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Simple and practical method for selective acylation of primary hydroxy group catalyzed by *N*-methyl-2-phenylimidazole (Ph-NMI) or 2-phenylimidazo[2,1-*b*]benzothiazoles (Ph-IBT)

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ABSTRACT

N-Methyl-2-phenylimidazole (**Ph-NMI**) and 2-phenylimidazo[2,1-*b*]benzothiazoles (**Ph-IBT**) catalyzed selective acylation of primary alcohols using acid anhydrides. The **Ph-NMI**- or **Ph-IBT**-catalyzed reaction using $(PhCO)_2O$ as an acylating agent could particularly acylate the primary hydroxy group of 1,n-diols ($n \geq 3$) with a high, synthetically useful selectivity.

Selective acylation of a primary hydroxyl group in the presence of secondary hydroxyl group(s) is often required as a discriminatory protection in organic synthetic schemes. Conventionally, processes which use a controlled amount of bulky acylation agents, such as pivalic acid derivatives, under mild reaction conditions have widely been accepted.[1] In addition, 3-acetylthiazolidine-2-thiones-NaH[2] and AcCl-hindered amine[3] have been employed for the selective acylation system for primary alcohols. Recently, Wakita and Hara developed *N*,*N*-diethyl-α,α-difluorobenzylamine as a selective agent of primary hydroxy benzoylation.[4] Besides such reagent-control systems, catalyst-control of the reaction has been realized by development of efficient catalyses with $Cu(OTf)_2$,[5] lanthanide trichlorides[6] such as $YbCl_3$ and $CeCl_3$, $Y_5(O\text{-}i\text{-}Pr)_{13}O$,[7] $InCl_3$,[8] $Sc(OTf)_3$,[9] TMSOTf,[9] $[ClBu_2SnOSnBu_2Cl]_2$,[10] $NaHSO_4/SiO_2$,[11] $KF\text{-}Al_2O_3$,[12] and iminophosphoranes.[13] Acylation catalyzed by enzymes such as lipases is also versatile, although the method is not necessarily general to substrate diversity.[14] With the exception of catalysis by TMSOTf, iminophosphoranes or enzymes, the methods have been developed based on using metallic compounds as catalysts and, somewhat surprisingly, catalysis based on organic compounds (organic catalysts) has been less explored. Here we report that *N*-methyl-2-phenylimidazole (**Ph-NMI**) and 2-substituted imidazo[2,1-*b*]benzothiazoles (**IBT**s) catalyzed the selective acylation of a primary hydroxy group in diols.

In the course of our research for catalytic acyl transfer reactions,[15,16] we discovered that imidazo[2,1-*b*]benzothiazole (**IBT**) catalyzed acylation of alcohols with acid anhydrides.

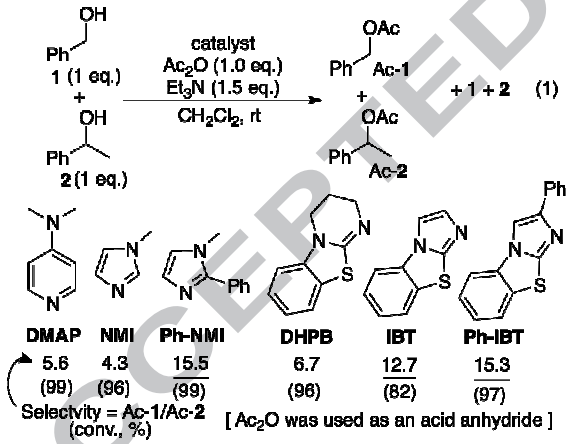
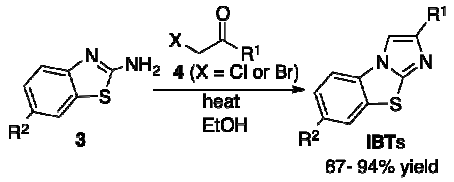


Figure 1. The results of the preliminary investigation of the acetylation of a mixture of **1** and **2**.

