Tetrahedron Letters, Vol.32, No.28, pp 3321-3324, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

RADICAL NITRILE TRANSFER WITH METHANESULFONYL CYANIDE OR P-TOLUENESULFONYL CYANIDE TO CARBON RADICALS GENERATED FROM THE ACYL DERIVATIVES OF N-HYDROXY-2-THIOPYRIDONE

Derek H. R. Barton*, Joseph Cs. Jaszberenyi and Emmanouil A. Theodorakis

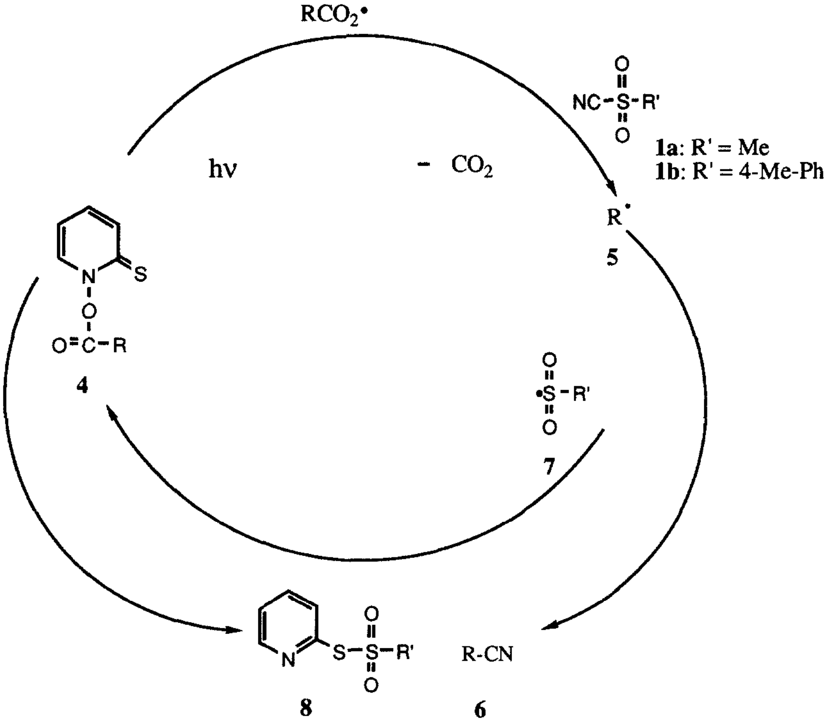
Department of Chemistry, Texas A&M University, College Station, Texas, 77843

Abstract: Reaction of methanesulfonyl cyanide or p-toluenesulfonyl cyanide with carbon radicals generated from the acyl derivatives of N-hydroxy-2-thiopyridone gives the corresponding nitriles in high yield. A mechanistic scheme is suggested.

There are many synthetic applications of carbon radicals generated from the acyl derivatives of N-hydroxy-2-thiopyridone[1]. Their easy synthesis and high reactivity make these compounds attractive tools in functional group transformations[2]. In the course of our synthetic studies in radical chemistry we have examined the reaction of sulfonyl cyanides (methanesulfonyl cyanide (**1a**) and p-toluenesulfonyl cyanide (**1b**)) with various carbon radicals generated from the corresponding acids (**2**) *via* the acyl derivatives (**4**) formed from N-hydroxy-2-thiopyridone (**3**) (Scheme 1). It is known that sulfonyl cyanides easily undergo homolytic cleavage between the sulfonyl sulfur and the nitrile carbon atom[3]. This, in principle, can be utilized for constructing a radical chain process. In this chain the carbon radical (**5**) is trapped by the sulfonyl cyanide (**1a** or **1b**), generating nitriles (**6**) and sulfonyl radicals (**7**). The latter then carry the radical chain by attacking **4** and producing **5** and thiosulfonates of type **8**. The synthetic use of this new radical method was demonstrated in reactions with primary, secondary and tertiary radicals generated from **4a**, **4b** and **4c**, respectively (Table 1).

The data in Table 1 indicate that this is indeed a good to high yielding new synthetic procedure for nitrile synthesis. The excess of the trapping agents (**1a** or **1b**) can be recovered after the reaction and used again. The yield of the nitriles is higher in the case of methanesulfonyl cyanide as radical trap. The difference can be explained as a combined effect of steric and energetic factors[4].

