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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · FEBRUARY 2004

Impact Factor: 4.72 · DOI: 10.1021/jo035412f · Source: PubMed

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Reactions on a Solid Surface. A Simple, Economical, and Efficient Acylation of Alcohols and Amines over Al_2O_3

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Received September 26, 2003

Abstract: Al_2O_3 brings about a rapid acylation of a range of alcohols and amines with acid chlorides and acid anhydrides, respectively. Amines are easily Boc- and Cbz-protected on reaction with Boc-anhydride and Cbz-Cl, respectively. The acylation of phenols is slow enough to allow chemoselective acylation of alcohols and amines in the presence of phenols.

The acylation, particularly the acetylation, of alcohols and amines is an important transformation in organic synthesis.[1] Although numerous methods to achieve acylation are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. Reactions on solid surfaces are particularly important because they allow easy recycling of the support. A recent report claims acetylation of carbinols, thiols, and amines using Ac_2O-pyridine$-Al_2O_3$ in solvent-free conditions under microwave irradiation.[2] Whereas the acetylation of phenols, thiophenols, amines, and anilines was reported, no example of the reaction of an alcohol has appeared. More recently, $HClO_4$ adsorbed on silica gel was demonstrated to efficiently catalyze the acetylation of phenols, thiols, alcohols, and aromatic amines with Ac_2O.[3] The acetylation of aliphatic amines, however, was not attempted. We have been interested in the development of methods for acylation that (a) would avoid the use of added acids and bases, (b) would avoid aqueous workup and chromatographic purification, (c) are easy to perform, and (d) are economical for application to large-scale preparations. In this pursuit, we have reported previously on the use of $KF-Al_2O_3$ as a solid support reagent for the acetylation of alcohols, amines, and phenols with $AcCl/Ac_2O$.[4] This method was found to be more efficient than most other often-used methods. We have now discovered that neutral Al_2O_3 alone promotes a very efficient acylation of alcohols and amines with noticeable differences from those of $KF-Al_2O_3$. Though Al_2O_3 has been previously demonstrated to promote the transesterification of alcohols with ethyl acetate,[5] the yields were generally poor and the reactions also took considerably long time. Furthermore, a significantly large amount of Al_2O_3 was used. Prompted by the recent reports, we present our results herein.

The results of the reactions of a diverse range of alcohols are collected in Table 1. Several features deserve comment. An acid chloride was preferred over the corresponding acid anhydride. The reaction with acid anhydride was too slow to have practical application. Both primary and secondary alcohols reacted very well; tertiary alcohols did not react. The conversion of propargyl alcohol into propargyl acetate on a 100 mmol scale (entry 6) proceeded just as well as the 1 mmol reaction. The reaction was conducive to the acetylation of silicon-containing alcohols; 3-trimethylsilyl-2-propyn-1-ol was conveniently transformed into its acetate (entry 7). Diols and triols having primary and secondary alcohol functions were conveniently transformed into diacetates and triacetates, respectively. Primary alcohols reacted at least 5 times faster than secondary alcohols; tertiary alcohols were completely resistant and did not undergo acetylation. Acid chlorides other than AcCl reacted slower as the reactions took comparatively longer time for completion.

The reactions of β-naphthol and *p*-bromophenol with AcCl (entries 16 and 17) were very slow in comparison to those of the aliphatic alcohols. Even after vigorous stirring for 16 h at 25 °C, the reactions were incomplete. β-Naphthol and *p*-bromophenol did not react at all with Ac_2O (entries 16 and 17). This is in contrast to the use of $KF-Al_2O_3$ that was very effective for the acetylation of phenols.[4] The poor reactivity of phenols with AcCl over Al_2O_3 raised a genuine possibility of selective acylation of primary and secondary alcohols in the presence of phenols. Indeed, 3-(2-hydroxyphenyl)propanol furnished only the expected monoacetate on reaction with 1.1 equiv of AcCl. Thus, the present method is comparable to the use of *Pseudomonus cepacia PS* lipase,[6] twisted amides,[7] and also the transesterification protocol that is catalyzed by distannoxane.[8]

The results of the acylation of amines are collected in Table 2. It is significant to note that acid anhydrides were preferred to the acid chlorides. All the amines reacted very rapidly within 5−10 min. Aromatic amines that were substituted by electron-attracting groups, e.g., *p*-nitroaniline (entry 2), reacted only a little slower than those that possessed electron-donating groups, e.g., *p*-chloroaniline (entry 1). Amines could also be Boc- and Cbz-protected conveniently by adopting the present protocol in excellent yields. Boc-anhydride and Cbz-Cl, respectively, were employed for the formation of Boc- and Cbz-derivatives (entries 5, 7, 12 and 13).

