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$FeCl_3$-catalyzed Ritter reaction. Synthesis of amides

Bruno Anxionnat, Amandine Guérinot, Sébastien Reymond *, Janine Cossy *

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10, Rue Vauquelin, 75231 Paris Cedex 05, France

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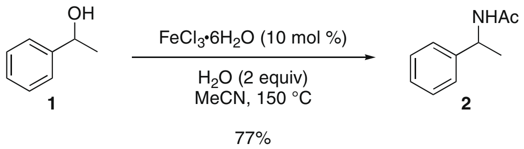
ABSTRACT

A safe and inexpensive synthesis of amides, from benzylic alcohols and nitriles and from *t*-butyl acetate and nitriles, using a Ritter reaction catalyzed by $FeCl_3·6H_2O$ is described.

The Ritter reaction is a well-known Name Reaction in which nitriles react with an in-situ generated carbocation to produce amides.[1] In recent examples, the Ritter reaction involving benzylic alcohols was found to be catalyzed by Brønsted acids,[2] Nafion[3] or Fe-Montmorillonite K10.[4] Furthermore, the Ritter reaction involving *tert*-butyl acetate was reported to be catalyzed by sulfuric acid[5] or bismuth triflate.[6] As it was recently demonstrated that $FeCl_3$ is able to activate benzylic alcohols to produce carbocation intermediates,[7–11] we have envisaged to synthesize amides from benzylic alcohols or *t*-butyl acetate by using a Ritter reaction catalyzed by $FeCl_3$.

When 1-phenylethanol (**1**) was treated with $FeCl_3·6H_2O$ (10 mol %) in MeCN at 150 °C for 30 min in the presence of water, amide **2** was produced. The best yield in **2**, 77%, was obtained when 2 equiv of water was added to the reaction medium (see Scheme 1).



Scheme 1.

The reaction is general and various benzylic amides were obtained using different nitriles and benzylic alcohols. The results are reported in Table 1. The reaction of **1** with PhCN led to the expected amide **6** in 54% isolated yield (Table 1, entry 1). Acrylonitrile appeared to be a suitable nitrile as **1** was transformed to the corresponding amide **7** in 66% yield (Table 1, entry 2). Benzhydrol **3** can also react smoothly with MeCN, PhCN and acrylonitrile to produce the corresponding amides **8**–**10** in 96%, 75% and 87% isolated yields, respectively (Table 1, entries 3–5). In the case of 1-phenyl-but-3-en-1-ol (**4**) (Table 1, entries 6 and 7), the $FeCl_3$-catalyzed Ritter reaction involving MeCN and acrylonitrile led to the expected amides in moderate yields (49% yield for **11** and 41% yield for **12**[12]) for a 90% conversion of **4**. It is worth noting that the formation of amide **13** from **5** and MeCN was only possible at 50 °C, and at higher temperatures, a complex mixture was observed (Table 1, entry 8).

In order to use nitriles as reagents, the Ritter reaction was examined in solvents such as $MeNO_2$, dioxane, toluene or cumene. The results are reported in Table 2. In $MeNO_2$ the transformation of **1** to **2**, by using 10 equiv of MeCN, in the presence of $FeCl_3·6H_2O$ (10 mol %) and water (2 equiv), at 110 °C or 50 °C was sluggish and the formation of many by-products was observed (Table 2, entries 1 and 2). On the contrary, when the reaction was performed at 110 °C in toluene or dioxane, a full conversion of **1** was observed after 6 h and **2** was isolated in 72% and 74% yields, respectively (Table 2, entries 3 and 4). Furthermore, when the reaction was achieved in cumene at 150 °C, after 1 h, the conversion of **1** was complete allowing the isolation of **2** in 73% yield (Table 2, entry 5).

