Safe and Efficient Ritter Reactions in Flow

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Abstract: Efficient mixing, temperature control and small environmental exposures allow reactions carried out in microfluidic devices to perform superior to their batch-type counterparts in conventional flasks. The Ritter reaction has been optimised for flow conditions leading to short reaction times and higher yields and also is more feasible with regards to safety, productivity and tolerance towards substrate functionalities.

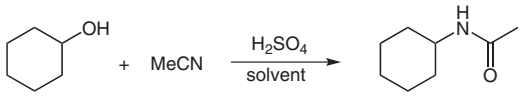
Key words: amide, carbocation, microreactor, Ritter Reaction, safety

One of the foremost advantages of microflow procedures in synthetic chemistry is the superior kinetic and thermodynamic control over the course of a reaction when compared to the batch process. Microfluidic mixing has been proven to be much more efficient and quicker than even rapid stirring in a flask. Additionally, the dimensions of the microstructured devices together with the flow rate can allow very short and very accurately adjusted reaction times. Thermodynamic control is facilitated as the large surface to volume ratio of the microreactor leads to optimal temperature exchange between the surrounding heat/cold source and the reactor. Constant reaction temperature can be easily implemented and the development of unwanted hotspots, which might occur in a flask, is suppressed. Therefore microreactors can help to gain better control over the avoidance or promotion of parallel and consecutive reactions, and recent publications have summarised these efforts.[1]

The Ritter reaction involves the nucleophilic attack of a nitrile or cyanide onto a carbenium ion and a subsequent hydrolysis resulting in the formation of amides.[2] Carbenium ions can be generated either from alkyl alcohols or alkenes by protonation. The generation of primary carbenium ions is difficult except for benzylic alcohols. The use of other primary alcohols is very limited and requires rigorous reaction conditions.[3] Secondary and tertiary alcohols are best suited as starting materials in the Ritter reaction, which serves as an excellent tool for the oxygen-to-nitrogen conversion. Very strong acidic conditions, hazards such as toxicity, especially for the use of cyanides, and the large exothermic character of the reaction are of concern especially when operating on a large scale, where the latter aspect allows the occurrence of hot-spots or even thermodynamic runaways. The problems appear to rise significantly with increasing batch size.[4] Several interesting protocols have been published recently that demonstrate strategies to improve and optimise the process, such as the use of mild Lewis acids or microwave irradiation[5] and diastereoselective Ritter reactions using trifluoromethanesulfonic acid in dichloromethane have been described[6] as well as fluoro Ritter reactions in microreactors.[7] Best conversions are achieved with excess of concentrated sulfuric acid, i.e. the conditions of the original work.[8] The Ritter reaction is therefore a challenging subject for microreactor technology[9] and we report herein that this approach is advantageous with regards to safety, productivity and tolerance towards substrate functionalities.

Secondary and tertiary alcohols are protonated relatively easily under strongly acidic conditions and the resulting carbocations can then be attacked by nucleophiles. Nitriles and cyanides are very good nucleophiles under these conditions and quickly form resonance-stabilised nitrilium ions which, after hydrolysis, result in the corresponding amides. The direct synthesis of tertiary amines from their corresponding alcohols is one of the less accessible conversions in modern organic chemistry despite the fact that tertiary amines are very important building blocks in the fine chemical and polymer industry.[10]

Initial optimisations were performed by reacting cyclohexanol (**1**) with acetonitrile to afford *N*-cyclohexylacetamide (**2**; Scheme 1). Solvents that have been described in the literature to be useful for Ritter reactions are nitrobenzene, dioxane, and acetic acid.



1 **2**

Scheme 1 Ritter reaction of cyclohexanol (**1**) with acetonitrile

The reaction was performed at 90 °C and with a residence time of about ten minutes. The results were analysed qualitatively with GC–MS. Use of nitrobenzene as solvent gave traces of the desired product, dioxane led to approximately 5–10% conversion to the desired amide with mainly cyclohexanol being recovered and acetic acid showed **2** as the main product with some cyclohexylamine. Dioxane and acetic acid both led to clean conver-

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sion without notable side products but it appeared that dioxane would require much longer reaction times; whereas the occurrence of cyclohexylamine in the acetic acid mixture indicates that shorter reaction times should be possible using this solvent. Therefore, all subsequent reactions were carried out in acetic acid as fast reactions can profit most from microreactor technology (Figure 1).

