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(P_2O_5/SiO_2): a useful heterogeneous alternative for the Ritter reaction

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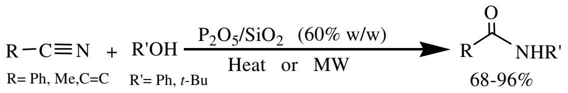
Abstract—Tertiary alcohols as well as primary and secondary benzylic alcohols react efficiently with nitriles to give the corresponding amides in good to excellent yields in the presence of P_2O_5/SiO_2 (60% w/w).

The Ritter reaction is an important carbon–nitrogen bond forming reaction used to prepare *N-tert*-butyl amides which are important amine precursors and pharmaceuticals.[1,2] The reaction of tertiary or benzylic alcohols with nitriles in concentrated sulfuric acid is known classically as the Ritter reaction. Some alternative acidic reagents used for this purpose are $(CF_3SO_2)_2O$,[3] $BF_3 \cdot Et_2O$,[4] $Fe(ClO_4)_3/SiO_2$,[5] $MeSO_3H/Al_2O_3$,[6] Nafion-H,[7] $CoCl_2/Ac_2O$,[8] Fe^{3+}-K10 montmorillonite,[9] heteropoly acids,[10] zeolites[11] and triflic anhydride.[12] Recently, modified Ritter reactions of nitriles have been reported using $Ph_2C^+ClSbCl_6^-$,[13] tertiary esters,[14] or trimethylsilyl cyanide[15] instead of alcohols or nitriles, respectively. However, disadvantages include limited applications of the reported methods and therefore, new versions of the Ritter reaction have been developed to overcome these drawbacks.

Heterogeneous organic reactions have been recently performed with immobilized reagents on solid supports. These procedures have advantages such as cleaner reactions, easier work up, reduced reaction times and eco-friendliness. These considerations are currently driving our efforts to develop heterogeneous organic transformations,[16] and herein we report a simple alternative procedure for the Ritter reaction to provide various amides using a mixture of (60% w/w) P_2O_5 and SiO_2 (Scheme 1).



Scheme 1.

P_2O_5/SiO_2 is more stable, less hygroscopic with much more activity than unsupported P_2O_5, and has been prepared via grinding 1.2 g of P_2O_5 and 0.8 g of preheated SiO_2 in a mortar for 1 min to give a homogeneous mixture. P_2O_5/silica gel has been used in acylation,[17,18] Fries-rearrangements,[19] protection and deprotection of aldehydes[20] or alcohols,[21] nitration,[22] oxidation[23] and Beckmann or Schmidt rearrangements.[24a,b]

Initially, in order to evaluate the efficiency of various acidic reagents in the Ritter reaction, we investigated their activities in a model reaction between acetonitrile (1.1 equiv) and benzyl alcohol (1 equiv) at 100 °C (Table 1). Among the acids screened, a mixture of P_2O_5 and silica gel (60% w/w) was found to be superior (Table 1, entry 11). The applicability of the present method to a large scale process was examined with 50 mmol of benzyl alcohol and acetonitrile which gave *N*-benzylacetamide in 88% yield.

The generality and scope of this new protocol was demonstrated by subjecting a wide range of secondary and primary benzylic alcohols, bearing both electron withdrawing and donating substituents, and *tert*-butanol, to the reaction with acetonitrile under these conditions.[25] In most cases, the reactions proceeded cleanly and the desired amides were obtained in good yields (Table 2, entries 1–9). The Ritter reaction of simple secondary alcohols with acetonitrile in the presence of P_2O_5/SiO_2 (60% w/w) afforded the corresponding

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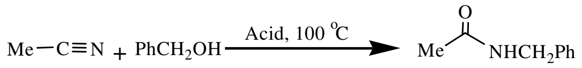
Table 1. Ritter reaction of benzyl alcohol with acetonitrile in different acidic media



Entry	Acid	Time (h)	Yield[a,b] (%)
1	H_2SO_4	5	50
2	$BF_3{\cdot}Et_2O$	8	53
3	CH_3SO_3H	8	60
4	CH_3SO_3H/Al_2O_3	5	82
5	NH_2SO_3H	5	55
6	Silica sulfuric acid	8	67
7	$H_3PW_{12}O_{40}$	5	75
8	P_2O_5	3.5	78
9	$P_2O_5/MeSO_3H$	5	75
10	P_2O_5/SiO_2(75% w/w)	2.5	91[c]
11	P_2O_5/SiO_2(60% w/w)	3	93
12	P_2O_5/Al_2O_3 (25% w/w)	8	55[c]
13	P_2O_5/Al_2O_3(60% w/w)	2.5	78[c]
14	P_2O_5/Al_2O_3(75% w/w)	2	80[c]
15	P_2O_5/Al_2O_3(50% w/w)	5	70
16	P_2O_5/SiO_2(50% w/w)	5.5	78

[a] Isolated yield.

