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Decarboxylative Radical Azidation Using MPDOC and MMDOC Esters

Erich Nyfeler and Philippe Renaud*

Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, CH-3012 Berne, Switzerland

philippe.renaud@ioc.unibe.ch

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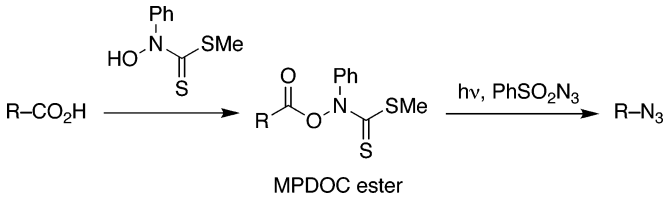
ABSTRACT



MPDOC ester

An efficient radical-mediated decarboxylative azidation of aliphatic carboxylic acids has been developed. The success of this transformation hinges on the use of a new type of thiohydroxamate esters (MPDOC esters). These esters are more stable than the classical Barton esters and less prone to rearrange under radical conditions. In the case of α-alkoxy and α-amino acids, optimal results are obtained with the even more stable MMDOC esters developed recently by Kim.

Barton has demonstrated that PTOC (PTOC = pyridine-2-thione-*N*-oxycarbonyl) esters are efficient precursors of alkyl radicals.[1] They have been applied to a wide range of reactions for the formation of C−H, C−C, and C−X bonds (X, = heteroatom such as O, N, S, Se, P, etc.).[2−4] Despite its obvious synthetic appeal, the formation of C−N bonds under decarboxylative conditions remains a formidable task. In an early attempt to run such a process, diazirines were used as radical traps by Barton.[5] More recently, Porter and Masterson[6] reported the decarboxylative azidation of β-silyl carboxylic acids via their PTOC-esters in moderate yield using ethanesulfonyl azide[7] as a radical trap. This transformation (i.e., converting a carboxylic acid into an azide) is unique and very attractive due to the versatility of the azide function.[8] However, synthetic applications of the azidation procedure involving PTOC esters are hampered by the formation of rearranged products (vide infra). Herein, we present a more general and efficient method for the decarboxylative azidation of alkanoic acids via the intermediacy less reactive *O*-acyl thiohydroxamates.

The radical azidation of *O*-adamantane-1-carbamoyl thiohydroxamates **1**−**3** (Scheme 1, eq 1) was chosen as a test reaction because the 1-adamantyl radical is known to react efficiently with the benzenesulfonyl azide radical trap.[7a] The PTOC ester **1** gave almost exclusively the rearranged *S*-pyridyl thioether **5** (Table 1, entry 1). Traces of the azide **4** were detected. This indicates that the PTOC ester **1** is more reactive than the benzenesulfonyl azide toward the adamantyl radical. Thus, successful azidation would entail either

(1) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Chem. Commun.* **1983**, 939.

(2) For reviews, see: (a) Motherwell, W. B.; Imboden, C. *Radicals in Organic Synthesis, Volume 1: Basic Principles*; Renaud, P., Sibi, M. P, Eds.; Wiley-VCH: Weinheim, 2001; p 107. (b) Barton, D. H. R.; Motherwell, W. B. *Heterocycles* **1984**, *21*, 1. (c) Crich, D. *Aldrichim. Acta* **1987**, *20*, 35. (d) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675. (e) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (f) Barton, D. H. R. *Tetrahedron* **1992**, *48*, 2529. (g) Barton, D. H. R. *Pure Appl. Chem.* **1994**, *66*, 1943.

(3) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979. (b) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron Lett.* **1985**, *26*, 5939.

(4) Barton, D. H. R.; Ozbalik, N.; Vacher, B. *Tetrahedron* **1988**, *44*, 3501.

(5) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 8050.

(6) Masterson, D. S.; Porter, N. A. *Org. Lett.* **2002**, *4*, 4253.

(7) (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717. (b) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496. For a review on radical azidation, see: (c) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem. Eur. J.* **2004**, *10*, 3606.

(8) For reviews on preparation and application of azides, see: (a) Bräse, S.; Gil, C.; Kneppner, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (c) L'Abbé, G. *Chem. Rev.* **1969**, *69*, 345.

