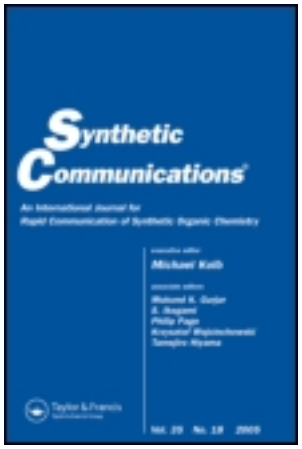

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Additive-Free Chemoselective Acylation of Amines

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Published online: 29 Dec 2009.

To cite this article: Andrea Temperini , Raffaella Terlizzi , Lorenzo Testaferri & Marcello Tiecco (2009): Additive-Free Chemoselective Acylation of Amines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:2, 295-302

To link to this article: http://dx.doi.org/10.1080/00397910902978007

Synthetic Communications®, 40: 295–302, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902978007

Taylor & Francis
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ADDITIVE-FREE CHEMOSELECTIVE ACYLATION OF AMINES

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Aliphatic and aromatic amines are efficiently acylated by acetic, pivalic, benzoic, phthalic, or maleic anhydrides in ethyl acetate at room temperature. Under the same experimental conditions, amino alcohols are chemoselectively acylated at the amino group.

Keywords: Acylation; amides; amines; amino alcohols; chemoselectivity

INTRODUCTION

Because of its basic and nucleophilic properties, the amino group is usually protected as the acyl derivative during a multistep reaction sequence. For this purpose, acid anhydrides are employed as the most common acyl sources because of their ready availability and stability. Thus, acetylation of amines is often carried out using acetic anhydride in the presence of bases,[1] acids,[2] or amphoteric catalysts.[3] Isolated examples of additive-free acetylation with acetic anhydride in different solvents have been reported in the literature, especially in the synthesis of drugs and organic intermediates.[4] Solvent- and additive-free acetylations of a limited number of simple aromatic and aliphatic amines with acetic anhydride have been also reported.[5] Of particular importance is the chemoselective acylation of the amino group in substrates holding other functionalities in the molecule; this is frequently required in organic synthesis.[6] In a search for a mild, additive-free, and chemoselective methodology of general application, we have investigated the simple reactions of several types of amine with different anhydrides in ethyl acetate at room temperature (Scheme 1). We have found that this procedure can be successfully applied to a variety of differently substituted amines.

Received December 22, 2008.

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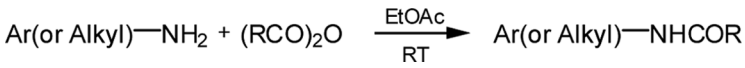


Scheme 1. Chemoselective acylation of amines with different anhydrides.

