

CONVERSION OF ALCOHOLS INTO AMIDES USING ALUMINA-METHANESULFONIC ACID (AMA) IN NITRILE SOLVENTS

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ABSTRACT: *The reaction of tertiary, secondary and benzylic alcohols with different nitriles in the presence of alumina-methanesulfonic acid (AMA) as a new reagent affords the corresponding amides in good yields (Table 1, 2). Conversion of 2,6-bis(hydroxymethyl)-4-halo anisoles into corresponding diamides in the range of 68-76% yields (Table 3) are also included in this paper.*

KEY WORDS: *Alumina-methanesulfonic acid, Amide, Alcohol, Nitrile, Diamides, Alcohol into amides, Conversion.*

INTRODUCTION

High yield and facile preparation of primary and secondary amines is important in organic synthesis. This goal may be achieved either by the hydrolysis or by the hydride reduction of amides. Amides and polyamides themselves are also important materials for different chemical purposes.

The reaction of alcohols with nitriles in sulfuric acid for preparation of amides is known as Ritter reaction [1]. This method has the disadvantage that it functions well only in the case of tertiary alcohols. Also, when the reaction of benzyl alcohol derivatives is carried out in the presence of acetic acid, both alkylation and esterification occurs in some instances [2]. Other methods which are available in the literature for the amidation of alcohols with nitriles are: chromium tricarbonyl complexes in sulfuric acid [3]

and boron trifluoride [4] which function only in the case of benzyl alcohol derivatives; trifluoromethane sulfonic anhydride [5] which in the case of tertiary alcohols elimination reaction compete with amidation; dichlorophosphate [6] that converts alcohols to amides in 10-22% yield; chlorodiphenylmethylum hexachloroantimoniate [7,8] and transition metal compounds [9] which are reported for primary and secondary aliphatic and alicyclic alcohols; Lewis base [10] and water [11] which convert methanol into N-methylacetamide in 21.7% and 40.3% yields respectively.

Recently, we reported alumina-methanesulfonic acid (AMA) as a new efficient reagent for direct acylation of phenols with carboxylic acid and Fries rearrangement [12]. In this paper we describe the

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Table 1 : Reaction of Benzyl Alcohol in the Presence of H_2SO_4 , $BF_3 \cdot Et_2O$ and AMA

Reagent	Solvent	Time(h)	Yield(%)	Product
H_2SO_4	CH_3CN	5	48	$PhCH_2NHCOCH_3$
"	$CH_2=CHCN$	5	50	$PhCH_2NHCOCH=CH_2$
$BF_3 \cdot Et_2O$	CH_3CN	8	50	$PhCH_2NHCOCH_3$
"	$PhCN$	10	48	$PhCH_2NHCOPh$
CH_3SO_3H	CH_3CN	8	60	$PhCH_2NHCOCH_3$
Al_2O_3	CH_3CN	24	—	—
AMA	CH_3CN	5	92 ^a	$PhCH_2NHCOCH_3$
"	$CH_2=CHCN$	3	87 ^a	$PhCH_2NHCOCH=CH_2$
"	$PhCN$	1	88 ^b	$PhCH_2NHCOPh$

a) Isolated according method A.

b) Isolated according method B.

Table 2 : Preparation of Amides 3(a-g).

Entry	ROH	$\frac{AMA}{ROH}$	Time(h)	Yield(%)	Product	mp(°C) or bp(°C)/torr
1	1 _a	5/1	5	80 ^a	3 _a	213/640
2	1 _b	5/1	2	95 ^a	3 _b	258/640
3	1 _c	1/1	8	75 ^a	3 _c	98-99(Lit: ⁵ 98-99)
4	1 _d	1/1	7	85 ^b	3 _d	127-128(Lit: ¹³ 126-128)
5	1 _c	1/1	7	86 ^b	3 _e	134-135(Lit: ¹⁴ 134-134.5)
6	1 _f	5/1	20	58 ^a	3 _f	101-103(Lit: ⁵ 102-103)
7	1 _g	5/1	15	54 ^a	3 _g	103-104(Lit: ⁵ 103-104)

a) Isolated according method A.

b) Isolated according method B.

amidation of tertiary, secondary and benzylic alcohols in different nitriles in the presence of AMA.

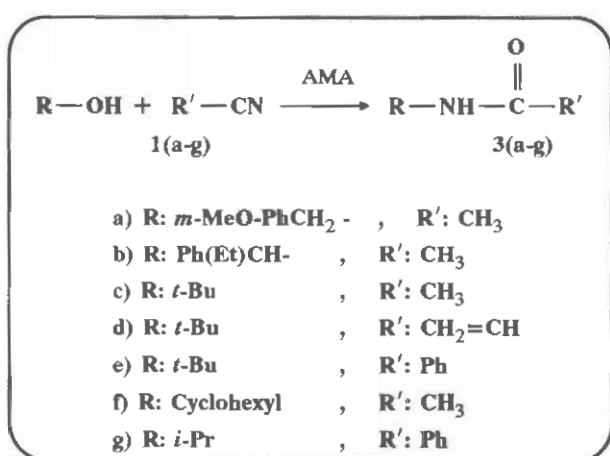
RESULTS AND DISCUSSION

In order to find a simple and suitable reagent for the amidation of alcohols with nitrile solvents, the reaction of benzyl alcohol was chosen as a model and its conversion to corresponding amide was studied in different conditions (Table 1). Treatment of benzyl alcohol with acetonitrile in the presence of H_2SO_4 at 60°C for 5 h produced N-benzyl acetamide in 48% and N-benzyl acrylamide in 50% yields with acrylonitrile [2]. Amidation of benzyl alcohol with acetonitrile and benzonitrile in the presence of $BF_3 \cdot Et_2O$

[4] gave 50% and 48% N-benzyl acetamide and N-benzyl benzamide respectively. Whereas, the reaction of benzyl alcohol with acetonitrile in the presence of methanesulfonic acid gave N-benzyl acetamide in 60% yield. No amidation takes place in reacting benzyl alcohol with acetonitrile in the presence of Al_2O_3 . Since attempts at the preparation of N-benzyl amide were unsuccessful, attention was turned to AMA which is a stable reagent even in highly boiling points. The reaction of benzyl alcohol with different nitriles was performed in the presence of AMA and produced corresponding amides in high yields (Table 1).

