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

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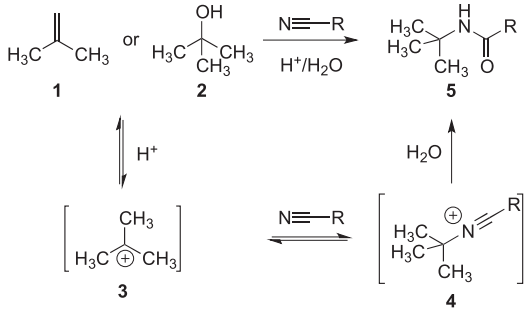
ABSTRACT

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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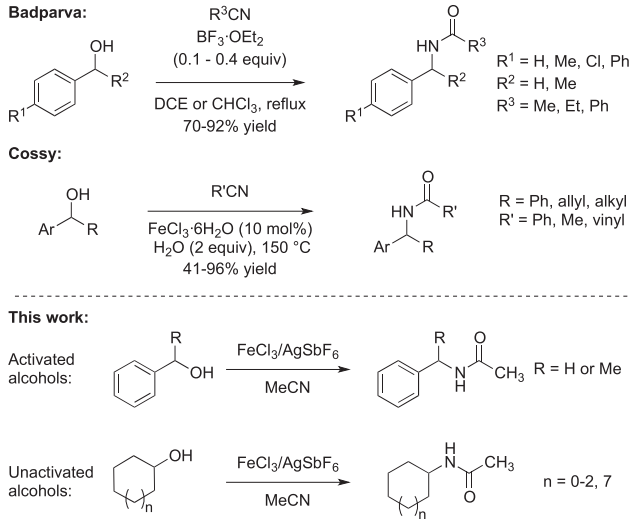


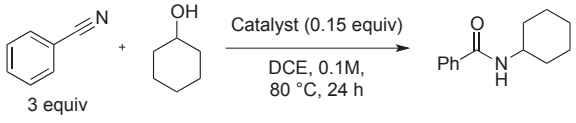
Scheme 2. Examples of Lewis acid-catalyzed Ritter reactions.

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



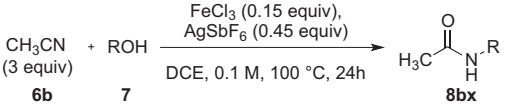
6a **7c** **8ac**

Entry	Catalyst	Yield %
1	$FeCl_3$	6
2	$FeCl_3·6H_2O$	9
3	$FeCl_3$ w/3$AgSbF_6$	36
4	$FeCl_2$	0
5	$Fe(BF_4)_2·3H_2O$	0
6	$FeF_3·3H_2O$	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	$FeCl_3·6H_2O$ w/3$AgSbF_6$	26
21	$FeF_3·3H_2O$ w/3$AgSbF_6$	7
22	HCl[a]	<5
23	TfOH	<5
24	pTSA·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



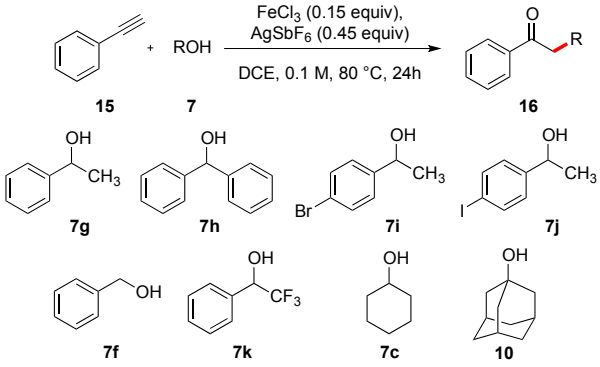
6b **7** **8bx**

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.

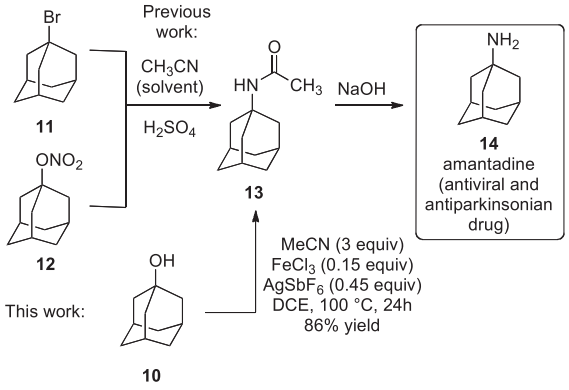
To explore the Ritter reaction in the context of a medicinally important small molecule, we chose a new route to adamantadine.

