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Hofmann Rearrangement by Using N-bromophthalimide-Silveracetate in DMF

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By using N-bromophthalimide (NBP) as halonium ion source for the Hofmann rearrangement, a series of primary amide could be converted to the corresponding carbamate in excellent yields. So NBP was thought to be very effective and practical halonium ion source for the Hofmann rearrangement.

Key words: N-bromophthalimide, N-bromosuccinimide, Dibromantine, Hofmann rearrangement, Primary amide, Carbamate, Halonium ion.

INTRODUCTION

The Hofmann rearrangement, converting primary amide to the corresponding primary amine of one less carbon by treatment with bromine and alkali, is applicable to the preparation of carbonyl compounds, halogenated compounds and valuable heterocyclic compounds (Wallis and Lane, 1946). Therefore this reaction has been thought to be a very useful method in organic synthesis. However, the synthetic utility of this reaction was limited in certain cases, owing to the troublesome side reactions such as unwanted halogenation and hydrolysis, caused by excess halogen, alkali and high reaction temperature. So recently new procedures, using the oxidizing reagents such as Pb $(OAc)_4$ (Baumgarten *et al.*, 1975; Acott *et al.*, 1968a, 1968b), $C_6H_5I(CF_3CO_2)$ (Boution and Loudin, 1984; Loduin *et al.*, 1984; Radhakrishna *et al.*, 1979), C_6H_5I (OTs)OH (Lazbin and Koser, 1986) or C_6H_5IO (Radhakrishna *et al.*, 1983) were developed in order to suppress such side reactions. But for the practical purposes, these methods have also some shortcomings due to their own reactivities.

Continuing our studies on the reaction of halonium ion or its equivalent with N-haloimidic compounds (Cook *et al.*, 1984, Cook *et al.*, 1983), we reported that the Hofmann rearrangement was carried out successfully in mild reaction condition by applying N-halolimides (e.g. N-bromo-succinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantion (dibromantine) as bromonium ion source, which is essential to the Hofmann rearrangement (Jew *et al.*, 1990). Although the mechanism of this procedure was not difined exactly, we thought that foresaid N-haloimide could act as a superb halonium ion or its equivalent for the Hofmann rearrangement by heterolytic cleavage of N-Br bond of that compound in aprotic polar solvent (e.g. N,N-Dimethylformamide or acetonitrile) as shown in Fig. 1.

From the formentioned studies, we found that those N-haloimides could serve as halonium ion for Hofmann rearrangement ideally. This fact was so impressive that we attempted to apply N-bromophthalimide (NBP), another N-haloimide compound, to our improved Hofmann rearrangement procedure as a bromonium ion source in order to extend its synthetic application.

We thought that NBP, having N-Br moeity similar to NBS and dibromantine, could act as an ideal bromonium ion source in this Hofmann rearrangement procedure in an analogous mode to foresaid N-haloimides as shown in Fig. 2.

In this paper we wish to report an another practical method of Hofmann rearrangement by using NBP as bromonium ion source.

MATERIALS AND METHODS

All melting point were uncorrected. IR spectroscopy were measured with a Beckmann IR 20A Infrared spectrometer and were reported in ν_{max} cm^{-1} and ^1H-NMR spectra were recorded on Perkin-Elmer R32 NMR spectrometer and were reported in δ from TMS as an internal standard. Only the strongest and structurally important peak were reported for IR and NMR spectra. All yields referred to chromatographically and spectros-

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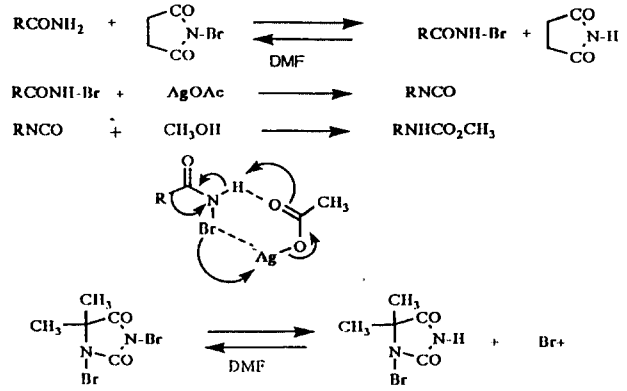


Fig. 1.