The reactions of amines with Ac_2O were so fast in comparison to those of the aliphatic alcohols that the

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10.1021/jo035412f CCC: $27.50
Published on Web 12/19/2003

TABLE 1. Acylation of Alcohols on Al_2O_3 Surface Using Acid Chlorides

entry	substrate	acylation reagent[a]	time (min)	reaction[b] (%)	yield[c] (%)
1	3-phenyl-1-propanol	CH_3COCl	10	100	96[d]
2	3-phenyl-1-propanol	CH_2=CHCOCl	105	100	99[d]
3	3-phenyl-1-propanol	C_6H_5COCl	90	100	99[d]
4	benzyl alcohol	CH_3COCl	15	100	99[e]
5	cinnamyl alcohol	CH_3COCl	10	100	96[e]
6	propargyl alcohol	CH_3COCl	15	100	99[e,f]
7	3-trimethylsilyl-2-propyn-1-ol	CH_3COCl	15	100	98[g]
8	methyl mandelate	CH_3COCl	15	100	99[h]
9	methyl mandelate	CH_2=CHCOCl	600	100	95
10	menthol	CH_3COCl	10	100	96[e]
11	menthol	C_6H_5COCl	120	100	96[d]
12	1,2-propanediol	CH_3COCl	15	100	98[e,i]
13	1,6-heptanediol	CH_3COCl	15	100	98[h,i]
14	1.6-heptanediol	CH_3COCl	15		*j*
15	glycerol	CH_3COCl	60	100	98[e,k]
16	*β*-naphthol	CH_3COCl	960	90	*l*
17	*p*-bromophenol	CH_3COCl	960	95	*h*
18	*β*-naphthol	Ac_2O	960		*m*
19	*p*-bromophenol	Ac_2O	960		*m*
20	3-(2-hydroxyphenyl)propanol	CH_3COCl	15	100	95[n,o]

[a] 2 equiv of the acylation reagent for every OH function was used unless indicated otherwise. [b] Reaction (%) indicates the percent of the starting material that had reacted. [c] Yield (%) is the isolated yield of the product. [d] Isihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. [e] Spectral data of the acetate/diacetate/triacetate correspond to those of commercially available materials. [f] The reaction was carried out on 100 mmol scale. [g] Taniguchi, Y.; Inaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229. [h] Yadav, V. K.; Ganesh Babu, K.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047. [i] The corresponding diacetate was prepared. [j] With the use of 1.1 equiv of CH_3COCl, the ratio of primary and secondary acetate was 5.3:1. [k] The corresponding triacetate was prepared. [l] *Handbook of proton-NMR Spectra and Data*; Asahi Research Center: Kyoto, 1985; Vol. 4, p 260. [m] Almost no reaction. [n] Only the aliphatic alcohol was acetylated with the use of 1.1 equiv of CH_3COCl. [o] Allevi, P.; Ciuffreda, P.; Longo, A.; Anastasia, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2915.

TABLE 2. Acylation of Amines on Al_2O_3 Surface

entry	substrate	acylation reagent[a]	time (min)	reaction[b] (%)	yield[c] (%)
1	*p*-chloroaniline	$(CH_3CO)_2O$	<5	100	98[d]
2	*p*-nitroaniline	$(CH_3CO)_2O$	40	100	98[e]
3	*t*-$BuNH_2$	$(CH_3CO)_2O$	<5	100	94[f]
4	*t*-$BuNH_2$	CH_2=CHCOCl	<5	100	96[g]
5	*t*-$BuNH_2$	$(Me_3CO)_2CO$	<5	100	95[h]
6	morpholine	$(CH_3CO)_2O$	<5	100	95[i]
7	morpholine	$PhCH_2OCOCl$	<5	100	96
8	morpholine	$(Me_3CO)_2CO$	<5	100	97
9	$H_2NCH_2CH_2CH_2OH$	$(CH_3CO)_2O$	10	100	95[j,k]
10	$H_2NCH_2CH_2CH_2CH_2OH$	$(CH_3CO)_2O$	10	100	97[j]
11	$MeNHCH_2CH_2OH$	$(CH_3CO)_2O$	10	100	96[l,m]
12	$MeNHCH_2CH_2OH$	$(Me_3CO)_2CO$	10	100	97[l]
13	$MeNHCH_2CH_2OH$	$PhCH_2OCOCl$	10	100	96[l]
14	4-aminophenol	$(CH_3CO)_2O$	10	100	97[g,l]