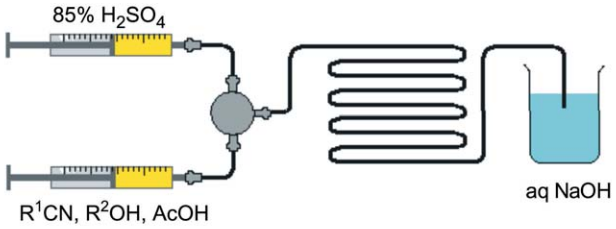
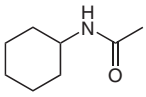
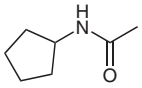
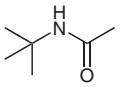
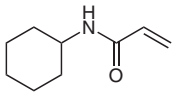
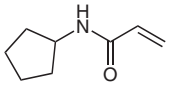
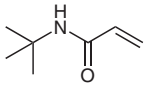
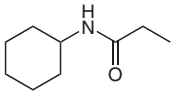
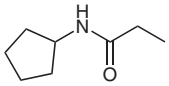
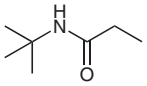
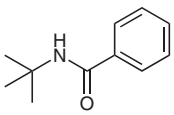


Figure 1 Set-up of a Ritter reaction in flow

Concentrated sulfuric acid is the most effective acid for Ritter reactions (Figure 1). Lewis acids such as BF_3 led to the exclusive formation of acetic acid cyclohexyl ester and not **2**. A protocol with short reaction times leading to reasonable yields (Table 1) was established based on the original findings that included reaction times of only two to ten minutes with heating to 45 °C for tertiary and 85 °C for secondary alcohols (benzyl alcohol showed distinctly lower selectivity and was not found to be effective). Under these conditions very clean products were obtained, usually without the need for further purification, although crystallisation from hexane–dichloromethane was performed in some cases. As concentrated sulfuric acid is used, PEEK tubing and mixers were not compatible. Teflon micromixers[11] were shown to be much more reliable for these reaction conditions[12] and they show long-term reliability as well.

The combination of simple alcohols and nitriles resulted in the synthesis of the corresponding amides in good yields (Table 1, entries 1–10). The very short reaction times allowed a departure from the classical substrates for Ritter reaction and some unexpected functional groups were tolerated, such as esters (Table 2, entry 1), ethers (Table 2, entry 2) as well as aryl and alkyl halides (Table 2, entries 3–5) and the amide products were formed in good yields. The use of cyanide salts under acidic conditions is often avoided and the development of one-pot protocols to enable such reactions is important.[13] The use of cyanides appears to be particularly promising in microreactor chemistry because they offer a safe alternative to the hazards in the large-scale batch use of hydrogen cyanide and heat. The formamides produced in these reactions are of high value as they can easily be cleaved and several publications report mild reaction conditions for such conversions.[14] The established protocol was slightly altered for this purpose. Sufficient water was added to the solution of starting materials to allow the sodium cyanide to dissolve completely and to ensure that sodium sulfate, which has a lower solubility, does not precipitate

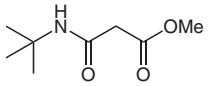
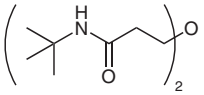
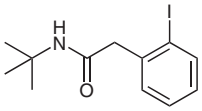
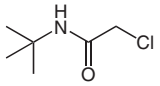
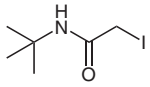
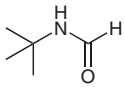
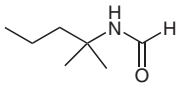
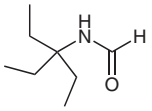
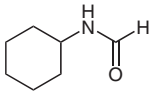
Table 1 Simple Ritter Reactions in Flow

Entry	Nitrile (1 equiv)	Alcohol (1 equiv)	Product	Yield (%)
1	MeCN	cyclohexanol	 **2**	69
2	MeCN	cyclopentanol	 **3**	65
3	MeCN	*t*-BuOH	 **4**	62
4	acrylonitrile	cyclohexanol	 **5**	76
5	acrylonitrile	cyclopentanol	 **6**	79
6	acrylonitrile	*t*-BuOH	 **7**	74
7	propionitrile	cyclohexanol	 **8**	62
8	propionitrile	cyclopentanol	 **9**	58
9	propionitrile	*t*-ButOH	 **10**	64
10	benzonitrile	*t*-BuOH	 **11**	66

in the reactor and cause a blockage. Tertiary alcohols reacted readily and cleanly under the optimised conditions and afforded the corresponding formamides in reasonable yields with fast reaction times and more safely than in a batch process (Table 2, entries 6–8). Secondary alcohols only give the corresponding acetates. This is surprising because with nitriles conversions were comparable to those when using tertiary alcohols. Other solvent systems did not improve the situation.