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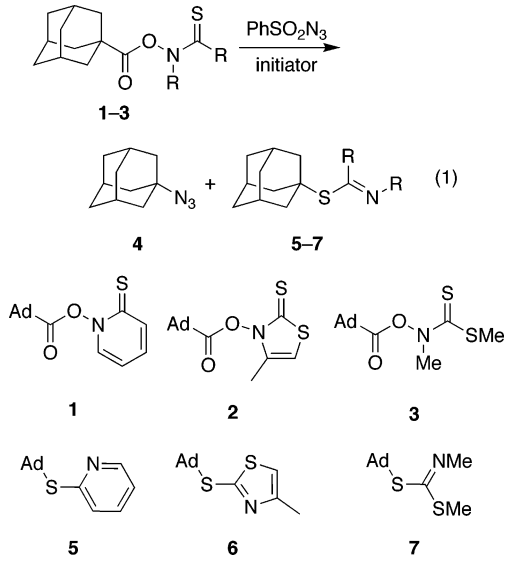
Scheme 1. First Attempts of Azidative Decarboxylation



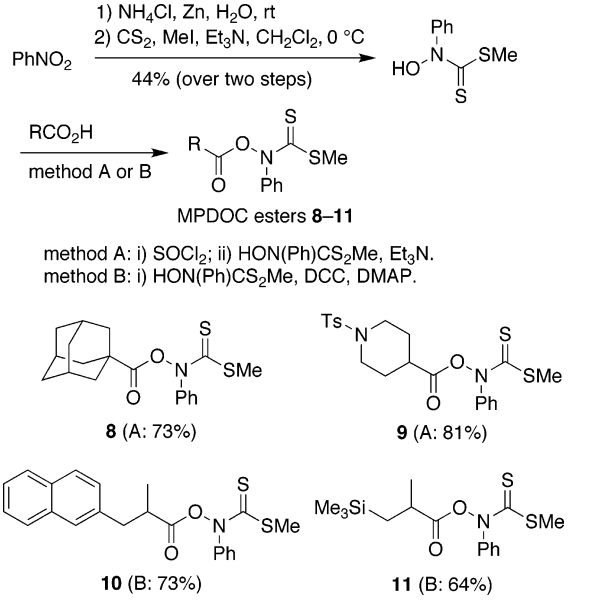
increasing the rate of the azidation or reducing the rate of the rearrangement. Unfortunately, the nature of the sulfonyl azide has little influence on the rate of the azidation process, presumably because the radical addition to the azide takes place at the remote γ-position.[9] Indeed, the use of ethanesulfonyl azide, 3-pyridinesulfonyl azide, and trifluoromethanesulfonyl azide did not favor the azidation reaction relative to the rearrangement. Therefore, we decided to investigate alternate thiohydroxamate radical precursors. The MTTOC (MTTOC = 4-methyl-1,3-thiazolin-2-thione-*N*-oxycarbonyl) ester **2**, which has been reported to rearrange slowly in benzene but rapidly in refluxing toluene,[10] affords the rearranged thioether **6** as the major product (entry 2) under photochemical initiation with a sunlamp. Kim and co-workers have obtained promising results for the decarboxylative acylation with the MMDOC (MMDOC = *N*,*S*-dimethyldithiocarbamoyl-*N*-oxycarbonyl) esters.[11] With the MMDOC ester **3**, high temperature initiation (refluxing toluene) is required, and interestingly, the desired adamantyl azide **4** is the only product isolated; the corresponding rearranged product **7** is not observed. However, the yield of **4** is moderate, presumably because of the high reaction temperature since benzenesulfonyl azide starts to decompose at 105 °C.[12] Although photochemical initiation with MMDOC esters has been reported at 300 nm with a low-pressure mercury lamp,[11b,13] this type of irradiation is incompatible with sulfonyl azides.

Table 1. Decarboxylative Radical Azidation Using Reported Thiohydroxamate Esters According to Scheme 1 (eq 1)

entry	precursor	initiation	temp (°C)	yield **4** + **5**–**7**	ratio **4**/**5**–**7**
1	**1**	sunlamp	5	77%	<1:15
2	**2**	sunlamp	5	n.d.	1:2
3	**3**	heat	110	52%	>15:1

We reasoned that replacement of the *N*−Me group of MMDOC esters by a *N*-Ph group would enable photochemical initiation using a standard sunlamp. This modification should cause only a moderate increase of reactivity as a radical trap and a marginal decrease of thermal stability. *N*-Hydroxy-*S*-methyl-*N*-phenyldithiocarbamate is easily prepared from nitrobenzene in two steps (44% overall yield). It is obtained as a yellowish solid after purification by column chromatography or recrystallization (Scheme 2). The

Scheme 2. Preparation of MPDOC Esters



MPDOC esters **8**−**11** (MPDOC = *S*-methyl-*N*-phenyl-1,3-dithiocarbamoyloxycarbonyl) are prepared from the corresponding carboxylic acids and *N*-hydroxy-*S*-methyl-*N*-phenyldithiocarbamate in good yields (Scheme 2). They are easily purified by column chromatography without using any special protection against daylight.

