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Short Communication

Additive-Free Chemoselective Acylation of Amines and Thiols

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Summary. Amines with different stereoelectronic nature were efficiently acylated at room temperature using acetic anhydride in the presence of no solvent or additive. Various thiols also react equally well under the same conditions. Chemoselective protection of amines in the presence of thiols, alcohols, and phenols and of thiols in the presence of alcohols, and phenols were achieved using competitive experiments.

Keywords. Solvent-free; Acetylation; Green chemistry; Amines; Thiols.

Introduction

With increasing global environmental concerns, design of green processes with no use of hazardous and expensive solvents, *i.e.* ''solvent-free'' reactions, has gained special attention by organic chemists [1]. As a result, many reactions are newly found to proceed cleanly and efficiently in solid state or under solvent-free conditions [2]. Less chemical pollution, lower expenses, and easier procedures to handle are the main reasons for recent years increasing popularity of solvent-free reactions.

Protection of amine functionalities is a fundamental maneuver in organic chemistry. The nucleophilic and basic nature of amines require their protection during many multi-step syntheses of biological targets [3]. In this context, N-acylation of amines is a very common synthesis practice and is usually conducted in the presence of acidic or basic additives using acetic acid [4], acyl transfer reagents [5], acyl halides [6], or anhydrides of carboxylic acids [7]. However, use of expensive reagents, harsh conditions requirement, presence of competitive side reactions or

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production of toxic waste are the drawbacks of many of these procedures [8]. Recent instances to tackle these limitations involve the use of catalysts under aqueous [9, 10] or neat [11–13] conditions or application of neutral acylating reagents [8]. In the framework of our investigations on the protection of various functional moieties [14], we recently noticed that amines could spontaneously convert to amides when they are exposed to acetic anhydride alone. Consequently, we were encouraged to investigate these observations extensively.

Results and Discussion

The isolated yields obtained for room-temperature acylation of selected amines in the presence of acetic anhydride and no additive are given in Table 1. When a mixture of aniline and acetic anhydride was stirred without solvent or additive, complete formation of *N*-phenylacetamide was observed within a few minutes (entry 1). The ^{1}H NMR spectrum showed the presence of N-acylated compound as the sole product of the reaction. The applicability of this method to other substrates was evaluated by subjecting electron-withdrawing (entry 2), electron-releasing anilines (entry 3), and disubstituted amines (entries 4–5) to the same conditions. In all cases, rapid formation of the respective amides was observed in high yields. Further generality of this procedure was demonstrated by convenient conversion of α-naphthylamine (entry 6), (*S*)-1-phenylethanamine (entry 7), N-alkylated or N-arylated aniline derivatives (entry 8), and aliphatic amines (entries 9–11) to their respective amides.

In the majority of these reactions, substrates bearing substituents with different electronic behavior led to spontaneous precipitation of products within few minutes illustrating the high efficiency of the method. Simple filtration led to separation of the desired amides as indicated in Table 1. With these in hands, we decided to use

Table 1. Additive-free acetylation of various amines

Entry	Amine	Amide	Yield/% [Ref.]
1	$C_6H_5NH_2$	C_6H_5NHAc	86 [9]
2	*p*-$XC_6H_4NH_2$	*p*-XC_6H_4NHAc	93 (X = Cl) [15]
			75 (X = Br) [15]
			92 (X = NO2) [9]
			90 (X = CO_2H) [9]
3	*p*-$XC_6H_4NH_2$	*p*-XC_6H_4NHAc	94 (X = *Me*) [9]
			90 (X = OH) [9]
			95 (X = NH_2) [9]
4	3,5-$Cl_2C_6H_3NH_2$	3,5-$Cl_2C_6H_3NHAc$	80 [16]
5	2,6-$Me_2C_6H_3NH_2$	2,6-$Me_2C_6H_3NHAc$	89 [16]
6	2-naphthyl-NH_2	2-naphthyl-$NHAc$	94 [15]
7	(*S*)-$C_6H_5CH(Me)NH_2$	(*S*)-$C_6H_5CH(Me)NHAc$	88 [13]
8	C_6H_5NHR	C_6H_5NRAc	87 (R = *Me*) [17]
			81 (R = *Ph*) [16]
9	cyclohexyl-NH_2	cyclohexyl-$NHAc$	82 [17]
10	morpholine	1-morpholinoethanone	77 [18]
11	*tert-Bu*NH_2	*tert-Bu*$NHAc$	81 [19]

