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Alcohols as electrophiles: iron-catalyzed Ritter reaction and alcohol addition to alkynes

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A R T I C L E I N F O

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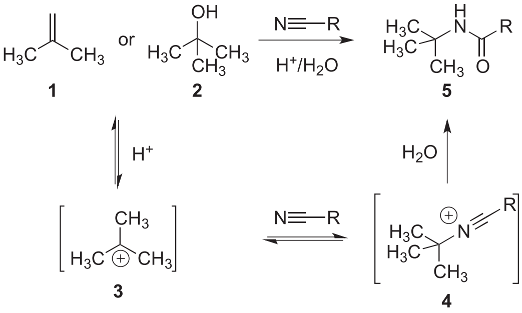
A simple, iron-based catalytic system allows for a straightforward method for the synthesis of primary, secondary, and tertiary amides. The system also allows the addition of benzyl alcohols across phenylacetylene to produce substituted phenyl ketones. This transformation improves and expands the substrate scope beyond that previously reported and proceeds under mild reaction conditions, tolerating air and moisture.

1. Introduction

The Ritter reaction, discovered at New York University in 1948,[1,2] offers a particularly atom-economical approach to the synthesis of amides (Scheme 1). In the traditional mechanistic paradigm, the reaction proceeds through the generation of a stable carbocation (e.g., **3**) followed by attack of the nitrile. The newly formed nitrilium ion (e.g., **4**) is then quenched by water to form the amide (e.g., **5**) after a tautomerization event. Since the Ritter reaction generally requires carbocation formation, it works best for the formation of sterically encumbered amides. Unfortunately, the traditionally harsh reaction conditions needed to form carbocations (e.g., stoichiometric sulfuric acid) limits the substrate scope of the reaction. Despite this limitation, the Ritter reaction has found widespread use in synthesis. For example, the Ritter reaction enabled the synthesis of aristotelone,[3] isocyanoallopupukeanane,[4] and Crixivan™.[5] Based on these critical applications, more broadly useful Ritter variants would be highly valuable to expand its use in synthesis.

The search for mild conditions capable of effecting a catalytic Ritter reaction resulted in the first Lewis acid-catalyzed Ritter reaction reported in 1994.[6] The amidation of secondary benzylic alcohols was catalyzed by 0.1–0.4 equiv of boron trifluoride etherate complex ($BF_3 \cdot OEt_2$) in good-to-excellent yields (Scheme 2). Secondary benzylic alcohols with electron-withdrawing groups, such as *p*-nitro, and secondary and tertiary aliphatic alcohols were unreactive under these conditions. In 2009, Cossy and co-workers reported an inexpensive, environmentally friendly Ritter reaction based on $FeCl_3 \cdot 6H_2O$ (Scheme 2).[7] This Ritter reaction provided the target amides in good yields, but the starting materials were limited to benzyl alcohols and *t*-butyl acetate as substrates. These reactions also required relatively high temperatures (150 °C).



Scheme 1. The Ritter reaction.

We recently reported the powerful dehydration properties of a $FeCl_3/AgSbF_6$ system in a formal Friedel–Crafts alkylation reaction.[8] Under our conditions, unactivated secondary alcohols were competent electrophiles in arene alkylation reactions for the first time and can provide enantioenriched products.[9] In an effort to further elucidate the utility of this catalytic system, we applied our conditions to the Ritter reaction. Here we report a general catalytic system for the Ritter reaction with acetonitrile.

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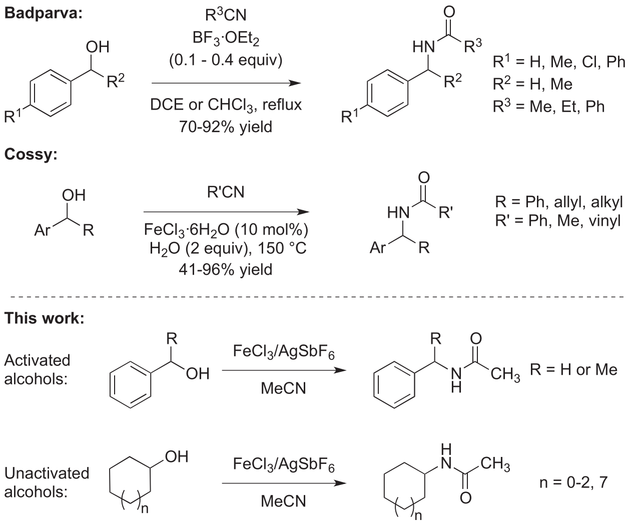


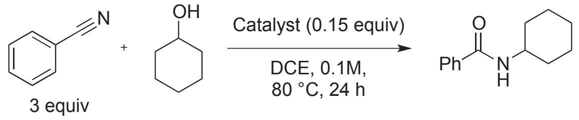
Scheme 2. Examples of Lewis acid-catalyzed Ritter reactions.

