

Ca(HSO₄)₂ Mediated Conversion of Alcohols into N-Substituted Amides under Heterogeneous Conditions: A Modified Ritter Reaction

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Tertiary, secondary, and benzylic alcohols react efficiently with nitriles in the presence of the catalyst calcium hydrogen sulfate, Ca(HSO₄)₂, to produce amides in high yields. In this study, a modified Ritter reaction using this solid acid catalyst is found to be an environmentally safe method for converting 2,6-bis(hydroxymethyl)-4-halo anisole into the corresponding diamides in CH₃CN.

Keywords: Calcium hydrogen sulfate, Alcohols, Nitriles, Heterogeneous conditions, N-substituted amides, Ritter reaction

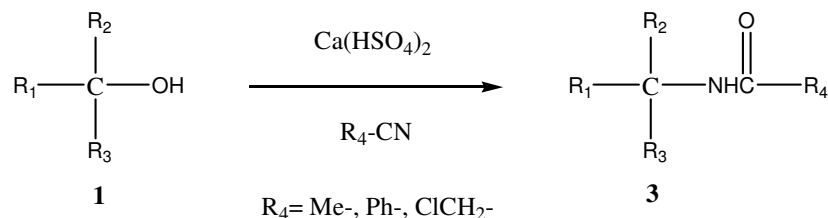
INTRODUCTION

One of the most important objectives now is to adapt classical processes so that pollution effects are kept to a minimum, with both a reduction in energy and consumption of raw materials. In this respect, heterogeneous systems are promising, and a new approach has been undertaken using solid acids chemistry. Solid acids have many advantages such as simplicity in handling, fewer reactor and plant corrosion problems, and more environmentally safe disposal in a variety of chemical processes. Also, wastes and by-products can be minimized or avoided using solid acids in the development of cleaner synthesis routes. On the other hand, any reduction in the amount of liquid acid needed and/or any simplification in handling procedures is required to achieve risk reduction, economic advantage and environmental protection [1], and using an applicable industrial catalyst that is safe and eco-friendly, green and simply recycled in the reaction mixtures has been attracting a great deal of attention. Thus, green

chemistry has been defined as a set of principles designed to reduce or eliminate the use or generation of hazardous substances throughout the entire life of chemical materials. Inorganic solid acidic salts, such as metal hydrogen sulfates or solid acids, play a prominent role in organic synthesis under heterogeneous conditions [2]. In order to promote environmental safety and due to their safe and eco-friendly nature, the importance of these solid acid catalysts is growing as attention is directed toward the development of clean and green technologies for important organic molecules.

In continuation of our studies in the use of inorganic metal hydrogen sulfate acidic salts in organic transformations [2-3], we have found that calcium hydrogen sulfate is suitable for the direct conversion of alcohols into their corresponding N-substituted amides by reacting them with nitriles under heterogeneous conditions. The amidation of alcohols, which is known as the Ritter reaction [4], is important for the preparation of primary and secondary amines. 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.

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Scheme 1

This method constitutes a very useful procedure for the preparation of N-alkyl amides with bulky substituents. The applied acidic reagents for this purpose are: H₂SO₄ [5], (CF₃SO₂)₂O [6], Ph₂CCl⁺SbCl₆⁻ [7], Fe(ClO₄)₃ [8], BF₃·Et₂O [9], nafion-H [10], CoCl₂-Ac₂O [11], Co(III)-DMG complex [12], Fe³⁺-montmorillonite [13], Mg(HSO₄)₂ [14], and Fe(ClO₄)₃-SiO₂ [15]. However, many of these methods suffer from at least one of the following disadvantages: unavailability of the reagent, vigorous reaction conditions, strong protic and aqueous media, high cost and toxicity of the reagent, tedious work-up procedure, unsatisfactory yields, inefficiency in amidation of saturated alcohols and hydroscopic nature of the reagent.

In conjunction with our interest in the use of metal hydrogen sulfates as efficient catalysts in various transformations [2-3], and also in continuation of our studies on the improvement of the Ritter reaction [16], herein, we report the reaction of different classes of alcohols with nitriles in the presence of Ca(HSO₄)₂ as an efficient heterogeneous mediator to produce the corresponding amides in high yields (Scheme 1).