In an effort to evaluate the range of applicability

of our method, we examined also some other alcohols. As shown in Scheme (1) and Table 2, tertiary and benzylic alcohols react with nitriles in the presence of AMA to give the corresponding amides in high yields. The reaction of secondary alcohols with nitriles in the presence of AMA affords corresponding amides in moderate yields, but no reaction takes place with primary alcohols. It is pertinent to mention that tertiary alcohols do not undergo elimination under the reaction conditions to produce olefins (GC and ^1H NMR).



Scheme (1)

2,6-Bis(hydroxymethyl)-4-halo anisoles were condensed smoothly with nitriles in the presence of AMA and obtained corresponding diamides in good yields (Table 3).

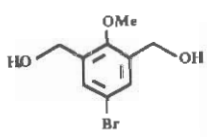
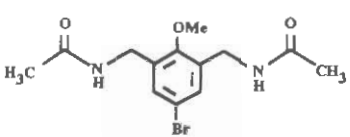
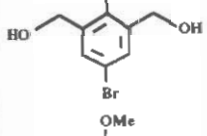
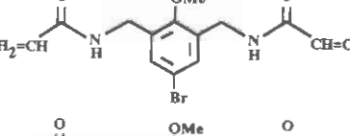
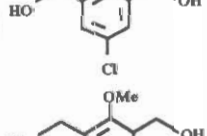
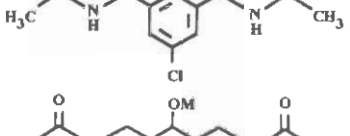
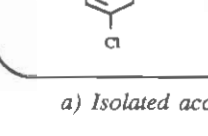
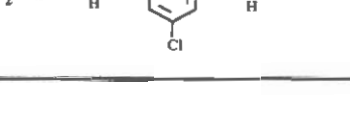
This method is generally applicable, because the reagent needed is readily available, the procedure is simple and the reaction times are relatively short, the reaction can be performed with tertiary, secondary, and benzylic alcohols under mild conditions in high yields and no elimination reaction taking place in the case of tertiary alcohols.

EXPERIMENTAL

Instrumentation, analyses and starting material

NMR spectra were recorded on a Bruker Avance DPX-250 in pure deuterated solvents. IR spectra were obtained on a Perkin-Elmer IR-157-G spectrophotometer. The purity of the substrates and reactions monitoring were determined by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-10A instrument with a flame ionization detector using a column of 15% Carbowax 20 M Chromosorb W acid washed 60-80 mesh. Melting points were determined in open capillary tubes in a Buchi-510 circulating oil melting points apparatus.

Table 3: Preparation of diamides

Substrate	RCN	AMA Sub.	Time(h)	Yield ^a (%)	Product	mp(°C)
	CH ₃ CN	5/1	7	70		228-230 (Lit: ¹⁵ 230)
	CH ₂ =CH-CN	5/1	2	76		200-202(Polym.) (Lit: ¹⁵ 204)(Polym.)
	CH ₃ CN	5/1	7	68		213-215 (Lit: ¹⁵ 214)
	CH ₂ =CH-CN	5/1	2	71		185-187 (Lit: ¹⁵ 186)

a) Isolated according method B

Alcohols, methanesulfonic acid, alumina acidic [Fluka, type 504 C] and other chemical materials were purchased from Fluka (Buchs, Switzerland) Aldrich (Milwaukee, WI, USA) and Merck (Darmstadt, Germany) in high purity and were used without further purification. Yields refer to isolated pure products after recrystallization. 2,6-Bis(hydroxymethyl)-4-haloanisoles were prepared according to established procedures, and their spectroscopic and physical data were compared with the literature data [15, 16]. All of the products are known compounds and their spectroscopic and physical data were compared with those of the literature [2,4,5,13-15].

General procedure for the amidation of alcohols with nitriles in the presence of AMA

To an ice-cooled suspension of alumina (0.13-1.3 g) and methanesulfonic acid (10-100 mmol) in nitrile (4-8 mL) was added alcohol (10 mmol) with stirring. Then, the reaction mixture was stirred in 60°C for 1-10 h. For isolation of products two methods were used:

a : The mixture was filtered and washed with ethyl acetate, then water (20 mL) was added to the solution and the mixture neutralized with 10% NaHCO₃ solution. The organic phase was then separated and the aqueous layer extracted with ethyl acetate (3×30 mL). The combined organic phases were evaporated under reduced pressure. The resulting crystals were purified by recrystallization in petroleum ether (60-80°C) to afford pure amides in 54-95% yields (Table 1,2).

b : The mixture was filtered, washed with diethyl ether, and the ether solution evaporated. Water (20 mL) was added to the residual and the solution neutralized with 10% NaHCO₃ solution. The resulting solid filtered, washed, dried and purified by recrystallization in proper solvent in 68-88% yields (Table 2,3).

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