This new reaction can be used to introduce labeled carboxyl groups into complicated and sensitive natural products. This has been shown using two model acids, linoleic acid (**2d**) and oleic acid (**2e**) (Scheme 2). The acids were transformed to the corresponding acyl derivatives **4d** and **4e** in 96% and 94% yield respectively. The derivatives thus obtained were then photolysed in CH_2Cl_2 at 0^oC with a tungsten lamp resulting in the formation of the nitriles **6d** and **6e** in > 95% yield (Table 2). After purification **6d** and **6e** were isolated (97% and 95% respectively), indicating that indeed the carbon radicals thus formed can be trapped selectively with sulfonyl cyanides. No interference of the starting thione or the double bond(s) was observed. Alkaline hydrolysis ($NaOH/EtOH/H_2O$/ boiling) of the nitriles thus obtained completed the cycle. Linoleic acid was obtained in 81%, oleic acid in 78% yield. These synthetic cycles would have allowed the introduction of a label in 74% and 70% overall yield (not optimized) into **2d** and **2e**[6] respectively.

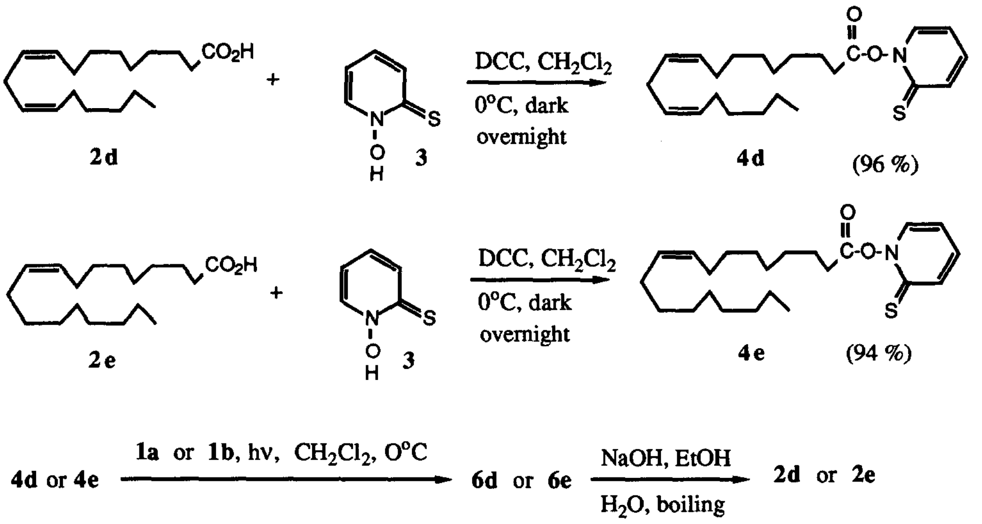


Scheme 1

Table 1 Radical nitrile transfer to the carbon radicals generated from **4a-c**

Radical source	Sulfonyl nitrile equivalents	Yield of the nitriles[a] % with **1a**	with **1b**
4a	1	78	65
	3	93	82
	5	-	91
4b	1	73	60
	3	88	86
	5	-	90
4c	1	65	55
	3	82	77
	5	-	84

[a] by ^{1}H NMR.



Scheme 2

Table 2 Nitrile transfer to the carbon radicals generated from linoleic acid (**2d**) and oleic acid (**2e**) with sulfonyl cyanides **1a** and **1b**

Radical source	Sulfonyl nitrile equivalents	Yield of the nitriles[a] % with **1a**	with **1b**
4d	1	80	60
	3	93	78
	5	> 95 (97)[b]	83
4e	1	77	62
	3	89	75
	5	95[b]	87

[a] by ^1H NMR.

[b] isolated yield, with 6 equivalents of **1a**.

Typical procedure:

To the solution of methanesulfonyl cyanide[5] (**1a**) (6 equivalents, 18 mmol, 1.9 g) in dry methylene dichloride (5 ml) was added the appropriate mixed anhydride (3 mmol) under argon at 0°C and the mixture photolysed with two tungsten lamps (GE, 150 W) in a Pyrex flask at 0-5°C (ice bath) until decoloration (5-10 minutes). Then the reaction mixture was concentrated in vacuum and the nitriles isolated by column chromatography on silica gel (hexanes: ether = 3:1).

Acknowledgements: We thank the NIH and the Schering-Plough Corporation for financial support. Mr. E.A. Theodorakis is a Schering Scholar.

