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A simple acylation of thiols with anhydrides

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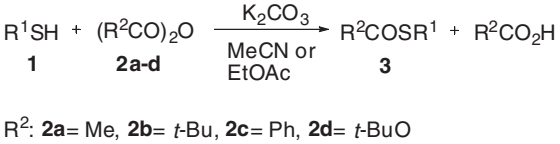
ABSTRACT

Different thiols were efficiently acylated at room temperature with different anhydrides in the presence of potassium carbonate. Chemoselective protection of thiol in the presence of hydroxy group was achieved using di-*tert*-butyl dicarbonate and isatoic anhydride.

Thiol esters are important intermediates in organic synthesis[1] as well as biologically active compounds because of the high reactivity toward various nucleophiles.[2] Furthermore protection of thiols as thiol esters is an important aspect in chemical self-assembly procedure employed in the fabrication of nano and macromolecular structures, nanoparticulate composites, surface immobilization of molecules, and metal surface modification.[3] Most preparations of thiol esters employ an activated acyl derivative such as acyl halides[4] with thiol salts or with thiols in the presence of a base. Alternatively mixed anhydrides of carboxylic acids as well as coupling reagents have been employed.[5] Commonly used reagents are anhydrides too,[6] especially in the presence of suitable basic or acidic catalysts although in the reaction one acyl moiety is lost. Furthermore, a few examples of solvent and catalyst free reaction of acetic anhydride with thiols at room temperature, or at 80 °C or under microwave induction have been reported.[7]

We now report a simple and general method for the acylation of thiols with different anhydrides in the presence of anhydrous potassium carbonate (Scheme 1). We began our investigation by treating thiophenol (1.0 equiv) with acetic anhydride (1.3 equiv) in ethyl acetate (8 mL/mmol thiol) at room temperature. The corresponding phenyl thioacetate was obtained in 95% yield after 19 h. The same reaction performed in dichloromethane or in tetrahydrofuran did not give satisfactory results. To assess the generality of the method, we investigated the scope and limitations of the reaction by treating various thiols **1** with nearly equimolecular amount of acetic anhydride **2a**, pivalic anhydride **2b**, benzoic anhydride **2c**, and di-*tert*-butyl dicarbonate **2d** at room temperature. In the case of benzoylation and *tert*-butoxycarbonylation the reactions were performed in acetonitrile to obtain better results. After complete conversion of the thiol, the crude reaction mixture was filtered, dried, and evaporated. The products were frequently obtained without any further purification giving satisfactory results on NMR and GC/MS analysis. Otherwise column chromatography (eluent: ethyl acetate–petroleum ether, silica gel) was used. The physical and spectroscopic data (mp, IR, NMR, and GC/MS) of the known compounds were found to be identical with those reported in the literature. Table 1 lists the substrates **1a–n** used for acylation, the acid anhydrides **2a–d** employed, and the acylation products **3a–v** obtained.

Acetylation, pivalation, benzoylation, and *tert*-butoxycarbonylation proceeded with excellent yields starting from aromatic and aliphatic thiols. The easy *tert*-butoxycarbonylation, especially for aliphatic thiols represents an improved procedure for the protection of the sulfhydryl group to be employed in orthogonal protection approach.[8] The mild experimental conditions employed are compatible with different functional groups such as ester (entry 11–13 and 17), alkoxysilyl (entry 14–16), and amide group (entry 17). In order to explore the generality and scope of the proposed method, the procedure has been extended to mercapto alcohols **1l–n**. Thus, it was observed that the reaction is chemoselective for the thiol group giving the *S*-*tert*-butoxycarbonyl derivatives **3t–v** in excellent yields. However, reaction of thiols **1l** and **1m** with equimolecular amount of acetic and pivalic anhydrides gave a mixture of the S-acylated and the S/O-diacylated products while



R^2: **2a**= Me, **2b**= *t*-Bu, **2c**= Ph, **2d**= *t*-BuO

Scheme 1. Acylation of thiols with different anhydrides.

