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Hypophosphorous Acid-Iodine: An Efficient and Mild Reagent for Cleavage of N–C Bond

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ABSTRACT

A mixture of hypophosphorous acid (H_3PO_2) and iodine in acetic acid can selectively cleave the *N*-alkyl bond in a variety of substituted heterocylic compounds in good to excellent yields without any damage to amide bond present in the substrates.

Key Words: Hypophosphorous and acid iodine; N-C bond cleavage.

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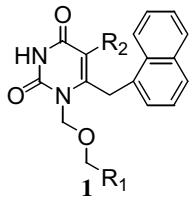
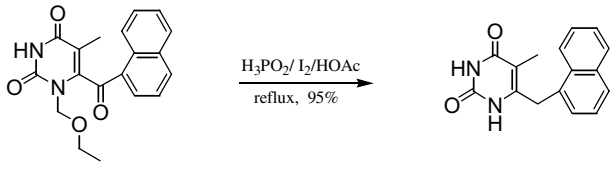
Although hypophosphorous acid was often used as reductive deazoniation reagent of aryldiazonium ions,[1] and sometimes hypophosphorous acid and its salts were reported for the chain deoxygenation, dehalogenation, and deamination of primary amine,[2] their extension as a synthetic reagent in organic chemistry has been very limited yet.[3] Until recently, there are several reports on the reductive ability of the mixture of hypophosphorous acid and iodine in refluxing acetic acid. This system reported by Hicks et al. is found to be able to convert diaryl ketones to the corresponding diarylmethylenes in high yields.[4]

In the course of the synthesis of series of 6-naphthylmethyl substituted 1-[2-(Hydroxyethoxymethyl)]-6-phenylthiothymine (HEPT) analogs (**1**)[5] (Fig. 1) as potential HIV reverse transcriptase (RT) inhibitors, we tried using the $H_3PO_2/HOAc/I_2$ system to reduce 1-ethoxymethyl-6-(1-naphthylcabonyl)thymine (**2**) to the 1-ethoxymethyl-6-(1-naphthylmethyl)thymine. The isolated product turned out to be 6-(1-naphthylmethyl)thymine (**3**) instead, which was identified by IR, ^{1}H NMR, and ^{13}C NMR (Sch. 1). Intrigued by the synthetic potential of this mild cleavage of *N*-alkyl group, we launched an investigation to establish its scope and limitation on various compounds, so as to make an enrichment of the dealkylation and debenzylation methods.[6]



1

Figure 1. Structure of 6-naphthylmethyl substituted HEPT analogs.



2 **3**

Scheme 1.

EXPERIMENTAL

Melting points were measured on a WRS-1 digital melting point instrument. Infrared spectra were recorded on a Nicolet FT-IR 360 spectrometer as KBr pellets. ^{1}H NMR spectra were obtained on a Bruker DMX 500 MHz spectrometer in DMSO-d_6 as solvent unless specified. Chemical shifts were reported in ppm units from TMS as an internal standard. ^{13}C NMR spectra were run on a Bruker DMX 500 MHz spectrometer using DMSO-d_6 as solvent except for specified as $CDCl_3$. Mass spectra were obtained on a HP 5989A spectrometer by direct inlet at 70 eV. Column chromatography was performed with silica gel G. Analytical TLC was performed with silica gel G plates. Reagents and solvents were all AR grade and used without further purification.

Typical Procedures

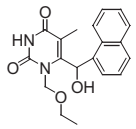
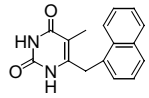
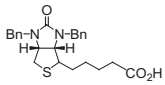
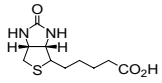
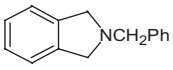
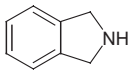
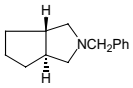
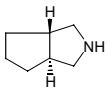
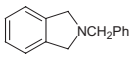
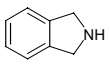
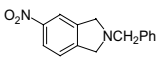
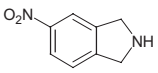
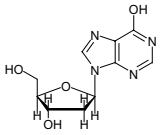
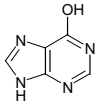
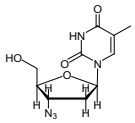
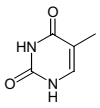
Iodine (16.7 mg, 0.67 mmol) and acetic acid (1 mL) were stirred together in a flask fitted with a condenser and a dropping funnel. Hypophosphorous acid, 50% aq. (33.3 μL, 0.32 mmol) was added. After the mixture was refluxed, a solution of 1-ethoxymethyl-6-(1-naphthylcarbonyl)thymine (67.6 mg, 0.2 mmol) in 1.6 mL of acetic acid was added slowly over 10 min. The mixture was then stirred and refluxed for an additional 12 h, cooled, diluted with water, and extracted with cyclohexane and dichloromethane respectively. The cyclohexane portion was discarded and the dichloromethane portion was dried over $MgSO_4$ and then evaporated under reduced pressure to give crude products, which was purified by flash chromatography to afford pure **3** as white crystals (49.5 mg, 93%); m.p. 279–281°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.655 (s, 3H), 4.223 (s, 2H), 7.131–8.117 (m, 7H), 10.751 (s, 1H), 11.098 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.929 (CH_3), 33.110 (CH_2), 106.852 (C_5), 148.928 (C_6), 157.406 (C_4), 165.291 (C_2), 123.724–133.801 (10C, 1-naphthyl). DEPT ($\theta = 45^\circ$, 125 MHz, DMSO-d_6): 9.951 (CH_3), 33.110 (CH_2), 123.745–129.044 (8C, naphthyl). MS (EI) m/z: 266 (M^+), 251, 141, 128.

RESULTS AND DISCUSSION

To our delight, treatement of the substrates with 50% of hypophoshorous acid (1.6 equiv.) and iodine (3.4 equiv.) in acetic acid for

12 h gave the dealkylated products in good to excellent isolated yields. The results are presented in Table 1. It was observed that the benzhydrol group in the substrate 1-ethoxymethyl-6-(1-naphthylhydroxymethyl)thymine was reduced to the methylene group simultaneously, resulting in the 6-(1-naphthylmethyl)thymine as the sole product (Entry 1). In addition, it is

Table 1. Dealkylation of substrates with $H_3PO_2/HOAc/I_2$.

Entry	Substrate	Reaction temp. (°C) time (h)	Product	Yield[a] (%)
1		60 12		93
2		110 12		85
3		110 12		66
4		Reflux 12		76
5		Reflux 12		75
6		Reflux 12		83
7		Reflux 12		79
8		Reflux 12		81

[a]Yield of isolated pure product.

important to note that the amide group in some substrates (Entries 1, 2, 7, and 8) was kept intact under these reaction conditions.

Next, using *N*,*N*-bisbenzylbiotin, a key intermediate for the synthesis of *d*-biotin, as model compound,[7] the effect of iodine has also been investigated. The result shows that the presence of iodine was critical to the successful transformation of this compound to *d*-biotin (Entry 2). No debenzylation was observed in its absence and reactions did not go to completion when the amounts of iodine were reduced.

CONCLUSION

In conclusion, we have developed a new and efficient method for the cleavage of *N*-alkyl group for various kinds of heterocyclic compounds using the H_3PO_2/HOAc/I_2 system without any damage on the amido bond. This method will be a new entry into the removal of *N*-alkyl as well as *N*-benzyl protection group.

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