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1,3-DIHYDRO-1,3-DIACETYL-2*H*-BENZIMIDAZOL-2-ONE : A NEW VERSATILE AND SELECTIVE ACETYLATING AGENT

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Abstract - 1,3-Dihydro-1,3-diacetyl-2*H*-benzimidazol-2-one (**4, DABI**) was proven to be a versatile and selective acetylating agent for amines. Selectivity and reactivity are not only superior than those of other known acetylating agents, but also products could be easily separated with excellent yield.

The acetylation of amines is one of the most fundamental reactions in organic synthesis.[1] Especially, selective acetylation is important reaction in diamino or polyamino compounds. Numerous studies have been performed to obtain more efficient acetylating agents or to extend the application of the existing ones.[2]

During the study on imidazolone derivatives which are useful and important building blocks in medicinal chemistry, [3] we have found that *N*-acetyl group could be easily removed by nucleophiles such as amines. From this result, we have synthesized several 1,3-dihydro-1,3-diacetyl-1*H*-imidazolone derivatives (Figure 1) to consider their acetyl transfer reactivity to amine.[4]

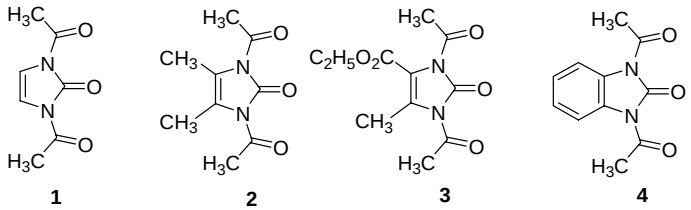


Figure 1. 1,3-Dihydro-1,3-diacetylimidazole-2-one derivatives

All of the compounds (**1-4**) showed excellent acetyl transferring properties (Tables 1 and 2). Among these,

4 showed the best reactivity. Compound (**4**) also has an additional advantage in its facile preparation (Scheme 1) through acetylation of commercially available 1,3-dihydro-2*H*-benzimidazol-2-one (**5**) with a corresponding acetyl chloride or acetic anhydride. *N*-Acetylated benzylamine and piperazine were efficiently separated by filtration of 1,3-dihydro-1-acetyl-2*H*-benzimidazol-2-one (**6**) by virtue of its low solubility in most organic solvents.

Table 1. Reactivity of 1,3-diacetylimidazolone derivatives with benzylamine

Agents	Amine	Conditions	Product	Yield(%)[a]
1	Benzylamine	CH_2Cl_2, rt, 3 h	*N*-Ac-benzylamine	91
2	Benzylamine	CH_2Cl_2, rt, 2.5 h	*N*-Ac-benzylamine	92
3	Benzylamine	CH_2Cl_2, rt, 1.5 h	*N*-Ac-benzylamine	95
4	Benzylamine	CH_2Cl_2, rt, 1.5 h	*N*-Ac-benzylamine	96

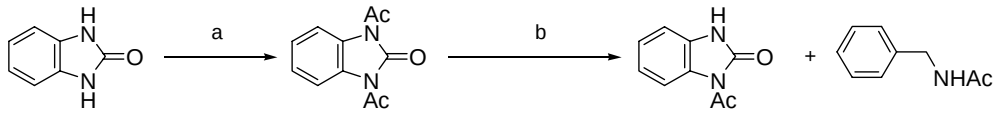
a) Isolated yield

Table 2. Reactivity of 1,3-diacetylimidazolone derivatives with piperazine

Agents	Amine	Conditions	Product	Yield(%)[a]
1	Piperazine	CH_2Cl_2, rt, 2.5 h	*N*-Ac-piperazine	85
2	Piperazine	CH_2Cl_2, rt, 2.5 h	*N*-Ac-piperazine	88
3	Piperazine	CH_2Cl_2, rt, 1.3 h	*N*-Ac-piperazine	94
4	Piperazine	CH_2Cl_2, rt, 1.4 h	*N*-Ac-piperazine	93

a) Isolated yield

Scheme 1. Preparation of **4** and reaction with benzylamine



5 **4** **6**

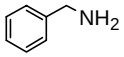
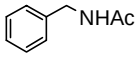
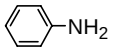
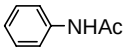
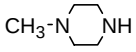
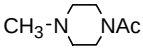
Reagents and conditions ; a) Ac_2O, reflux, 6 h, 97 %; AcCl (2.05 eq), $(C_2H_5)_3N$, reflux, 5 h, 94 %
b) benzylamine (1 eq), CH_2Cl_2, rt, 1.5 h, 96 %

In order to confirm the selectivity and reactivity of **4**, three other known acetylating agents, *N*-acetyl-*N*-acyl-3-aminoquinazoline (**A**), [2a] 2-trifluoromethyl-*N*,*N*-diacetylaniline (**B**) [2b] and *N*-methoxydiacetamide (**C**) [2f] were compared with **4**. Although **B** showed good selectivity, its reaction condition and yield were not recommendable. **4** also have advantages on the aspect of facile product isolation.

It was important to confirm the diacetyl transfering ability of **4** to various amine. The monoacetyl and diacetyl transferring abilities of **4** to various amines are summarized in Table 3. All of the amines required harsh conditions with 0.5 equivalent of **4** but proceeded under mild conditions with 1.0 equivalent.