[b] The products were isolated by addition of water (10 ml) and extraction with ethyl acetate (10 ml).

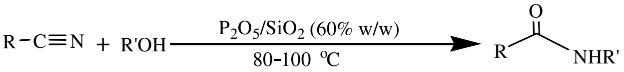
[c] Dibenzyl ether was also formed as a side product.

amides in moderate yields (30–68%). No Ritter reaction took place with simple primary alcohols.

Benzonitrile and acrylonitrile gave the desired products in good yields under similar conditions (Table 2, entries 10–18). Similarly, we have applied the present methodology for the amidation of malononitrile and found that the conversion to the corresponding bisamides was highly dependent on steric factors due to the alcohols. Thus, *tert*-butyl alcohol gave the desired bisamide, whereas benzyl alcohol afforded a mixture of four products containing both mono and bismalonoamides (Table 2, entries 19 and 20). Heterocyclic nitriles such as 3 or 4-cyanopyridine remained completely unreactive and no amides were formed even after 12 h.

The feasibility of microwave assisted[26] Ritter reactions of various alcohols in the presence of 60% w/w P_2O_5/SiO_2 was also demonstrated (Table 2, entries 1–4 and 11–14) under microwave irradiation using an unmodified domestic MW oven at 475 W for 120 s. Almost all of the alcohols were rapidly converted into the corresponding amides in yields comparable to the thermal conditions in very short times. The acceleration of the reaction under microwave irradiation may be rationalized on the basis of the high polarity of the reaction mix-

Table 2. P_2O_5/SiO_2 mediated Ritter reaction of alcohols with nitriles at ambient temperature[a]



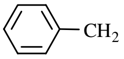
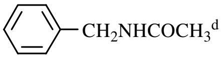
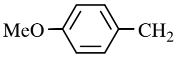
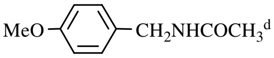
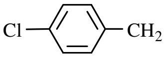
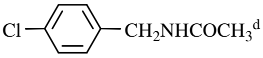
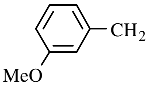
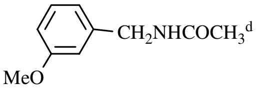
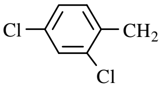
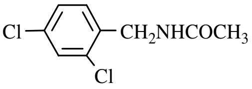
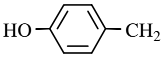
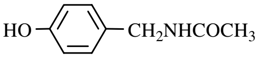
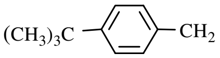
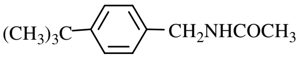
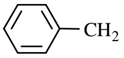
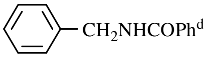
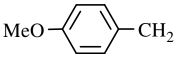
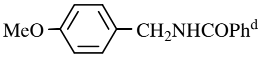
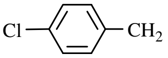
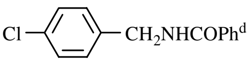
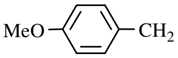
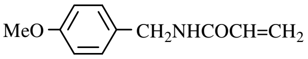
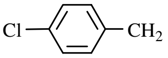
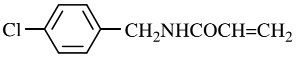
Entry	R	R′	Temperature (°C)	Product	Time (h)/yield[c] (%)	References
1	CH_3[b]		100	 [d]	2.5/92	6
2	CH_3[b]		90	 [d]	2/91	5
3	CH_3[b]		90	 [d]	3/88	27
4	CH_3[b]		90	 [d]	3/85	27
5	CH_3		100		2.5/78	28
6	CH_3[b]		90		1.5/91	27
7	CH_3[b]		100		3/91	28
8	CH_3[b]	$(CH_3)_3C$–	100	$(CH_3)_3C$–$NHCOCH_3$	2.5/90	28
9	CH_3[b]	Ph_2CH	100	Ph_2CH–$NHCOCH_3$	3/96	5
10	Ph	Ph_2CH	80	Ph_2CH–NHCOPh	3/68	5
11	Ph		90	 [d]	3.5/90	29
12	Ph		80	 [d]	3.5/73	29