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. IR spectra were run on a Shimadzu infrared spectrophotometer, model IR-435. The ¹H NMR was run on an Avance Bruker model AQS 300 MHz spectrometer. The reactions were followed by TLC using silica gel SILG/UV 254 plates. The 2,6-bis(hydroxymethyl)-4-haloanisoles were prepared according to a previously reported procedure [16]. The products are known compounds and were identified by comparison of their spectral data (IR, ¹H NMR

and physical properties with those of authentic samples.

General Procedure

In a round-bottomed flask equipped with a condenser and a magnetic stirrer, calcium hydrogen sulfate (1 mmol) was added to a nitrile solution (4 ml) in 1 mmol alcohol. The resulting heterogeneous mixture was stirred at 80 °C until the alcohol was completely consumed (Table 1). The reaction mixture was concentrated under reduced pressure. Water (20 ml) was added to the resulting mixture, which was then extracted with ethyl acetate (3 × 20 ml). The organic layer was separated, dried over anhydrous Na₂SO₄ and the solvent was evaporated *in vacuo*. The resulting crude products were crystallized from *n*-hexane.

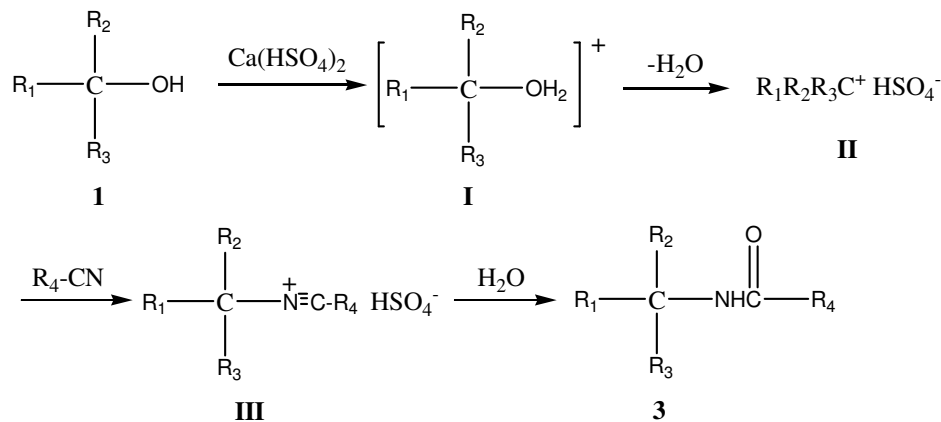
Typical Procedure

Preparation of N,N'-diacetyl-4-bromo-2,6-di(amino-methyl) anisole (**5b**) was carried out as follows. In a round-bottomed flask equipped with a condenser and a magnetic stirrer, calcium hydrogen sulfate (0.468 g, 2 mmol) was added to a solution of 4-bromo-2,6-bis(hydroxymethyl) anisole (0.247 g, 1 mmol) in CH₃CN (4 ml). The mixture was stirred at 80 °C for 2 h. Then, the mixture was concentrated under reduced pressure and H₂O (20 ml) was added to the resulting mixture upon which precipitates were formed. The precipitates were filtered, washed with water and dried to give 0.27 g (82%) of **5b** (Table 1, entry 19). Recrystallization from ethanol gave an analytical sample of **5b**, m.p.: 230 °C [16]. ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 1.93 (s, 6H), 3.76 (s, 3H), 4.30 (d, 4H, J = 5.7 Hz), 7.32 (s, 2H), 8.35 (b, 1H).

Selected Spectral Data

N-Benzyl-2-chloroacetamide (3b). ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 4.11 (s, 2H), 4.29 (d, 2H, J = 5.52 Hz), 7.17-

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Scheme 2

7.34 (m, 5H), 8.71 (b, 1H).

N-(4-chlorobenzyl)-2-chloroacetamide (3e). ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 4.11 (s, 2H), 4.28 (d, 2H, J = 5.71 Hz), 7.28 (d, 2H, J = 8.1 Hz), 7.39 (d, 2H, J = 8.1 Hz), 8.75 (b, 1H).

N-(4-bromobenzyl)-2-chloroacetamide (3g). ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 4.12 (s, 2H), 4.27 (d, 2H, J = 5.8 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.51 (d, 2H, J = 8.0 Hz), 8.73 (b, 1H). ¹³C NMR (75 MHz): δ (ppm) 42.31, 43.06, 120.41, 129.98, 131.64, 138.84, 166.56.