Fig. 2.

copically homogeneous materials. N-bromophthalimide were available from Aldrich Co. and amides were prepared from the corresponding carboxylic acid according to the literature (Shriner *et al.*, 1964).

General procedure of Hofmann rearrangement

A typical procedure is as follows; To a solution of benzamide (100 mg, 0.82 mmol) and AgOAc (160 mg, 0.98 mmol) in 5 ml of DMF, methanol (1 ml) was added, followed by addition of a solution of NBP (216 mg, 0.98 mmol) in 3 ml of DMF at 0℃ under Ar atmosphere. After the reaction mixture was stirred for 2 hrs at 0℃ and 10 hrs at room temperature. This reaction mixture was evaporated under reduced pressure; the residue was diluted with 300 ml of EtOAc; washed with H_2O (30 cc×2), 5% HCl (30 cc×2); dried over anhydrous $MgSO_4$; and evaporated to give 125 mg of yellow semisolid. This was purified with silica gel column chromatography (hexane: EtOAc=3 : 1) to give 121 mg of amorphorous solid. mp. 44-46℃, (lit. 47℃, Kizber and Glagoleva, 1953) (yield 100%).

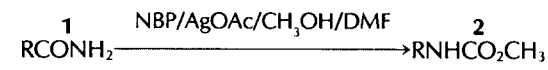
Methyl N-phenylcarbamate

Benzamide (100 mg), AgOAc (160 mg), NBP (216 mg); yield: 125 mg, quant. mp. 44-46℃: IR (nujol)cm^{-1}; 3300 (NH), 1700 (CO); NMR($CDCl_3$)δ: 6.9-7.4 (m, 5H, C_6H_5), 6.70 (br, 1H, NH), 3.68 (m, 5H).

Methyl N-benzylcarbamate

Phenylacetamide (100 mg), AgOAc (146 mg), NBP (197 mg), methanol (1 ml); yield; quant. solid; mp. 62-63℃; IR (nujol) cm^{-1} 3320 (NH), 1700 (CO); NMR ($CDCl_3$) δ: 7.30 (s, 5H, C_6H_5), 5.00 (br, 1H, NH), 4.36 (d, 2H, CH_2, J=6 Hz), 3.70 (s, 3H, CH_3O)

Table I. The conversion of amide **1** to carbamate **2**



R	Yield of carbamate 2(%)
C_6H_5	Quant.
$C_6H_5CH_2$	Quant.
3-Pyridyl	97
p-$NO_2C_6H_4$	93
$CH_3(CH_2)_7$	88
$CH_3(CH_2)_8$	93
Cyclohexyl	92

Methyl N-(3-pyridyl) carbamate

Nicotinamide (100 mg), AgOAc (164 mg), NBP (219 mg), methanol (1 ml); yield: 120 mg (97%), yellow solid; mp. 115-116℃; IR (nujol) cm^{-1}: 3200 (NH), 1700 (CO); NMR ($CDCl_3$) δ: 7.20-8.62 (m, 4H, Ar-H), 7.07 (br, 1H, NH), 3.78 (s, 3H, CH_3O).

Methyl N-(p-nitrophenyl) carbamate

p-nitrobenzamide (100 mg), AgOAc (120 mg), NBP (163 mg), methanol (1 ml); yield 110 mg (93%); mp. 178-179℃; IR (nujol) cm^{-1}: 3440 (NH), 1740 (CO); NMR ($CDCl_3$) δ 8.14 (d, 2H, 2Ar-H (m to NO_2), J=9 Hz), 7.48 (d, 2H, 2Ar-H (o to NO_2), J=9 Hz), 6.85 (br, 1H, NH), 3.76 ((s, 3H, CH_3O).

