[Chem. Pharm. Bull. 31(10)3724—3727(1983)]

1-Substituted Imidazoles as Useful Catalysts for Acylation of Alcohols

TETSUHIDE KAMIJO, RYOJI YAMAMOTO, HIROMU HARADA, and KINJI IIZUKA*

Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., 19–48, Yoshino, Matsumoto-shi, Nagano 399–65, Japan

(Received March 15, 1983)

Acylation of alcohols with acid anhydrides or acid halides could be considerably accelerated by adding 1-substituted imidazoles as catalysts. The acylation with acid halides required the addition of triethylamine to capture the resulting acid. 1-Isopropyl-5-methylimidazole and 1-(4-methoxybenzyl)-5-methylimidazole showed higher catalytic activities than 4-dimethylaminopyridine (DMAP) for acylation of primary and secondary alcohols.

Keywords——1-substituted imidazole; acylating catalyst; 1-isopropylimidazole; 1-isopropyl-5-methylimidazole; 1-(4-methoxybenzyl)-5-methylimidazole; 4-dimethylaminopyridine

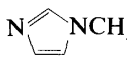
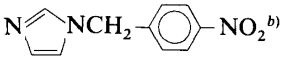
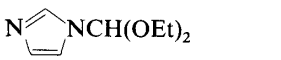
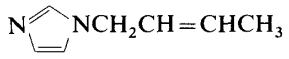
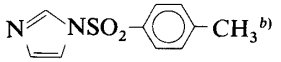
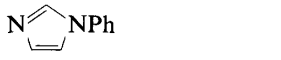
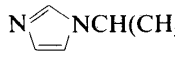
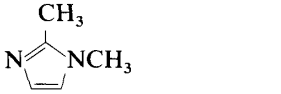
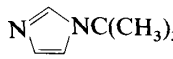
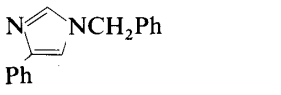
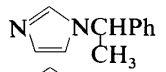
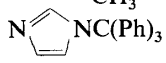
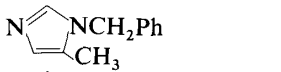
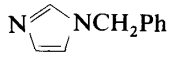
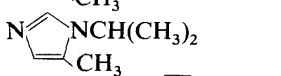
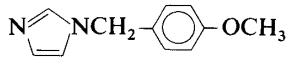
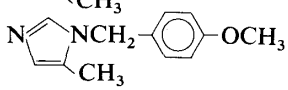
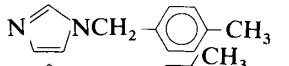
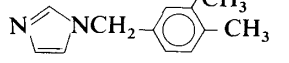
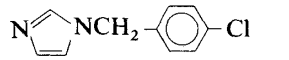
Connors *et al.*[1] and Pandit *et al.*[2] have reported that 1-methylimidazole has catalytic activity similar to that of 4-dimethylaminopyridine (DMAP) for acylation of alcohols with acid anhydrides or acid halides. The mechanism of the acylation has been considered to be as follows: 1-methylimidazole and acid halides yield small amounts of the 1-acyl-3-methylimidazolium halides, and then the acyl moieties of the salts are transferred to the alcohols. We examined the catalytic activities of 1-substituted imidazoles for acylation of alcohols and found that some of them have considerably higher catalytic activities than 1-methylimidazole.

We now report the structure–catalytic activity relationships of 1-substituted imidazoles for the acylation of alcohols. The acylation of alcohols was carried out with 1.1 eq of acid anhydrides or acid halides and 0.02—0.1 eq of 1-substituted imidazoles.

As shown in Table I, 1-phenethylimidazole showed the highest catalytic activity among the 1-substituted imidazoles with straight chain alkyl or aralkyl groups (entries 1—4), and 1-isopropylimidazole showed the highest activity among the 1-substituted imidazoles with branched chain alkyl or aralkyl groups (entries 5—8). The yields of acetate were improved by increasing the amount of the catalyst (0.02→0.05 eq) (entry 5). In the case of 1-benzylimidazoles with various substituents on the benzene ring, electron-donating groups increased the catalytic activities, while electron-withdrawing groups lowered them (entries 9—14). Furthermore, 1-substituted imidazoles with electron-withdrawing groups such as diethoxymethyl and tosyl groups showed very weak catalytic activities (entries 15 and 16). 1-Phenylimidazole, 1,2-dimethylimidazole and 1-benzyl-4-phenylimidazole also showed weak catalytic activities (entries 17—19), but 1-substituted imidazoles with a methyl group at the 5 position, such as 1-benzyl-5-methylimidazole (**20**), 1-isopropyl-5-methylimidazole (**21**), and 1-(4-methoxybenzyl)-5-methylimidazole (**22**), showed the highest catalytic activities among the tested 1-substituted imidazoles. Compounds **21** and **22**, especially, showed higher catalytic activities than DMAP.