The formation of ethers from benzylic alcohols in the presence of $FeCl_3$[10,11] or $Fe(NO_3)_3$[14] was previously observed. Similarly, during the course of the Ritter reaction involving **1**, the formation of ether **14** was observed at 70 °C, whereas at 150 °C, only amide **2** was produced. Furthermore, when ether **14** was treated at 150 °C under the previous established conditions [MeCN,

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* Corresponding authors. Tel.: +33 1 40 79 46 59; fax: +33 1 40 79 46 60 (J.C.).
E-mail addresses: sebastien.reymond@espci.fr (S. Reymond), janine.cossy@espci.fr (J. Cossy).

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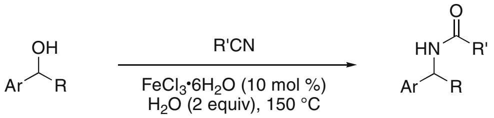
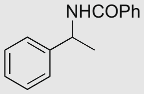
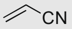
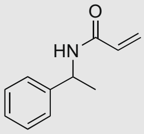
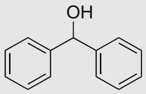
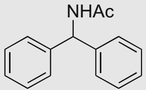
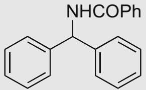
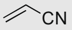
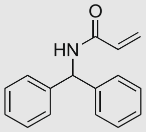
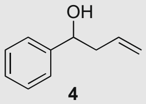
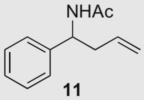
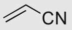
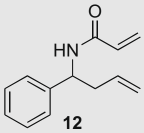
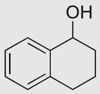
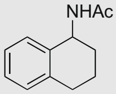
Table 1
Ritter reaction of various alcohols and nitriles catalyzed by $FeCl_3{\cdot}6H_2O$[13]



Entry[a]	Alcohol	Nitrile	Amide	Time (h)	Yield[b] (%)
1	**1**	PhCN	 **6**	1.0	54
2[c]	**1**	 	 **7**	1.0	66
3	 **3**	MeCN	 **8**	0.5	96
4	**3**	PhCN	 **9**	0.5	75
5[c]	**3**	 	 **10**	1.0	87
6	 **4**	MeCN	 **11**	4.5	49[e]
7[c]	**4**	 	 **12**	2.0	41[e]
8[d]	 **5**	MeCN	 **13**	15.0	52[e]

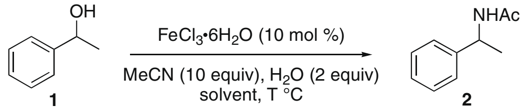
[a] Alcohol (1 mmol), nitrile (1 mL), 150 °C, sealed tube.
[b] Isolated yield.
[c] Alcohol (1 mmol), nitrile (3 equiv), cumene (1 mL), 150 °C, sealed tube.
[d] At 50 °C.
[e] 90% conversion.

$FeCl_3{\cdot}6H_2O$ (10 mol %), water (2 equiv), 150 °C], amide **2** was isolated in 75% yield (Scheme 2).

According to these results, it can be speculated that amide **2** can come from ether **14** as the latter can be polarized by $FeCl_3$ to gen-

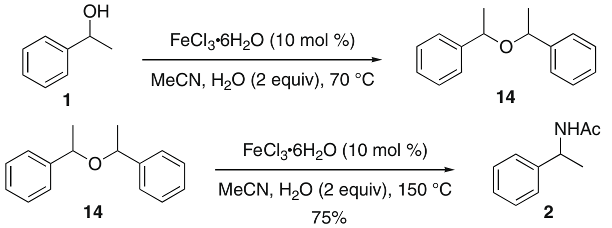
Table 2

$FeCl_3·6H_2O$-catalyzed Ritter reaction of **1** with MeCN in different solvents



