the versatile *N*-containing compounds.

Previously, we reported that the new *N*-alkylation method by using sodium triacetoxyborohydride [$NaBH(OAc)_3$] with the corresponding carboxylic acids as alkyl source [3]. In the process of traditional reductive *N*-alkylation, aldehydes are used for alkyl source, but carboxylic acids are typically more stable than aldehydes as chemical species, which are easier to handle. Thus, carboxylic acids have come to draw attention as *N*-alkylational material. Our methodology had been revealed to have some advantages that the alkyl group was introduced only into the basic nitrogen atoms, not non-basic nitrogen like pyrrole nor indole, and the carbonyl moiety in the target molecule remained without reduction through the reaction unlike the other reported similar *N*-alkylation procedure by use of carboxylic acid [4]. In addition, it was found that different type of products from reported ones were given by using unsaturated carboxylic acid [3,4]. However, only aromatic amines were examined in our previous work as the first trial. Hence, in this paper, we investigate the further possibility of our method; the solvent effect, the application to aliphatic amines and induction of 4-hydroxybutyl group found through the process.

## Results and discussion

As mentioned above, the tested substrates were limited within the aromatic amine, aniline derivatives, in our previous report in spite of the effectiveness of $NaBH(OAc)_3$ with carboxylic acid as an alkyl source for *N*-alkylation. Thus, in order to show the further usefulness of our method, we planned to apply it to aliphatic amines. Before the trial, we examined the solvent effect for the reaction using aromatic amine, *p*-chloroaniline, and formic acid basically in accordance with the previous procedure, at first. But in order to compare the status of the progress of reaction easily, the reaction term was a little shorter than ever. In brief, 10 mg of *p*-chloroaniline was dissolved into 1.6 mL of solvent, then treated with 45 μL of HCOOH and 250 mg of $NaBH(OAc)_3$. The reaction mixture was stirred at rt for 24 h even if the starting material remained. Among *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), acetonitrile, 1,4-dioxane, tetrahydrofuran (THF), dichloromethane, and toluene, more polar solvent tended

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to give the better conversion yield for formic acid-related products, although formic acid and acetate-part derived from $NaBH(OAc)_3$ competitively reacted. Exceptionally, DMF resulted in recovery of most of starting material along with small amount of single methylated product and dimethylsulfoxide (DMSO) was disclosed not to support the reaction to recover the stating material almost completely (Table S1). Thus, we presumed that formyl sub-structure in DMF rather than amide seriously interfere the reaction mechanism because the ethyl and the formyl products were observed in DMA and that the oxidative property of DMSO might contradict the reductive reagent. In addition to the solvents shown in Table S1, acetone gave an *N*-isopropyl product naturally through the traditional reductive *N*-alkylation pathway and contrarily THF kept without antioxidant BHT surprisingly produced the relatives bearing *N*-(4-hydroxybutyl) moiety [5].

This 4-hydroxybutyl fragment induced to the nitrogen atom was suggested to be brought from 2-hydroperoxytetrahydrofuran (**6**) as a peroxidic THF relatives in reference to the researches reported by Russell et al. and Lippard et al. because formate **5** was also isolated from the reaction mixture which is presumed to be generated from **6** (Fig. 1) [6]. It could be also proved by the fact that THF stabilized with BHT didn't lead the production of *N*-(4-hydroxybutyl) derivatives at all (Table S1). For the validation of proposed mechanism, the reproducibility and the generality, we tried some substrates for this 4-hydroxybutyl-inducing reaction in THF containing **6** as shown in Table S2. Surprisingly, *p*-anisidine (**24**) was converted to *N*,*N*-di(4-hydroxybutyl) derivative in high yield within only 10 min reaction time at room temperature. Similarly, di-substituted product was also found from 2,4-dimethylaniline (**25**) as the major product. Thus, the electron-donating group on aromatic ring was revealed to tend to enhance the reactivity of anilines for this reaction. The secondary amine, indoline (**26**), and the aliphatic amine, 1-octadecylamine (**7**), also successfully reacted as well to furnish the corresponding *N*-(4-hydroxybutyl) products (Table S2). In 2018, Li et al. reported introducing 4-hydroxybutyl group to nitrogen atom in preparation for *N*-aryl amino alcohols [7]. By our method, the *N*-(4-hydroxybutyl) compounds were accidentally revealed to be directly produced in the single step whereas they contained two steps. The concentration of **6** was estimated by the protocol for detection of peroxidic-impurity in the organic reagents like 2-propanol mentioned in The Japanese Pharmacopeia 17th edition [8]. Namely, the sample THF was treated with potassium iodide for 15 min, then the resultant iodine was titrated by sodium thiosulfate under the colorization by starch. Consequently, THF proceeding induction of 4-hydroxybutyl group was assessed to contain **6** at the concentration