Table 2 (*continued*)

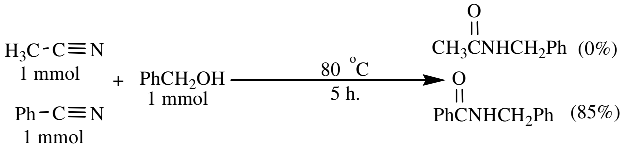
Entry	R	R′	Temperature (°C)	Product	Time (h)/yield[c] (%)	References
13	Ph		90		4.5/84	5
14	Ph	$(CH_3)_3C$–	100	$(CH_3)_3C$–NHCOPh	2.5/92	30
15	C=C	$(CH_3)_3C$–	90	$(CH_3)_3C$–NHCOCH=CH_2	3/88	28
16	C=C	$PhCH_2$	90	$PhCH_2NHCOCH=CH_2$	3/90	6
17	C=C		80		3/89	28
18	C=C		90		4/93	28
19	$CNCH_2$–	$(CH_3)_3C$	80	$(CH_3)_3CNHCOCH_2CONHC(CH_3)_3$	3/89	28
20	$CNCH_2$–	$PhCH_2$	80	Mixture of products	—	—

[a] The alcoholic substrate (1 mmol) was stirred with nitrile (1 mmol) in the presence of 0.2 g of freshly prepared P_2O_5/SiO_2 (60% w/w) under neat conditions at 50–100 °C.

[b] Acetonitrile (1.2 mmol) was used.

[c] Isolated yields.

[d] These alcohols underwent microwave assisted Ritter reaction using an unmodified domestic MW oven at 475 W for 120 s and produced the corresponding amides in comparable yields to thermal conditions. All products are known and were identified by their melting points, IR and in some cases ^{1}H NMR spectra.



Scheme 2.

tures. The results obtained show that P_2O_5/SiO_2 (60% w/w) provides an excellent heterogeneous media for the Ritter reaction both under thermal conditions or microwave irradiation.

Additionally, the chemoselectivity of the reaction was evaluated via competitive P_2O_5/SiO_2-catalyzed Ritter reaction of benzyl alcohol (1 mmol) with a mixture of benzonitrile and acetonitrile. It was found that benzonitrile reacted with benzyl alcohol in high yield and selectively in the presence of acetonitrile and that the reaction temperature extensively affected the chemoselectivity (Scheme 2). However, no chemoselectivity was observed for benzyl alcohol versus benzhydrol.

In conclusion, this simple efficient P_2O_5/SiO_2-catalyzed Ritter reaction offers several advantages including generality and simplicity, easy work up, clean reactions, scale up, selectivity and improved yields.