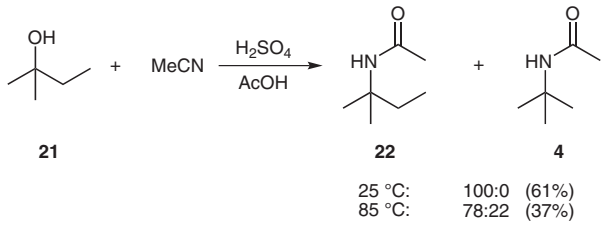
The reaction of 2-methyl-2-butanol (**21**) with acetonitrile under the optimised reaction conditions produced amide **22** in 61% yield. If the same reaction was performed at

Table 2 Advanced Ritter Reactions in Flow

Entry	Nitrile (1 equiv)	Alcohol (1 equiv)	Product	Yield (%)
1	Methyl 2-cyanoacetate	*t*-BuOH	 **12**	64
2	bis(2-cyanoethyl)ether	*t*-BuOH (2 equiv)	 **13**	36
3	2-iodophenyl acetonitrile	*t*-BuOH	 **14**	80
4	chloroacetonitrile	*t*-BuOH	 **15**	73
5	iodoacetonitrile	*t*-BuOH	 **16**	61
6	NaCN (1.5 equiv)	*t*-BuOH	 **17**	81
7	NaCN (1.5 equiv)	2-methyl-2-pentanol	 **18**	68
8	NaCN (1.5 equiv)	3-ethyl-3-pentanol	 **19**	64
9	NaCN (1.5 equiv)	cyclohexanol	 **20**	63

higher temperatures, a side product was observed (up to 8%, Scheme 2). This side product was identified to be **4** and apparently resulting from Ritter reaction of acetonitrile with a *tert*-butyl cation.

We found this partial degradation of substrate **21** in reactions with several nitriles. However, the transfer of these reaction conditions (85 ºC) to a batch process resulted, only in decomposition and polymerisation.



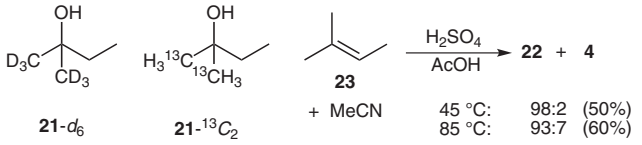
Scheme 2 Ritter reaction of 2-methyl-2-butanol (**21**) with acetonitrile

This unusual loss of a methylene group is not easily explained. The driving force for this side reaction is most likely the high stability of the *tert*-butyl cation intermediate.[15] We assume that the cleavage of the terminal carbon–carbon bond in the ethyl moiety leads to the formation of the *tert*-butyl cation as cleavage of any other carbon–carbon bond would require a subsequent rearrangement or migration.

To find proof for this assumption, we synthesised the deuterated compound **21**-d_6 by addition of ethylmagnesium iodide to acetone-d_6. However, Ritter reaction of **21**-d_6 with acetonitrile generated reaction products **22** and **4** with zero to six deuterated positions due to scrambling under the strong acidic conditions. The ^{13}C-labelled com-

pound **21**-$^{13}C_2$ was prepared by addition of ^{13}C-methylmagnesium iodide to methyl propanoate. Ritter reaction of this furnished **22** and **4** with either no or two ^{13}C labels.

