Pergamon

Tetrahedron Letters 43 (2002) 1397–1399

TETRAHEDRON
LETTERS

Lower primary alkanols and their esters in a Ritter-type reaction with nitriles. An efficient method for obtaining *N*-primary-alkyl amides

Mikhail Y. Lebedev* and Mark B. Erman

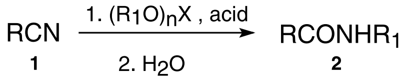
Millennium Specialty Chemicals, PO Box 389, Jacksonville, FL 32201, USA

Received 16 November 2001; revised 2 January 2002; accepted 4 January 2002

Abstract—*N*-Primary-alkyl amides $RCONHR_1$ were obtained by a Ritter-type reaction of nitriles RCN with lower primary alkanols R_1OH or their esters in the presence of acids. © 2002 Elsevier Science Ltd. All rights reserved.

The Ritter reaction in its original version involves electrophilic alkylation of nitriles with carbenium ions generated from olefins, or tertiary or secondary alcohols in the presence of acids, and results in *N*-monosubstituted amides.[1–3] Applicability of this reaction to primary alcohols has been limited to those capable of producing fairly stable carbenium ions, for example benzylic alcohols[4] and adamantyl carbinols.[5] Inability of primary alkanols to participate in the 'classic' Ritter reaction has been confirmed in a number of publications[1,3,6] and is currently considered common knowledge.[7] Therefore, several alternative Ritter-type methodologies for introduction of a primary alkyl group have been developed which involve strong alkylating agents.[6,8]

Our primary goal was to find an economical method for the conversion of nitrile **1a** into the corresponding *N*-monosubstituted amide **2a**–a commercially important compound possessing a physiological cooling effect.[9] A direct Ritter-type reaction certainly appeared the shortest and most attractive approach (Scheme 1). First, we attempted to apply the very original Ritter procedure[2] consisting of heating nitriles with alcohols and sulfuric acid in glacial acetic acid medium. The reaction gave only a negligible amount of amide **2a** (Table 1, entry 1), nevertheless encouraged us to extend the search to other sets of conditions and substrates. Surprisingly, simple treatment of nitrile **1a** with excess amounts of methanol and concentrated sulfuric acid showed a 60–70% conversion into amide **2a** (entries 2–4). Functionally substituted analogs of **1a**-nitriles **1b**,**c** were converted into the corresponding amides **2b**,**c** similarly (entries 5–7). Practically no alkyl exchange was observed: in the reaction of nitrile **1c** with methanol only ethoxycarbonyl *N*-methylamide **2c-Me** was obtained.



$$\underset{\mathbf{1}}{RCN} \xrightarrow[2.\ H_2O]{1.\ (R_1O)_nX\ ,\ acid} \underset{\mathbf{2}}{RCONHR_1}$$

R_1 = Me; Et; n-Bu;
acid = H_2SO_4; "115%" polyphosphoric; $MeSO_3H$; $ClSO_3H$.
X = H; or: X = SO_2 (n=2); P=O (n=3); C=O (n=2); B (n=3); SO_2Me (n=1); $(C{=}O)_2$ (n=2); Ac (n=1).

Scheme 1.

The carbenium ion intermediacy in these reactions could be ruled out for obvious reasons. We assumed that the reactive intermediate is monomethyl sulfate $MeHSO_4$ reversibly formed in situ from MeOH and sulfuric acid. The water formed could have been consumed through the formation of a by-product *N*-unsubstituted amide (see footnote c to Table 1).

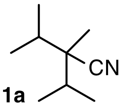
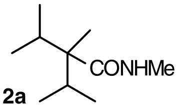
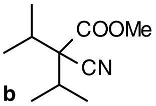
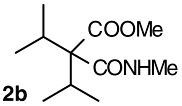
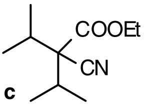
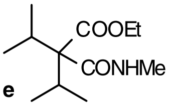
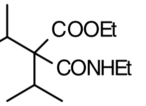
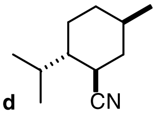
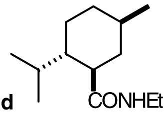
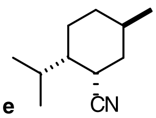
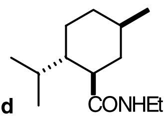
Indeed, a reaction of nitrile **1a** with a quadruple excess of $MeHSO_4$ obtained from equimolar amounts of Me_2SO_4 and H_2SO_4 in entry 8 gave a significantly better yield of amide **2a** compared to the entries 2–4. Further yield improvement was achieved by substitution of polyphosphoric acid for sulfuric acid in entry 9. In this case, a variety of acid alkyl phosphates and polyphosphates can be considered the reactive species.