Methyl N-heptylcarbamate

Octanamide (100 mg), AgOAc (148 mg), NBP (200 mg), methanol (1 ml); yield 88%, oil; IR (neat) cm^{-1}: 3340 (NH), 1700 (CO); NMR ($CDCl_3$) δ: 4.82 (br, 1H, NH), 3.58 (s, 3H, CH_3O), 3.07 (m, 2H, CH_2N), 1.18-1.21 (m, 10H, 5×CH_2), 0.80 (t, CH_3, J=6 Hz).

Methyl N-nonylcarbamate

Decanamide (100 mg), AgOAc (122 mg), NBP (161 mg), methanol (1 ml); yield: 110 mg (93%), yellow oil; IR (neat) cm^{-1}: 3340 (NH), 1700 (CO); NMR ($CDCl_3$): 4.74 (br, 1H, NH), 3.57 (s, 3H,O OCH_3), 3.08 (m, 2H, CH_2N), 1.00-1.60 (m, 14H, CH_2×7), 0.81 (t, 3H, CH_3CH_2, J=6.8 Hz).

Methyl N-cyclohexylcarbamate

Cyclohexancarboxamide (100 mg), AgOAc (156 mg), NBP (211 mg), methanol (1 ml); yield: 92%, yellow solid; mp. 74℃; IR (nujol) cm^{-1}: 3340 (NH), 1700 (CO), NMR ($CDCl_3$) δ: 4.56 (br, 1H, NH), 3.69 (s, 3H, CH_3O), 3.39 (m, 1H, CH), 0.80-2.20 (m, 10H, 5×CH_2).

RESULTS AND DISCUSSION

As described in experimental section, we investigated the reaction of a series of amide with NBP in various reaction conditions. And the results were summarized in Table I.

As shown in Table I, all the aromatic amides were converted to the corresponding carbamate in excellent yields. Interestingly phenylacetamide, which suffered unwanted oxidation of active methylene when treated with $Pb(OAc)_4$, gave good yield of carbamate without such side reaction. Although this observation could not be explained clearly, we thought that the heterolytic cleavage of N-Br bond in NBP occured in equilibrium under our reaction condition so ideally as to prevent the presence of excess bromonium ion which might bring about troublesome oxidation of active methylene.

It was reported that benzamide could not be transformed to the corresponding carbamate by using the recently devised reagents such as $C_6H_5I(CF_3CO_2)_2$. C_6H_5IO and $C_6H_5I(OTs)OH$. But in our procedure, the Hofmann rearrangement of benzamide was carried out successfully without any side product.

In case of nicotinamide, Acott and Baumgarter reported that ethyl N-pyridylcarbamate was obtained in low yield by using $Pb(OAc)_4$. But using our method this could be converted to methyl N-pyridylcarbamate nearly quantitatively.

p-Nitrobenzamide was known to be suffered unwanted hydrolysis in drastic alkaline medium of classical Hofmann rearrangement. But under our neutral and anhydrous reaction condition this amide could be converted to the corresponding carbamate in excellent yield.

To our knowledge the Hofmann rearrangement of higher aliphatic amide is accompanied with side product such as urea derivatives. But in our Hofmann rearrangement, all the aliphatic amide could be converted to the corresponding carbamate without any side products.

CONCLUSION

In conclusion, we have found that NBP is a superb reagent for carrying out the conversion of amides into the corresponding carbamates. Especially the successful conversion of aromatic amides such as phenylacetamide and *p*-nitrobenzamide to the corresponding carbamate is particulary meaningful in that it illustrate the applicability of this reaction procedure to organic synthesis.

From the above discussion, it is clear that our reaction method of applying NBP as bromoniumion source affords an useful and practical alternative to our improved Hofmann rearrangement procedure.

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