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The Ritter Reaction under Truly Catalytic Brønsted Acid Conditions

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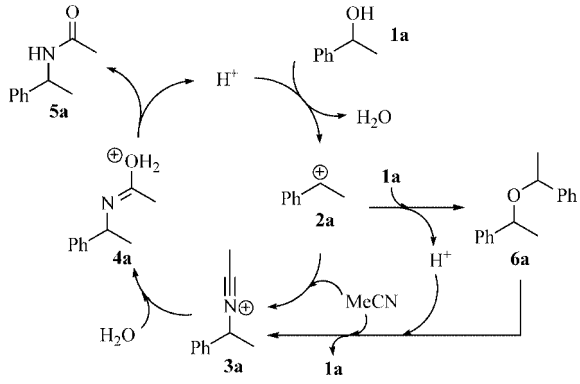
Simple organic acids like 2,4-dinitrobenzenesulfonic acid (DNBSA) catalyze the Ritter reaction of secondary benzylic alcohols giving rise to the corresponding *N*-benzylacetamides in usually high yields. Reactions can be conducted without exclusion of oxygen and without the need of dry solvents. With tertiary α,α-dimethylbenzylic alcohols a different pathway involving a formal dimerization reaction takes place under the acid-catalytic conditions used.

Introduction

The Ritter reaction is a general method for the amidation of alcohols or alkenes with nitriles.[1] The reaction typically requires a strongly ionizing solvent and a stoichiometric amount of a strong acid (usually sulfuric acid), thus limiting its applicability to compounds with groups that survive such harsh conditions.[2] This reaction works well in the case of tertiary alcohols but, the reaction proves more challenging with less substituted centres due to the instability of the intermediate carbocation.[3] For instance, 2-methyl-1-phenylpropan-1-ol affords only moderate yields (ca. 35%) of *N*-(1,1-dimethyl-2-phenylethyl)acetamide or *N*-(2-methyl-1-phenylpropyl)acetamide depending on the reaction conditions,[3b] showing the tendency of molecular rearrangements in the course of Ritter reactions with secondary alcohols. Different procedures have been developed to promote the reaction of less substituted centres, most of them employing heteroatoms.[4] However, in the last years Brønsted acid-mediated reactions of different alcohols with nitriles have been shown to be useful for the preparation of interesting amides.[5]

Although in the past some alternative methodologies have been developed for the Ritter reaction where sulfuric acid is replaced by metal complexes,[6] triflic anhydride,[7] $BF_3{\cdot}Et_2O$,[8] or inmobilized reagents on solid supports,[9] most of these methods suffer from drawbacks such as the use of compounds that are corrosive, toxic, or expensive, whereas others involve anhydrous conditions. The Ritter reaction is supposed to proceed through a catalytic cycle such as that shown in Scheme 1.



Scheme 1. Proposed catalytic cycle for the Ritter reaction of **1a**.

The reaction of a benzylic alcohol such as **1a** with an acid forms the carbocation **2a**. This is trapped with a molecule of acetonitrile to generate the nitrilium cation **3a**, which is captured by the water produced in the first step of the process to afford **4a** regenerating a molecule of acid. So, in principle, the acid could be used in a catalytic amount.

However, as mentioned before, the standard conditions to perform the reaction involve the use of stoichiometric amounts of concentrated sulfuric acid and, to the best of our knowledge, there is no general method reported in the literature for the Ritter reaction using only catalytic amounts of a Brønsted acid. In this context, we have recently found that simple Brønsted acids like *p*-toluenesulfonic acid (PTS) or triflic acid (TfOH) are able to catalyze the direct nucleophilic substitution of propargylic alcohols,[10] as well as benzylic and allylic ones.[11] In the following we wish to report that simple organic Brønsted acids when used in catalytic amounts efficiently promote the Ritter reaction of secondary benzylic alcohols.

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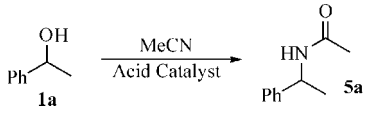
Results and Discussion

In the course of our studies about the nucleophilic substitution of 1-phenylethanol **1a** with different nucleophiles under Brønsted acid catalysis, we had observed that the use of acetonitrile as solvent gave mainly rise to *N*-(1-phenylethyl)-acetamide (**5a**), precluding the substitution by the external nucleophile.[11a] So, we decided to investigate in depth the model reaction of **1a** with acetonitrile to give acetamide **5a** by using several different Brønsted acids as catalysts (Table 1).