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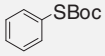
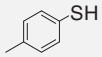
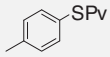
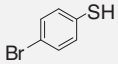
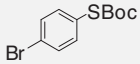
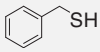
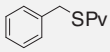
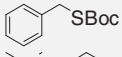
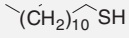
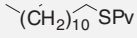
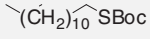
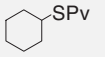
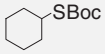
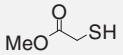
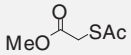
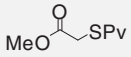
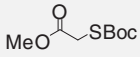
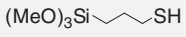
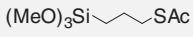
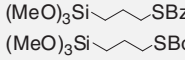
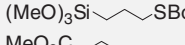
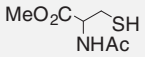
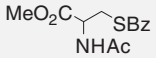
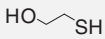
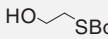
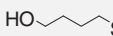
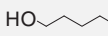
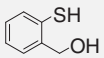
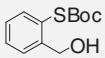
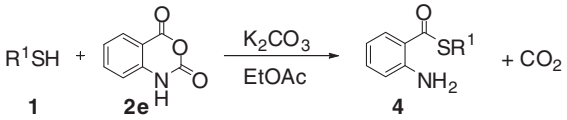
Table 1
Acylation[a] of thiols **1a–n** with anhydrides **2a–d** at room temperature in EtOAc or MeCN[b]

Entry		Thiol **1**[c]	Anhydride **2**	Time (h)		Product **3**[d]	Yield[e] (%)	Lit. yield[f,g] (%)
1	**1a**		$(PhCO)_2O$ **2c**	23	**3a**		89	(94)[4a]
2	**1a**		$(t\text{-BuOCO})_2O$ **2d**	22	**3b**		96	96[8b]
3	**1b**		$(t\text{-BuCO})_2O$ **2b**	24	**3c**		96	(91)[9]
4	**1c**		**2d**	23	**3d**		93	75[8c]
5	**1d**		**2b**	8	**3e**		96	95[6e]
6	**1d**		**2d**	24	**3f**		94	(60)[10]
7	**1e**		**2b**	18	**3g**		98	
8	**1e**		**2d**	24	**3h**		87[h]	
9	**1f**		**2b**	24	**3i**		95	(97)[11]
10	**1f**		**2d**	24	**3l**		85[h]	75[8a]
11	**1g**		$(MeCO)_2O$ **2a**	8	**3m**		91	(85)[12]
12	**1g**		**2b**	15	**3n**		97	
13	**1g**		**2d**	24	**3o**		92	
15	**1h**		**2a**	9	**3p**		96	
16	**1h**		**2c**	21	**3q**		84	
17	**1h**		**2d**	36	**3r**		88	
18	**1i**		**2c**	26	**3s**		84	
19	**1l**		**2d**	19	**3t**		89	
20	**1m**		**2d**	24	**3u**		88	
21	**1n**		**2d**	24	**3v**		90	(70)[13]

[a] Reaction conditions: **1**/**2b** or **2c** (1:1.1), anhydrous K_2CO_3 (2 equiv) for pivalic anhydride **2b** and benzoic anhydride **2c**; **1**/**2a** (1:1.3), anhydrous K_2CO_3 (2 equiv) for acetylation and **1**/**2d** (1:1), anhydrous K_2CO_3 (2 equiv) for di-*tert*-butyl dicarbonate **2d**.
[b] MeCN was used for acylation with benzoic anhydride **2c** and with di-*tert*-butyl dicarbonate **2d**.
[c] Thiols were used as received (purity ranging from 95% to 99%).
[d] All the products were characterized by IR, ^1H and ^{13}C NMR and GC/MS. Ac = MeCO; Pv = *t*-BuCO; Bz = PhCO; Boc = *t*-BuOCO.
[e] Yields of isolated products; ⩾97% pure material by ^1H NMR.
[f] Literature yields refer to catalyzed acylation with anhydrides.
[g] Value in parentheses refers to the best result which do not employ anhydrides.
[h] The product was purified by SiO_2 gel chromatography.

reaction of **1l** with a twofold excess of acetic anhydride gave the expected diacetylated product in 93% yield. Finally the thiols **1b–e**, **1g–l**, and **1o** were reacted with isatoic anhydride **2e** (Scheme 2) under the same experimental conditions and with comparable reaction times.