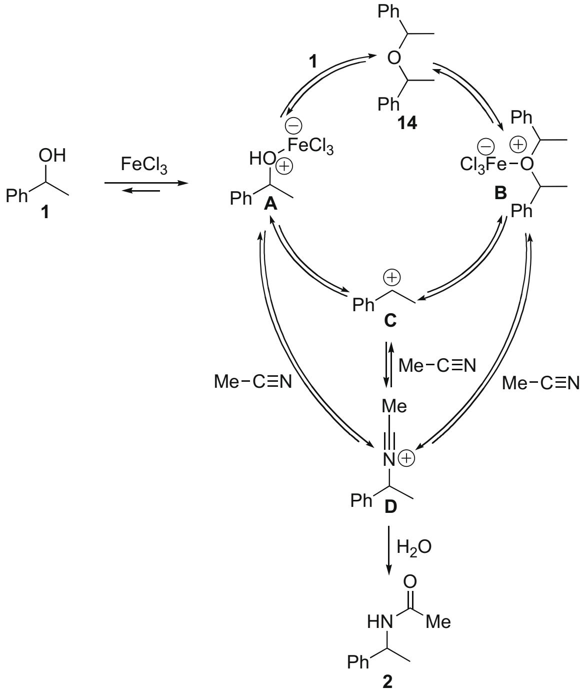
Entry[a]	Solvent	T (°C)	Time (h)	Conversion[c] (%)	Yield[d] (%)
1	$MeNO_2$	110	5.0	50	–
2	$MeNO_2$	50	5.0	6	–
3	Toluene	110	6.0	100	72
4	Dioxane	110	6.0	100	74
5[b]	Cumene	150	1.0	100	73

[a] Alcohol **4** (1 mmol), solvent (1 mL), sealed tube.
[b] Alcohol **4** (1 mmol), solvent (0.5 mL), sealed tube.
[c] Conversion of **4** determined by GC/MS.
[d] Isolated yield.

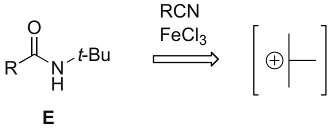


Scheme 2.

erate the benzylic carbocation **C** which can be trapped by MeCN. However, we cannot exclude that **A** or **B** can be attacked by MeCN to produce **D**, or that **A** can generate the carbocation **C** directly (Scheme 3).[11b]



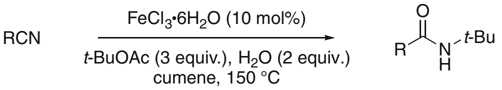
Scheme 3.

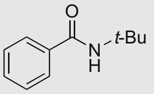
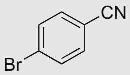
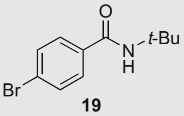
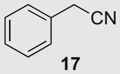
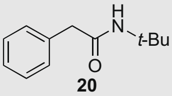
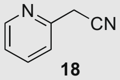
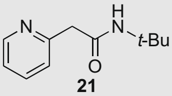


Scheme 4.

Table 3

Ritter reaction of various nitriles with *t*-butyl acetate catalyzed by $FeCl_3·6H_2O$[16]



Entry[a]	Nitrile	Amide	Time (h), yield[b] (%)
1	PhCN	 **15**	1.5, 69
2	 **16**	 **19**	1.0, 61
3	 **17**	 **20**	1.0, 65
4[c]	 **18**	 **21**	6.0, 45

[a] Nitrile (1 mmol), *t*-Bu-OAc (3 equiv), cumene (0.6 mL), 150 °C, sealed tube.
[b] Isolated yield.
[c] Nitrile (1 mmol), *t*-Bu-OAc (6 equiv), $FeCl_3·6H_2O$ (20 mol %), 150 °C, sealed tube.

As *tert*-butyl amides of type **E** can be valuable synthetic intermediates as they can be deprotected to the corresponding primary amides,[15] we turned our attention to the possible $FeCl_3$-catalyzed synthesis of amides **E** from nitriles and from a synthetic equivalent of the *tert*-butyl carbocation (Scheme 4).