Table 1. Catalyst screening for the Ritter reaction of 1-phenylethanol (**1a**).



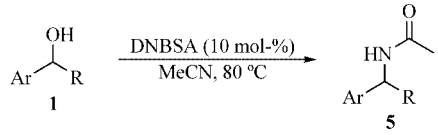
Entry	Acid catalyst	Amount [mol-%]	*T* [°C]	*t* [h]	Yield [%][a]
1	PTS	10	reflux	48	84
2	DNBSA	10	reflux	12	85
3	TfOH	10	reflux	12	85
4	H_2SO_4	10	reflux	15	82
5	DNBSA	5	reflux	24	75[b]

[a] Isolated yields based on starting alcohol **1a**; >95% conversion was observed for all the cases. [b] A 7:1 mixture of **5a**/**6a** was determined by ^{1}H NMR analysis of the crude reaction mixture.

Gratifyingly, the amidation reaction of **1a** took place by using different Brønsted acids as catalysts (10 mol-%). The only difference observed between these acids was the reaction time required for complete conversion of the starting material (Table 1, entries 1–4). As shown, the temperature of the reaction was raised to reflux in order to obtain the final amide in reasonable time. It is also interesting to note that in all cases we observed the initial formation of bis(1-phenyethyl) ether **6a** and its progressive transformation into the final amide **5a** (see Scheme 1). After this study, we decided to use 2,4-dinitrobenzenesulfonic acid (DNBSA)[12] (10 mol-%) as catalyst in the successive experiments due to its high activity and easiness of handling. Lowering the catalyst loading from 10 mol-% to 5 mol-% (Table 1, entries 2 and 5) resulted in a significant increase in the reaction time required for the formation of **5a** (the transformation of the initially formed ether **6a** into amide **5a** is slower under these conditions).

The generality of the reaction was explored with functionalized 1-arylethanols **1b**–**h**. These experiments usually gave high yields of the desired *N*-(1-arylethyl)acetamides **5b**–**h** (Table 2, Entries 2–8).[13] In order to check if this approach could be applied to multigram synthesis, 3.77 g of **5a** (77% isolated yield) were easily prepared in one batch from 3.66 g of 1-phenylethanol (**1a**) by using 10 mol-% of DNBSA as catalyst. Moreover, benzylic alcohols **1i**–**n**, substituted with primary- (Entries 9–12), secondary- (Entry 13), or tertiary-alkyl groups (Entry 14) were shown to be appropriate starting materials for the catalyzed Ritter reaction and only small amounts of the corresponding elimination products were obtained in some cases. Interestingly, 2-methyl-1-phenylpropan-1-ol (**1m**) afforded *N*-(2-methyl-1-phenylpropyl)acetamide (**5m**) in high yield (Table 2, entry 13). By contrast, under the standard stoichiometric conditions reported for the Ritter reaction, the use of this substrate was shown to be problematic.[3b]

Table 2. Preparation of *N*-benzylacetamides **5** from benzylic alcohols **1**.



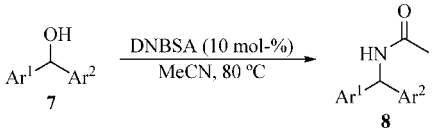
Entry	Alcohol	Ar	R	Amide	*t* [h]	Yield [%][a]
1	**1a**	Ph	Me	**5a**	15	82
2	**1b**	4-FC_6H_4	Me	**5b**	24	83
3	**1c**	4-ClC_6H_4	Me	**5c**	48	70[b]
4	**1d**	4-BrC_6H_4	Me	**5d**	30	74[b]
5	**1e**	3-$MeOC_6H_4$	Me	**5e**	24	66
6	**1f**	2-BrC_6H_4	Me	**5f**	50	62
7	**1g**	2-IC_6H_4	Me	**5g**	72	82[b]
8	**1h**	2-naphthyl	Me	**5h**	9	80[b]
9	**1i**	4-BrC_6H_4	Et	**5i**	24	63[b]
10	**1j**	Ph	*n*Pr	**5j**	15	75[c]
11	**1k**	Ph	*n*Bu	**5k**	48	62[c,d]
12	**1l**	4-ClC_6H_4	*n*Bu	**5l**	24	55[c]
13	**1m**	Ph	*i*Pr	**5m**	15	89
14	**1n**	Ph	*t*Bu	**5n**	30	66

[a] Isolated yields after chromatography based on starting alcohol **1**. [b] Trace amounts (< 5%) of the corresponding styrene derivatives were also observed. [c] A ca. 10% of the corresponding styrene derivatives were also isolated. [d] Under PTS catalysis ca. 20% of the elimination product was obtained.