2-Chloro-N-(1-phenylethyl) acetamide (3l). ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 1.37 (d, 3H, J = 7.0 Hz), 4.06 (s, 2H), 4.90 (q, 1H, J = 7.0 Hz), 7.23-7.32 (m, 5H), 8.63 (b, 1H).

N-Adamantyl acetamide (3o). ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 1.59 (s, 6H), 1.72 (s, 3H), 1.89 (s, 6H), 1.97 (s, 3H), 7.27 (s, 1H). ¹³C NMR (75 MHz): δ (ppm) 24.21, 29.25, 36.52, 41.46, 50.95, 168.95.

N-Adamantyl-2-chloroacetamide (3p). ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 1.61 (s, 6H), 1.91 (s, 6H), 2.00 (s, 3H), 3.94 (s, 2H), 7.65 (s, 1H). ¹³C NMR (75 MHz): δ (ppm) 29.21, 36.36, 41.14, 43.92, 51.61, 165.23.

RESULTS AND DISCUSSION

Benzylic alcohols with electron-releasing and electron-withdrawing substituents react efficiently with acetonitrile, benzonitrile and chloroacetonitrile to produce the corresponding amides in excellent yields (Table 1). The reports on high yielding amidation of saturated alcohols by

Ritter reactions are scarce in the literature [17]. However, by the present method, *tert*-butanol, adamantanol, 3-pentanol and cyclohexanol are converted to the corresponding N-substituted amides under mild and heterogeneous conditions in good yields (Table 1, entries 10-17). We have also attempted the amidation of primary saturated alcohols; however these attempts were not successful by this method. By these observations we presume that this reaction may proceed *via* an intimate carbanion ion (II), upon which an immediate attack by the nitrile molecule produces the nitrilium intimate ion (III). After hydration, the nitrilium intimate ion (III) produces the proper amide (Scheme 2).

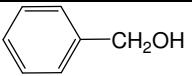
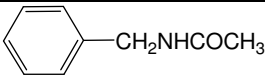
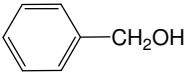
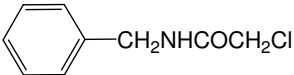
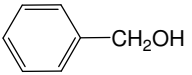
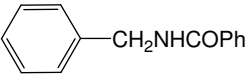
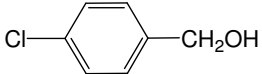
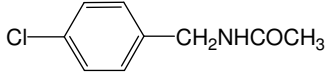
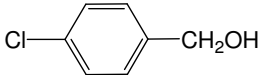
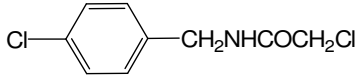
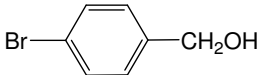
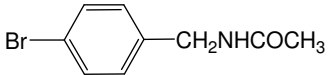
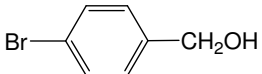
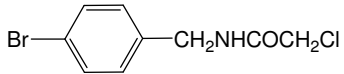
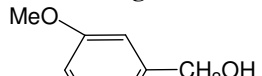
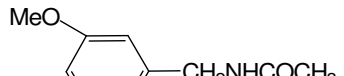
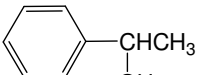
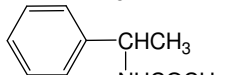
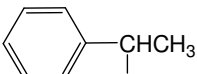
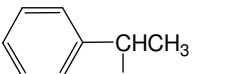
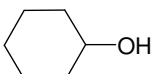
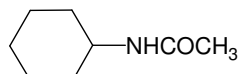
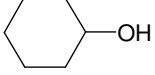
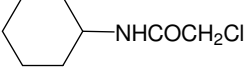
By this method the conversion of bis-2,6-dihydroxymethyl-4-halo anisoles into the corresponding N-substituted diamides was investigated in acetonitrile in the presence of an equimolar amount of Ca(HSO₄)₂. The reaction proceeded smoothly with high yields and short reaction times (Scheme 3, Table 1, Entries 18, 19).

In conclusion, we have presented a highly efficient mediation of Ca(HSO₄)₂ for the one-pot conversion of alcohols into N-substituted amides under heterogeneous conditions. The work-up of the method is easy and the yields of the products are high. However, Ca(HSO₄)₂ cannot catalyze the amidation of primary alcohols.

