Tetrahedron Letters 51 (2010) 4827–4829

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$HBF_4{\cdot}OEt_2$ as a mild and versatile reagent for the Ritter amidation of olefins: a facile synthesis of secondary amides

B. V. Subba Reddy *, N. Sivasankar Reddy, Ch. Madan, J. S. Yadav

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 22 May 2010
Revised 1 July 2010
Accepted 6 July 2010
Available online 8 July 2010

Keywords:
Ritter amidation
Alkenes
Nitriles
$HBF_4{\cdot}OEt_2$
α-Aryl ethyl amides

ABSTRACT

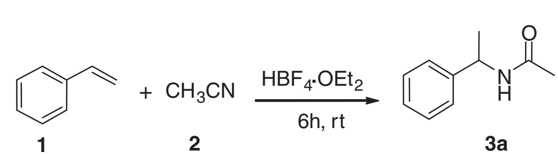
A variety of alkenes undergo smooth amidation with nitriles in the presence of $HBF_4{\cdot}OEt_2$ at room temperature under mild conditions to afford the corresponding secondary amides in good to excellent yields. This is a highly efficient method for the preparation of α-aryl ethyl amides especially from vinyl arenes without any side reactions such as olefin polymerization. The use of readily available and easy to handle reagent $HBF_4{\cdot}OEt_2$ makes this method simple, convenient, and practical.

The conversion of hydroxyl groups into amides is often known as the Ritter reaction which is one of the most direct and important methods for the introduction of an amino functionality onto an organic molecule.[1] Generally, strong acids such as sulfuric acid and formic acid are known to catalyze this reaction.[2] In order to circumvent serious side reactions in the sulfuric acid approach, several modifications and improvements have been made and the protic acid is often replaced by Lewis acids.[3] A variety of Lewis acids such as $AlCl_3$, $FeCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ have been used for the selective amidation of benzyl alcohols.[4] Subsequently, solid acid catalysts such as clays, rare earth exchanged HY-zeolite, and heteropoly acids have also been utilized for the conversion of alcohols into amides.[5] Although a variety of acid catalysts have been explored for the amidation of alcohols, only a few catalysts are known for the amidation of olefins with nitriles.[6] Recently, various modifications of the original Ritter reaction have also been reported for the amidation.[7] In particular, haloamidation of olefins, Betti–Ritter reaction, Mannich–Ritter reaction, and Prins–Ritter reaction are noteworthy.[8] However, to the best of our knowledge, there have been no reports on the amidation of olefins with nitriles using $HBF_4{\cdot}OEt_2$.

Following our interest on the use of $HBF_4{\cdot}OEt_2$ in organic synthesis,[9] we herein report a versatile and mild alternative method for the synthesis of secondary amides from olefins and nitriles using a ethereal solution of tetrafluoroboric acid. Initially, we have attempted the coupling of styrene (**1**) with acetonitrile (**2**) using $HBF_4{\cdot}OEt_2$ under neat conditions. The reaction went to completion in 6 h at room temperature and the corresponding *N*-(1-phenylethyl)acetamide **3a** was isolated in 85% yield (Scheme 1).

This result encouraged us to extend this process to various alkenes and nitriles. Interestingly, various vinyl arenes such as *p*-chloro-, *p*-methyl-, and *p*-*tert*-butyl styrenes underwent smooth coupling with nitriles to give the corresponding *N*-(1-arylethyl)acetamide derivatives in high yields (Table 1, entries b–g). This method is also effective for sterically hindered substrates such as, for example, 2-vinyl naphthalene (Table 1, entry l). Furthermore, dihydronaphthalene and indene also participated well in this reaction (Table 1, entries k and m). In the case of dihydronaphthalene, indene, and vinyl arenes, the nitrile attacked the benzylic position (Table 1, entries a–m). Next, we examined the reaction of cycloalkenes with nitriles under similar conditions. For example, the treatment of cyclohexene and cyclopentene with acetonitrile in the presence of $HBF_4{\cdot}OEt_2$ gave 1-acetamidocylohexane and 1-acetamidocyclopentane respectively in good yields (Table 1, entries n and o, Scheme 2).