With MPDOC esters **8**−**11** in hand, we examined their reactivity in radical reactions. For example, irradiation of a solution of **8** in CH_2Cl_2 with a 300 W sunlamp at 5 °C affords the rearranged product **12** in good yield (Scheme 2, eq 2, Table 2, entry 1). Similar yields are obtained with the MPDOC esters **9**−**11** that afford the corresponding sulfides **13**−**15** (Table 2, entries 2−4). However, when the MPDOC esters **8**−**11** are irradiated at 5 °C in the presence of benzenesulfonyl azide (eq 3), they give the corresponding azides **4** and **16**−**18** as major products (Table 2, entries 1−4); the only side product observed in theses reactions are the rearranged products **12**−**15** (10−20% yield).

(9) Masterson, D. S.; Shackleford, J. P. *Synlett* **2007**, 1302.
(10) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.
(11) (a) Kim, S.; Lim, C. J.; Song, S.-E.; Kang, H.-Y. *Synlett* **2001**, *5*, 688. (b) Kim, S.; Lim, C. J.; Song, S.-E.; Kang, H.-Y. *Chem. Commun.* **2001**, 1410.
(12) Dermer, O. C.; Edmiso, M. T. *J. Am. Chem. Soc.* **1954**, *77*, 70.
(13) Fenner, T.; White, J. M.; Schiesser, C. H. *Org. Biomol. Chem.* **2006**, *4*, 466.

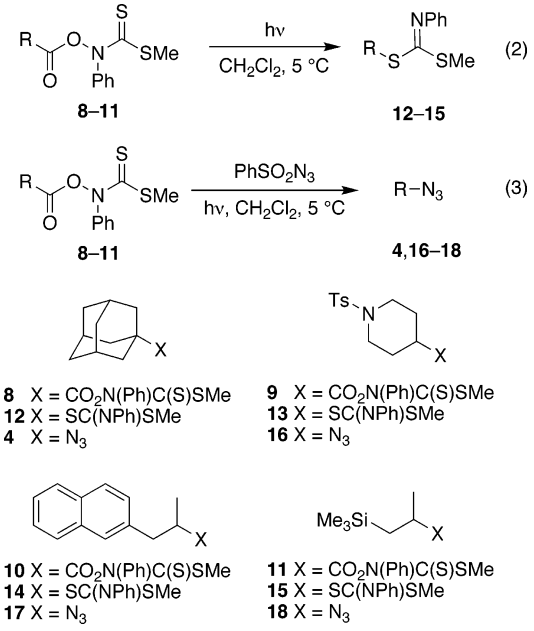
Table 2. Decarboxylative Rearrangement and Azidation of MPDOC Esters with Benzenesulfonyl Azide According to Scheme 3 (eqs 2 and 3)

entry	precursor	eq 2, yield	eq 3, yield[a]
1	**8**	**12**, 73%	**4**, 67%
2	**9**	**13**, 84%	**16**, 38%
3	**10**	**14**, 76%	**17**, 53%
4	**11**	**15**, 66%	**18**, 52%

[a] Rearranged products **12**−**15** are also produced in 10−20% yield.

The decarboxylative rearrangement of MPDOC esters represents a practical method for the transformation of carboxylic acids into thiols as exemplified by reductive treatment of rearranged product **14** with $LiAlH_4$ in THF to afford **19** (Scheme 4, eq 4). To further demonstrate the utility

Scheme 3. Decarboxylative Rearrangement and Azidation of MPDOC Esters

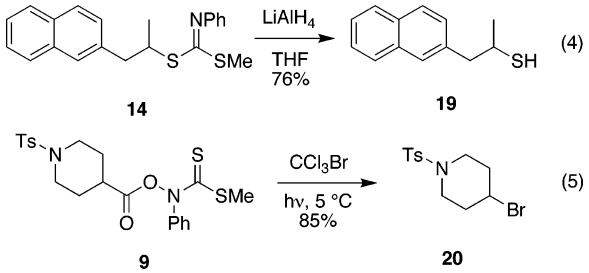


of MPDOC esters, radical bromination using CCl_3Br was investigated (Scheme 4, eq 5).[14] Treatment of ester **9** with CCl_3Br at 5 °C affords the expected bromide **20** in 85% yield.

The reaction involving MPDOC esters was also examined in cyclization processes (Scheme 5). In preliminary experiment with ester **21**, irradiation at 5 °C with a sunlamp afforded the cyclized product **22** in 80% yield (eq 6). When the same reaction was run in the presence of benzenesulfonyl azide, the cyclic azide **23** was isolated in 41% yield (eq 7).

