THE RITTER REACTION IN LIQUID SULFUR DIOXIDE

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INTRODUCTION

Ritter reaction is associated with a one-pot process for amide bond formation, that involves nitrile and a group, capable of giving a relatively stable carbenium ion (originally - alcohol or alkene) in strongly ionizing acidic medium.[1] The classical Ritter reaction involves use of at least stoichiometric amounts of a corrosive Brønsted acid (i.e., conc. H_2SO_4), thus often limiting its applicability to compounds containing acid labile functional groups.[2] Nevertheless because of its atom economy and easy application Ritter reaction proved to be useful in synthesis of different biological molecules and pharmaceuticals.[3] Over past two decades a huge progress has been made in development of catalytic variations of the Ritter reaction.[4]

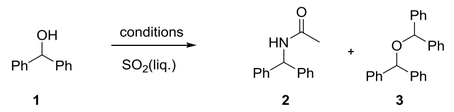
SO_2 is a colorless, non-combustible gas, that makes up about one part per billion (ppb) by volume in atmosphere. It has also found its application as a food preservative, for example, as an antioxidant and anti-microbial in wine manufacture. Gaseous SO_2 can be easily liquefied to give a colorless, mobile liquid ($SO_{2(liq.)}$) with relatively low vapor pressure (about 3 bar at 20 ^oC), that can be used as a commercially acceptable solvent or reagent for synthetic chemistry preparations.[5] Unique characteristics of $SO_{2(liq.)}$ as a reaction medium has previously been observed by P. Walden[6] and G. A. Olah.[7] One of such properties that was found particularly attractive is the ability to facilitate formation of carbenium ions.[8]

Having regard of the aforementioned unique properties of $SO_{2(liq.)}$ as a solvent reported we became interested in possible application of $SO_{2(liq.)}$ as a solvent for the Ritter reaction. To the best of our knowledge the sole example of the Ritter reaction that was carried out in $SO_{2(liq.)}$ refers to work of Bakke and Knudsen,[9] who studied dicyclopentadiene-derived carbenium ion rearrangements during the Ritter reaction and concluded that in $SO_{2(liq.)}$ the reaction can be performed at lower temperature with well-defined configuration of resulting nitrile adduct.

RESULTS AND DISCUSSIONS

In order to investigate the ability of $SO_{2(liq.)}$ to advance the formation of carbenium ions and further Ritter reaction without using any Lewis or Brønsted acidic additives benzhydryl alcohol (**1**) was exposed to $SO_{2(liq.)}$ as a solvent at elevated temperatures (Table 1). As a result formation of corresponding ether (**3**) was observed by GC-MS. However, in presence of 5 equivalents of acetonitrile however full conversion to Ritter product was observed, hence amide **1** was isolated in excellent yield.

Table 1. Ritter reaction of benzhydryl alcohol in $SO_{2(liq.)}$ in the absence of catalyst



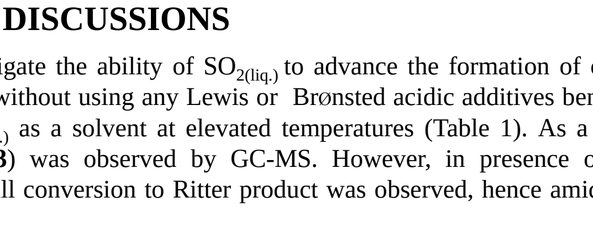
1 **2** **3**

Entry	Time (h)	Temperature (^oC)	Conditions[a]	Conversion, % **2** (GC-MS)	Conversion, % **3** (GC-MS)
1	29	+150	-	0	89
2	24	+150	MeCN (5 equiv.)	>99 (97[b])	0

[a] reactions were performed in a pressure reactors; [b] isolated yield.

To evaluate the capability of various Brønsted and Lewis acids to catalyze the Ritter reaction in $SO_{2(liq.)}$ solution, benzyl alcohol (**4**) was treated with variety of potential catalysts in the presence of 5 equivalents of acetonitrile at 60 ^oC. Product composition was determined by GC-MS (Table 2). The formation of dibenzyl ether (**7**) was also observed during the course of these reactions. The latter is considered to be an active intermediate capable of generating carbenium ion in reaction medium, that is further converted into desired Ritter reaction product.

Table 2. Catalyst screening for the Ritter reaction of benzyl alcohol in $SO_{2(liq.)}$

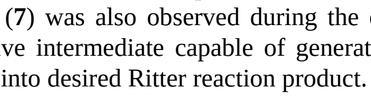


Entry	Catalyst[a]	Time (h)	Conversion, % **6** (GC-MS)	Conversion, % **7** (GC-MS)
1	TfOH	30	47	25
2	H_2SO_4[b]	26	48	27
5	$FeCl_3 \cdot 6H_2O$[c,d]	16	31	20
6	$Cu(OTf)_2$	28	36	31
7	**$In(OTf)_3$**	**23**	**68 (57[e])**	**21**
8	$Sc(OTf)_3$	23	23	18
9	$Al(OTf)_3$	23	47	18
10	$Bi(OTf)_3$	22	52	22
11	$Fe(OTf)_3$	21	55	23

[a] reactions were performed in a pressure reactors at 60 ^oC if not stated otherwise; [b]0.5 equiv; [c]90 ^oC; [d]Benzyl chloride was verified as a side product of the reaction; [e]isolated yield.

It was found that conventional Brønsted acids along with inorganic triflates provided best results. $In(OTf)_3$ showed obvious preference over other catalysts in terms of conversion and therefore was used for further investigations. To demonstrate the superiority of combination of $SO_{2(liq.)}$ with selected Lewis and Brønsted acids, the latter were employed also with AcOH and MeCN as solvents (Table 3). Results verified our expectations, proving that better conversion can be achieved when $SO_{2(liq.)}$ as a solvent compared to more conventional conditions for the Ritter reaction.