Initially, we studied the selectivity for acetylation of a primary alcohol in the presence of a secondary alcohol by the catalytic reaction of a mixture of benzyl alcohol (**1**) and 2-phenylethanol (**2**) with acetic anhydride (Ac_2O) using 5 mol% of 4-*N*,*N*-dimethylaminopyridine (**DMAP**), *N*-methylimidazole (**NMI**), *N*-methyl-2-phenylimidazole (**Ph-NMI**),[17] 2,3-dihydro-4*H*-pyrimido[2,3-*b*]benzothiazole (**DHPB**),[15,18] **IBT** or its 2-phenyl derivative **Ph-IBT** (Equation 1). The selectivity for acylation of the primary alcohol was evaluated as a value of Ac-**1**/Ac-**2** (Figure 1). We found that **Ph-NMI** and **Ph-IBT** exhibited high Ac-**1**/Ac-**2** values of more than 15, due to the bulkiness of the 2-Ph group. Interestingly, **IBT** also exhibited a high selectivity (12.7), however, the selectivity of **DHPB**, with a similar thioguanidine structure, was low.

Following these results, we studied the selectivity for primary alcohol acylation catalyzed by **Ph-NMI**, **IBT** and its derivatives. In this study, substituted imidazo[2,1-*b*]benzothiazoles (**IBT**s) were readily synthesized in good yields from commercially available 2-aminobenzothiazoles **3** and α-haloketones **4** according to previously reported procedures[19] (Scheme 1).

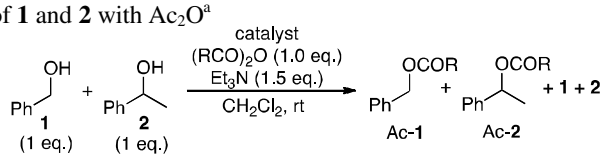
Table 1 shows results of the competitive reaction of a mixture of **1** and **2** with Ac_2O in the presence of various **IBT**s as catalysts. Comparing the results of entries 5–7, the substitution at the 2-position of **IBT** increased the selectivity; however, the deference between **Me-IBT** and **Ph-IBT** was not large in this acetylation reaction. As previously mentioned, **Ph-NMI** was also assessed as a selective catalyst (entry 4). The use of more sterically demanding acid anhydrides enhanced the selectivity (entries 12–14). In toluene and 1,2-dichloroethane a somewhat enhanced selectivity was observed (entries 8 and 9). Interestingly, reactions under higher concentrations or with a larger loading of catalyst exhibited higher selectivity (entries 10 and 11). Substitution at the 7-position of **IBT** affected the rate and selectivity of the reaction (entries 15 and 16). The selectivity was improved by the substitution, and an electron-withdrawing group at the 7-position decreased the reaction rate (entry 16).



IBT (R^1, R^2 = H) **Ph,MeO-IBT** (R^1 = Ph, R^2 = OMe)
Me-IBT (R^1 = Me, R^2 = H) **Ph,NO_2-IBT** (R^1 = Ph, R^2 = NO_2)
Ph-IBT (R^1 = Ph, R^2 = H)

Scheme 1. Preparation of imidazobenzothiazoles.

Table 1. Reaction of a mixture of **1** and **2** with Ac_2O[a]



entry	catalyst (mol%)	acid anhydride	Ac-**1**/**1**/Ac-**2**/**2**[b]	selectivity, Ac-**1**/Ac-**2**[b]	total conversion, %[b]
1	**DMAP** (5)	Ac_2O	84/16/15/85	5.6	99
2	**NMI** (5)	Ac_2O	78/32/18/82	4.3	96
3	**DHPB** (5)	Ac_2O	60/40/9/91	6.7	96
4	**Ph-NMI** (5)	Ac_2O	93/7/6/94	15.5	99
5	**IBT** (5)	Ac_2O	76/24/6/94	12.7	82
6	**Me-IBT** (5)	Ac_2O	91/9/6/94	15.2	97
7	**Ph-IBT** (5)	Ac_2O	92/8/6/94	15.3	98
8	**Ph-IBT** (5) [toluene][c]	Ac_2O	80/20/5/95	16.0	85
9	**Ph-IBT** (5) [$Cl(CH_2)_2Cl$][d]	Ac_2O	72/28/4/96	18.0	76
10	**Ph-IBT** (5) [2.0 M][e]	Ac_2O	78/22/4/96	19.5	82
11	**Ph-IBT** (20)	Ac_2O	79/21/3/97	26.0	82
12	**Ph-IBT** (5)	$(EtCO)_2O$	80/20/3/97	26.7	83
13	**Ph-IBT** (5)	$(i\text{-}PrCO)_2O$	71/29/2/98	35.5	73
14	**Ph-IBT** (5)	$(PhCO)_2O$	96/4/3/97	32.0	99
15	**Ph,MeO-IBT** (5)	Ac_2O	86/14/5/95	17.2	91
16	**Ph,NO_2-IBT** (5)	Ac_2O	55/45/3/97	18.3	58

[a]The reaction was performed at room temperature for 24 h. Unless other wise indicated, the concentration (**1** or **2** in CH_2Cl_2) was 1.0 M.

