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N-METHYL-2-DIMETHYLAMINOACETOHYDROXAMIC ACID AS A NEW REAGENT FOR THE SELECTIVE CLEAVAGE OF ACTIVE ESTERS UNDER NEUTRAL CONDITIONS

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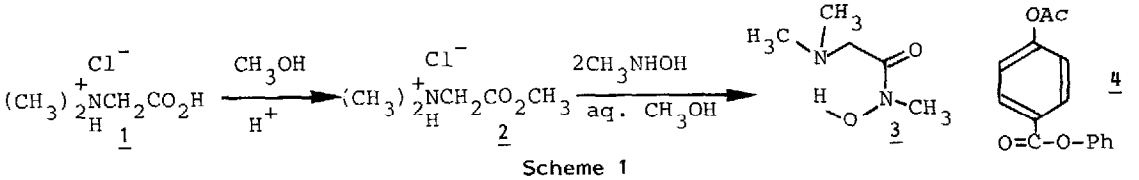
Summary: A new reagent, N-methyl-2-dimethylaminoacetohydroxamic acid 3 was developed for the selective cleavage of active esters under neutral conditions. The kinetic studies and the applications of 3 are described.

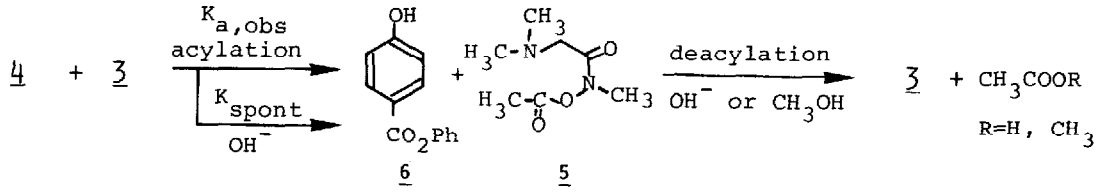
It is known[1] that anionic nucleophiles such as thiolate, hydroxamate, and oximate anions show remarkably high reactivities toward p-NPA in cationic micellar systems. On the other hand, Bender et al.[2] and Kunitake et al.[3] have suggested that the introduction of a second functionality into hydroxamic acid makes a catalytic activity toward p-NPA increase in non-micellar systems. However, little is known about the applications of these observations into the selective deprotection of active esters without affecting other alkali sensitive groups in organic synthesis. Continuing with our efforts in this area,[4] we wish to report that the title compound 3 serves as one of versatile bifunctional catalyst[5] for the selective cleavage of active esters under neutral conditions.

N-Methyl-2-dimethylaminoacetohydroxamic acid 3 (m.p. 94-97 °C; pKa_1= 7.3, pKa_2= 10.9),[6] which exhibits strong amphiphilic property, is conveniently obtainable from N,N-dimethylglycine hydrochloride 1 in high yield according to the route illustrated in Scheme 1.



Scheme 1

In the first place we examined the selective cleavage of ester 4 (m.p. 84-85 °C). The results are presented in Table 1. Treatment of 4 with the equivalent amount of 3 in THF/aqueous phosphate buffer (pH= 7.6) or MeOH at 30 °C gave 6 (m.p. 180 °C) in a regioselective manner (run 1 and 2). It is to be noted that the reaction proceeds even in the solvent systems non-buffered, affording 6 quantitatively within 1 h (run 5). When 3 was allowed to react with a twofold excess of 4 in THF/buffer, the appearance of 6, followed by HPLC, obeyed strictly the pseudo-first order kinetics for at least 72% of the cleavage with K_{total}= 1.18 x 10^{-3} sec^{-1}



Scheme 2

Table 1. Comparison of the effects of 3 and other additives on the release of 6 from ester 4 at 30 °C.

Run	Additive (mol. eq.)	Solvent	$K_{a,obs}$, M^{-1} sec^{-1}	K_{total}, sec^{-1}[a]	Products/%[b]
1	3 (1.0)[c]	THF/buffer[c] (1 : 1)	1.23×10^{-1}	2.48×10^{-3}	6 (95)
2	3 (1.0)[c]	MeOH	1.52×10^{-1}	3.05×10^{-3}	6 (98)
3	3 (0.75)	THF/buffer (1 : 1)	1.22×10^{-1}	1.85×10^{-3}	6 (98)
4	3 (0.5)[d]	THF/buffer (1 : 1)	1.18×10^{-1}	1.19×10^{-3}	6 (91)
5	3 (1.0)	THF/H_2O (1 : 1)	1.25×10^{-1}	2.52×10^{-3}	6 (95)
6	3 (0.3)	THF/buffer (1 : 1)	1.20×10^{-1}	7.29×10^{-4}	6 (72), 4 (19)
7	none	THF/buffer (1 : 1)		1.44×10^{-5}	6 (3), 4 (93)
8	MeCON(Me)OH[7] (1.0)	THF/buffer	1.73×10^{-2}	3.45×10^{-4}	6 (60), 4 (36)
9	imidazole[8] (1.0)	THF/buffer	5.30×10^{-3}	1.06×10^{-4}	6 (22), 4 (64)
10	$C_4H_9NH_2$[9] (1.0)	benzene			6 (41), 4 (36)

a. $K_{a,obs}$ was determined by the following equations: $K_{a,obs} = (K_{total} - K_{spont})/(3)_o$; $\log(P_\infty - P_t) = -K_{total} \times t/2.303 + \log P_\infty$, where P_∞ is the amount of 6 at the infinite reaction time and P_t is the amount of time t.