At first, the generation of the *tert*-butyl cation from *t*-BuOH was examined. Disappointingly, when PhCN was treated with *t*-BuOH in the presence of $FeCl_3·6H_2O$ (10 mol %), a low conversion of PhCN was observed. However, *t*-butyl acetate appeared to be a better source of *t*-butyl carbocation (Table 3). The reaction of PhCN with *t*-BuOAc in cumene at 150 °C in the presence of $FeCl_3·6H_2O$ (10 mol %) produced amide **15** in 69% isolated yield (Table 3, entry 1), the reaction was stopped after 1 h (89% conversion of PhCN) as for longer reaction times, the degradation of amide **15** was observed. In the case of nitriles **16** and **17** (Table 3, entries 2 and 3), the expected amides **19** and **20** were isolated in 61% and 65% yields, respectively, and with nitrile **18**, the reaction was still possible but required 20 mol % of $FeCl_3·6H_2O$ and 6 equiv of *t*-BuOAc to produce **21** in 45% yield after 6 h (Table 3, entry 4).

In conclusion, we have described that $FeCl_3·6H_2O$ catalyzes the Ritter reaction of nitriles with benzylic alcohols as well as the Ritter reaction of nitriles with *t*-BuOAc producing, respectively, benzylic amides and *t*-butyl protected primary amides. This catalytic reaction is an inexpensive and eco-friendly process allowing the preparation of various amides that can be useful synthons.

Acknowledgement

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References and notes

1. (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045; (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.
2. See for recent examples: (a) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Guitérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642; (b) Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Eur. J. Org. Chem.* **2009**, 430.
3. Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 2661.
4. Lakouraj, M. M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* **2000**, *30*, 821.
5. (a) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453; (b) Baum, J. C.; Milne, J. E.; Murry, J. A.; Thiel, O. R. *J. Org. Chem.* **2009**, *74*, 2207.
6. Callens, E.; Burton, A. J.; Barrett, A. G. M. *Tetrahedron Lett.* **2006**, *47*, 8699.
7. Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913.
8. Rubenbauer, P.; Bach, T. *Adv. Synth. Catal.* **2008**, *350*, 1125.
9. Zhan, Z.-p.; Yu, J.-l.; Liu, H.-j.; Cui, Y.-y.; Yang, R.-f.; Yang, W.-z.; Li, J.-p. *J. Org. Chem.* **2006**, *71*, 8298.
10. Salehi, P.; Iranpoor, N.; Kargar Behbahani, F. *Tetrahedron* **1998**, *54*, 943.
11. (a) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858; (b) Jana, U.; Biswas, S.; Maiti, S. *Eur. J. Org. Chem.* **2008**, 5798; (c) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065; (d) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160.
12. It is worth noting that an amide of type **12** is a suitable substrate for Ring Closing Metathesis (RCM). See: Fiorelli, C.; Savoia, D. *J. Org. Chem.* **2007**, *72*, 6022.
13. *Typical experimental procedure*: A mixture of alcohol (1 mmol), nitrile (1 mL) and $FeCl_3 \cdot 6H_2O$ (10 mol %, 27 mg) was placed in a sealed tube and warmed to 150 °C. The reaction medium was concentrated and diluted with AcOEt (4 mL) and H_2O (0.5 mL). Celite was added and the mixture was filtered and dried over Na_2SO_4 to furnish the desired amides. When necessary, the obtained amides were purified by flash chromatography.
14. Namboordiri, V. V.; Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 8839.
15. Mahalingam, A. K.; Wu, X.; Alterman, M. *Tetrahedron Lett.* **2006**, *47*, 3051.
16. *Typical experimental procedure*: A mixture of nitrile (1 mmol), *t*-Bu-OAc (3 mmol), cumene (0.6 mL) and $FeCl_3 \cdot 6H_2O$ (10 mol %, 27 mg) was placed in a sealed tube and warmed to 150 °C. The reaction medium was concentrated and diluted with AcOEt (4 mL) and H_2O (0.5 mL). Celite was added and the mixture was filtered and dried over Na_2SO_4. The obtained *t*-butyl amides were purified by flash chromatography.