[b]Determined by ^1H NMR analysis of the crude mixture.

[c]The reaction was conducted in toluene instead of CH_2Cl_2.

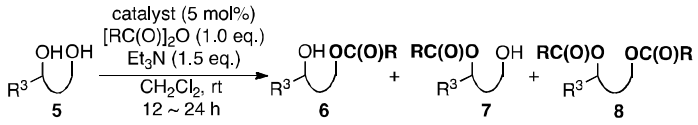
[d]The reaction was carried out in 1,2-dichloroethane instead of CH_2Cl.

[e]The concentration of **1** or **2** in CH_2Cl_2 was 2.0 M.

Having these results in hand, the **Ph-NMI**- and **Ph-IBT**-catalyzed reactions of 1,n-diols **5** (n = 2, 3, 4 and 5) with Ac_2O, $(i\text{-}PrCO)_2O$ or $(PhCO)_2O$ were investigated and the results are summarized in Table 2. The reaction yielded a mixture of primary ester **6**, secondary ester **7**, and diester **8**. The selectivity for acylation of a primary hydroxy group was evaluated by comparison of (**6** + **8**)/(**7** + **8**) values.

The reaction of 1,2-diol (1,2-butanediol, **5a**) proceeded selectively at primary hydroxyl group; however, the selectivity was unfortunately not high and thus inapplicable for practical use, even when sterically demanding anhydrides were employed (entries 1–3). Meanwhile, 1,n-diols (n ≥ 3) were acylated with a high primary-selectivity (entries 7 and 11–22). In the acetylation reaction of 1,3-diol **5b** (1,3-butanediol), **Ph-NMI** and **Ph-IBT** demonstrated better selectivity (entries 4–6, 8, and 9). The reactions with $(PhCO)_2O$ catalyzed by **Ph-NMI** or **Ph-IBT** exhibited high selectivity in producing the desired **6** with formation of a small amount of **8** (entries 7 and 12). **Ph-IBT**-catalyzed reactions of other 1,3-diols **5c** and **5d** with $(PhCO)_2O$ afforded the primary ester **6** with a high, synthetically useful selectivity (entries 14 and 16). Similarly, 1,4-diols **5e** and **5f** (entries 18 and 20) and 1,5-diol **5g** (entry 22) could be converted by **Ph-IBT**-catalyzed reactions with $(PhCO)_2O$ to the desired primary esters with a high selectivity.

Table 2. Acylation of diols[a]

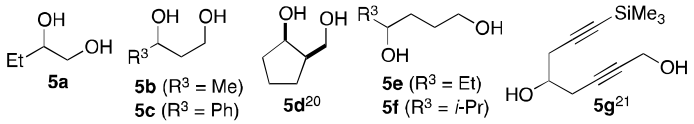


	entry	**5**[b]	catalyst	acid anhydride	**6**:**7**:**8**[c]	selectivity (**6**+**8**)/(**7**+**8**)[c]	conversion, %[c]
1,2-diol	1	**5a**	**Ph-NMI**	$(PhCO)_2O$	83:13:4	5.1	92
	2	**5a**	**Ph-IBT**	$(i\text{-PrCO})_2O$	72:25:3	2.7	93
	3	**5a**	**Ph-IBT**	$(PhCO)_2O$	75:20:5	3.2	91
1,3-diols	4	**5b**	**DMAP**	Ac_2O	64:34:2	1.9	93
	5	**5b**	**NMI**	Ac_2O	78:17:5	3.8	91
	6	**5b**	**Ph-NMI**	Ac_2O	92:4:4	12	98
	7	**5b**	**Ph-NMI**	$(PhCO)_2O$	97:0:3	33.3	95
	8	**5b**	**Me-IBT**	Ac_2O	77:5:18	4.1	80
	9	**5b**	**Ph-IBT**	Ac_2O	90:3:7	9.7	85
	10	**5b**	**Me-IBT**	$(i\text{-PrCO})_2O$	85:2:13	6.5	86
	11	**5b**	**Ph-IBT**	$(i\text{-PrCO})_2O$	96:1:3	24.8	91
	12	**5b**	**Ph-IBT**	$(PhCO)_2O$	96:0:4	25.0	92
	13	**5c**	**Ph-IBT**	$(i\text{-PrCO})_2O$	96:2:2	24.5	86
	14	**5c**	**Ph-IBT**	$(PhCO)_2O$	97:0:3	33.3	95
	15	**5d**	**Ph-IBT**	$(i\text{-PrCO})_2O$	96:1:3	24.8	96
	16	**5d**	**Ph-IBT**	$(PhCO)_2O$	97:2:1	32.7	96
1,4-diols	17	**5e**	**Ph-IBT**	$(i\text{-PrCO})_2O$	94:2:4	16.3	90
	18	**5e**	**Ph-IBT**	$(PhCO)_2O$	96:1:3	24.8	95
	19	**5f**	**Ph-IBT**	$(i\text{-PrCO})_2O$	97:2:1	32.7	91
	20	**5f**	**Ph-IBT**	$(PhCO)_2O$	98:1:1	49.5	91
1,5-diol	21	**5g**	**Ph-IBT**	$(i\text{-PrCO})_2O$	97:1:2	33.0	91
	22	**5g**	**Ph-IBT**	$(PhCO)_2O$	98:1:1	49.5	95