On the other hand, benzhydrylamine derivatives are important structural features of various physiologically active compounds and are also used as protecting groups.[14] The classical syntheses of diarylmethylamines form benzhydrol precursors involve their previous transformation into chlorides or mesylates, followed by substitution with ammonia.[15] Interestingly, a synthesis of *para* di- and monosubstituted benzhydrylamines has been developed from beznhydrol precursors and phenyl carbamate under acidic conditions.[16] In order to get this kind of compounds in a simple way, we thought of applying the Ritter reaction under the catalytic conditions previously described, i.e. a catalytic amount of DNBSA in MeCN at reflux temperature. Indeed, *N*-benzhydrylacetamides **8** were obtained in high yields from several benzhydrol derivatives **7** (Table 3). Remarkably, even when strong electron-withdrawing groups are present in the starting alcohol **7** (Table 3, Entries 2–4), high yields of the corresponding acetamides **8** were obtained.

Finally, we decided to study the catalyzed Ritter reaction of a tertiary benzylic alcohol like 2-phenylpropan-2-ol **9a** (Ar = Ph; R = H) (Scheme 2). However, under DNBSA catalysis in MeCN at reflux, the reaction with **9a** did not afford the expected *N*-benzylic acetamide **10a**. Instead of it, a 1.3:1 mixture of dimeric compounds **11a** and **12a** (Ar = Ph) was obtained in combined 66% yield (Scheme 2 and Table 4, entry 1). This kind of dimerization has previously

Table 3. Preparation of *N*-benzhydrylacetamides **8** from benzhydrol derivatives **7**.

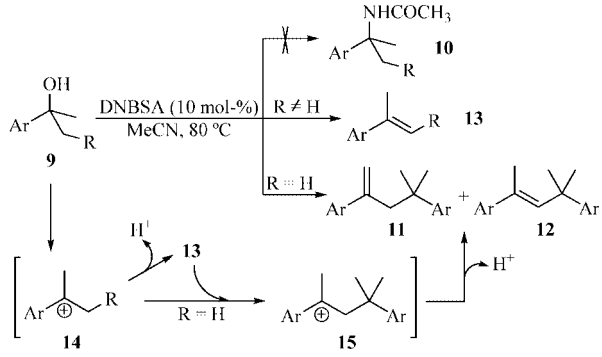


Entry	Alcohol	Ar^1	Ar^2	Amide	*t* [h]	Yield [%][a]
1	**7a**	Ph	Ph	**8a**	15	86
2	**7b**	4-FC_6H_4	4-FC_6H_4	**8b**	30	88
3	**7c**	4-ClC_6H_4	4-ClC_6H_4	**8c**	15	80
4	**7d**	Ph	4-$NO_2C_6H_4$	**8d**	15	82
5	**7e**	Ph	4-BrC_6H_4	**8e**	24	91
6	**7f**	Ph	4-ClC_6H_4	**8f**	15	87
7	**7g**[b]	2,2′-(C_6H_4-C_6H_4)		**8g**	15	82

[a] Isolated yields after chromatography based on starting benzhydrol **7**. [b] 9-Fluorenol.

been carried out under metal catalysis,[17] with aminium salts acting as one electron oxidants,[18] and with excess of concd. aqueous H_2SO_4 or HCl.[19] In this context, we have recently reported a similar process for the formal dimerization of styrenes under TfOH catalysis of the corresponding secondary benzylic alcohols in $MeNO_2$.[11b] The formation of isomeric compounds **11a** and **12a**[20] could be understood through protonation of **9a** and formation of α-methylphenylethyl cation **14a** (Ar = Ph; R = H), which could undergo an elimination reaction producing α-methylstyrene **13a** (Ar = Ph; R = H). Its addition to the benzylic carbocation **14a** would afford the dimer carbocation **15a** (Ar = Ph). Subsequent elimination of a proton which could take place in two different ways, accounts for the generation of the final compounds (Scheme 2).

