

Amides from Nitriles using Basic Hydrogen Peroxide under Phase-Transfer Catalysed Conditions

S. CACCHI, D. MISITI

Istituto di Chimica Organica, via Castro Laurenziano 9, I-00161 Roma, Italy

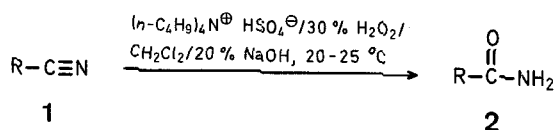
F. LA TORRE

Istituto Superiore di Sanità, Lab. Chimica del Farmaco, Viale Regina Elena 299, I-00161 Roma, Italy

The hydrolysis of nitriles to amides is one of the best methods for the preparation of the latter compounds. Basic and acidic conditions were described to catalyze the water addition to the carbon-nitrogen triple bond, as well the presence of certain metal ions or complexes¹. Even basic hydrogen peroxide was reported to give good results using suitable mixtures of solvents².

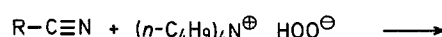
We have found that this last reaction may be conveniently carried out under phase-transfer catalysed conditions. Thus, a number of aromatic, aliphatic, and vinylic nitriles 1 were converted into the corresponding amides 2 in good yield at room temperature.

In a typical small scale run, a 2.0–3.0 molar dichloromethane solution of the nitrile 1 was treated with an excess of basic 30% hydrogen peroxide in the presence of a catalytic amount (20 mol%) of *n*-tetrabutylammonium hydrogen sulfate. After 0.5–1.5 h the organic layer was separated, washed with water, and worked up. The results are summarised in the Table.

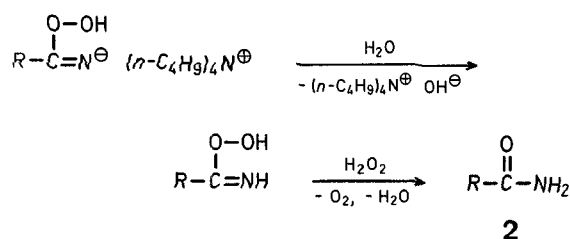


Control experiment revealed that the ammonium salt greatly enhances the reaction rate, presumably, if the reac-

tion occurs according to the mechanism proposed by Wi-berg³, affecting only the first step.



1



Without the addition of the catalyst, only 30% of benzonitrile is converted into the corresponding amide after 80 min. The effectiveness of the ammonium catalyst varies with the nature of the starting nitrile: as an example, if the catalyst is omitted, only 10% of *m*-toluamide was isolated from the reaction of *m*-tolunitrile under the reported conditions after 90 min.

As expected, this method does not work with nitriles containing electron-withdrawing substituents bonded to the carbon atom α to the cyano group as the abstraction of the α -hydrogen atom prevents the nucleophilic attack of the hydroperoxide ion.

Melting points are uncorrected and were determined with a Büchi apparatus. The starting nitriles are commercially available and were used without further purification. Only nitrile 1n was prepared in good yield from commercially available *p*-nitrophenylacetone through methylation with an excess of methyl iodide under PTC conditions. Tetrabutylammonium hydrogen sulfate was purchased from Fluka and used as such. The reaction products were purified on silica gel columns (SiO₂-60, 70–230 mesh, Merck), eluting with ethyl acetate. All the reported reactions were carried out on a 3.5–5.5 mmol scale.

Table. Amides 2 from Nitriles 1 using Basic Hydrogen Peroxide

Nitrile 1 No.	R	Reaction time [min]	Yield [%] of 2 ^{a,b}	m.p. [°C]	
				found	reported
1a	C ₆ H ₅	80	92	125–127	125–126 ⁴
1b	2-H ₃ C–C ₆ H ₄	100	97	140–142	137–140 ⁴
1c	3-H ₃ C–C ₆ H ₄	90	92	93–95	93–94 ⁵
1d	4-H ₃ C–C ₆ H ₄	90	95	161–163	159–160 ⁴
1e	3-O ₂ N–C ₆ H ₄	30	90	140–141	141.5–142.5 ⁶
1f	4-Cl–C ₆ H ₄	80	97	178–180	177–179 ⁷
1g	2-naphthyl	80	96	192–194	196–196.5 ⁸
1h	C ₆ H ₅ CH=CH	90	80	142–144	141–142 ⁹
1i	<i>c</i> -C ₆ H ₁₁	100	79	183–184	184–185 ¹⁰
1l	<i>c</i> -C ₈ H ₉	70	85	174–175	174–176 ¹¹
1m	C ₆ H ₅ (CH ₂) ₃	80	95	90–92	84–85 ¹²
1n ^c	4-O ₂ N–C ₆ H ₄ –C(CH ₃) ₂	80	87	113–114	— ^d