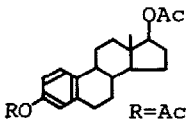
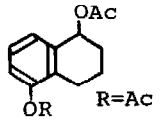
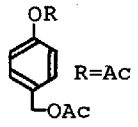
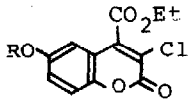
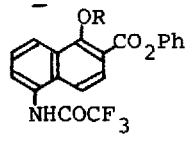
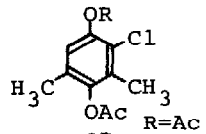
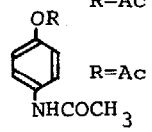
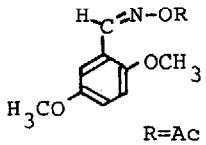
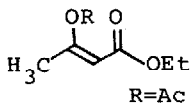
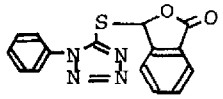
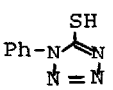
b. Yields estimated by HPLC analysis after 1 h.

c. 50 v/v% THF-0.1M phosphate buffer (pH= 7.6), (3) = (4) = 2.0×10^{-2}M

d. (3) = 1.0×10^{-2}M, (4) = 2.0×10^{-2}M

(run 4). Under the same conditions in the absence of 3, the initial rate for the hydrolysis was 1.44×10^{-5} sec^{-1}, and the prolonged treatment led to a loss of the regioselectivity of the cleavage (run 7). That is, the selective hydrolysis of 4 was catalyzed 80-fold by 3 under these turnover conditions. Usefulness of 3 was also demonstrated in the comparison of the apparent rate constants ($K_{a,obs}$ and K_{total}) with other additives reported (run 8, 9, and 10). The absence of a large kinetic solvent isotope effect using buffered THF/D_2O (pD= 7.6) supports the nucleophilic mechanism[7] and may suggest that there is no accumulation of the acetyl intermediate 5 because of faster deacylation[3] (K_{H_2O}/K_{D_2O}= 1.2 ± 0.05) in the conditions.

Table 2. Results of the selective cleavage of several esters by 3

Entry	Substrate	3(mol. eq.)	Solvents	Temp/°C	Time/h	Product(Yield/%)[a]
1	 R=Ac	2.5	CH_3OH	45	3	R = H; 82 m.p. 215-217 °C
2	 R=Ac	1.0	THF/buffer[b] (1 : 1)	45	4	R = H; 84 m.p. 66 °C
3	 R=Ac	1.0	CH_3OH	50	1.5	R = H; 80 oil
4	 7 R=Ac	0.5	THF/buffer (2 : 1)	R.T.	1	R = H; 95 m.p. 235-237 °C
5	 R=Ac	0.5	THF/buffer (1 : 1)	R.T.	1	R = H; 92 m.p. 175-177 °C
6	 R=Ac	1.0	THF/buffer (3 : 1)	45	2	R = H; 82 m.p. 82-83 °C
7	 R=Ac	1.0	EtOH	45	1	R = H; 80 m.p. 158-160 °C
8	 R=Ac	1.5	THF/CH_3OH/ buffer (5 : 1 : 5)	50	2	R = H; 79 m.p. 108-110 °C
9	 R=Ac	0.5	EtOH	R.T.	2	R = H; 91 oil
10		1.0	THF/DMF/ buffer (3 : 1 : 1)	40	3	 86 m.p. 154-157 °C

a) Yields of purified products; b) 0.1M aqueous phosphate buffer (pH= 7.6)

The successful deprotection reactions listed in Table 2 indicate a reasonable applicability for alkali labile and/or oxygen sensitive compounds. Thus, protected phenols (entries 1-4), naphthol (entry 5), hydroquinones (entries 6 and 7), oxime (entry 8), and enol (entry 9) were smoothly deprotected by treatment of 3 (0.5-2.5 equiv.) to regenerate the corresponding hydroxyl function without affecting other functional groups.

A typical procedure is as follows: To a solution of ester 7 (m.p. 130 °C; 310 mg, 1 mmol) in THF (10 cm^3) was added a solution of 3 (66 mg, 0.5 mmol) in aqueous phosphate buffer (5 cm^3; pH= 7.6). The reaction mixture was stirred at room temperature for 1 h, poured into water (50 cm^3) and brine (50 cm^3) and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give crystals of ethyl 3-chloro-7-hydroxy-4-coumarincarboxylate (m.p. 235-237 °C; 253 mg).

The authors wish to thank Miss Haruko Shimizu for carrying out the kinetic determination.

References and Notes

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6) The pKa values were determined by the potentiometric titration in 20 v/v% water in EtOH.

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8) M. L. Bender and B. W. Turnquest, J. Am. Chem. Soc., 79, 1652 (1957); T. C. Bruce and J. M. Sturtevant, J. Am. Chem. Soc., 81, 2860 (1959); C. G. Overberger and C. M. Shen, J. Am. Chem. Soc., 93, 6992 (1971); T. Kunitake and Y. Okahata, Chem. Lett., 1974, 1057.

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