Table 3
Substrate scope of the alcohol addition to alkynes



Entry	ROH	Product	Isolated yield
1	**7g**	**16g**	60%
2	**7h**	**16h**	92%
3	**7i**	**16i**	95%
4	**7j**	**16j**	73%
5	**7f**	**16f**	50%
6	**7k**	**16k**	0%
7	**7c**	**16c**	0%
8	**10**	**16l**	72%

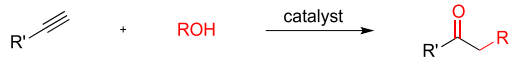
Adamantadine (**14**), originally approved for use against the Asian flu in 1966, is now used widely as both an antiviral and anti-parkinsonian drug.[11–14] While the drug has been prepared through the Ritter reaction, previous syntheses utilize 1-adamantyl bromide (**11**) and adamantyl-1-nitrate (**12**) as starting materials (Scheme 2). With the technology described above, we envisioned the use of 1-adamantol (**12**) directly in the synthesis of adamantadine. We were delighted to find the treatment of 1-adamantol (**10**) with catalytic $FeCl_3/AgSbF_6$ in the presence of 3 equiv of acetonitrile produced amide **14** in 86% yield (Scheme 3). This reaction avoids the use of oleum and large excess of acetonitrile. Due to the greater scarcity of acetonitrile supplies, this has become a considerable issue.



Scheme 3. The synthesis of amide **13**.

2.2. Benzyl alcohol addition to alkynes

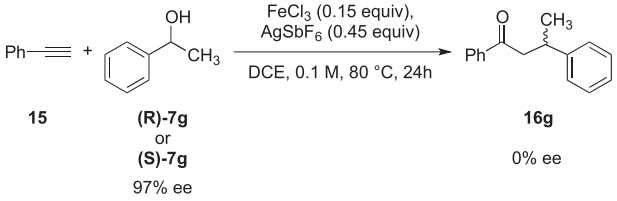
Another atom-economical reaction is the alcohol addition to alkynes (Scheme 4). In this reaction, loss of water leads to the formation of a new carbon–carbon bond followed by a hydration of an alkyne to provide ketone products. Such a reaction seemed ideally suited to demonstrate the capability of our new dehydration system. Cognizant of the recent report by Jana and co-workers describing the addition of benzyl alcohols to alkynes using $FeCl_3$ as the catalyst,[16] we were pleased to find our system provided significantly better yields.



Scheme 4. The addition of alcohols to alkynes.

As can be seen in Table 3, the reaction worked well with phenylacetylene and various benzylic alcohols. For substrates **7g** and **7h** (entries 1 and 2, Table 3), the addition of $AgSbF_6$ proved critical for high yields.[16] When election poor substrate **7k** was employed, the reaction recovered starting material. As a testament to the power of this new dehydration system, primary alcohol **7f** produced ketone **16f** in 50% yield (entry 6, Table 3) in contrast to previous reports where **7f** was unreactive.[16] Based on our experience with unactivated secondary alcohols,[8] cyclohexanol (**7c**) was subjected to the reaction conditions (entry 7, Table 3). Surprisingly, none of desired ketone **16c** was detectable in the reaction. While explanations for failure abound, one possibility is that the secondary alcohols do not pass through carbocation intermediates while benzylic alcohols access carbocations en route to product. Finally, adamantanol (**10**) also performed well in the reaction, providing adamatyl phenyl ketone **16l** in 72% yield (entry 8, Table 3).

As part of a cursory mechanistic investigation, enantioenriched alcohols (**R**)-**7g** and (**S**)-**7g** were subjected to the optimized reaction conditions (Scheme 5). The resulting phenyl ketone **16g** was isolated as a racemic mixture. The erosion of enantioenrichment is consistent with the intermediacy of benzylic carbocations. Based on these results, a mechanistic hypothesis is provided in Scheme 6.