Table 2. Additive-free acetylation of thiols

Entry	*R*SH	*R*S*Ac*	Yield/% [19]
1	C_6H_5SH	C_6H_5SAc	90
2	*p*-ClC_6H_4SH	*p*-ClC_6H_4SAc	93
3	2-naphthyl-SH	2-naphthyl-S*Ac*	88

this chemistry for the protection of thiols because of the importance of their masking in organic chemistry [12, 13, 19] especially in peptide and protein syntheses [3]. Moreover, bioorganic [20] and electrochemical [21] applications make the protection of thiols more attractive. Therefore, several thiols were conveniently acylated within few hours under the conditions similar to those employed for amines (Table 2).

Further studies showed that alcohols and phenols do not react with acetic anhydride under the conditions employed. This behavior and the observation that thiols are acetylated slower than amines persuaded us to evaluate the feasibility of selective protection of amines and thiols in the presence of other competing functionalities. Thus, when a 1:1:1 mixture of aniline, thiophenol, and acetic anhydride was treated at room temperature, formation of *N*-phenylacetamide was detected as the major acylated product (Table 3, entry 1). Similar competition between aniline and phenol also resulted in nearly exclusive formation of the same product (entry 2). Interestingly, intramolecular competition between NH_2 and OH groups in *p*-aminophenol resulted in exclusive formation of *N*-(*p*-hydroxyphenyl)acetamide, a very common analgesic drug and industrially important material known as paracetamol (entry 3) [22].

Next, selective protection of diamines was explored using *p*- (entry 4) and *o*-phenylenediamine (entry 5), and ethylendiamine (entry 6). Use of deficient amounts of Ac_2O resulted in formation of mono protected amines as the major product. Alternatively, double protected diamines could be obtained in an efficient manner when an equimolar amount of acetic anhydride was used. Finally, when mixtures of *n*-pentanol with aniline (entry 7) or with thiophenol (entry 8) were treated with an equimolar amount of acetic anhydride, only formation of *N*-phenylacetamide or *S*-phenyl ethanethioate was detected.

Table 3. Competitive acetylation of various functional groups with Ac_2O

Entry	Product **1**	Product **2**	**1**:**2**
1	C_6H_5NHAc	C_6H_5SAc	>95:5
2	C_6H_5NHAc	C_6H_5OAc	>99:1
3	*p*-HOC_6H_4NHAc	*p*-$H_2NC_6H_4OAc$	99:1
4	*p*-$H_2NC_6H_4NHAc$	*p*-$AcHNC_6H_4NHAc$	>90:10
5	*o*-$H_2NC_6H_4NHAc$	*o*-$AcHNC_6H_4NHAc$	>90:10
6	$H_2NCH_2CH_2NHAc$	$AcHNCH_2CH_2NHAc$	>90:10
7	C_6H_5NHAc	*n*-$C_5H_{11}OAc$	>99:1
8	C_6H_5SAc	*n*-$C_5H_{11}OAc$	>99:1

In conclusion, we disclose the additive-free conversion of various amines and thiols to their respective acyl protected products in high yields and short reaction times. High chemoselectivity and generality of the procedure, lack of formation of side products, easy work-up, and the environmental safety of the reactions are among the advantages of the present methodology.

Experimental

General Procedure

An equimolar mixture of acetic anhydride and the amine (thiol) was stirred at room temperature until TLC showed complete disappearance of the starting amine (thiol). The precipitated product was filtered off, washed with dilute $NaHCO_3$ solution, and dried. Physical and spectral data of the products were obtained and compared with those available in the references provided in the Tables 1 and 2.

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