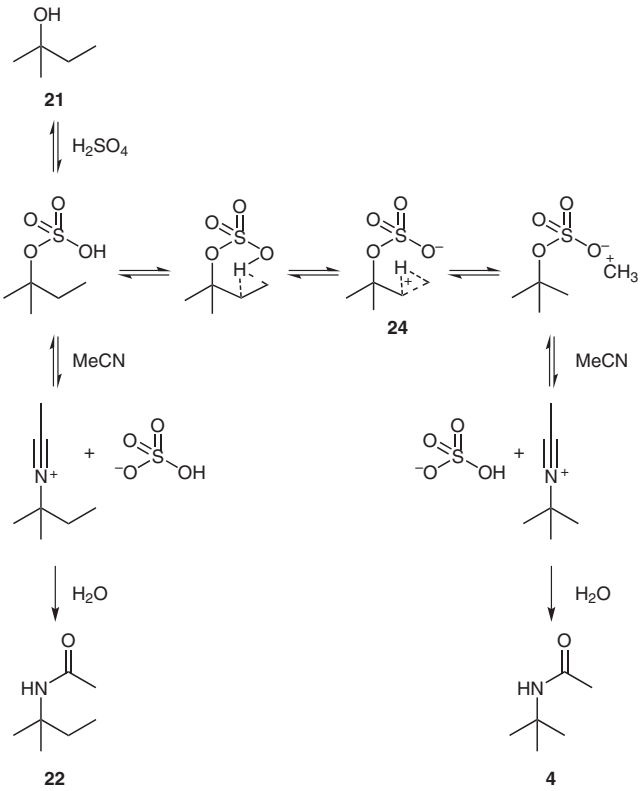
Additional evidence came from the reaction using 2-methyl-2-butene (**23**) as a starting material (Scheme 3). Similar product ratios were obtained using the microreactor setup, whereas only product **22** was formed in 66% yield when the reaction was performed as a batch process.



Scheme 3 Ritter reaction of 2-methyl-2-butene (**23**) with acetonitrile

It has been reported that methane and methyl radicals eliminate from small radical cations of alkanes when formed in a mass spectrometer, but a considerable amount of energy is required for the initial formation of the radical cation.[16] A more conclusive explanation could be an acid-catalysed cracking. This can occur via either a carbenium or a carbonium ion. In the first case, classical bimolecular cracking occurs via a hydride transfer from the adduct alkane to a smaller carbenium ion or a Lewis acid followed by β-scission. The latter case has been observed in superacids at low temperatures or with solid Lewis acid catalysts (zeolites) at very high temperatures.[17] The temperature difference is normally associated with the necessity to compensate for the lower pH levels of the solid acids. We cannot be sure that our reaction conditions of heated and rather concentrated sulfuric acid are sufficient to allow the formation of carbonium ions.

The dominance of any of these mechanisms in a certain process has been found to be highly dependent upon the set-up conditions and parameters. However, often several mechanisms can be assumed to occur concurrently.[18] The classic pathway via the carbenium ion would involve the β-scission directly after the dehydroxylation and would give one equivalent of isobutene and a methyl cation. Isobutene would be immediately protonated and give **4** (Scheme 4), but the existence of methyl cations in the reaction mixture should lead to the formation of the corresponding amide which has not been detected. The existence of a carbonium transition state would imply the protonation of the *tert*-pentyl cation to form a dication. This species is considered to be surprisingly stable in the gas phase as described in a recent and detailed theoretical investigation.[19] Additionally, the stabilisation of the cation with a hydrogen sulfate ion is possible and could, in this case, improve charge separation and stabilise the transition state. The decomposition of the dication would most likely result in the elimination of a methane equivalent. This would coincide with our observation of gas formation in the microreactor under these conditions, however, two positive charges would remain on the *tert*-



Scheme 4 Possible reaction mechanism for the generation of **4** from alcohol **21**

butyl moiety and it is not clear how a necessary hydride transfer to form the *tert*-butyl cation could be sustained under these conditions. Considering the very harsh conditions, the selectivity of this process is high as only the side product **4** and the main product **22** are formed. However, a definitive mechanistic description of the side reaction still eludes us.

In conclusion, we have described the fast synthesis of amides and formamides as important building blocks in synthesis by minimising the hazards involved in the classical Ritter reaction under microfluidic conditions.

Acknowledgment

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References and Notes

(1) (a) *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, **2008**. (b) *Flash Chemistry*; Yoshida, J.-I., Ed.; Wiley: Chichester, **2008**.
(2) Bishop, R. In *Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 261–300.
(3) Lebedev, M. Y.; Erman, M. B. *Tetrahedron Lett.* **2002**, *43*, 1397.

