Note

N-Alkylation Using Sodium Triacetoxyborohydride with Carboxylic Acids as Alkyl Sources

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Received September 4, 2017; accepted October 5, 2017

A versatile *N*-alkylation was performed using sodium triacetoxyborohydride and carboxylic acid as an alkyl source. The combination of these reagents furnished products different from those given previously by a similar reaction. Moreover, the mild conditions of our method allowed some functional groups to remain through the reaction, whereas they would react and be converted into other moieties in the similar reductive *N*-alkylation reported previously. Herein, we provide a new procedure for the preparation of various compounds containing nitrogen atoms.

Key words sodium triacetoxyborohydride; *N*-alkylation; carboxylic acid

Many nitrogen-containing compounds have been discovered and are currently being used in medicinal, agricultural and industrial chemistry. Accordingly, it is important to develop *N*-alkylation methods specific to the *N*-containing compound being targeted, and thus there is a demand for novel procedures to prepare alkylated amines. One of best known of the traditional *N*-alkylation methods is reductive amination using carbonyl compounds with reductive reagents. Thus, we attempted to induce methyl groups to *p*-chloroaniline (**1**) by sodium triacetoxyborohydride ($NaBH(OAc)_3$) with 1,3,5-trioxane as a methyl source under an acidic condition with acetic acid,[1] but *N*,*N*-diethyl-*p*-chloroaniline (**2**) was obtained as a major product (Fig. 1). Acetyl or acetoxyl groups were assumed to be consumed for the *N*-ethylation. Previous reviews[2,3] of reductive amination methods using carbonyl compounds have briefly mentioned such phenomena as side reactions, and similar reactions using carboxylic acids with amines in the presence of sodium borohydride have already been reported.[4–7] In addition, other recent studies achieved an improvement of *N*-alkylation using carboxylic acids as the alkyl source by a single step reaction under a reductive condition.[8–10] Considering the various disadvantages of the traditional reductive amination by carbonyl derivatives—such as the instability of aldehydes, low reactivity of ketone carbonyl and necessity of a stepwise protocol—carboxylic acids should be a useful material, because they are normally more stable in air than aldehydes, and because various carboxylic acids are readily available. Thus, we further investigated *N*-alkylation by $NaBH(OAc)_3$ with carboxylic acids as the alkyl source and herein report the features of this reaction, which were different from those of the recently presented reactions.[8,10]

Results and Discussion

Carboxylic acids (R-COOH) were readily reacted with anilines in the presence of $NaBH(OAc)_3$ to furnish corresponding *N*-CH_2R derivatives. In the case of formic acid, *N*-formyl (*N*-CHO) products were also given as well as *N*-methyl ones. Treatment of anilines with only $NaBH(OAc)_3$ without any carboxylic acids also gave *N*-ethylanilines, but the reaction was very slow. In this case, the acetyl group in the reagent was presumed to be employed as an ethyl moiety. Moreover, during the screening to investigate the reactivity, $NaBH(OAc)_3$ was revealed to display a different reactivity from the recently reported reagents for *N*-alkylation using carboxylic acids,[8,10] as shown in Tables 1 and 2. The introduction of a methyl group to the nitrogen in indole (**3**) by $NaBH(OAc)_3$ with formic acid hardly proceeded, resulting in full recovery of **3**, whereas the reported reagents gave *N*-methylindoline (**4**)[10] (Table 1, entry 1). Moreover, pyrrole (**5**) could not be readily alkylated by $NaBH(OAc)_3$ but indoline (**6**) could be (entries 2, 3). Hence, it was suggested that the amines to be alkylated by $NaBH(OAc)_3$ with carboxylic acid should have some basicity. Next, we found that the acetyl group on the aromatic ring in the substrate remained after *N*-alkylation by $NaBH(OAc)_3$, but was reductively removed by the previously reported reagents[8] (entries 4, 5). This selectivity that *N*-alkylation was faster than reductive elimination of carbonyl moiety was confirmed by the reactions of 4-aminobenzophenone (**13**) and *p*-aminopropiophenone (**15**) (entries 6, 7). Thus, a carbonyl group next to aromatic ring was strongly suggested to endure in our *N*-alkylation procedure. Additionally, as depicted in Table 2, levulinic acid (**17**) and *p*-chloroaniline (**1**) were treated with $NaBH(OAc)_3$ to give a γ-lactam (**18**) as a major product, while a cyclic amine (**19**) was mainly obtained through reductive removal of the carbonyl moiety under a previously reported condition[10] (Table 2, entry 1). Neither conversion from acetanilide nor that from *p*-chloroacetanilide into the corresponding ethylphenylamines proceeded by $NaBH(OAc)_3$. Thus, the mild reductive activity of $NaBH(OAc)_3$ was suggested to allow the carbonyl moiety in the amide group to survive under the *N*-alkylation reaction condition. When unsaturated carboxylic acids, *i.e.*, acrylic acid (**20**) or propiolic acid (**23**), were used