Other nitrile derivatives such as benzonitrile, benzyl cyanide, and acrylonitrile also underwent smooth addition on styrene to give the corresponding α-phenylethyl amide derivatives in high

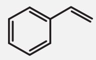
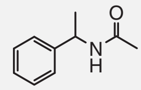
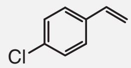
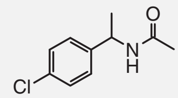
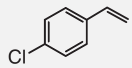
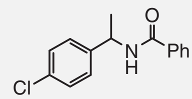
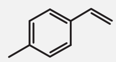
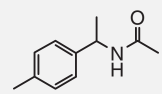
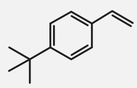
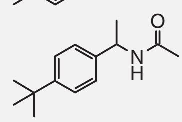
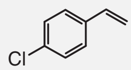
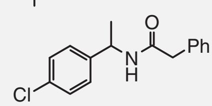
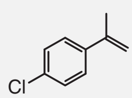
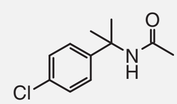
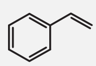
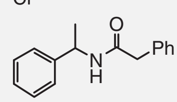
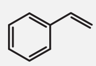
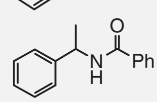
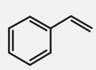
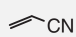
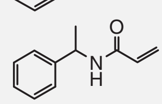
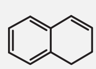
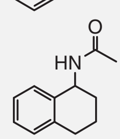
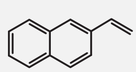
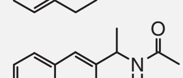
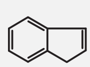
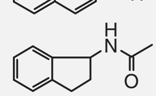
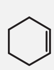
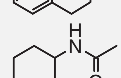
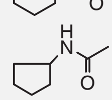


Scheme 1. Preparation of *N*-(1-phenylethyl)acetamide.

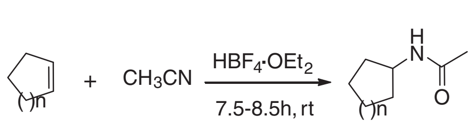
* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: basireddy@iict.res.in (B.V. Subba Reddy).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.032

Table 1
Direct synthesis of amides from olefins and nitriles using $HBF_4{\cdot}OEt_2$

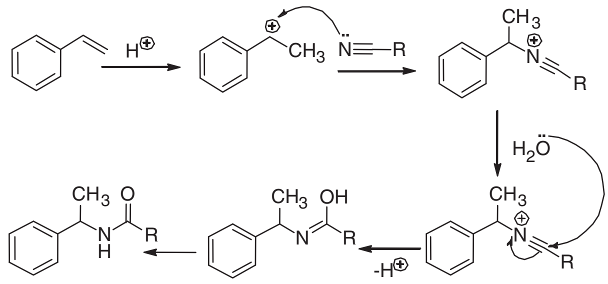
Entry	Olefin (**1**)	Nitrile (**2**)	Product (**3**)[a]	Time (h)	Yield[b] (%)
a		CH_3CN		6.0	85
b		CH_3CN		7.0	80
c		PhCN		6.5	82
d		CH_3CN		6.5	85
e		CH_3CN		7.0	90
f		$PhCH_2CN$		7.5	89
g		CH_3CN		6.5	80
h		$PhCH_2CN$		7.0	91
i		PhCN		6.5	85
j				6.0	81
k		CH_3CN		7.0	85
l		CH_3CN		8.0	75
m		CH_3CN		8.0	70
n		CH_3CN		7.5	72
o		CH_3CN		8.5	70

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2. Preparation of cyclohexyl and cyclopentyl acetamides.

yields (Table 1, entries c, f, h, i and j). Furthermore, α-substituted styrene also reacted well with acetonitrile under identical conditions (Table 1, entry g). However, no reaction was observed in the absence of $HBF_4{\cdot}OEt_2$ even after an extended reaction time (12 h). In all cases, the reactions proceeded rapidly at room temperature under mild conditions and the products were obtained in good to excellent yields. As shown in Table 1, this method works well with both terminal as well as internal olefins. In all cases, secondary amides were obtained exclusively without the formation of any side products such as fluorinated compounds under the



Scheme 3. A plausible reaction mechanism.

present reaction conditions. The scope and generality of this process is illustrated with respect to various alkenes and nitriles and the results are presented in Table 1.[10]

Mechanistically, we assume that the reaction likely proceeds via the protonation of alkene by $HBF_4{\cdot}OEt_2$. The resulting carbocation might be trapped by nitrile to give the nitrilium cation which subsequently reacts with water to furnish the desired amide as shown in Scheme 3.

In summary, we have developed a simple, convenient, and efficient method for the preparation of secondary amides by means of amidation of olefins with nitriles using $HBF_4{\cdot}OEt_2$. This method offers significant advantages including mild conditions, simplicity of the reagent, and no formation of by-products. This method provides an easy access to a wide variety of secondary amides.

Acknowledgment

N.S.R. and Ch.M. thank Director, IICT, for the financial assistance.