Table II shows the results of acylation of alcohols with acid chlorides. The reaction was carried out by the addition of a catalytic amount of 1-substituted imidazole [1-isopropylimidazole (**5**), 1-isopropyl-5-methylimidazole (**21**), and 1-(4-methoxybenzyl)-5-methyl-

TABLE I. $(CH_3)_2CHCH_2\underset{\underset{OH}{|}}{C}HCH_3 + Ac_2O \xrightarrow[CCl_4,\ 40°C\ 3h]{\text{catalyst (0.02 eq)}} (CH_3)_2CHCH_2\underset{\underset{OAc}{|}}{C}HCH_3$

Entry	Catalyst		Yield[a] (%)	Entry	Catalyst		Yield[a] (%)
1		**1**	73.5	14		**14**	62.0
2		**2**	75.0	15		**15**	<5
3		**3**	72.0	16		**16**	<5
4		**4**	80.0	17		**17**	28.0
5		**5**	83.0 88.0[c] 92.0[d]	18		**18**	9.0
6		**6**	80.5	19		**19**	<5
7		**7**	71.5				
8		**8**	20.0	20		**20**	85.5
9		**9**	70.5	21		**21**	96.0
10		**10**	80.0	22		**22**	96.0
11		**11**	76.0	23	Pyridine		<5
12		**12**	78.5	24	Et_3N		<5
13		**13**	65.5	25	DMAP		94.0

a) The yields were calculated from NMR spectra.
b) Sparingly soluble in CCl_4.
c) Yield with 0.03 eq of 1-isopropylimidazole.
d) Yield with 0.05 eq of 1-isopropylimidazole.

imidazole (**22**)] and 1.1 eq of triethylamine to capture the resulting acid. The catalytic activities of these imidazoles (**5**), (**21**), and (**22**) were considerably higher than that of DMAP.

Chart 1 shows the acylation of a sterically hindered alcohol, *tert*-butanol. DMAP gave the best yield in the reaction with Ac_2O.

$$(CH_3)_3COH + Ac_2O \xrightarrow[CCl_4,\ \text{reflux 24 h}]{\text{catalyst (0.1 eq)}} (CH_3)_3COAc$$

catalyst	yield (%)
21	71.0
22	64.0
DMAP	84.0
pyridine	35.5

Chart 1

From these results, it is suggested that introduction of an electron-donating substituent into the 1 position of the imidazole ring considerably increases the catalytic activity, while the

TABLE II. $PhCH_2CHCH_3$ (OH) + RCOCl $\xrightarrow[CCl_4]{\text{catalyst}}$ $PhCH_2CHCH_3$ (OCOR)

Entry	RCOCl (1.1 eq)	Catalyst	(eq)	Et_3N (eq)	Conditions		Ester yield[a] (%)
					Temp. (°C)	Time (h)	
26a	PhCOCl	**5**	0.05		Reflux	3	17.0
26b	PhCOCl	**5**	0.05	1.1	Reflux	3	Quant.
26c	PhCOCl	**21**	0.05	1.1	Reflux	3	Quant.
26d	PhCOCl	**22**	0.05	1.1	Reflux	3	88.0
26e	PhCOCl	DMAP	0.05		Reflux	3	14.5
26f	PhCOCl	DMAP	0.05	1.1	Reflux	3	81.5
26g	PhCOCl			1.1	Reflux	3	39.0
27a	$(CH_3)_3CCOCl$	**5**	0.02	1.1	Reflux	3	82.0
27b	$(CH_3)_3CCOCl$	**21**	0.05	1.1	Reflux	3	Quant.
27c	$(CH_3)_3CCOCl$	**22**	0.05	1.1	Reflux	3	88.0
27d	$(CH_3)_3CCOCl$	DMAP	0.02	1.1	Reflux	3	82.0

a) The yields were calculated from NMR spectra.

introduction of an electron-withdrawing substituent lowers the catalytic activity for acylation. Furthermore, introduction of a substituent into the 2 or 4 position of 1-substituted imidazoles greatly decreases the catalytic activities because of the steric hindrance at the nitrogen atom at the 3 position of the substituted imidazoles. In contrast, introduction of an electron-donating substituent into the 5 position of 1-substituted imidazole increases the catalytic activities because of the increase of the electron density of the imidazole ring.

Thus, 1-isopropyl-5-methylimidazole and 1-(4-methoxybenzyl)-5-methylimidazole showed higher catalytic activities than DMAP for the acylation of primary and secondary alcohols, and in the case of reaction of sterically hindered tertiary alcohols, DMAP showed the highest catalytic activity among the compounds tested.

Experimental

The infrared (IR) spectra were obtained with a Hitachi 260-10 infrared spectrophotometer. The nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-22 high-resolution nuclear magnetic resonance spectrometer in $CDCl_3$ or $(CD_3)_2SO$ with Me_4Si as an internal standard. The melting points were measured with Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed with a Yanaco CHN Corder MT-2.