(4) (a) Chang, S.-J. *Org. Process Res. Dev.* **1999**, *3*, 232. (b) Baum, J. C.; Milne, J. E.; Murray, J. A.; Thiel, O. R. *J. Org. Chem.* **2009**, *74*, 2207.
(5) (a) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Gutierrez, J. M.; Rodrígez, F. *Eur. J. Org. Chem.* **2007**, 4642. (b) Veverková, E.; Toma, S. *Chem. Pap.* **2005**, *59*, 8.
(6) Rubenbauer, P.; Bach, T. *Chem. Commun.* **2009**, 2130.
(7) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611.
(8) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.
(9) Poechlauer, P.; Kotthaus, M.; Vorbach, M.; Deak, M.; Zich, T.; Marr, R. PCT Int. Appl. WO 2006125502, **2006**.
(10) Szmant, H. H. *Organic Building Blocks of the Chemical Industry*; John Wiley & Sons: New York, **1989**.
(11) The micromixing device 'Comet X-01', available from Techno Applications Co., Ltd, 34-16-204, Hon, Denenchofu, Oota, Tokyo 145-0072, Japan, was used.
(12) Syringe A was loaded with 85% H_2SO_4 (5 mL). Syringe B was loaded with alcohol (6 mmol) and nitrile (6 mmol), diluted with acetic acid to 5 mL. The PTFE micromixer and the attached PTFE tubing (2 m, 0.5 mm inner diameter) were inserted into the heating bath and the temperature was adjusted to 45 °C (85 °C for secondary alcohols). The flow rate was set at 0.1 mL/min (reaction time: 3 min). The crude product was quenched by dropping into excess of ice–2 M NaOH. After the reaction, the tube was flushed with EtOAc and the crude mixture was washed with aq 2 M NaOH (80 mL) and EtOAc (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure.
Selected Spectroscopic Data:
3,3′-Oxybis[*N*-(*tert*-butyl)propanamide] (**13**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 18 H, Me), 2.34 (t, 4 H, *J* = 6.0 Hz, CH_2), 3.66 (t, 4 H, *J* = 6.0 Hz, CH_2), 5.85 (s, 2 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.8, 37.8, 51.0, 67.1, 170.2. EI–MS: *m*/*z* (%) = 272 [M$^+$](3), 257 (48), 242 (6), 229 (3), 217 (49), 207 (7), 200(100), 183 (18). HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{29}N_2O_3$: 273.2173; found: 273.2177. IR (neat): 3549, 3460, 3330, 3067, 2979, 2927, 2897, 1664, 1639, 1547, 1455, 1361, 1227, 1109 cm^{-1}.
N-(*tert*-Butyl)-2-(2-iodophenyl)acetamide (**14**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 9 H, Me), 3.61 (s, 2 H, CH_2), 5.22 (s, 1 H, NH), 6.98 (m, 1 H, ArH), 7.34 (m, 2 H, ArH), 7.86 (d, 1 H, *J* = 7.7 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.7, 49.6, 51.4, 101.0, 128.8, 128.9, 130.8, 138.8, 139.8, 168.6. EI–MS: *m*/*z* (%) = 318 [M$^+$](4), 302 (13), 281 (4), 262 (28), 244 (100), 232 (6). HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}INO$: 318.0349; found: 318.0349. IR (neat): 3378, 3276, 2972, 2960, 1643, 1552, 1466, 1448, 1417, 1360, 1341, 1288, 1259, 1155, 1014 cm^{-1}.
(13) Jirgensons, A.; Kauss, V.; Kalvinsh, I.; Gold, M. R. *Synthesis* **2000**, 1709.
(14) Ge, Y.; Hu, L. *Tetrahedron Lett.* **2007**, *48*, 4585.
(15) Kato, T.; Reed, C. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2908.
(16) (a) Hudson, C. E.; McAdoo, D. J. *Int. J. Mass Spectrom.* **2002**, *214*, 315. (b) Traeger, J. C.; McAdoo, D. J.; Hudson, C. E.; Giam, C. S. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 21. (c) Bowen, R. D.; Harrison, A. G. *Org. Mass Spectrom.* **1981**, *16*, 180. (d) Wendelboe, J. F.; Bowen, R. D.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 2333.
(17) (a) Xu, T.; Haw, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 7753. (b) Lercher, J. A.; van Santen, R. A.; Vinek, H. *Catal. Lett.* **1994**, *27*, 91. (c) Yang, S.; Kondo, J. N.; Domen, K. *Chem. Commun.* **2001**, 2008.
(18) (a) Boronat, M.; Corma, A. *Appl. Catal. A* **2008**, *336*, 2. (b) Kotrel, S.; Knözinger, H.; Gates, B. C. *Microporous Mesoporous Mater.* **2000**, *35-36*, 11. (c) Hunter, K. C.; East, A. L. L. *J. Phys. Chem. A* **2002**, *106*, 1346. (d) Williams, B. A.; Ji, W.; Miller, J. T.; Snurr, R. Q.; Kung, H. H. *Appl. Catal. A* **2000**, *203*, 179.
(19) Olah, G. A.; Prakash, G. K. S.; Rasul, G. *Dalton Trans.* **2008**, 521.