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Studies on a New Usage of Hypophosphorous Acid-iodine System in N-C Bond Cleavage

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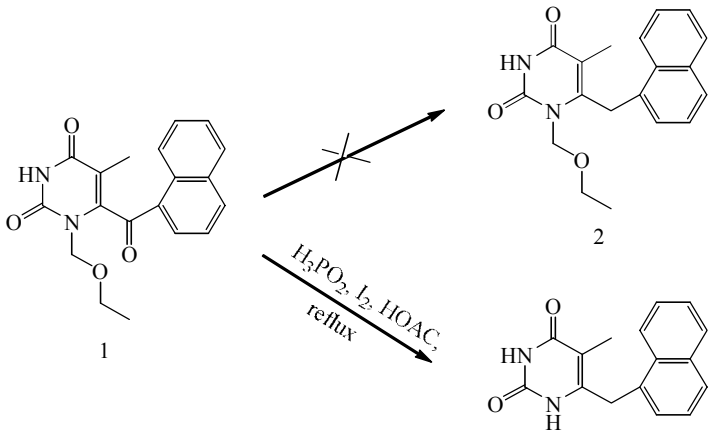
Absrtact: A mixture of hypophosphorous acid (H_3PO_2) and iodine in acetic acid can cleave the *N*-alkyl bond in a variety of *N*-1 substituted pyrimidine derivative in relatively high yields, without any damage to the amido bond in the non-nucleosides pyrimidine base skeleton.

Keywords: Hypophosphorous acid, iodine, carbon-nitrogen bond cleavage.

The reductive ability of the mixture of hypophophorous acid and iodine in refluxing acetic acid has been reported recently[1]. Hicks L.D. *et al.* reported that this system could convert diaryl ketones and benzhydrols to the corresponding diarylmethylenes in high yields[2].

When we tried to use this system to transform the 1-ethoxymethyl-6-(1-napthyl carbonyl)thymine **1** to 1-ethoxymethyl-6-(1-napthylmethyl) thymine **2**, which had been designed as anti-HIV-RT nonnucleoside inhibitors by computer[3], to our surprise, 6-(1-napthylmethyl)thymine **3** was obtained instead (**Scheme 1**).

Scheme 1



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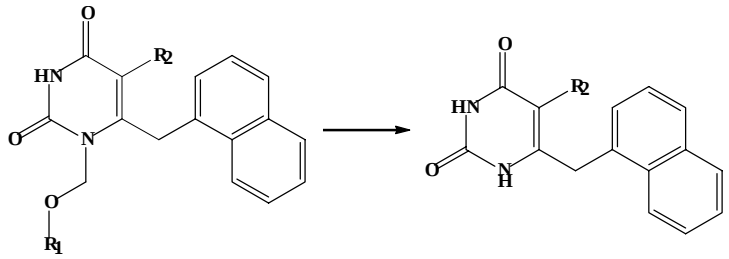
This unusual result inspired us to undertake further investigation on the generality of dealkylation with this system. A series of 1-alkoxyl-5-alkyl-6-(1-naphthylmethyl) uracils was tested to evaluate the scope and limitation of this reaction. The results were shown in **Table 1**.

Table 1 Dealkylation of the model substrates with H_3PO_2/HOAc/I_2 system



4 **5a-d**

a: R_2 = Me, b: R_2 = Et, c: R_2 = *iso*-Pr, d: R_2 = *n*-Pr[4]

Entry	**4**		Products	Reaction time	Yield (%)[a]
	R_1	R_2	**5**	(h)	
1	Me	Me	**5a**	4.5	91
2	Me	Et	**5b**	8	83
3	Me	*iso*-Pr	**5c**	9.5	75
4	Me	n-Pr	**5d**	9.	76
5	Et	Me	**5a**	5	93
6	Et	Et	**5b**	8.5	72
7	Et	*iso*-Pr	**5c**	11	63
8	Et	n-Pr	**5d**	10	65
9	Bn	Me	**5a**	5.5	73
10	Bn	Et	**5b**	6	64
11	Bn	*iso*-Pr	**5c**	13	55
12	Bn	n-Pr	**5d**	11	58
13	$HOCH_2CH_2$	Me	**5a**	5	76
14	$HOCH_2CH_2$	Et	**5b**	5.5	61
15	$HOCH_2CH_2$	*iso*-Pr	**5c**	12	56
16	$HOCH_2CH_2$	n-Pr	**5d**	10	60

a: Yield of isolated pure product.