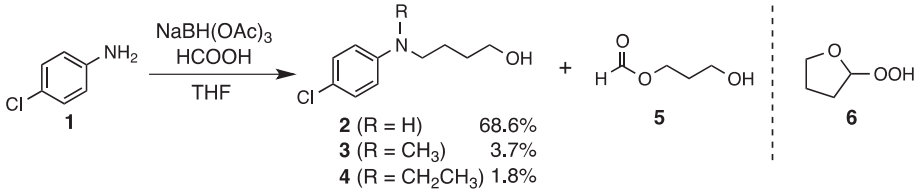
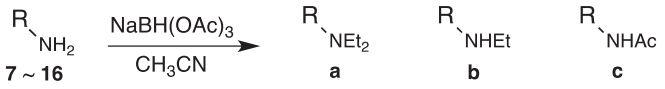
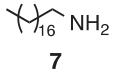
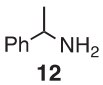
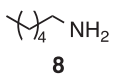
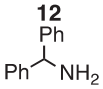
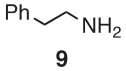
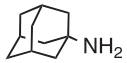
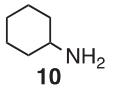
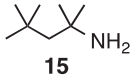
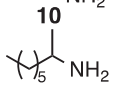
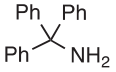



**Fig. 1.** Weird products through *N*-alkylation in THF by $NaBH(OAc)_3$ with formic acid.

**Table 1**
Application of our *N*-alkylation procedure to aliphatic amines.




| | Yield (%)* | | | | Yield (%)* | | |
|---|---|---|---|---|---|---|---|
| | **a*** -$NEt_2$ (%) | **b*** -NHEt (%) | **c*** -NHAc (%) | | **a*** -$NEt_2$ (%) | **b*** -NHEt (%) | **c*** -NHAc (%) |
|  **7** | 94.6 | – | 1.1 |  **12** | 80.8 | – | 3.3 |
|  **8** | 81.8 | – | 12.3 |  **13** | 82.2 | – | 12.6 |
|  **9** | 86.2 | – | 6.5 |  **14** | 73.4 | 20.5 | – |
|  **10** | 71.1 | – | 18.5 |  **15** | 80.2 | 12.0 | – |
|  **11** | 75.6 | trace | 11.3 |  **16** | – | 99.9 | – |

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of *ca.* 11.3 mM whereas freshly opened THF held 0.15 mM of **6**. Anyhow, old THF involving **6** demanded caution due to its explosibility and reactivity to create the unexpected products.

From the results of investigation for solvent effect shown in Table S1, we found that acetonitrile, 1,4-dioxane, and THF lead comparatively better conversion yield despite mixed products. Considering the solubility of each reagent in addition to conversion yield, next we examined the *N*-ethylation reaction to aliphatic amines by $NaBH(OAc)_3$ in acetonitrile. As shown in Table 1, the primary, secondary, and tertiary alkyl amines were treated with $NaBH(OAc)_3$ at 60 °C to furnish the desired *N*,*N*-diethylamines with good yields except triphenylmethylamine (**16**). Therefore, it was validated that our methodology can be applied to not only aromatic but also aliphatic amines. In case of the primary and secondary alkyl amines [1-octadecylamine (**7**), 1-hexylamine (**8**), 2-phenylethanamine (**9**), cyclohexylamine (**10**), 2-octylamine (**11**), 1-phenylethanamine (**12**), and benzhydrylamine (**13**)], the *N*,*N*-diethyl products were mainly obtained with a little amount of acetylamides, but mono-ethyl products were hardly detected. On the other hand, *N*-ethylation procedure which was applied to the tertiary alkyl amines [1-adamantylamine (**14**) and 2,4,4-trimethyl-2-pentylamine (**15**)] gave *N*,*N*-diethylamines as major products along with a little amount of mono-ethyl products, but acetylamides were scarcely found. Although the steric hindrance of tertiary alkyl amines was supposed to interfere with the induction of second ethyl group to nitrogen atom to afford the small amount of mono-ethyl amines, the reason why the acetylated products weren't found remained to be uncovered. Furthermore, only one ethyl group, not two, could be introduced into triphenylmethylamine (**16**), thus it was presumed that the bulkiness of triphenyl structure kept off the introduction of the second ethyl group. Anyway, our methodology was disclosed to applicable to aliphatic amines and to hold the potency to construct various *N*-containing compounds by using corresponding carboxylic acid.

