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N-METHOXYDIACETAMIDE: A NEW SELECTIVE ACETYLATING AGENT

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Summary: A simple and efficient method for the direct chemoselective acetylation of primary amines in the presence of alcohols or secondary amines using a new reagent N-methoxydiacetamide is described.

Acetylation is one of the most basic reactions in synthetic organic chemistry and selective acetylation of amino groups in the presence of other functional groups which can be acetylated by acetic anhydride has great practi cal utility.[1]

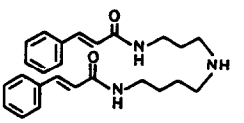
We wish to report here a new acetylating agent, N-methoxydiacetamide (**1**), which is useful for chemoselective acetylation of amino groups of compounds which possess both amino and other acetylatable groups.

$(RCO)_2NOCH_3$

1: R=CH_3

2: R=C_6H_5

3: R=$C_6H_5CH{=}CH_2$(trans)



Maytenine

1 is a new compound and readily synthesized from acetic anhydride and methoxyamine in high yield. **1** is fairly stable in hydroxylic solvents due to the electron-donating effect of a methoxy group and slowly decomposed in weak alkaline water.

Chemoselective Acetylation of Amino Groups in the Presence of Hydroxy Groups. **1**, applied in 2 molar equiv., acetylates smoothly primary and secondary amino groups in neat, N,N-dimethylformamide (DMF), and water at ordinary temperature in high yields liberating N-methoxyacetamide, while hydroxy compounds such as 3-phenyl-1-propanol cannot be acetylated with **1** overnight at ordinary temperature. Addition of triethylamine[1c] does not enhance the reactivity of **1**. After acetylation the products are obtained with usual work-up. Excess **1** is decomposed, if necessary, with the addition of 10% aqueous ammonia in 20-30 min to give acetamide and N-methoxyacetamide which are easily removed by washing with water. The results are presented in Table. Although several methods of chemoselective N-acetylation are available,[1] our method has the advantages of high yields, cheap and easily handled reagent, and easy work-up.

Table. Selective Acetylation of Amines with N-Methoxydiacetamide (1)[a]

run	amine	solvent	time (h)	product (%, yield)[b]
1	$C_6H_5NH_2$	--	0.7[c]	C_6H_5NHAc (94)
2	$C_6H_5(CH_2)_2NH_2$	--	0.3[c]	$C_6H_5(CH_2)_2NHAc$ (99)
3	$C_6H_5(CH_2)_2NH_2$	--	0.5	$C_6H_5(CH_2)_2NHAc$ (97)
4	$C_6H_5(CH_2)_2NH_2$	DMF	3.3	$C_6H_5(CH_2)_2NHAc$ (97)
5	$C_6H_5CH(OH)CH_2NH_2$	H_2O	1.2	$C_6H_5CH(OH)CH_2NHAc$ (89)
6	$C_6H_5CH_2NHCH_3$	--	4.4	$C_6H_5CH_2N(CH_3)Ac$ (92)
7	$C_6H_5CH_2NHCH_3$	DMF	2.3	$C_6H_5CH_2N(CH_3)Ac$ (96)
8	p-$HOC_6H_4(CH_2)_2NH_2$	DMF	4.0	p-$HOC_6H_4(CH_2)_2NHAc$ (96)
9	D-Glucosamine·HCl	H_2O[d]	26.5[e]	N-Ac-D-glucosamine (66)[f]
10	c-$C_6H_{11}NH(CH_2)_3NH_2$	H_2O	20.3	c-$C_6H_{11}NH(CH_2)_3NHAc$ (80)
11	$C_6H_5CH_2NH(CH_2)_2NH_2$	H_2O	40	$C_6H_5CH_2NH(CH_2)_2NHAc$ (85)
12	$H_2N(CH_2)_3NH(CH_2)_3NH_2$	H_2O	4	$AcNH(CH_2)_3NH(CH_2)_3NHAc$ (75)
13	DL-Phe	dioxane[g]	19	Ac-DL-Phe (81)
14	L-Tyr-OCH_3	DMF	3.5	Ac-L-Tyr-OCH_3 (96)[h]
15	L-Lys	dioxane[g]	15.5	N^{ε}-Ac-L-Lys (88)[i]