In general, primary and secondary aliphatic amines including cyclic amines (Entries **1** and **4**) were easily acetylated in quantitative yield. Aromatic amines (Entry **2**) and sterically hindered aliphatic amines

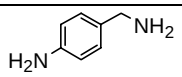
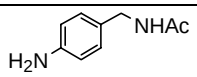
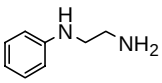
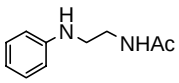
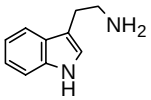
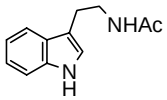
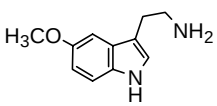
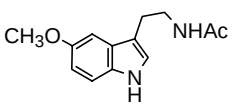
Table 3. Reaction of 1,3-dihydro-1,3-diacetyl-2*H*-benzimidazol-2-one (DABI) with amines*

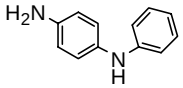
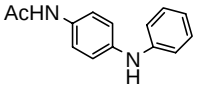
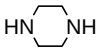
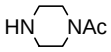
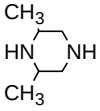
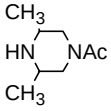
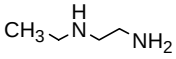
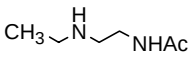
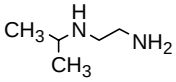
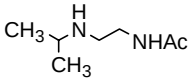
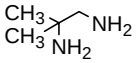
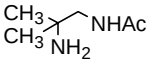
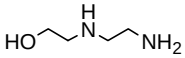
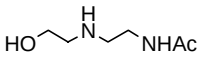
Entry	Amine	Product	DABI(0.5 eq)[a],Yield(%)[b]	DABI(1 eq)[c], Yield(%)[b]
1			rt, 6 h, 95	25 min, 99
2			30 h, 93	150 min, 94
3			60 h, 48.	4 h, 97
4			5 h, 96	30 min, 98
5			25 h, 97	120 min, 96

* All experiments were carried out in reagent grade THF. a)The mixture was refluxed. b)Isolated yield. c)The reaction proceeded at room temperature.

(Entry **5**) required slightly harsher reaction conditions. In contrast, sterically hindered *N*- methylaniline (Entry **3**) was incompletely acetylated with 0.5 equivalent of reagent, but proceeded completely under mild conditions with the 1.0 equivalent. The substantial reactivity difference depending on the nucleophilicity and steric hindrance of amines encouraged us to examine selective acetylation in a series of structurally diverse diamino compounds possessing aromatic and aliphatic, or primary and secondary amino groups (Table 4). As shown in Table 4, the aliphatic amino group was selectively acetylated in the presence of aromatic amines (Entries **6, 7,** [5] **8,** and **9**). In the case of aliphatic diamino compounds consisting of primary and secondary amino moieties, monoacetamides of primary amino groups were selectively obtained in good yields (Entries **14**, **15**, [6] and **16**). Compound (**4**) showed good regio- and chemoselectivity (Entry **17**), and transferred acetyl group to imidazole[7] itself (Entry **11**). From this result, we have found compound (**4**) has more powerful acetyl transfer reactivity than those of imidazole.

Table 4. Reaction of 1,3-dihydro-1,3-diacetyl-2*H*-benzimidazol-2-one (DABI) with diamines*

Entry	Amines	Product	DABI(0.5 eq)[a], Yield(%)[b]	DABI(1 eq)[a], Yield(%)[b]
6			15 h, 97	25 min, 97
7			12 h, 96	20 min, 96
8			12 h, 95	20 min, 95
9			12 h, 93	18 min, 93

10			48 h, 95	120 min, 95
11			reflux, 12 h, 75	20 min, 80
12			12 h, 75	20 min, 95
13			reflux, 6 h, 95	18 min, 98
14			5 h, 96	15 min, 96
15			6 h, 97	15 min, 97
16			7 h, 95	18 min, 95
17			6 h, 94	15 min, 94

* All experiments were carried out in reagent grade THF. a)Reaction was performed at room temperature. b)Isolated yield.

In conclusion, 1,3-dihydro-1,3-diacetyl-2*H*-benzimidazol-2-one (**4**) is a convenient regio- and chemoselective acetylating reagent with many advantages due to its facile preparation, good reactivity, stability and easy work-up process.

REFERENCES AND NOTES

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3. N. A. Meanwell, S. Y. Sit, J. Gao, H. S. Wong. Q. Gao, R. St. L. Denis, and B. Neelakantan, *J. Org. Chem*., 1995, **60**, 1565.
4. R. Duchinsky and L. A. Dolan, *J. Am. Chem. Soc*., 1946, **68**, 2350; B. B. Corson and D. Blum, *Chem. Ber*., 1957, **90**, 391.
5. All new compounds exhibited satisfactory analytical and spectroscopic data. Selected data for **7** : brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61-7.21 (m, 5H), 5.91 (br s, NH), 4.01 (br s, NH), 3.48 (t, *J* = 5.7 Hz, 2H), 3.28 (t, *J* = 5.7 Hz, 2H), 1.98 (s, 3H); MS m/z 178 (M+); HRMS *m/z* $[M]^+$ calcd for

$C_{10}H_{14}N_2O$, 178.1106, found 178.1106.

6. Selected data for **15** : yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (br s, NH), 3.33(q, *J* = 5.7 Hz, 2H), 2.78 (m, 1H), 2.72 (q, *J* = 5.7 Hz, 2H), 1.97 (s, 3H), 1.59 (br s, NH), 1.04 (d, *J* = 6.4 Hz, 6H); HRMS *m/z* $[M]^+$ calcd for $C_7H_{16}N_2O$, 144.1262, found 144.1261.

7. R. Paul and G. W. Andonon, *J. Am. Chem. Soc*., 1960, **82**, 4596; H. A. Staab, *Angew. Chem. Int., Ed*. *Engl*., 1962, **7**, 351; A. Saito and B. Shimizu, *Bull. Chem. Soc. Jpn*., 1983, **56**, 2974.