[a] 1.1 equiv of the acylation reagent was used throughout. [b] Reaction (%) indicates the percent of the starting material reacted. [c] Yield (%) is the overall yield of the product. [d] *Handbook of proton-NMR Spectra and Data*; Asahi Research Center: Kyoto, 1985; Vol. 3, p 82. [e] *Handbook of proton-NMR Spectra and Data*; Asahi Research Center: Kyoto, 1985; Vol. 3, p 89. [f] Yadav, V. K.; Ganesh Babu, K.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047. [g] ^{1}H NMR corresponded to that of commercially available material. [h] Pirkle, W. H.; Simmons, K. A.; Boeder, C. W. *J. Org. Chem.* **1979**, *44*, 4891 [i] *Handbook of proton-NMR Spectra and Data*; Asahi Research Center: Kyoto, 1986; Vol. 6, p 242. [j] The amines in 3-aminopropanol and 4-aminobutanol were acylated 10 times faster than the alcohol. [k] Kim, J. K.; Souma, Y.; Beutow, B.; Ibbeson, C.; Caserio, M. C. *J. Org. Chem.* **1989**, *54*, 1714. [l] This reaction was highly chemoselective as only the amine had reacted. [m] Deslongchamps, P.; Dubé, E.; Lebreux, C.; Patterson, D. R.; Taillefer, R. J. *Can. J. Chem.* **1975**, *53*, 2791.

selective protection of an amine in the presence of an aliphatic alcohol appeared to be a distinct possibility. This has indeed been demonstrated from the entries 9−11. It is indeed gratifying to note that the reaction of 2-(*N*-methyl)amino ethanol with Boc-anhydride was complete in 10 min (entry 12). The same reaction took 15 h for completion in $CHCl_3$ as solvent without any catalyst.[9] The amino group in aminophenols was selectively acetylated (entry 14).

A comparison of the present protocol with selected previously known protocols is collected in Table 3 to demonstrate that the present protocol is indeed superior to several of the other protocols. Menthol is completely acetylated in less than 10 min at 25 °C in 96% isolated yield using the present protocol. Most of the other protocols listed take either longer time for completion or require prior preparation of the catalyst support or use dangerous materials with generally reduced isolated

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TABLE 3. Comparison of Protocols for the Acylation of Alcohols and Amines

entry	substrate	reagent/catalyst	acylating agent	time (min)	*T* (°C)	yield (%)	ref
1	(−)-menthol	Al_2O_3	AcCl	10	25	96	*a*
		$HClO_4-SiO_2$	Ac_2O	5	25	90	3
		Py/Al_2O_3 (basic)	Ac_2O				2[b]
		HBF_4-SiO_2	Ac_2O	360	25	83	10
		$InCl_3$	Ac_2O	45	25	70	11
		$Mg(ClO_4)_2$[c]	Ac_2O	30	25	100	12
2	cinnamyl alcohol	Al_2O_3	AcCl	10	25	96	*a*
		$KF-Al_2O_3$	Ac_2O	840	25	*d*	4
		$KF-Al_2O_3$	AcCl	60	25	98	4
		Py/Al_2O_3 (basic)	Ac_2O				2[b]
		$Mg(ClO_4)_2$[c]	Ac_2O	60	25	100	12
3	morpholine	Al_2O_3	Ac_2O	<5	25	95	*a*
		Py/Al_2O_3 (basic)	Ac_2O	2	105	98	2
4	2-(*N*-methylamino) ethanol	Al_2O_3	Ac_2O	10	25	97	*a*
		no catalyst	Ac_2O	900	25	100	9