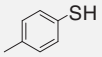
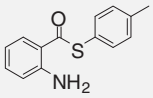
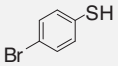
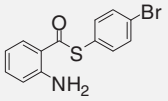
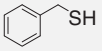
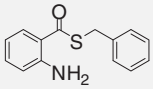
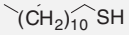
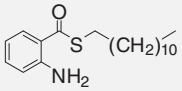
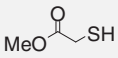
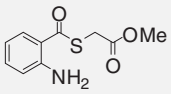
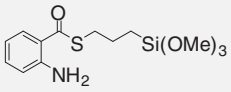
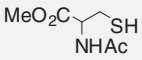
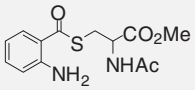
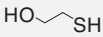
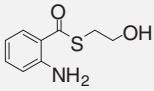
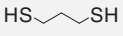
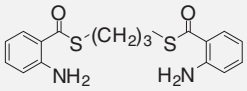
All reactions of **2e** with these thiols proceed by attack to the ester-type carbon[14] to give thiol esters **4** of anthranilic acid as confirmed by ^1H and ^{13}C spectroscopic data as well as by the formation of the N-acetylated derivative **5** from **4d**. Aliphatic, aromatic, and functionalized thiol esters **4** were obtained in high yields in all cases (Table 2). These antranilic thiol ester derivatives are useful substrates for the cross-coupling with organostannanes to give ketones.[15] As previously reported for the *tert*-butoxycarbonylation, the reaction of isatoic anhydride with mercapto alcohol **1l** occurred selectively at the sulfhydryl group without involving the hydroxyl group. Furthermore the reaction of dithiol **1o** with 2.2 equiv of isatoic anhydride gave the interesting diprotected derivative **4o** in excellent yield.



Scheme 2. Reaction of thiols with isatoic anhydride.

We have developed a simple and efficient procedure for the protection of different thiols as thiol esters by simple reaction with anhydrides in ethyl acetate or acetonitrile, in the presence of potassium carbonate and at room temperature. Moreover the reaction is chemoselective involving the sulfhydryl group without affecting other functionalities present in the molecule. Tacking into account the role of thiol esters as acylating agent in biochemical process, their high reactivity with various nucleophiles and the

Table 2
Acylation of thiols **1**with isatoic anhydrides **2e** at room temperature in EtOAc[a]

Entry	Thiol **1**	Time (h)	Product **4**[b]	Yield[c] (%)
1	**1b** 	22	**4b** 	98 (92)[15]
2	**1c** 	24	**4c** 	94
3	**1d** 	24	**4d** 	98[d]
4	**1e** 	20	**4e** 	90[e]
5	**1g** 	19	**4g** 	95
6	**1h** 	23	**4h** 	94
7	**1i** 	18	**4i** 	80[e]
8	**1l** 	10	**4l** 	97[d]
9	**1o** 	20	**4o** 	95

[a] Reaction conditions: **1**/**2e** (1:1.1), anhydrous K_2CO_3 (2 equiv).
[b] All the products were characterized by IR, ^1H and ^{13}C NMR and GC/MS.
[c] Yields of isolated products; ⩾97% pure material by ^1H NMR. Value in parentheses refers to the best result in the literature.
[d] No yield was reported in the literature.[14,16]
[e] The product was purified by SiO_2 gel chromatography.

increasingly important prerequisites in the development of chemical self-assembly methods, the simplicity of our procedure can favorably compete with existing methods.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.126.

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