RESULTS AND DISCUSSION

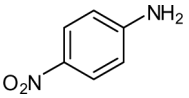
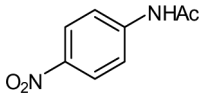
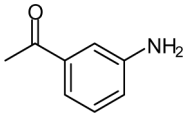
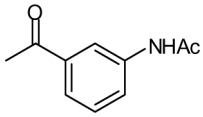
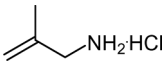
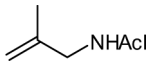
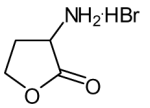
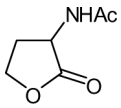
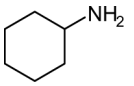
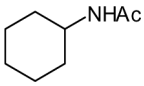
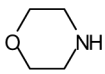
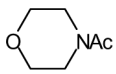
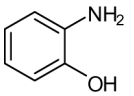
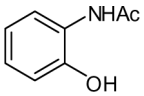
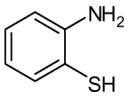
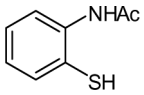
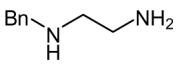
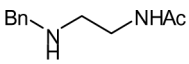
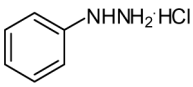
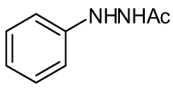
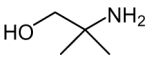
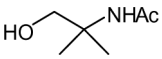
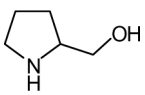
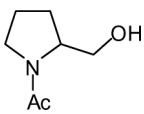
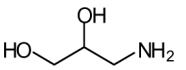
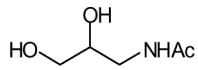
Preliminary experiments were carried out on aniline in different solvents. The reaction performed in acetonitrile, tetrahydrofuran (THF), or dichloromethane (DCM) did not give satisfactory results. In contrast, the reactions in ethyl acetate or in a mixture of ethyl acetate and methanol or dioxane were all successful. When a mixture of commercially available amine (1 equiv) and acetic anhydride (1.1 equiv) in ethyl acetate (2 mL/mmol amine) was stirred at room temperature, complete conversion into the N-acetamide was observed (2–20 h, monitored by thin-layer chromatography, TLC). Depending on the acid–base properties of the starting amines or of the reaction products, the solubility of the products or their stability, three different workup procedures were employed. After complete conversion of the amine, the crude reaction mixture was evaporated and then dried in vacuum with a potassium hydroxide trap (method A). In other cases, anhydrous potassium carbonate (2 equiv) was added to the reaction mixture to neutralize the acetic acid, and the mixture was filtered, evaporated, and dried in vacuum (method B). In the cases in which the by-products were not volatile, the reaction mixtures were poured in a 10% solution of potassium carbonate, extracted with ethyl acetate, and dried over sodium sulfate (method C).

The products were isolated practically pure, and chromatographic purification was necessary only in a few cases. The physical and spectroscopic data [mp, infrared (IR), NMR and gas chromatography–mass spectrometry (GC-MS)] of the known compounds were identical with those reported in the literature. The results obtained are collected in Table 1.

The first experiments refer to differently substituted aromatic or aliphatic amines (entries 1–6), which can be acylated in almost quantitative yields. The mild experimental conditions employed are compatible with different functional groups such as double bonds and ester groups (entry 3 and 4).

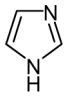
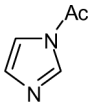
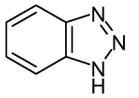
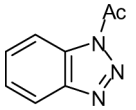
The N-acetylation of 2-aminophenol (entry 7) was completely chemoselective and involved the amino group exclusively, leaving the hydroxyl group unaffected. This different reactivity between the two functional groups was already observed using a different acetylation procedure.[2b] A similar chemoselectivity was not observed in the case of the 2-aminobenzenethiol (entry 8). When the latter was treated with 1.1 equiv. of acetic anhydride in ethyl acetate and in the presence of potassium carbonate (1.1 equiv., modified method B), the N-acetylated product and the N,S-diacetylated product were obtained in 65% and 20% isolated yields, respectively, after column chromatography. The same reaction carried out in water in the presence of sodium dodecyl sulfate (SDS) is reported to afford 2-methyl-benzothiazole as the major reaction product.[7] The same result was observed by us in the case in which the reaction was effected in the absence of potassium carbonate. These different selectivities were also investigated by effecting intermolecular competitive acetylation experiments. Thus, an equimolecular mixture of aniline and phenol were

Table 1. Acetylation of aromatic and aliphatic amines, diamines, aminoalcohols, and heteroaromatic bases with acetic anyhydride in ethyl acetate at room temperature

Entry	Substrate	Product[a]	Time (h)	Method	Yield (%)[b]
1			20	A	98
2			7	B	92
3			8	B[c]	99
4			6	B[c]	92
5			6	B	98
6			12	B	95
7			6	A	98
8			8	B	65[d]
9			9	A	88[e]
10			7	B[c]	82
11	$HO(CH_2)_5–NH_2$	$HO(CH_2)_5–NHAc$	2	A	99
12			18	B	98
13			8	B	94
14			7	A[f]	96

(*Continued*)