This catalytic and metal-free alternative for the formal dimerization of α-methylstyrenes could be of interest and so, we prepared several 2-arylpropan-2-ol derivatives **9b–e** and treated them under Brønsted acid-catalyzed conditions. Substrates **9b–d** containing electron-withdrawing substituents produced the unsaturated dimers **11b–d** and **12b–d** in high overall yields (Table 4, entries 2–4). Reaction times with these alcohols were longer than that for the parent alcohol **9a** and also, small amounts of the corresponding α-methylstyrenes **13b–d** were isolated, indicating a lower stabilization for carbocations **14b–d** compared with **14a**. On the other hand, alcohol **9e** containing one electron-donating substituent gave the expected open chain unsaturated dimers **11e** and **12e** along with a small amount of 1,1,3,5-tetramethyl-3-*p*-tolylindan, the corresponding cyclodimer of intermediate carbocation **15e** (Table 4, entry 5). Finally, we treated alcohol **9f** (Ar = Ph, R = Pr) under DNBSA catalysis, but only the elimination product, i.e. styrene **13f**, was obtained showing that β-substitution in the intermediates **13** and **14** (R ≠ H) inhibits the dimerization process (Table 4, entry 6).



Scheme 2. Formation of 2,4-diarylpentene derivatives **11** and **12** from 2-aryl-2-propanol derivatives **9** (R = H) under Brønsted acid-catalyzed conditions.

Conclusions

In summary, we have found that simple organic acids like DNBSA catalyze the amidation of secondary benzylic alcohols.[21] The reaction is tolerant towards air and moisture. This metal-free method represents a clean and environmentally friendly alternative to the established use of metallic catalysts or stoichiometric amounts of Brønsted acids. The method is also amenable to large scale synthesis. On the other hand, 2-arylpropan-2-ols undergo formal dimerization through the corresponding styrenes under Brønsted acid catalysis.

Experimental Section

General Procedure for DNBSA-Catalyzed Amidation of Alcohols 1 and 7: To a solution of the corresponding alcohol **1** or **7** (2 mmol) in analytical grade MeCN (5 mL), DNBSA[22] (59 mg, 0.2 mmol) was added. The reaction mixture was stirred at reflux and the completion of the reaction was monitored by GC-MS (see reaction times in Tables 2 and 3). The solvent was removed under reduced pressure and the residue was purified by column chromatography

Table 4. Brønsted acid-catalyzed reaction of tertiary benzylic alcohols **9**.

Entry	Alcohol	Ar	R	*t* [h]	Products	Ratio[a]	Yield [%][b]
1	**9a**	Ph	H	12	**11a+12a**	1.3:1	66
2	**9b**	4-FC_6H_4	H	24	**11b+12b+13b**	8:10:1	77
3	**9c**	4-ClC_6H_4	H	24	**11c+12c+13c**	1.8:1:1	72
4	**9d**	4-BrC_6H_4	H	24	**11d+12d+13d**	1.5:1:1	67
5	**9e**	4-MeC_6H_4	H	12	**11e+12e**	1.6:1	70[c]
6	**9f**	Ph	Pr	12	**13f**	–	74

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Combined isolated yields for **11** + **12** after chromatography based on starting alcohol **9**. [c] About 15% of 1,1,3,5-tetramethyl-3-*p*-tolylindane was also produced.

on silica gel (eluent: hexane/ethyl acetate), affording the corresponding acetamides **5** and **8**.

Supporting Information (see also the footnote on the first page of this article): Spectroscopic and characterization data for all compounds.

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[20] Under DNBSA catalysis at room temperature, a 2:1 mixture of **11a/12a** was formed, showing the poor reproducibility on the ratio of **11/12**.

[21] We have also checked the reaction by using other nitriles different from acetonitrile. For example, positive results were obtained in the reaction of 1-phenylethanol (**1a**) with benzonitrile. Details on this work will be published at due time.

[22] We used 2,4-dinitrobenzenesulfonic acid hydrate (Aldrich, 556971). Its elemental analysis gave the molecular formula $(NO_2)_2C_6H_3SO_3H{\cdot}2.5H_2O$.

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