Materials——1-Methylimidazole (**1**) and 1,2-dimethylimidazole (**18**) were commercial products. 4-Dimethylaminopyridine and 1-substituted imidazole derivatives except (**20**), (**21**), and (**22**) were prepared by the reported procedures.[3]

1-(4-Methoxybenzyl)-5-methylimidazole (22)——A mixture of 1-acetyl-4-methylimidazole[4] (1.24 g), 4-methoxybenzyl chloride (1.57 g), sodium iodide (1.50 g), and dry acetonitrile (30 ml) was stirred at room temperature for 18 h, then concentrated under reduced pressure. The residual oil was dissolved in $CHCl_3$, and the solution was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was purified by silica gel column chromatography ($CHCl_3$ as eluent) to obtain 1-(4-methoxybenzyl)-5-methylimidazole (**22**) (1.25 g, 62% yield). IR (neat): 1615, 1515, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.02 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.92 (s, 2H, CH_2), 6.75—7.10 (m, 5H), 7.43 (m, 1H, imidazole H); *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.50; H, 6.95; N, 13.60.

By similar procedures, 1-benzyl-5-methylimidazole (**20**) and 1-isopropyl-5-methylimidazole (**21**) were prepared. 1-Benzyl-5-methylimidazole (**20**): mp 98.5—101.5 °C; IR (KBr): 1490, 1445, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.02 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 6.78 (m, 1H, imidazole H), 6.90—7.50 (m, 6H); *Anal.* Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.52; H, 7.10; N, 16.15. 1-Isopropyl-5-methylimidazole (**21**): IR (neat); 2990, 1490 cm^{-1};

^{1}H NMR ($CDCl_3$) δ: 1.42 (d, 6H, J=7 Hz, CH_3), 2.12 (s, 3H, CH_3), 4.00—4.33 (m, 1H, CH), 6.70 (m, 1H, imidazole H), 7.45 (m, 1H, imidazole H); *Anal.* Calcd for $C_7H_{12}N_2$: C, 67.70; H, 9.74; N, 22.56. Found: C, 67.85; H, 9.70; N, 22.41.

A Typical Acylation Procedure——A solution of 4-methyl-2-pentanol (5.1 g), acetic anhydride (5.6 g), and 1-isopropylimidazole (0.28 g, 0.05 eq) in CCl_4 (50 ml) was stirred at 40 °C for 3 h. The reaction solution was washed with dil. HCl, aq. $NaHCO_3$, and water, then dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was distilled (51.5—52.5 °C/21.5 mmHg) to obtain 4-methyl-2-pentylacetate (6.5 g, 90%): IR (neat): 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ:0.89 (d, 6H, J=6 Hz, CH_3), 1.16 (d, 3H, J=6 Hz, CH_3), 1.20—1.70 (m, 3H), 1.96 (s, 3H, $COCH_3$), 4.97 (m, 1H, CH).

By similar procedures, the esters listed in Tables I, II, and Chart 1 were prepared. 1-Phenyl-2-propylbenzoate: IR (neat); 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.25 (d, 3H, J=6 Hz, CH_3), 2.88 (t, 2H, J=7 Hz, CH_2), 5.30 (m, 1H, CH), 7.12—8.20 (m, 10H, aromatic H). 1-Phenyl-2-propylpivalate: IR (neat); 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (s, 9H, CH_3), 1.12—1.32 (m, 3H, CH_3), 2.78 (m, 2H, CH_2), 5.02 (m, 1H, CH), 7.17 (m, 5H, aromatic H).

References

1) K. A. Connors and N. K. Pandit, *Anal. Chem.*, **50**, 1542 (1978).
2) N. K. Pandit and K. A. Connors, *J. Pharm. Sci.*, **71**, 485 (1982).
3) *a*) A. F. Pozharskii, B. K. Martsokha, and A. M. Simonov, *Chem. Abstr.*, **59**, 7515*e* (1963); *b*) H. Schubert, W. Berg, and H. Andrae, *Chem. Abstr.*, **60**, 14494*g* (1964); *c*) F. Pierre, D. C. Paul, and L. Etieene, *Chem. Abstr.*, **69**, 106622*u* (1968); *d*) G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem. Int. Ed. Engl.*, **17**, 569 (1978); *e*) N. J. Curtis and R. S. Brown, *J. Org. Chem.*, **45**, 4038 (1980); *f*) J. M. Eijk, R. J. Nolte, and J. W. Zwikker, *J. Org. Chem.*, **45**, 547 (1980); *g*) T. Kamijo, R. Yamamoto, H. Harada, and K. Iizuka, *Chem. Pharm. Bull.*, **31**, 1213 (1983).
4) *a*) J. H. Boyer, *J. Am. Chem. Soc.*, **74**, 6274 (1952); *b*) H. A. Staab, *Angew. Chem. Int. Ed. Engl.*, **1**, 351 (1962).