As shown in **Table 1**, all the substrates, which have different *N*-1-alkoxylmethyl side chain, can undergo the dealkylation reaction with relatively high yields. The amido group in pyrimidine skeleton was kept intact during the process. It also can be drawn from the **Table** that the compounds with the bulkier *N*-1 side chains and *C*-5 substitutes often need longer reaction time and have the lower isolated yields. The 6-naphthylmethyl substitution of α- and β-, almost have no effect on this cleavage under these conditions.

The effect of I_2 in this reaction was also evaluated. We tried the reaction with

H_3PO_2 and acetic acid without I_2. It was found that the raw material remained unchanged after 5 hours, and also the reaction did not go to complete when reduced amount of I_2 was used. It should be pointed out that our method has the advantages such as the mild reaction condition, convenient work-up, and the reagent hypophosphorous acid, acetic acid and iodine are cheap.

In conclusion, we have successfully implemented the system of H_3PO_2/HOAc/I_2 to the cleavage of *N*-alkoxymethyl bond of the *N*-1-substituted pyrimidine derivatives. This reaction is competitive in terms of yield, convenience and general synthetic utility with the traditional processes[5] for cleaving the *N*-alkoxymethyl bond in pyrimidine. The present method will be a new method for removal of *N*-alkoxymethyl on the pyrimidine substrates, outside of which without carbonyl group. If there is a carbonyl group, then it will be reduced to methylene group under these reaction conditions

General procedure

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. 50 % aq. solution of hypophosphorous acid, (33.3 μl, 0.32 mmol) was added and the mixture was heated to reflux. 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 minutes. The mixture was then stirred and refluxed for several hours, monitored by TLC, cooled, diluted with water and extracted with cyclohexane and dichloromethane subsequently. The cyclohexane portion was discarded and the dichloromethane portion was dried over $MgSO_4$. The filtrate was evaporated in reduced pressure to give a yellowish white precipitates. The precipitates thus obtained was purified by chromatography to afford a pure product (32 g, 93 %). Analysis by IR, MS and NMR spectrometry showed that the product was 6-(1-naphthylmethyl)thymine.

References and Notes

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4. The selected spectroscopic data of the products (**5a** and **5c**) are available as follows.
   5a. 6-(1-naphthylmethyl)thymine white cubic crystal; mp 266-268°C (from abs. EtOH).
   FT-IR (KBr): ν 3417 (NH), 2829 (Me), 1737 (C=O), 1660 (C=O) cm^{-1}. ^1H NMR (500

MHz): δ 1.65 (s, 3 H, Me), 4.22 (s, 2H, CH_2 naphthyl), 7.12-8.12 (m, 7H, naphthyl), 10.76 (s, 1H, N-1H), 11.11 (s, 1H, N-3H). ^{13}C NMR (500 MHz): δ 9.9 (Me), 33.1 (CH_2), 106.8 (C-5), 123.7-133.8 (8C, naphthyl), 148.9 (C-6), 151.4 (C-4), 165.3 (C-2). DEPT (θ45°C, 500 MHz): 9.9 (CH_3), 33.1 (CH_2), 123.7-129.1 (8C, naphthyl). EI-MS: *m/z* (%) 266 (100), 251 (34.50), 141 (36.89), 128 (82.98). HRMS: *m/z* Calcd. for $C_{16}H_{14}N_2O_2$: 266.1055. Found: 266.1051. Anal. calcd. for $C_{17}H_{16}N_2O_2$ (280.3): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.22; N, 10.44.

5c. 5-Isopropyl-6-(1-naphthylmethyl)uracil, white cubic crystal; mp 199-203°C (from EA). FT-IR (KBr): ν 3420 (NH), 2961 (Me), 1708 (C=O), 1647 (C=O) cm^{-1}. ^{1}H NMR (500 MHz): δ 1.06 (d, 6H, *J*=7.7, 2 Me), 2.50 (m, 1H, *J*=7.7, CH), 4.23 (s, 2H, CH_2), 7.12-8.13 (m, 7H, naphthyl), 10.70 (s, 1H, N-1H), 10.99 (s, 1H, N-3H). ^{13}C NMR (500 MHz): δ 20.6 (2Me), 27.0 (CH), 33.2 (CH_2), 115.7 (C-5), 123.8-133.8 (8C, naphthyl), 148.2 (C-6), 151.6 (C-4), 164.3 (C-2). EI-MS: *m/z* (%) 294 (74.62), 279 (100), 141 (56.01), 128 (24.37). HRMS: *m/z* Calcd. for $C_{18}H_{18}N_2O_2$: 294.1368. Found: 294.1346. Anal. calcd. for $C_{18}H_{18}N_2O_2$ (294.3): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.23; H, 6.14; N, 9.35.

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