[a] Present work. [b] No alcohol was attempted in this work. [c] It can cause irritation of skin and mucous membranes. [d] The reaction was incomplete.

yields. The present protocol is effective in causing complete acetylation of cinnamyl alcohol in less than 10 min. The same transformation requires 60 min for completion using either $KF-Al_2O_3$ or Ac_2O−magnesium perchlorate. Morpholine is acetylated completely in less than 5 min using the present protocol. The use of pyridine−Al_2O_3 is equally effective. However, it requires elevated temperature. That Al_2O_3 indeed catalyses the reaction is demonstrated from the reaction of 2-(*N*-methylamino)ethanol. Without Al_2O_3, the reaction time was considerably prolonged.

In conclusion, we have presented a simple, economical, and efficient protocol for the acylation of alcohols and amines. Further, an alcohol can be acetylated in the presence of phenols with very high selectivity. Primary alcohols react at least five times faster than secondary alcohols, and the tertiary alcohols do not react. This allowed for the selective acetylation of primary alcohols in the presence of secondary and tertiary alcohols. Also, the *N*-Ac-, *N*-Boc-, and *N*-Cbz-derivatives can be selectively prepared in the presence of alcohols. Unlike the Ac_2O−pyridine−Al_2O_3 protocol,[2] the present protocol does not require high temperature. Furthermore, the present protocol is more efficient than the $HClO_4$−silica gel−Ac_2O protocol[3] for the acetylation of alcohols (cf. acetylation of benzyl alcohol). The present protocol can be effectively used for a rapid Boc- and Cbz-protection of amines, and thus, it is likely to find application in peptide synthesis as well.

Experimental Section

^1H and ^{13}C spectra were recorded in $CDCl_3$. The signal positions are reported in ppm (δ scale) relative to TMS used as an internal standard. For every OH function in the substrate, 1.5 equiv of column grade neutral Al_2O_3 (Acme's Laboratory Chemicals, India) and 2.0 equiv of an acid chloride were used. Likewise, for every NH function in the substrate, 1.5 equiv of Al_2O_3 and 1.1 equiv of an acid anhydride or 1.1 equiv of CbzCl were employed. The solvents were evaporated under reduced pressure on a rotovap. The chromatographic separations, whenever required, were performed by silica gel (100−200 mesh) column chromatography (EtOAc/hexanes).

General Procedure for the Acylation of Monohydric Aliphatic Alcohols. Neutral Al_2O_3 (0.153 g, 1.5 mmol) was added to an alcohol (stirring not required) and then mixed with an acid chloride (2.0 mmol) in one portion. The resultant dispersion was stoppered tightly and kept aside unstirred at 25 °C, and the progress of the reaction was monitored by TLC. When the reaction was complete, the dispersion was taken with EtOAc (2 × 3 mL) and filtered. The solvent was removed to furnish the product.

General Procedure for the Acylation of Aliphatic Diols. An acid chloride (4.0 mmol for diols and 6.0 mmols for triols) was added, in one portion, to the mixture of a diol/triol (1.0 mmol) and neutral Al_2O_3 (0.306 g, 3.0 mmol for diol; 0.460 g, 4.5 mmol for triol). The resultant dispersion was stoppered tightly and kept aside unstirred at 25 °C, and the progress of the reaction was monitored by TLC. When the reaction was complete, it was taken with EtOAc (2 × 3 mL for diol; 2 × 5 mL for triol) and filtered. The solvent was removed to furnish the product.

Chemoselective Monoacetylation of an Aliphatic Diol and a Hydroxyalkylphenol. AcCl (1.1 mmol) was added, in one portion, to a mixture of the substrate (1.0 mmol) and neutral Al_2O_3 (0.153 g, 1.5 mmol). The resultant dispersion was stoppered tightly, kept aside unstirred at 25 °C for 15 min, taken with EtOAc (2 × 3 mL), and filtered. The solvent was removed, and the crude material was purified by silica gel chromatography (EtOAc/hexanes).