---

* Corresponding author. Tel.: 1-904-924-2885; fax: 1-904-924-2743; e-mail: mike.lebedev@millenniumchem.com

PII: S0040-4039(02)00057-6

Table 1. The Ritter reaction of nitriles with primary alkanols or their esters in the presence of acids[a]

Entry	Nitrile (1 mole)	Alcohol or ester (moles)	Acid (moles)	t, °C (time, h)	Conv., %	Product	GLC yield, %	Isolated yield, %[b]
1	 **1a**	MeOH (2)	H_2SO_4 (2); AcOH (17)	100 (47)	70	 **2a**	1.2[c]	-
2	**1a**	MeOH (3)	H_2SO_4 (3)	100 (15)	95	**2a**	62[c]	-
3	**1a**	MeOH (6)	H_2SO_4 (6)	100 (1)	96	**2a**	67[c]	-
4	**1a**	MeOH (8)	H_2SO_4 (8)	100 (1)	97	**2a**	73[c]	-
5	 **1b**	MeOH (4)	H_2SO_4 (4)	100 (11.5)	79	 **2b**	75	62
6	 **1c**	MeOH (4)	H_2SO_4 (4)	100 (17)	81	 **2c-Me**	75	60
7	**1c**	EtOH (4)	H_2SO_4 (4)	100 (17)	77	 **2c-Et**	57	48
8	**1a**	$MeHSO_4$ (4)[d]		100 (3)	99	**2a**	92	-
9	**1a**	MeOH (1.5)	PPA (3)[e]	150 (10)	100	**2a**	99	92
10	**1a**	MeOH (2)	$ClSO_3H$ (4)[f]	85 (4)	100	**2a**	79	73
11	**1a**	$(MeO)_3PO$ (2)	H_2SO_4 (3)	120 (6)	100	**2a**	92	-
12	**1a**	$(MeO)_2CO$ (1)	PPA (3)[e]	140 (10)	100	**2a**	Quant.	95
13	**1a**	$(MeO)_3B$ (2)	H_2SO_4 (2.5)	100 (8)	95	**2a**	58[c]	50
14	**1a**	$(COOMe)_2$ (2)	H_2SO_4 (4)	100 (3)	99	**2a**	66[c]	-
15	**1a**	MeOAc (4)	H_2SO_4 (4)	100 (24)[g]	65	**2a**	35[c]	-
16	**1a**	$(MeO)_3PO$ (2)	$MeSO_3H$ (5)	140 (5)	100	**2a**	99	91
17	 **1d**	$(EtO)_3PO$ (1.8)	PPA (3)[e]	140 (7)	100	 **2d**	Quant.	-
18	**1d**	$EtOSO_2Me$ (4)	$MeSO_3H$ (4)	140 (6)	100	**2d**	97	86
19	 **1e**	$(EtO)_3PO$ (1.7)	PPA (3)[e]	140 (4.5)	97	 **2d**	92	78
20	PhCN	$MeOSO_2Me$ (4)	$MeSO_3H$ (4)	100 (18)	78	PhCONHMe	75	-
21	MeCN	$(n\text{-}BuO)_3PO$ (1)	$MeSO_3H$ (3)	140 (5)	100	MeCONH-n-Bu	29	-

[a] Nitrile was added to the other reagents in all entries, except for entry 2, where alcohol was added to a mixture of nitrile and acid, and entry 9, where acid was added to a mixture of alcohol and nitrile.

[b] Based on total amount of nitrile taken into reaction.

[c] Major by-product is the corresponding N-unsubstituted amide.

[d] Obtained from equimolar amounts of Me_2SO_4 and H_2SO_4.

[e] "115%" Polyphosphoric acid; quantity given in weight parts per 1 part of nitrile.

[f] Alcohol was carefully added to chlorosulfonic acid (cooling), and the mixture was stirred until evolution of HCl subsided (about 2 hours) before the addition of nitrile.

[g] Efficient reflux condenser.

In the case of MeOH and an excess of chlorosulfonic acid (entry 10), the reactive intermediate is probably methyl chlorosulfate $MeOSO_2Cl$ (see Ref. 10).

In a further modification of the method, various alkyl esters were successfully used as the donors of the alkyl group in combinations with sulfuric, polyphosphoric, and methanesulfonic acid (entries 11–16). In the latter case, the most likely reactive species is methyl mesylate.

Table 1 illustrates numerous available options for the economical and relatively environmentally benign conversion of nitrile **1a** into *N*-methylamide **2a**. Although this study has been originally focused at the nitriles with a quaternary α-carbon, the resulting method is not limited to only this family of substrates. Thus, menthylnitrile **1d** was successfully converted into the corresponding *N*-ethylamide **2d** in entries 17 and 18. An isomeric *neo*-menthyl nitrile **1e** gave a good yield of the same amide **2d**, apparently due to a rapid epimerization at the α-carbon (entry 19). Benzonitrile gave *N*-methylbenzamide in a good yield (entry 20). The synthetic applicability of the method to α-unbranched nitriles warrants further investigation (see entry 21).