As an additional discovery noticed through these trials, ethylamine, diethylamine or their ammonium salt were sometimes found from the reaction mixture. They were assumed to be derived from acetonitrile *via* reduction although $NaBH(OAc)_3$ has never reported to enable to convert cyano moiety (–CN) to aminomethylene ($–CH_2NH_2$). Accidental contamination of water wasn't supposed the reason because the premeditated addition of water to the reaction mixture didn't give these ethylamine derivatives constantly. Thus, the reason and mechanism of this result remain to be dissolved.

## Conclusion

In conclusion, the mild reductive *N*-alkylation procedure by using $NaBH(OAc)_3$ with carboxylic acid which we previously investigated for aromatic amines was proved to be also effective for aliphatic amines. Furthermore, it was shown that the polarity of solvents for the reaction might be relative with the reactivity and **6** induced the ω-hydroxybutyl unit to nitrogen atom. About our this method, much more still remains to be clear, for example, mechanism of the reaction, variation of carboxylic acid, internal reaction on the compounds bearing both amino and carboxyl moiety, and so on. In particular, the reaction using the reagents prepared *in situ* from $NaBH_4$ and the carboxylic acid are deriving the interesting outcomes. These trials to verify the effectiveness of our procedure are now ongoing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151919.

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[5] 2: colorless oil. 1H NMR (CDCl3, 500 MHz) δ: 7.11 (2H, d, J = 8.6 Hz), 6.52 (2H, d, J = 8.6 Hz), 3.70 (2H, t, J = 5.8 Hz), 3.13 (2H, t, J = 6.3 Hz), 1.69 (4H, m). 13C NMR (CDCl3, 125 MHz) δ: 146.8, 129.0, 121.8, 113.8, 62.5, 43.9, 30.2, 25.9. HR-MS [electrospray ionization (ESI)] m/z [M+H]+: 200.0841 (Calcd for C10H1535ClNO: 200.0837). 3: colorless oil. 1H NMR (CDCl3, 500 MHz) δ: 7.15 (2H, d, J = 9.2 Hz), 6.61 (2H, d, J = 9.2 Hz), 3.67 (2H, t, J = 6.3 Hz), 3.32 (2H, t, J = 7.2 Hz), 2.90 (3H, s), 1.62 (4H, m). 13C NMR (CDCl3, 125 MHz) δ: 147.9, 128.9, 121.1, 113.5, 62.7, 52.8, 38.6, 30.2, 23.1. HR-MS (ESI) m/z [M+H]+: 214.0995 (Calcd for C11H1735ClNO: 214.0993). 4: colorless oil. 1H NMR (CDCl3, 500 MHz) δ: 7.14 (2H, d, J = 9.1 Hz), 6.59 (2H, d, J = 9.1 Hz), 3.68 (2H, t, J = 6.3 Hz), 3.32 (2H, q, J = 7.4 Hz), 3.26 (2H, t, J = 6.9 Hz), 1.62 (4H, m), 1.13 (3H, t, J = 7.4 Hz). 13C NMR (CDCl3, 125 MHz) δ: 146.5, 129.0, 120.5, 113.5, 62.7, 50.4, 45.4, 30.3, 23.9, 12.1. 1H NMR (acetone-d6, 500 MHz) δ: 7.11 (2H, d, J = 8.6 Hz), 6.68 (2H, d, J = 8.6 Hz), 3.58 (2H, brt, J = ca. 6 Hz), 3.53 (1H, brs), 3.38 (2H, q, J = 6.9 Hz), 3.32 (2H, t, J = 7.7 Hz), 1.66 (2H, quint-like, J = 7.7 Hz), 1.55 (2H, m), 1.12 (3H, t, J = 6.9 Hz). 13C NMR (acetone-d6, 125 MHz) δ: 147.7, 129.6, 120.0, 113.9, 62.3, 50.9, 45.5, 31.0, 24.7, 12.4. HR-MS (ESI) m/z [M+H]+: 228.1151 (Calcd for C12H1935ClNO: 228.1150).

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