Table 1. Continued

Entry	Substrate	Product[a]	Time (h)	Method	Yield (%)[b]
15			9	B	94
16			6	B	98

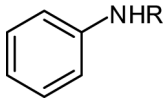
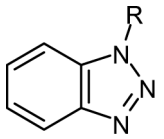
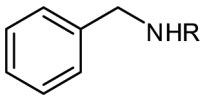
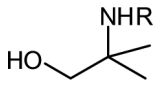
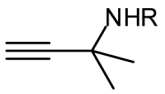
[a]All the products were characterized by ^{1}H and ^{13}C NMR and mass spectroscopy.
[b]Yields of the isolated products; ≥97% pure material by ^{1}H-NMR.
[c]Anhydrous K_2CO_3 (2.2 mmol) was added with acetic anhydride.
[d]20% of the N, S diacetylated product was also obtained after column chromatography separation.
[e]Based on monoacetylated product after column chromatography separation.
[f]The reaction was performed in 4:1 mixture of EtOAc/ MeOH.

allowed to react with 1 equivalent of acetic anhydride. The aniline was selectively acetylated, leaving the phenol unaffected. A similar experiment between aniline and thiophenol gave slightly different results. In this case, aniline was completely acetylated, whereas thiophenol remained unchanged. Obviously, thiophenol alone can be easily acetylated using the present procedure (90% yield). Aliphatic thiols, like benzyl mercaptan, could not be acetylated.

The selective protection of aliphatic diamines was then explored (entry 9). In the case of N-benzylethane-1,2-diamine, the acetylation of the primary NH_2 occurred with complete selectivity, making our procedure a valuable alternative to the previous methods reported in the literature.[8] Phenyl hydrazine was also selectively monoacetylated at the unsubstituted nitrogen atom in good yield (entry 10). The selectivity of this acetylation reaction in the case of aminoalcohols was also investigated (entries 11–14). As indicated in Table 1, the acetylation reaction produced the corresponding acetamides without involving the hydroxy group. In general, the reactions are very clean. This chemoselective acetylation of primary and secondary amino groups in amino alcohols is of considerable synthetic importance because in general it requires more complex reaction conditions.[6] Finally, good results were also obtained from the acetylation of the heteroaromatic bases imidazole and benzotriazole, which gave the useful acetyl transfer agents acetylimidazole and acetylbenzotriazole[9] (entries 15 and 16).

To extend the scope of the present method, the acylation of some representative amines with pivalic and benzoic anhydrides was carried out under conditions identical to those described for acetic anhydride. In these cases, the workup procedure of method C was employed because of the low volatility of the pivalic and benzoic acids by-products. Thus aliphatic, aromatic, and functionalized amines gave the corresponding N-pivaloyl and N-benzoyl derivatives in excellent yields (Table 2, entries 1, 2, 5–8, 11, and 12). As in the case of the acetylation reaction, the benzoylation of an aminoalcohol (entry 11) occurred selectively at the amino group without involving the hydroxyl group.

Table 2. Reaction of amines with pivalic, benzoic, phthalic, or maleic anyhydrides in ethyl acetate at room temperature

Entry	Substrate	Reaction product[a]	R[b]	Time (h)	Method	Yield (%)[c]
1	aniline		Piv	8	C	96
2			Bz	12	C	96
3			Pht	8	A	98
4			Mal	17	A	99
5	1H-1,2,3-benzotriazole		Piv	8	C	75
6			Bz	8	C	98
7	benzylamine		Piv	6	C	97
8			Bz	8	C	96
9			Pht	10	A	98
10			Mal	10	A	97
11	2-amino-2-methylpropan-1-ol		Bz	12	C	90
12	2-methylbut-3-yn-2-amine		Bz	16	C	80
13			Pht	16	A	97
14			Mal	15	A	98

[a]All the products were characterized by ^{1}H and ^{13}C NMR and mass spectroscopy.
[b]Piv = *t*-buCO; Bz = PhCO; Pht = $COC_6H_4CO_2H$; Mal = COCH=$CHCO_2H$.
[c]Yields of the isolated products; ≥97% pure material by ^{1}H-NMR.