There is not enough data yet for a discussion of the intimate mechanism of the reaction between the esters and nitriles in acidic medium at elevated temperatures. However, based on the generally accepted model for the Ritter-type processes,[1] we can assume that the protonated ester reacts with the nitrile producing an imidate intermediate $RC(OX)=NR_1$. The latter is further converted into the *N*-substituted amide during the hydrolytic work-up. The role of acids in the reaction may not be limited to the protonation only: they also serve as solvents, especially when taken in excess with respect to the other reagents.[11]

In a typical procedure, alcohol or ester was carefully added to an acid (**CAUTION**: exothermic reaction, especially with alcohols), followed by the addition of the nitrile.[12] The resulting mixture was stirred under conditions specified in Table 1 and periodically sampled for GLC analysis. Upon completion, the reaction mixture was cooled, carefully quenched with water, neutralized with dilute aqueous NaOH, and extracted with ether or heptane.[13] After evaporation of the solvent, the product was purified by distillation or recrystallization.[14,15]

In summary, we have developed a simple and efficient procedure for obtaining *N*-primary-alkyl amides by a Ritter-type reaction of nitriles with lower primary alkanols or their esters in acidic medium.

References

1. For reviews on the Ritter reaction, see: (a) Krimen, L. I.; Cota, D. J. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1969; Vol. 17; pp. 213–325; (b) Bishop, R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Eds.; Pergamon Press: New York, 1991; Vol. 6, pp. 261–300.
2. Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048.
3. Benson, F. R.; Ritter, J. J. *J. Am. Chem. Soc.* **1949**, *71*, 4128–4129.
4. (a) Parris, C. L.; Christenson, R. M. *J. Org. Chem.* **1960**, *25*, 331–334; (b) Sanguigni, J. A.; Levine, R. *J. Med. Chem.* **1964**, *7*, 573–574.
5. Sasaki, T.; Eguchi, S.; Toru, T.; Ito, K. *Bull. Chem. Soc. Japan.* **1970**, *43*, 1820–1824.
6. Barton, D. H. R.; Magnus, P. D.; Garbarino, J. A.; Young, R. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2101–2107.
7. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley–Interscience: New York, 2001; p. 1244.
8. (a) Olah, G. A.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1979**, 274–276; (b) Garcia Martinez, A.; Martinez Alvarez, R.; Teso Vilar, E.; Garcia Fraile, A.; Haneck, H.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *37*, 581–582.
9. Watson, H. R.; Hems, R.; Rowsell, D. G.; Spring, D. J. *J. Soc. Cosmet. Chem.* **1978**, *29*, 185–200.
10. Suter, C. M. *The Organic Chemistry of Sulfur*; John Wiley & Sons: New York, 1944, pp. 6, 19.
11. The importance of acids in the process can be further emphasized by our unsuccessful attempt to obtain amide **2a** using dimethyl sulfate alone, in the absence of acid. Heating nitrile **1a** with a triple molar excess of Me_2SO_4 for 37 h at 100°C gave only about 18% conversion of **1a** and 5% yield of **2a** (GLC).
12. Addition sequence is not important in most cases, however see, Table 1, footnote f for procedures involving chlorosulfonic acid.
13. Amount of heptane should be sufficient to ensure complete extraction: some of the products have a limited solubility in heptane.
14. Amides **2a**, **2d**, *N*-methylbenzamide and *N*-methylacetamide were identified by a comparison with the authentic samples. For **2a**, see: Rowsell, D. G.; Spring, D. J.; Hems, R. Brit. Patent 1,421,744, 1976; *Chem. Abstr.* **1976**, *84*, 150224. For **2d**, see: Watson, H. R.; Rowsell, D. G.; Spring, D. J. Brit. Patent 1 351 762, 1972; *Chem. Abstr.* **1974**, *81*, 47583.
15. Amide **2b**: mp 88.5–89°C (from heptane); ^1H NMR ($CDCl_3$) δ 0.87 d, (6.9 Hz, 6H), 0.89 d (6.9 Hz, 3H), 2.60 septet (6.9 Hz, 2H), 2.79 d (4.7 Hz, 3H), 3.71 s (3H), 7.76 br. s (1H). Amide **2c-Me**: ^1H NMR ($CDCl_3$) δ 0.87 d (6.8 Hz, 6H), 0.89 d (6.8 Hz, 6H), 1.27 t (7.3 Hz, 3H), 2.59 septet (6.8 Hz, 2H), 2.77 d (4.9 Hz, 3H), 4.17 q (7.3 Hz, 2H), 7.83 br. s (1H). Amide **2c-Et**: ^1H NMR ($CDCl_3$) δ 0.88 d (6.8 Hz, 6H), 0.90 d (6.8 Hz, 6H), 1.11 t (7.0 Hz, 3H), 1.27 t (7.0 Hz, 3H), 2.60 septet (6.8 Hz, 2H), 3.28 m (2H), 4.17 q (7.0 Hz, 2H), 7.83 br. s (1H).