Scheme 5. Racemization of enantioenriched **7g** under standard conditions.

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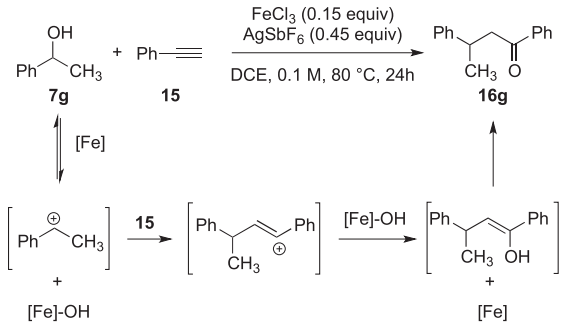

Scheme 6. A mechanistic hypothesis for alcohol addition to alkynes.

3. Conclusions

In conclusion, we present a simple method to access primary, secondary, and tertiary amides via the Ritter reaction. The powerful dehydration conditions also permit the addition of benzyl alcohols across phenylacetylene in significantly higher yields than previously reported. The reaction is simple and based on a low-cost iron catalyst. Further, it provides an atom-economical synthesis of amides and phenyl ketones.

4. Experimental section

4.1. *N*-Cyclohexylbenzamide (8ac)

To an oven dried 20 mL vial containing $FeCl_3$ (24.3 mg, 0.15 equiv) was added a solution of cyclohexanol (1 mmol) in DCE (10 mL) and allowed to stir until $FeCl_3$ was completely dissolved (10–15 min). To this solution was added the phenylnitrile (3 mmol, 3 equiv) immediately followed by the $AgSbF_6$ (154.6 mg, 0.45 equiv), which was then capped and put into mechanical shaker at 80 °C for 24 h. The reaction was quenched with water (30 mL) extracted with DCM (3×30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and silica chromatography (hexanes:EtOAc=9:1) to yield **8ac** (72.8 mg, 36%) as a yellow oil whose ^1H and ^{13}C NMR matches the reported spectra.[15] ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=7.4 Hz, 2H), 7.48 (t, J=7.3 Hz, 1H), 7.41 (t, J=7.5 Hz, 2H), 6.13 (s, 1H), 4.12–3.83 (m, 1H), 2.03 (d, J=9.4 Hz, 2H), 1.76 (dd, J=10.0, 3.6 Hz, 2H), 1.66 (dd, J=9.3, 3.7 Hz, 1H), 1.49–1.35 (m, 2H), 1.33–1.15 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 135.1, 131.2, 128.5, 126.9, 48.7, 33.2, 25.6, 24.9.

4.2. 2-(Adamantan-1-yl)-1-phenylethan-1-one (17i)

To an oven dried vial containing $FeCl_3$ (24.3 mg, 0.15 mmol) was added a solution of adamantanol (152.3 mg, 1 mmol) in DCE (10 mL) and allowed to stir until $FeCl_3$ was completely dissolved. To this solution was added phenylacetylene (0.17 mL, 1.5 mmol) immediately followed by the $AgSbF_6$ (154.6 mg, 0.45 mmol), which was then capped and put into a mechanical shaker at 80 °C for 24 h. The reaction was quenched with water (30 mL) extracted with DCM (3×30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated to give the residue. The residue was purified by silica flash chromatography using hexane and ethyl acetate (9:1) to give desired product *2-(adamantan-1-yl)-1-phenylethan-1-one* **16l** (184.2 mg, 72% yield) as a yellow oil; R_f (hexanes:EtOAc=9:1)=0.60; ν_{max} (liquid film) 2900, 2848, 1674 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 7.94 (d, J=7.3, 1.7 Hz, 2H), 7.58–7.50 (m, 1H), 7.45 (dd, J=8.4, 6.9 Hz, 2H), 2.72 (s, 2H), 1.94 (q, J=3.1 Hz, 3H), 1.74–1.59 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) 200.3, 138.9, 132.7, 128.4, 128.3, 51.2, 43.0, 36.7, 33.9, 28.7; HRMS: $C_{15}H_{22}$ requires 254.1671, found: 254.1666.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.072.

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