Table 3. Screening of various conditions for the Ritter reaction of benzyl alcohol with acetonitrile.



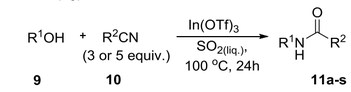
Entry	Catalyst[a]	Time (h)	Solvent	Conversion, % **6** (GC-MS)	Conversion, % **7** (GC-MS)	Conversion, % **8** (GC-MS)
1	H_2SO_4	28	AcOH[b]	0	0	100
2	H_2SO_4	27	MeCN[c]	9	3	-
3	$Al(OTf)_3$	24	AcOH[b]	0	0	100
4	$Al(OTf)_3$	23	MeCN[c]	19	10	-
5	$In(OTf)_3$	24	AcOH[b]	0	0	100
6	$In(OTf)_3$	24	MeCN[c]	2	0	-

[a] under atmosphere of argon; [b]0.2 M in **4**; [c]0.2 M in **4** (excess of acetonitrile).

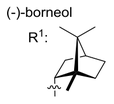
Further we investigated reactivity of various secondary and tertiary alcohols in our newly developed catalytic conditions of the Ritter reaction ($In(OTf)_3/SO_{2(liq.)}$).

For the purpose of full conversion to the desired amides all reactions were carried out at +100 ^oC. Results are summarized in Table 4. Different secondary and tertiary alcohols were subjected to our newly developed catalytic conditions. No more than 20 mol-% (down to 5-mol% in the case of **11a** and **11b**) of catalyst was necessary to afford desired *N*-alkyl amides in yields up to 97%.

Table 4. $In(OTf)_3$ catalyzed Ritter reaction in $SO_{2(liq.)}$.



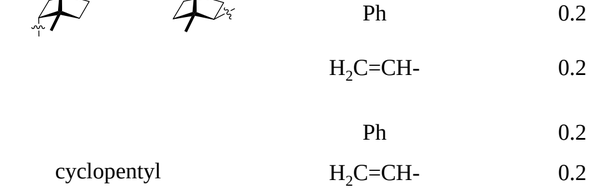
9 **10** **11a-s**

Entry[b]	R^1	R^2	$In(OTf)_3$ (equiv.)	Amide, yield
1		Ph	0.05	**11a**, 82%
2		Me	0.05	**11b**, 85%
3		Me	0.1	**11c**, 86%
4		H_2C=CH-	0.1	**11d**, 83%
5		$ClCH_2$-	0.1	**11e**, 79%
6		Ph	0.1	**11f**, 80%
7		*n*-Pr	0.1	**11g**, 79%
8	(-)-borneol R[1]:  *rac*-product R[1]: 	Me	0.2	**11h**, 87%
9		$ClCH_2$-	0.2	**11i**, 71%
10		Ph	0.2	**11j**, 66%
11		H_2C=CH-	0.2	**11k**, 68%
12		Ph	0.2	**11l**, 60%
13	cyclopentyl	H_2C=CH-	0.2	**11m**, 48%
14		$ClCH_2$-	0.2	**11n**, 71%
15		Ph	0.2	**11o**, 61%
16	cyclohexyl	H_2C=CH-	0.2	**11p**, 26%
17		$ClCH_2$-	0.2	**11q**, 66%
18		Ph	0.2	**11r**, 96%
19		$ClCH_2$-	0.2	**11s**, 97%

[a] reactions were performed in a pressure reactors; [b] in case of entries 1-7 5.0 equivalents of nitrile was used and in case of entries 8-19 3.0 equivalents of nitrile was used.

N-Adamantyl amides **11c-g** were obtained in excellent yields using only 10 mol-% of $In(OTf)_3$. Synthesis of amides **11c** and **11e**[10] can be viewed as particularly useful, since those are considered as precursors of antiviral and anti-parkinsonian drug Amantadine.[11] Interestingly less activated secondary alcohols can also be subjected to the Ritter reaction using $In(OTf)_3/SO_{2(liq.)}$ catalytic system to give desired amides in good to excellent yields (Table 4, entries 12, 14, 17). It was proved experimentally, that excess of nitrile has to be decreased to 3 equivalents and catalyst loading must be increased to 20 mol-% in order to achieve full conversion in similar conditions. 2-Adamantanol proved to be the most viable substrate among tested secondary alcohols and, consequently, amides **11r** and **11s** were isolated in almost quantitative yields (Table 4, entries 18, 19).

Relative stereochemistry of borneol-derived Ritter products **11h** and **11i** (Table 4, entries 8, 9) was determined by single crystal X-Ray analysis (Figure 1). Also the latter showed that the isolated single crystals belong to the racemic group. To the best of our knowledge there has been no previous reports on obtaining amides **11h-k** through direct Ritter reaction of L-(-)-borneol with nitriles.



11h **11i**

Figure 1. X-Ray structures of Ritter products of L-(-)-borneol

In conclusion, we have discovered that the Ritter reaction can profit from being run in liquid sulfur dioxide as a solvent. $In(OTf)_3$ was found to be the best catalyst among the tested catalytic additives. $SO_{2(liq.)}$ as a reaction medium plays a crucial role in facilitating the Ritter reaction and shows apparent preference over conventional solvents in terms of catalytic activity of different Lewis and Brønsted acidic additives. Other synthetic processes that can profit from the use of $SO_{2(liq.)}$ as reaction medium is underway in our laboratory and will be reported elsewhere.

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