References and notes

1. (a) Ritter, J. J.; Minier, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045; (b) Krimen, L. I.; Cota, D. J. *Org. React. (NY)* **1969**, *17*, 213.
2. (a) Top, S.; Jaouen, G. *J. Org. Chem.* **1981**, *46*, 78; (b) Garcia Martinez, A.; Martinez Alvarez, R.; Teso Vilar, E.; Garcia Fraile, A.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581; (c) Barton, D. H. R.; Magnus, P. D.; Young, R. N. *J. Chem. Soc., Chem. Commun.* **1973**, 331; (d) Barton, D. H. R.; Magnus, P. D.; Garbarino, J. A.; Young, R. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2101; (e) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453.
3. Kacan, M.; McKillop, A. *Synth. Commun.* **1993**, *23*, 2185.
4. Firouzabadi, H.; Sardarian, A. R.; Badparva, H. *Synth. Commun.* **1994**, *24*, 601.
5. (a) Kumar, H. M. S.; Reddy, B. V. S.; Anjaneyulu, S.; Reddy, E. J.; Yadav, J. S. *New J. Chem.* **1999**, *23*, 955; (b) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642; (c) Yadav, J. S.; Reddy, B. V. S.; Pandurangam, T.; Reddy, Y. J.; Gupta, M. K. *Catal. Commun.* **2008**, *9*, 1297; (d) Wang, G. W.; Shen, Y. B.; Wu, X. L. *Eur. J. Org. Chem.* **2008**, 4367.
6. (a) Trost, B. M.; Fleming, I.; Martin, F. In *Comprehensive Organic Synthesis*; Pergamon press: Oxford, 1991; Vol. 4, p 292; (b) Clarke, T.; Devine, J.; Dicker, D. W. *J. Am. Oil. Chem. Soc.* **1964**, *41*, 78.
7. Cazorla, C.; Métay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 6855.
8. (a) Rawal, G. K.; Kumar, A.; Tawar, U.; Vankar, Y. D. *Org. Lett.* **2007**, *9*, 5171; (b) Yeung, Y. Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644; (c) Yadav, J. S.; Reddy, B. V. S.; Chary, D. N.; Chandrakanth, D. *Tetrahedron Lett.* **2009**, *50*, 1136; (d) Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 788; (e) Bahulayan, D.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 5735; (f) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Kumar, G. G. K. S. N.; Madhavi, C.; Kunwar, A. C. *Tetrahedron* **2008**, *64*, 3025; (g) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Reddy, G. M. *Tetrahedron Lett.* **2007**, *48*, 4903.
9. (a) Yadav, J. S.; Reddy, B. V. S.; Anusha, B.; Reddy, U. V. S.; Reddy, V. V. B. *Tetrahedron Lett.* **2010**, *51*, 2872; (b) Yadav, J. S.; Reddy, B. V. S.; Ramesh, K.; Kumar, G. G. K. S. N.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 1578.
10. *Typical procedure*: a mixture of styrene (1 mmol), acetonitrile (1 mmol), and $HBF_4{\cdot}OEt_2$ complex (1 mmol) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by the purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5–9.5) gave the pure *N*-(1-phenylethyl)acetamide. The products thus obtained were characterized by IR, NMR, and mass spectroscopy. Spectral data for selected compounds: compound **3a**: *N-(1-phenylethyl)acetamide*: pale yellow solid, mp 63–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H), 5.84 (br s, 1H), 5.07 (m, 1H), 1.94 (s, 3H), 1.49 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 143.2, 128.4, 127.1, 126.1, 48.6, 23.1, 21.6; IR (KBr): ν 3265, 1644, 1552, 1447, 1374, 700 cm^{-1}; EIMS: m/z: 163 $[M]^+$. Compound **3b**: *N-(1-(4-chlorophenyl)ethyl)-acetamide*: white solid, mp 89–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.36 (m, 4H), 5.57 (br s, 1H), 5.0–5.16 (m, 1H), 1.96 (s, 3H), 1.47 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 141.7, 132.8, 128.6, 127.4, 48.1, 23.2, 21.6; IR (KBr): ν 3293, 1648, 1551, 1369, 828, 738 cm^{-1}; EIMS: m/z: 197 $[M]^+$. Compound **3h**: *(2-phenyl-N-(1-phenylethyl)acetamide*: white solid, mp 93–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10–7.36 (m, 5H), 5.51 (br s, 1H), 5.02–5.13 (m, 1H), 3.53 (s, 2H), 1.39 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 142.9, 129.2, 128.8, 128.4, 127.1, 125.8, 48.6, 43.7, 21.7; IR (KBr): ν 3313, 1647, 1532, 1245, 698; EIMS: m/z: 240 $[M+H]^+$.