Acknowledgement

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References and notes

1. (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045; (b) Benson, F. R.; Ritter, J. J. *J. Am. Chem. Soc.* **1949**, *71*, 4128.
2. Samguigni, J. A.; Levins, R. *J. Med. Chem.* **1964**, *7*, 573.
3. Garcia Martinez, A.; Martinez Alvarez, R.; Teso Vilar, E.; Garcia Fraile, A.; Hanach, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581.
4. Firouzabadi, H.; Sardarian, A. R.; Badparva, H. *Synth. Commun.* **1994**, 601.
5. Salehi, P.; Rostamian Motlagh, A. *Synth. Commun.* **2000**, 671.
6. Sharghi, H.; Niknam, Kh. *Iran J. Chem. Chem. Eng.* **1999**, *18*, 36.
7. Olah, G. A.; Yamato, T.; Lyer, S. *Mater. Chem. Phys.* **1987**, *17*, 21.
8. (a) Mukhopadhyay, M.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *J. Org. Chem.* **1995**, *60*, 2670; (b) Mukhopadhyay, M.; Iqbal, J. *J. Org. Chem.* **1995**, *62*, 1843.
9. Lakourag, M. M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* **2000**, 821.
10. Okuhara, T.; Chen, X.; Matsuda, H. *Appl. Catal. A: Gen.* **2000**, *200*, 109.
11. Chen, X.; Okuhara, T. *J. Catal.* **2002**, *207*, 194.
12. (a) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077; (b) Justribo, V.; Colombo, M. I. *Tetrahedron Lett.* **2003**, *44*, 8023.
13. Barton, D. H. R.; Magnus, P. D.; Garbarino, J. A.; Young, R. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2101.
14. Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453.
15. Chen, H. G.; Goel, O. P.; Kesten, S.; Knobelsdrof, J. *Tetrahedron Lett.* **1996**, *37*, 8129.
16. Tamaddon, F.; Amrollahi, M. A.; Sharafat, L. *Tetrahedron Lett.* **2005**, *46*, 7841.
17. (a) Eshghi, H.; Rafei, M.; Karimi, M. *Synth. Commun.* **2001**, 771; (b) Hajipour, A. R.; Zarei, A.; Khazdooz, L.; Pourmoousavi, S. A.; Mirjalili, B. F.; Ruoho, A. E. *Phosphorus Sulfur Silicon* **2005**, *180*, 2029.
18. Eshghi, H.; Rafei, M.; Gordi, Z.; Bohloli, M. *J. Chem. Res. (s)* **2003**, *12*, 763.
19. (a) Eshghi, H.; Gordi, Z. *Phosphorus Sulfur Silicon* **2005**, *180*, 1553; (b) Eshghi, H.; Shafieyoon, P. *J. Chin. Chem. Soc.* **2005**, *52*, 155.
20. Eshghi, H.; Shafieyoon, P. *Phosphorous Sulfur Silicon* **2004**, *179*, 2149.

21. Eshghi, H.; Shafieyoon, P. *J. Chem. Res. (s)* **2004**, *12*, 802.
22. Hajipour, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2005**, *46*, 8307.
23. Hajipour, A. R.; Koshki, B.; Ruoho, A. E. *Tetrahedron Lett.* **2005**, *46*, 5503.
24. (a) Eshghi, H.; Hassankhani, A. *Synth. Commun.* **2006**, 2211; (b) Eshghi, H.; Gordi, Z. *Synth. Commun.* **2003**, 2971.
25. *General experimental procedure for the Ritter reaction*: To a stirred mixture of the alcohol (5 mmol) and nitrile (5 mmol, 5.5 mmol for acetonitrile) in a round-bottomed flask equipped with condenser at 100 °C was added 1 g of a homogeneous mixture of P_2O_5/SiO_2 (60% w/w) and the reaction was heated for the given time (Table 2). For microwave-assisted reactions the above premixed mixture was irradiated at 475 W in a domestic MW oven. The progress of reaction was followed by TLC. After completion of the reaction (Table 2), the resulting mixture was extracted with EtOAc (2×20 mL). The organic layer was washed with 10% $NaHCO_3$ and water, dried with Na_2SO_4 and concentrated to give the products in 78–96% yields. All product amides are known and were characterized by comparison of their spectral or physical data with those of authentic samples.
26. Thierny, J. P.; Lisdstrom, P. *Microwave Assisted Organic Synthesis*; Blackwell, 2005.
27. Hosseini Sarvari, M.; Sharghi, H. *Tetrahedron* **2005**, *61*, 10903.
28. (a) Rappaport, Z. *CRC, Handbook of Tables for Organic Compounds Identification*, 3rd ed.; The Chemical Rubber Co.: Ohio, 1967; (b) Shriner, R. L.; Fuson, R. C.; Curtin, D. Y.; Morrill, T. C. In *The Systematic Identification of Organic Compounds*; John Wiley: New York, 1980; p 538; (c) Weast, R. C. *CRC, Handbook of Chemistry* & *Physics* 54th ed.; The Chemical Rubber Co.: Ohio, 1983 or Lide, David R. *CRC Handbook of Chemistry* & *Physics*, Internet version 2005. CRC press: Boca Raton, FL, 2005. http://www.hcpnetbase.com.
29. Srinivas, K. V. N. S.; Das, B. *J. Org. Chem.* **2003**, *68*, 1165.
30. Olah, J. A.; Narang, S. C.; Luna, A. G. *Synthesis* **1980**, *8*, 661.