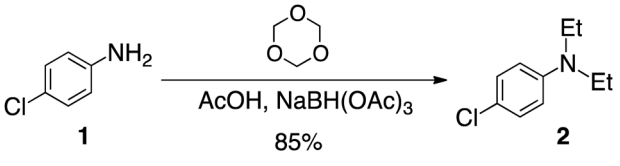

Fig. 1. *N*-Ethylation by $NaBH(OAc)_3$ with Acetic Acid

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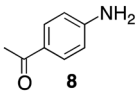
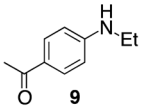
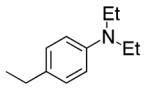
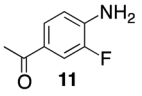
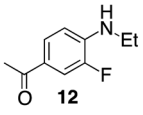
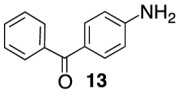
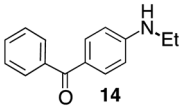
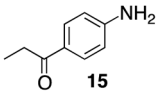
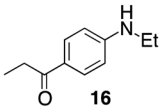
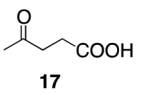
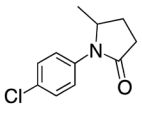
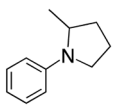
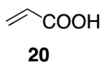
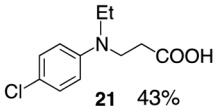
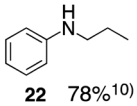
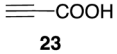
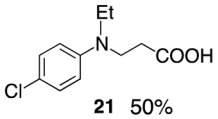
Table 1. Comparison of Reactivity for Various *N*-Containing Compounds

Entry	Starting substrate	Product	Reported product in previous condition
1	 **3**	NR	 **4** Me 81%[10]
2	 **5**	NR	———
3	 **6**	 **7** Et 91%	———
4	 **8**	 **9** 79%	 **10** 62%[8]
5	 **11**	 **12** 72%	———
6	 **13**	 **14** 88%	———
7*	 **15**	 **16** 79%	———

NR: no reaction. —: no data. *Reaction condition: at 40°C for 5 h in $(CH_2Cl)_2$.

Table 2. Comparison of Products by Using Various Carboxylic Acids as Alkyl Sources

Entry	Carboxylic acid	Product*	Reported product in previous condition**
1	 **17**	 **18** 78%	 **19** 86%[10]
2	 **20**	 **21** 43%	 **22** 78%[10]
3	 **23**	 **21** 50%	———

—: no data. **p*-Chloroaniline was used as a starting substrate. **Aniline was used as a starting substrate.

for the *N*-alkylation by $NaBH(OAc)_3$, Michael addition by the amine proceeded prior to reductive amination to afford carboxylic acids, although the reported condition resulted in *N*-alkylation and hydrogenation to furnish a product in which nitrogen was substituted with a saturated alkyl group (entries 2, 3).[10] This result allowed us to presume that *N*-alkylation by $NaBH(OAc)_3$ and carboxylic acid was a slower reaction than nucleophilic attack by the amines.

The mechanism of action was discussed in an article that reported a similar reductive *N*-alkylation; the authors suggested that the mechanism was formation of an amide linkage, followed by reductive removal of the carbonyl moiety by hydride reagents.[8] However, our approach was not expected to proceed in this manner, because the $NaBH(OAc)_3$ used in our reaction produced the lactam product and could not reduce the acetanilides to ethylphenylamines. The elucidation of the detailed mode of action is ongoing.

In conclusion, our *N*-alkylation by $NaBH(OAc)_3$ and carboxylic acid showed milder reactivity than a similar reaction condition reported previously. So, our condition and the previous condition sometimes furnished different products. Therefore, a much wider range of compounds can be applied to *N*-alkylation by $NaBH(OAc)_3$. For example, a carbonyl group next to aromatic ring, an amide carbonyl and a non-basic nitrogens such as pyrrole could exist in the substrates and remain throughout the *N*-alkylation under our condition. In this way, our approach could be very useful for the preparation of various compounds containing nitrogen, although further optimization of the reaction condition is necessary.