General Procedure for the Acylation of Amines. An acid anhydride (1.1 mmol) was added, in one portion, to the mixture of an amine (1.0 mmol) and neutral Al_2O_3 (0.153 g, 1.5 mmol). The resultant dispersion was stoppered tightly and kept aside unstirred at 25 °C, and the progress of the reaction was monitored by TLC. When the reaction was complete, it was taken with EtOAc (2 × 3 mL) and filtered. The solvent was removed to obtain the product.

General Procedure for the Chemoselective Monoacetylation of Amino Alcohols. Ac_2O (1.1 mmol) was added, in one portion, to the unstirred mixture of an amino alcohol (1.0 mmol) and neutral Al_2O_3 (0.153 g, 1.5 mmol). After 10 min, the reaction mixture was taken with EtOAc (2 × 3 mL) and filtered. The solvent was removed to furnish the product.

General Procedure for the Reaction of Amines with *t*-Boc Anhydride. *t*-Boc anhydride (1.1 mmol) was added, in one portion, to the unstirred mixture of an amine (1.0 mmol) and neutral Al_2O_3 (0.153 g, 1.5 mmol). The resultant dispersion was stoppered tightly, kept aside unstirred at 25 °C, taken with EtOAc (2 × 3 mL) after the reaction was complete, and filtered. The solvent was removed to obtain the product.

General Procedure for the Reaction of Amines with Cbz-Cl. Cbz-Cl (1.1 mmol) was added, in one portion, to the unstirred mixture of an amine (1.0 mmol) and neutral Al_2O_3 (0.153 g, 1.5 mmol). The resultant dispersion was stoppered tightly, kept aside unstirred at 25 °C, taken with EtOAc (2 × 3 mL) after the reaction was complete, and filtered. The solvent was removed to obtain the product.

Methyl mandelate acrylate: colorless liquid; ^1H NMR δ 7.51−7.47 (2H, m), 7.41−7.37 (3H, m), 6.53 (1H, dd, J = 17.3,

1.2 Hz), 6.24 (1H, dd, J = 17.3, 10.5 Hz), 6.02 (1H, s), 5.92 (1H, dd, J = 10.5, 1.2 Hz), 3.72 (3H, s); ^{13}C NMR δ 169.1, 165.2, 133.7, 132.2, 129.2, 128.7, 127.6, 127.4, 74.4, 52.5. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.43; H, 5.50. Found: C, 65.35; H, 5.40.

N-*tert*-Boc-morpholine: mp 56−58 °C; ^{1}H NMR δ 3.63 (4H, t, J = 4.9 Hz), 3.41 (4H, t, J = 4.9 Hz), 1.47 (9H, s); ^{13}C NMR δ 154.6, 79.7, 66.5, 43.8, 28.2. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.72; H, 9.16. Found: C, 57.55; H, 9.05.

***N*-Carbobenzyloxymorpholine:** mp 47−49 °C; ^{1}H NMR δ 7.37−7.26 (5H, m), 5.14 (2H, s), 3.64 (4H, bs), 3.48 (4H, t, J = 4.9 Hz); ^{13}C NMR δ 155.2, 136.4, 128.5, 128.0, 127.9, 67.2, 66.5, 44.1. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.84. Found: C, 65.00; H, 6.75.

***N*-*t*-Boc-*N*-methyl-2-aminoethanol:** colorless liquid; ^{1}H NMR δ 3.72 (2H, t, J = 5.5 Hz), 3.38 (2H, t, J = 5.12 Hz), 3.18 (1H, bs), 2.92 (3H, s), 1.46 (9H, s); ^{13}C NMR δ 157.1, 79.8, 61.0, 51.2, 35.3, 28.3. Anal. Calcd for $C_8H_{17}NO_3$: C, 54.82; H, 9.78. Found: C, 54.70; H, 9.65.

***N*-Carbobenzyloxy-*N*-methyl-2-aminoethanol:** colorless liquid; ^{1}H NMR δ 7.35−7.26 (m, 5H), 5.11 (s, 2H), 3.74 (2H, t, J = 5.4 Hz), 3.43 (2H, t, J = 5.4 Hz), 2.98 (3H, s). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.13; H, 7.23. Found: C, 63.07; H, 7.14.

Acknowledgment. We thank the Council of Scientific & Industrial Research, Government of India, for financial support. One of us (K.G.B.) thanks CSIR for the award of a Senior Research Fellowship.

JO035412F