[a] Unless otherwise noted, all reactions were carried out according to the general procedure described in the text. All new compounds have satisfactory spectroscopic data and elemental analysis. [b] Isolated yield. [c] At 100 °C. [d] Plus 1 molar equiv. of NaOAc to an amine. [e] At 65 °C. [f] $[\alpha]_D^{22}$ +42.8 ° (c=0.57, H_2O); Lit.[2] $[\alpha]_D^{24}$ +41 ° (c=2, H_2O). [g] Plus 1 molar equiv. of 2N NaOH to an amino acid. [h] $[\alpha]_D^{24}$ +28.5 ° (c=3, MeOH); Lit.[3] $[\alpha]_D^{20}$ +29.7 ° (c=0.41, MeOH). [i] $[\alpha]_D^{23}$ +22.0 ° (c=3, 5N HCl); Lit.[4] $[\alpha]_D^{23}$ +22.1 ° (c=1, 5N HCl).

Diacetamide was employed for the acetylation of phenethylamine under the same reaction conditions (run 4) to recover the starting material (54%) in addition to N-acetylphenethylamine (22%), which indicates that the methoxy group plays an important role for the stabilization of **1** in protic solvents and the enhancement of acetylating ability. N-Methoxydibenzamide (**2**), a congener of **1**, can benzoylate amino groups; however, the chromatographic separation of the resulting N-methoxybenzamide from products is needed.

Chemoselective Acetylation of Primary Amines in the Presence of Secondary Amines. In the field of polyamine chemistry the direct chemoselective N-acylation of primary amines has been performed in the presence of secondary amines upon treatment with poly(3-acyl-2-oxazolone),[1d] 3-acyl-1,3-thiazoline-2-thion,[1e] 1-hydroxy-piperidine active esters,[5a] acylimidazoles,[5b] and acyl cyanides.[5c] **1** acetylates smoothly primary amino groups in the presence of secondary amino groups in water as shown in Table. It is noteworthy that N-methoxydicinnamamide (**3**), easily synthesized from cinnamoyl chloride and methoxyamine, reacts with spermidine to give the naturally occuring polyamine maytenine [$\underline{N}^1$, $\underline{N}^8$-bis(<u>trans</u>-cinnamoyl)spermidine][1e, 5c] in 85.4% yield. This seems the simplest method because of easy access of **3** and technical simplicity.

Acetylation of Amino Acids. α-Amino groups of amino acids and an amino acid ester are acetylated with **1** under weakly alkaline and neutral conditions, respectively. Optical purity was retained in every case. Selective N^{ε}-acetylation of lysine was performed with **1** in high yield with simple operation (run 15). The procedure is simpler than the improved methods which include the removal of copper from the copper salt of product with gaseous hydrogen sulfide[6a] or with sequestering agents.[6b]

Preparation of 1. Triethylamine (239 mmol) was mixed with $MeONH_2 \cdot HCl$ (59.7 mmol) in CH_2Cl_2 (50 mL) with cooling and to this solution was added dropwise acetic anhydride (149 mmol) during 30 min. The reaction mixture was stirred overnight at room temperature. After the usual work-up, the residue was distilled to give **1** [78.3%, bp 72-74 °C (12 mmHg)]: ^{1}H NMR ($CDCl_3$)δ 2.34 (s, 6H), 3.76 (s, 3H); IR (neat) 1720 cm^{-1}; MS, m/e 131 (M^+).

A Typical Procedure. A mixture of 2-amino-1-phenylethanol (1.5 mmol) and **1** (3.0 mmol) in H_2O (1 mL) was stirred for 1.25 h at room temperature. H_2O (4 mL) was added to the mixture and it was extracted with AcOEt (20 mLx3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (EtOAc-benzene, 10:1) to give 2-acetamido-1-phenylethanol (88.5%): mp 123-124 °C (EtOH)(lit.[7] mp 118-119 °C).

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