References and notes:

1. The early results: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc. Chem. Commun.* **1983**, 939., Idem, *Tetrahedron Lett.* **1983**, *24*, 4979. Barton, D. H. R.; Kretzschmar, G. *ibid.* **1983**, *24*, 5889. Barton, D. H. R.; Crich, D.; Kretzschmar, G. *ibid.* **1984**, *25*, 1055. Idem, *J. Chem. Soc. Perkin Trans. I* **1986**, 39. Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron* **1985**, *41*, 5507. Idem, *Tetrahedron Lett.* **1985**, *26*, 6349. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. Barton, D. H. R.; Garcia, B.; Togo, H.; Zard. S. Z. *Tetrahedron Lett.* **1986**, *27*, 1327. Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2325. Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron Lett.* **1986**, *27*, 4309. Barton, D. H. R.; Crich, D. *J. Chem. Soc. Perkin Trans. I*, **1986**, 1603. Idem, *ibid.*, **1986**, 1613. Examples of synthetic applications in other laboratories: Della, E. W.; Tsanaktsidis, J. *Aust. J. Chem.* **1986**, *39*, 2061. Idem, *ibid.* **1989**, *42*, 61. Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Durner, G.; Zimmermann, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771. Stofer, E.; Lion, C. *Bull Soc. Chim. Belg.* **1987**, *96*, 623. Flanagan, D. M.; Jouillie, M. M. *Heterocycles*, **1987**, *26*, 2247. Strazewski, P.; Tamm, C. *Synthesis* **1987**, 298. Eaton, P. E.; Maggini, M. *J. Am. Chem. Soc.* **1988**, *110*, 7230. Dauben, W. G.; Kowalczyk, B. A.; Bridon, D. P. *Tetrahedron Lett.* **1989**, *30*, 2461, Alfonso, C. M.; Barros, M. T.; Godinho, L.; Maycock, C. D. *ibid.* **1989**, *30*, 2707. For nitrogen-centered radicals see: Newcomb, M.; Park, S. U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651, Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163. Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317. Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *ibid.* **1990**, *46*, 2329. Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *ibid.* **1990**, *46*, 2345. Newcomb, M.; Kumar, M. U. *Tetrahedron Lett.*, **1990**, *31*, 1675. For oxygen centered radicals: Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415. Idem, *ibid.* **1989**, *111*, 230. Boivin, J.; Crépon, E.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 6869., Newcomb, M.; Kumar, M. U.; Boivin, J.; Crépon, E.; Zard, S. Z. *ibid.* **1991**, *32*, 45. Beckwith, A. L. J.; Davison, I. G. E. *ibid.* **1991**, *32*, 49. Barton, D. H. R.; Jaszberenyi, J. Cs.; Morrell, A. I. *ibid.* **1991**, *32*, 311.

2. Barton, D. H. R.; Zard, S. Z. *Phil. Trans. R. Soc. Lond.* **1985**, *B311*, 505. Idem. *Pure Appl. Chem.* **1986**, *58*, 675. Idem, *Janssen Chimica Acta* **1987**, *4*, 3. Crich, D. *Aldrichimica Acta* **1987**, *20*, 35. Barton, D. H. R. *ibid.* **1990**, *23*, 3, and references cited therein. Crich, D.; Quintero, L. *Chem. Rev.* **1988**, *89*, 1413, and references cited therein.

3. Pews, R. G.; Evans, T. E. *J. Chem. Soc. Chem. Commun.* **1971**, 1397. Fang, J.-M.; Chen, M.-Y. *Tetrahedron Lett.* **1987**, *28*, 2853. Fang, J.-M.; Chen, M.-Y.; Cheng, M.-C.; Lee, G.-H.; Wang, Y.; Peng, S.-M. *J. Chem. Res. (S)* **1989**, 272, *J. Chem. Res. (M)* **1989**, 2101.

4. Benson, S. W. *Chem. Rev.* **1978**, *78*, 23. Chatgilialoglu, C. Sulfonyl Radicals. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C. J. M. Eds.; John Wiley and Sons, Inc.: New York, 1988; pp. 1089-1113.

5. Synthesized by applying the method of Vrijland, M. S. A. *Org. Synth.* **1977**, *57*, 88. The ClCN was prepared according to the method of Schröder, H. *Z. Anorg. Allg. Chem.* **1958**, *297*, 298.

6. In an earlier study we had shown the value of isonitriles for the addition of one carbon atom to a radical (Barton, D. H. R.; Ozbalik, N.; Vacher, B. *Tetrahedron* **1988**, *44*, 3501). In fact methanesulfonyl cyanide is a superior reagent for this transformation.

(Received in USA 1 February 1991)