Aliphatic and aromatic amines also react successfully with 1 equiv. of phthalic and maleic anhydrides, giving the desired products in good yields (Table 2, entries 3, 4, 9, 10, 13, and 14). Because of the acidity of the phthalamic and maleamic acids thus obtained, the workup of the reaction mixtures was carried out as indicated in method A. These compounds have some practical interest because of their biological activities[10] and surfactant properties.[11]

CONCLUSION

In conclusion, we have described a mild and convenient procedure for the N-acylation of different amines with anhydrides in ethyl acetate at room temperature. The reactions are easy to perform and give very clean reaction products that do not require chromatographic purification. Moreover, the reaction is very chemoselective, involving the amino group without touching other functionalities present in the molecule. The ethyl acetate can be considered a good solvent to perform these acylation reactions because of its low toxicity and low vapor pressure. Although procedures exist for the acylation of amines, the simplicity of our procedure can favorably compete with the existing methods especially for N-selective acylations. The present methodology can find applications in large-scale preparations.

EXPERIMENTAL

Materials

All the reactions were carried out without any special precautions in an atmosphere of nitrogen. Starting materials are commercially available and used as received. In almost all the acylation reactions, essentially pure materials were obtained without further purification. The ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker Avance DR 200. Fourier transform (FT)–IR spectra were recorded with a Jasco model 410 spectrometer equipped with a diffuse reflectance accessory. GC-MS analyses were effected with an HP-6890 gas chromatograph (dimethyl silicon column; 12.5 m) equipped with an HP-5973 mass selective detector at an ionizing voltage of 70 eV.

Acetylation

Acetic anhydride (0.20 mL, 2.2 mmol) was added to a solution of 2-amino-2-methylpropan-1-ol (0.18 g, 2.0 mmol) in 4 mL of EtOAc. The resulting mixture was stirred, under nitrogen, for 18 h. Anhydrous potassium carbonate (0.55 g, 4.0 mmol) was added, and stirring was continued for few minutes (method B). The reaction mixture was then filtered through a celite path and the filtrate was concentrated. *N*-(2-Hydroxy-1,1-dimethyl)acetamide[3b] was obtained in 98% isolated yield (Table 1, entry 14).

Pivalation

Pivalic anhydride (0.40 mL, 2.2 mmol) was added to a solution of 1*H*-1,2,3-benzotriazole (0.24 g, 2.0 mmol) in 4 mL of EtOAc. The resulting mixture was stirred, under nitrogen, for 8 h. The reaction was then quenched by addition of 10% aq potassium carbonate solution (10 mL). The reaction mixture was then extracted with ethyl acetate (3×6 mL), and the combined organic layers were dried over anhydrous sodium sulfate and then evaporated (method C). 1-(2,2-Dimethylpropanoyl)-1*H*-1,2,3-benzotriazole[9] was obtained in 75% isolated yield (Table 2, entry 5).

Phthaloylation

Powdered phtalic anhydride (0.14 g, 1 mmol) was added to a stirred solution of 2-methylbut-3-yn-2-amine (0.09 g, 1.0 mmol) in ethyl acetate (2 ml) at room temperature. The progress of the reaction was monitored by TLC. The reaction was complete within 16 h. The reaction was concentrated under reduced pressure (method A) and then dried under vacuum with a potassium hydroxide trap.

2-{[(1,1-Dimethylprop-2-yn-1-yl)amino]carbonyl}benzoic acid (Table 2, entry 13) was obtained as a white solid in 97% yield. Mp 135–138°C; FT-IR (KBr): 2984, 2840, 2105, 1699, 1666, 1645, 1541, 1300, 923 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 11.78$ (br s, 1H), 8.39 (s, 1H), 7.86–7.63 (m, 1H), 7.60–7.25 (m, 3H), 3.08 (s, 1H), 1.58 (s, 6H). ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 168.0$, 167.7, 138.7, 131.0, 130.7, 129.1, 128.8, 127.8, 88.2, 70.6, 46.5, 28.7(2C). GC-MS (EI): m/z 231 (M^+, 7%), 216

(10), 203 (77), 188 (34), 146 (56), 130 (100), 104 (52), 76 (45), 56 (27). Anal. calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.96. Found: C, 67.78; H, 5.89; N, 6.73.

ACKNOWLEDGMENTS

Financial support from MIUR, National Projects PRIN2005, Consorzio CINMPIS (National Interuniversity Consortium for Innovative Methodologies and Synthetic Process), Bari, and University of Perugia is gratefully acknowledged.

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