2. Results and discussion

2.1. The Ritter reaction

To test the viability of unactivated secondary alcohols in the Ritter reaction, cyclohexanol (**7c**) was treated with a variety of Lewis acids in dichloroethane at 80 °C (Table 1). As can be seen in Table 1, only iron(III) chloride (entry 1 and 2, Table 1), bismuth(III) triflate (entry 8, Table 1), and aluminum(III) chloride (entry 9, Table 1) provided detectable quantities of amide **8ac**. Since we have established that $AgSbF_6$ salts can dramatically increase the dehydrating power of $FeCl_3$,[8] the reaction was run with $FeCl_3$ in the presence of $AgSbF_6$ (entry 13, Table 1). To our delight, we observed the formation of amide **8ac** in 36% yield. Unfortunately, additional optimization studies did not provide higher yields.

Table 1
Examination of Lewis acids in the Ritter reaction



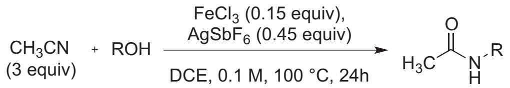
6a **7c** **8ac**

Entry	Catalyst	Yield %
1	$FeCl_3$	6
2	$FeCl_3 \cdot 6H_2O$	9
3	$FeCl_3$ w/3$AgSbF_6$	36
4	$FeCl_2$	0
5	$Fe(BF_4)_2 \cdot 3H_2O$	0
6	$FeF_3 \cdot 3H_2O$	0
7	$BiCl_3$	0
8	$Bi(OTf)_3$	19
9	$AlCl_3$	<5
10	CuOTf	0
11	$CuCl_2$	0
12	$ZnCl_2$	0
13	$AgSbF_6$	<5
14	$FeCl_3$ w/3$AgAsF_6$	18
15	$FeCl_3$ w/3$AgPF_6$	<5
16	$FeCl_3$ w/3AgOTf	<5
17	$FeCl_3$ w/3$AgNO_3$	0
18	$FeCl_3$ w/3AgOAc	0
19	$FeCl_2$ w/3$AgSbF_6$	7
20	$FeCl_3 \cdot 6H_2O$ w/3$AgSbF_6$	26
21	$FeF_3 \cdot 3H_2O$ w/3$AgSbF_6$	7
22	HCl[a]	<5
23	TfOH	<5
24	$pTSA \cdot H_2O$	<5
25	H_2SO_4	12
26	$HSbF_6$[b]	<5

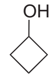
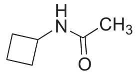
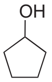
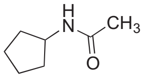
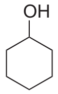
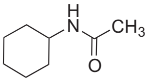
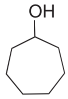
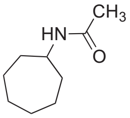
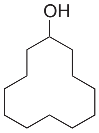
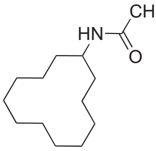
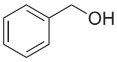
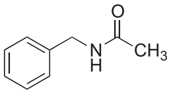
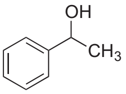
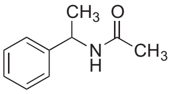
[a] 4.0 M in 1,4-dioxane.
[b] In 65–70% aqueous solution.

With the optimum conditions in hand, we explored the scope of the reaction of acetonitrile with various activated and unactivated alcohols (Table 2). We were pleased to find that our reaction conditions provided the desired Ritter products across a range of cyclic, secondary alcohols (entries 1–5, Table 2). Although benzyl alcohols represent a common substrate for the Ritter reaction,[10] primary benzylic alcohols remain rare.[6,10] Consequently, we were interested in comparing the reactivity of both primary and secondary benzylic alcohols. Both benzyl alcohol (**7f**) and 1-phenylethanol (**7g**) performed well in the reaction, returning products **8bf** and **8bg** in 83% and 87% yield, respectively. In cases where the reaction provides modest yields (e.g., entry 3, Table 3), increasing the catalyst loading to 25 mol % provides synthetically useful yields (e.g., 63% yield of **8bc**). Unfortunately, catalyst loadings higher than 25% did not provide any further improvements in yield. Consequently, these conditions provide a promising method for use in the Ritter reaction with activated and unactivated alcohols.

Table 2
Substrate scope of the Ritter reaction



6b **7** **8bx**

Entry	7		Product (8)		Isolated yield (%)
1		**7a**		**8ba**	Trace
2		**7b**		**8bb**	34
3		**7c**		**8bc**	36 63[a]
4		**7d**		**8bd**	37
5		**7e**		**8be**	23
6		**7f**		**8bf**	83
7		**7g**		**8bg**	87

[a] 25 mol % $FeCl_3$ and 75 mol % $AgSbF_6$ used.

To explore the Ritter reaction in the context of a medicinally important small molecule, we chose a new route to adamantadine.