Experimental

Materials and Instruments All reagents and solvents were used as received from commercial suppliers without any further purification. All reactions were carried out under an argon atmosphere using magnetic stirring. Reactions were analyzed by TLC with detection under UV light (λ=254 nm) and/or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed on silica gel 60N (spherical neutral, particle size 100–210 μm) for purification of products. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA500 spectrometer.

General Experimental Procedure All reactions were carried out according to the procedure written below unless otherwise noted. The starting anilines (0.1 mmol) in dry CH_2Cl_2 (2.5 mL) was treated with carboxylic acid (1.3 mmol) and $NaBH(OAc)_3$ (1.6 mmol) at room temperature overnight. Saturated aqueous $NaHCO_3$ was dropped into the reaction mixture, and then the mixture was stirred until the foaming stopped. After extracting with EtOAc, the organic layer was dried over $MgSO_4$. Removal of solvent from EtOAc extract under reduced pressure by a rotary evaporator gave crude products that were purified by column chromatography. The obtained products, 4-chloro-*N*,*N*-diethylaniline (**2**),[11] *N*-ethylindoline (**7**),[12] 1-(4-ethylaminophenyl)ethanone (**9**),[13] 4-ethylaminobenzophenone (**14**),[14] and *N*-(4-chlorophenyl)-5-methyl-2-pyrrolidone (**18**)[15] were confirmed by the previously reported spectroscopic data.

1-(4-Ethylamino-3-fluorophenyl)ethanone (12) Pale yellow oil, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7.4 Hz), 2.50 (3H, s), 3.27 (1H, dq, J=5.7, 7.4 Hz), 4.37 (1H, br s), 6.64 (1H, dd, J=8.1, 8.6 Hz), 7.59 (1H, dd, J=2.3, 12.6 Hz), 7.67 (1H, dd, J=2.3, 8.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.5, 26.0, 37.6, 109.7 (d), 114.0 (d), 126.8, 141.2 (d), 149.4, 151.3, 195.7. IR (KBr) cm^{-1}: 3438, 1666, 1611, 1537. Electrospray ionization-time-of-flight (ESI-TOF)-MS *m*/*z*: 182.0977 (Calcd for $C_{10}H_{13}FNO$: 182.0976). MS *m*/*z*: 182 ([M+H]$^+$).

1-(4-Ethylaminophenyl)propan-1-one (16) Colorless amorphous powder, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.20 (3H, t, J=7.4 Hz), 1.28 (3H, t, J=6.9 Hz), 2.89 (2H, q, J=7.4 Hz) 3.22 (2H, dq, J=2.9, 6.9 Hz), 4.14 (1H, br s), 6.55 (2H, d, J=8.8 Hz), 7.84 (1H, d, J=8.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 8.8, 14.6, 30.9, 37.8, 111.2, 126.1, 130.4, 152.0, 199.1. IR (KBr) cm^{-1}: 3351, 1653, 1592, 1565. ESI-TOF-MS *m*/*z*: 178.1234 (Calcd for $C_{11}H_{16}NO$: 178.1226). MS *m*/*z*: 178 ([M+H]$^+$).

***N*-(4-Chorophenyl)-*N*-ethyl-*β*-alanine (21)** Colorless amorphous powder, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.13 (3H, t, J=6.9 Hz), 2.61 (2H, t, J=6.9 Hz), 3.35 (2H, q, J=6.9 Hz), 3.58 (2H, t, J=6.9 Hz), 6.67 (2H, d, J=8.6 Hz), 7.18 (2H, d, J=8.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 12.1, 32.0, 45.9, 46.4, 114.7, 122.4, 129.2, 145.6, 177.2. IR (KBr) cm^{-1}: 2971, 1714, 1593, 1501. ESI-TOF-MS *m*/*z*: 226.0639 (Calcd for $C_{11}H_{13}{}^{35}ClNO_2$: 226.0640). MS *m*/*z*: 226 ([M−H]$^-$).

Acknowledgments We are thankful to Mr. S. Inagaki (Iwate Medical University) for measurement of MS spectra and Dr. T. Tsujihara (Iwate Medical University) for measurement of IR spectra.

Conflict of Interest The authors declare no conflict of interest.

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