ACKNOWLEDGMENTS

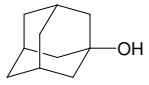
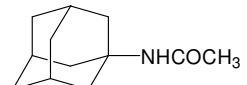
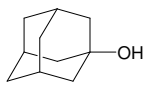
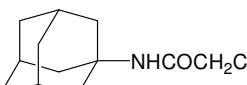
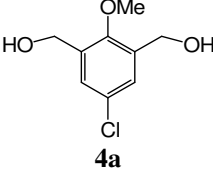
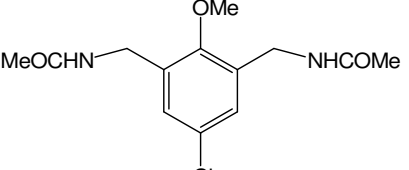
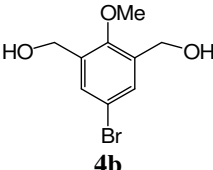
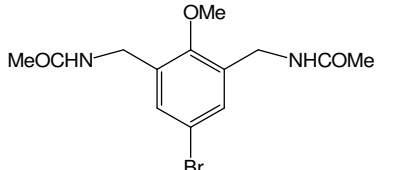
We are thankful to the Persian Gulf University Research Council for partial support of this work.

Table 1. Conversion of Alcohols into Corresponding Amides in the Presence of $\text{Ca}(\text{HSO}_4)_2$ in Nitriles under Heterogeneous Conditions

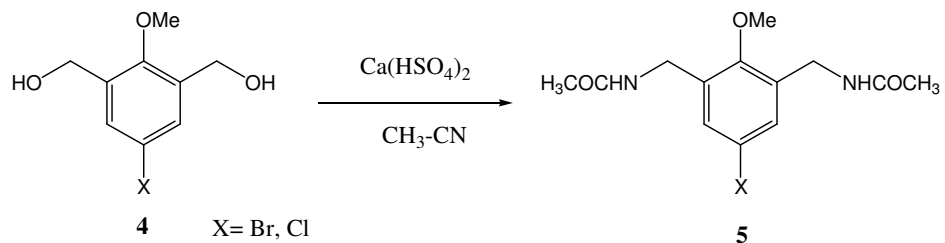
Entry	Substrate	Nitrile	Time (h)	Product	Yield (%) ^a
1	 1a	CH_3CN	2.5	 3a	89
2	 1b	ClCH_2CN	2.5	 3b	90
3	 1c	PhCN	2.0	 3c	90
4	 1d	CH_3CN	2.5	 3d	91
5	 1e	ClCH_2CN	2.5	 3e	89
5	 1f	CH_3CN	2.0	 3f	90
6	 1g	ClCH_2CN	2.0	 3g	87
7	 1j	CH_3CN	3.0	 3j	85
8	 1k	CH_3CN	2.0	 3k	86
9	 1l	ClCH_2CN	2.0	 3l	85
10	 1m	CH_3CN	2.2	 3m	82
11	 1m	ClCH_2CN	2.2	 3m	80

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Table 1. Continued

12	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3 \\ \\ \text{OH} \\ \mathbf{1n} \end{array}$	ClCH ₂ CN	2.5	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3 \\ \\ \text{NHCOCH}_2\text{Cl} \\ \mathbf{3n} \end{array}$	87
13	 $\mathbf{1o}$	CH ₃ CN	1.5	 $\mathbf{3o}$	91
14	 $\mathbf{1p}$	ClCH ₂ CN	2.5	 $\mathbf{3p}$	90
15	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{OH} \\ \\ \text{CH}_3 \\ \mathbf{1q} \end{array}$	CH ₃ CN	2.0	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{NHCOCH}_3 \\ \\ \text{CH}_3 \\ \mathbf{3q} \end{array}$	93
16	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{OH} \\ \\ \text{CH}_3 \\ \mathbf{1r} \end{array}$	ClCH ₂ CN	2.0	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{NHCOCH}_2\text{Cl} \\ \\ \text{CH}_3 \\ \mathbf{3r} \end{array}$	92
17	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{OH} \\ \\ \text{CH}_3 \\ \mathbf{1s} \end{array}$	PhCN	2.0	$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{C}-\text{NHCOPh} \\ \\ \text{CH}_3 \\ \mathbf{3s} \end{array}$	91
18	 $\mathbf{4a}$	CH ₃ CN	2.0	 $\mathbf{5a}$	81
19	 $\mathbf{4b}$	CH ₃ CN	2.0	 $\mathbf{5b}$	82

^aIsolated yield.



Scheme 3

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