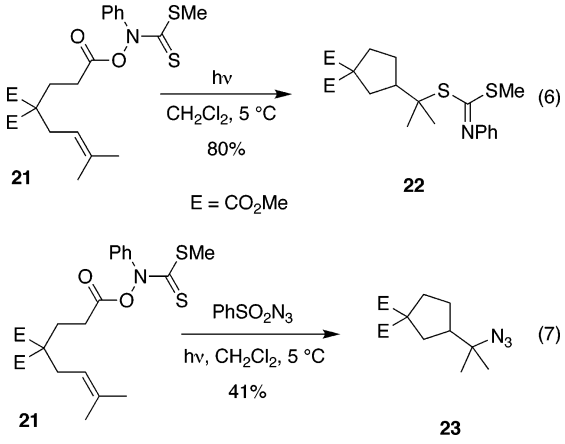
Decarboxylation of α-amino and α-alkoxy acids using the classical Barton PTOC esters is possible but experimentally

Scheme 4. Preparation of Thiols and Bromides



difficult to realize due to the instablity of the corresponding esters.[15] All of our attempts to run an azidation process with PTOC esters derived from amino acids failed. Therefore, the use of the MPDOC esters was investigated but their stability is not sufficiently enhanced compared to PTOC esters to solve the problem. Finally, best results are obtained by using Kim's MMDOC esters (Scheme 6). Preparation and purification of the esters **24**−**26** (Table 3) are possible although some decomposition on silica gel is observed. Initiation of the radical reaction is best achieved in this case with AIBN in refluxing benzene. In the presence of benzenesulfonyl azide or 3-pyridinesulfonyl azide,[16] good yield of azides **27**−**29** were obtained.

Scheme 5. Decarboxylative Cyclization and Cyclization-Azidation Reaction of the MPDOC Ester **21**



The reaction of ester **26** affords only **29**, the product of direct azidation, in 63% yield. No product resulting from a 6-exo-cyclization process is observed. Interestingly, in all the azidation reactions involving MMDOC esters **24**−**26**, no rearranged product is observed.

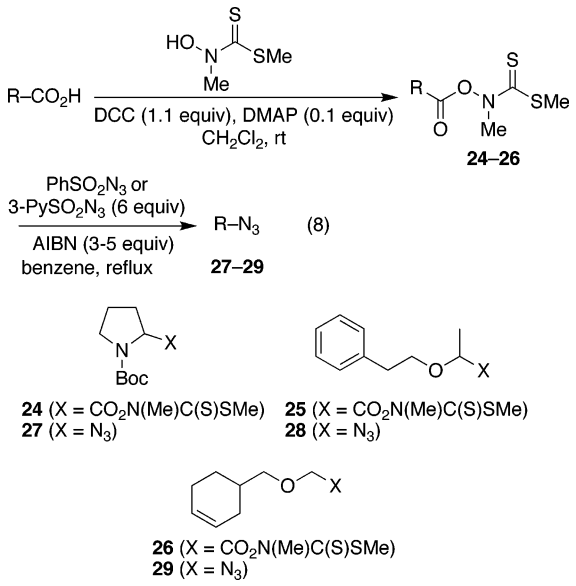
In conclusion, we have developed thiohydroxamic acid esters, the MPDOC esters, which are particularly suitable for the generation of alkyl radicals. They are stable and can be purified by classical flash chromatography but they

(14) Barton, D. H. R.; Crich, D.; Motherwell, W. *Tetrahedron* **1985**, *41*, 3901.

(15) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479.

(16) Panchaud, P.; Renaud, P. *Adv. Synth. Catal.* **2004**, *346*, 925.

Scheme 6. MMDOC Esters from α-Amino- and α-Hydroxyesters



undergo facile homolytic fragmentation under thermal and photochemical initiation with a standard 300 W sunlamp. Because they are less reactive than the classical Barton PTOC esters, they are particularly useful for reactions with slow radical traps such as sulfonyl azides. For the generation of α-aminoalkyl and α-alkoxyalkyl radicals, the use of Kim's even less reactive MMDOC esters is recommended.

Table 3. Preparation and Azidation of MMDOC Ester According to Scheme 6 (eq 8)

entry	MMDOC, yield	azide, yield
1	**24**, 85%	**27**, 61%[a]
2	**25**, 60%	**28**, 70%[b]
3	**26**, 62%	**29**, 63%[b]

[a] $PhSO_2N_3$ was used as radical trap. [b] 3-$PySO_2N_3$ was used.

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Supporting Information Available: Full experimental procedures, spectral data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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