^a Yield of pure, isolated product; not optimised.

^b The I.R. and ¹H-N.M.R. spectra of products 2a–m were identical with those of authentic samples; satisfactory microanalyses were also obtained (C ± 0.27, H ± 0.20, N ± 0.22).

^c C₁₀H₁₀N₂O₂ calc. C 63.15 H 5.30 N 14.73 (190.2) found 63.01 5.31 14.76

¹H-N.M.R. (CDCl₃/TMS): δ = 1.77 [s, 6H, C(CH₃)₂]; 8.02 ppm (AA'BB', 4H_{arom}, J_{AB} = 9 Hz).

^d C₁₀H₁₂N₂O₃ calc. C 57.68 H 5.81 N 13.46 (208.2) found 57.83 5.82 13.48

¹H-N.M.R. (CDCl₃/TMS): δ = 1.61 [s, 6H, C(CH₃)₂]; 5.68 (br s, 2H, NH₂); 7.87 ppm (AA'BB', 4H_{arom}, J_{AB} = 9 Hz).

***o*-Toluamide (2b); Typical Procedure:**

To a magnetically stirred dichloromethane solution (1.5 ml) of *o*-tolunitrile (**1b**; 0.5 g, 4.27 mmol) cooled in an ice bath, are added 30% hydrogen peroxide (2.0 ml), tetrabutylammonium hydrogen sulfate (0.290 g, 0.85 mmol), and a 20% aqueous solution of sodium hydroxide (1.6 ml). The reaction mixture is allowed to warm to room temperature and maintained under stirring. After 1.6 h, dichloromethane is added, the organic layer is separated, washed with saturated sodium chloride solution, and dried with sodium sulphate. The solvent is removed under reduced pressure to leave a white solid from which pure *o*-toluamide is obtained by chromatography on silica gel; yield: 0.485 g (97%).

Received: October 20, 1979

- ¹ J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, McGraw-Hill, Intern. Stud. Ed., 2nd Ed., 1977, p. 809, and references therein.
- ² Br. Radziszewski, *Ber. Dtsch. Chem. Ges.* **18**, 355 (1885).
C. R. Noller, *Org. Synth. Coll. Vol. II*, 586 (1943).
J. S. Buck, W. S. Ide, *Org. Synth. Coll. Vol. II*, 44 (1943).
- ³ K. B. Wiberg, *J. Am. Chem. Soc.* **75**, 3961 (1953).
- ⁴ H. R. Snyder, C. T. Elston, *J. Am. Chem. Soc.* **76**, 3039 (1954).
- ⁵ M. L. Van Scherpenzeel, *Recl. Trav. Chim. Pays-Bas* **20**, 162 (1901).
- ⁶ L. Field, P. B. Hughmark, S. H. Shumaker, W. S. Marshall, *J. Am. Chem. Soc.* **83**, 1983 (1961).
- ⁷ C. R. Hauser, D. S. Hoffenberg, *J. Org. Chem.* **20**, 1448 (1955).
- ⁸ P. Fitzgerald, J. Packer, J. Vaughan, A. F. Wilson, *J. Chem. Soc.* 170 (1956).
- ⁹ S. Sugawara, H. Shigehara, *J. Pharm. Soc. Jpn.* **62**, 531 (1942).
- ¹⁰ S. Olsen, Engel-Margarete Enkemeyer, *Chem. Ber.* **81**, 359 (1948).
- ¹¹ H. Adkins, S. H. Watkins, *J. Am. Chem. Soc.* **73**, 2184 (1951).
- ¹² G. R. Lappin, *J. Am. Chem. Soc.* **71**, 3966 (1949).