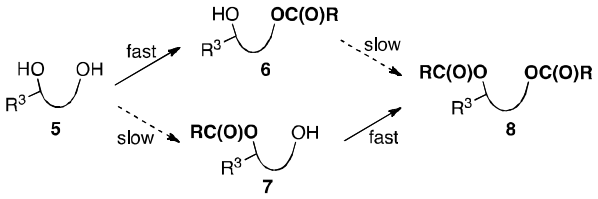
[a]The reaction was performed at room temperature for 12-24 h. The concentration of **5** in CH_2Cl_2 was 1.0 M.

[b]For the structure of diols **5**, see below.

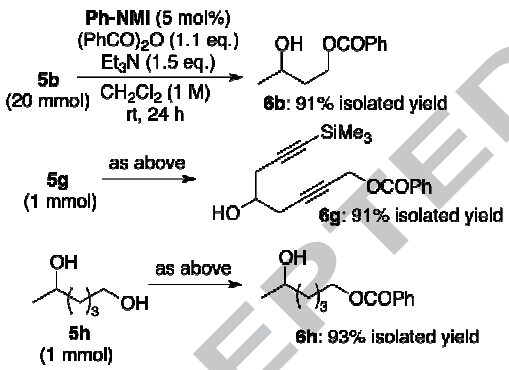
[c]Determined by ^1H NMR analysis of the crude mixture.



As a result, the reaction with $(PhCO)_2O$ catalyzed by **Ph-NMI** or **Ph-IBT** acylated the primary hydroxy group of 1,n-diols ($n \geq 3$) with a high synthetically useful selectivity. In an actual synthesis, isolation of the desired **6** from diester **8** by column chromatography will be easier than from **7** because of the difference of their polarity. The minimum generation of **7** in **Ph-NMI**- or **Ph-IBT**-catalyzed reactions was a characteristic of the method, which might be attained by the reasonably fast reaction rate of conversion of **7** to **8** (Scheme 2). For instance, using a slightly excess amount of $(PhCO)_2O$ in the **Ph-NMI**-catalyzed reactions, **6b**, **6g**, and **6h** were obtained in good isolated yields from diols **5b**, **5g**, and **5h**, respectively, by column chromatography (Scheme 3). In the 20 mmol scale reaction of **5b**, the desired **6b** was isolated in a good yield.



Scheme 2. Formation pathway of **6**, **7** and **8**.



Scheme 3. Examples of actual synthesis.

In summary, we demonstrated that *N*-methyl-2-phenylimidazole (**Ph-NMI**) and 2-phenylimidazo[2,1-*b*]benzothiazoles (**Ph-IBT**) catalyzed selective acylation of primary alcohols using acid anhydrides. In particular, the **Ph-NMI**- or **Ph-IBT**-catalyzed reaction, using $(PhCO)_2O$ as an acylating agent, acylated a primary hydroxy group of 1,n-diols ($n \geq 3$) with a high synthetically useful selectivity.[22]

Acknowledgments

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22. **General Procedure for Selective Primary Acylation of Diols**. To a mixture of diol **5** (1.0 mmol) and **Ph-IBT** (12.5 mg, 0.05 mmol, 5 mol%) in solvent (0.5 or 1.0 mL) was added $(i\text{-}PrCO)_2O$ or $(PhCO)_2O$ (1.0 or 1.1 mmol) at room temperature. The resulting mixture was stirred at ambient temperature. After checking the reaction progress by TLC analysis, saturated aqueous NH_4Cl was added and the mixture was extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was chromatographed on silica gel to separate the corresponding mono-ester **6**.

Graphical abstract