6496 *J. Am. Chem. Soc.* **2000,** *122,* 6496−6497

Formation of Carbon−Nitrogen Bonds via a Novel Radical Azidation Process

Cyril Ollivier and Philippe Renaud*

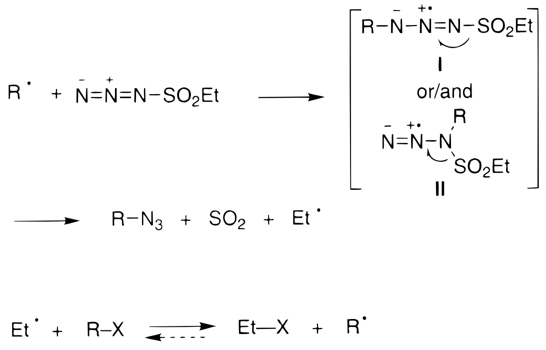
Université de Fribourg, Institut de Chimie Organique
Pérolles, CH-1700 Fribourg, Switzerland

Received February 24, 2000

Radical reactions are nowadays a very useful tool for organic synthesis as demonstrated by their frequent application in the preparation of natural products.[1] The majority of these processes are based on very efficient formation of carbon−hydrogen and carbon−carbon bond. The formation of a carbon−heteroatom bond from a carbon-centered radical is also well-documented when the heteroatom is sulfur, halogen, and oxygen.[2] The amination of alkyl radicals was investigated, too, and even though many different radical traps were tested, the preparative procedures that arose from this work are of limited scope.[3] In this contribution, we report preliminary results concerning a novel and unique azidation process of simple alkyl iodides and dithiocarbonates based on the use of ethanesulfonylazide as radical trap.

Ethanesulfonylazide, easily prepared from ethanesulfonylchoride and sodium azide, is a stable liquid that can be heated at 100 °C without decomposition. Our hypothesis was that addition of alkyl radicals in the α or γ position of ethanesulfonylazide should lead to intermediate nitrogen-centered radicals (**I** or **II**). These radicals should fragment to give alkyl azides and the ethanesulfonyl radical that decomposes readily to give sulfur dioxide and the ethyl radical (Scheme 1).[4,5] Since the ethyl radical is known to be an efficient promoter of iodine atom and dithiocarbonate transfer reactions, this reaction sequence is expected to be suitable for radical azidation of iodides and dithiocarbonates.[6] Dilauroyl peroxide (DLP) has already proved to be an excellent initiator for the transfer of iodine atoms and dithiocarbonates.[7,8] Therefore, it should also be efficient for the azidation reaction.

Scheme 1



The reaction was tested first with different alkyl iodides (equation 1) and results are summarized in Table 1. Cyclic secondary alkyl iodides such as **1a** and **1b** are efficiently converted into the corresponding azides **2a** and **2b** by treatment with 3 equiv of ethanesulfonylazide and a substoichiometric amount of DLP[9] in a mixture of chorobenzene and heptane as solvent (method A, entries 1 and 2). Sterically more hindered secondary cyclic iodides such as **1c** and **1d** are efficiently converted into azides **2c** and **2d** by treatment with 5 equiv of ethanesulfonylazide (method B, entries 3 and 4). Tertiary alkyl iodides such as **1e** are also suitable substrates for this azidation reaction (entry 5), in this case, total conversion is achieved with 0.35 equiv of DLP (87% yield according to ^{1}H NMR, 77% isolated yield). As expected, primary alkyl iodides gave only low yields as demonstrated by the conversion of **1f** to **2f** (entry 6). Indeed, with this substrate, the iodine transfer between the ethyl radical and the primary iodide is nearly thermoneutral; therefore, the chain reaction cannot be very efficient. Iodides resulting from an iodolactonization process are of synthetic interest; however, the presence of a β-acyloxy group slows the reaction,[10] under optimized conditions (method B) yields of 60 and 56% have been reached (entries 7 and 8). When method A was used with these substrates, formation of reduction product (X = H) was observed, presumably occurring by hydrogen atom abstraction from heptane. For substrate **1h**, it is of interest to mention that the classical ionic substitution reaction with sodium azide failed to give the corresponding azide **2h**.[11]

---

(1) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(2) For general review on radical reactions, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1988. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Synthesis*; Wiley: Chichester, 1995. Chatgilialoglu, C.; Renaud, P. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; p 501.

(3) Several reagents have been tested for radical amination. Nitric oxide: Okamoto, T.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1984**, 289. Patel, V. F.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1451. Ghosez, A.; Göbel, T.; Giese, B. *Chem. Ber.* **1988**, *121*, 1807. Veit, A.; Giese, B. *Synlett* **1990**, 166. Nitrite esters: Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1 and references therein. Bertrand, M.-P.; Surzur, J.-M. *Bull. Soc. Chim. Fr.* **1973**, 2393. Kizil, M.; Murphy, J. A. *Tetrahedron* **1997**, *53*, 16847. Girard, P.; Guillot, N.; Motherwell, W. B.; Hay-Motherwell, R.; Potier, P. *Tetrahedron* **1999**, *55*, 3573. Azo compounds: Huisgen, R.; Pohl, H. *Chem. Ber.* **1960**, *93*, 527. Shah, A.; George, M. V. *Tetrahedron* **1971**, *27*, 1291. Baigraie, B. D.; Cadogan, J. I. G.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1065. Beckwith, A. L. J.; Wang, S.; Warkentin, J. *J. Am. Chem. Soc.* **1987**, *109*, 5289. Wang, S. F.; Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1988**, *110*, 7235. Kunka, C. P. A.; Warkentin, J. *Can. J. Chem.* **1990**, *68*, 575. Leardini, R.; Lucarini, M.; Nanni, A.; Nanni, D.; Pedulli, F. G.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1993**, *58*, 2419. Diazirines: Barton, D. H. R.; Jaszberenyi, J. Cs.; Theodorakis, E. A.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 8050. Hydrazine derivatives: Barton, D. H. R.; Le Greneur, S.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 1601. Intramolecular amination via radical addition to imines: Han, O.; Frey, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 8982. Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. Tomaszewski, M. T.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123. Tomaszewski, M. T.; Warkentin, J. *J. Chem. Soc., Chem. Commun.* **1993**, *11*, 966. Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149. Gioanola, M.; Leardini, R.; Nanni, D.; Pareschi, P.; Zanardi, G. *Tetrahedron* **1995**, *51*, 2039. Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. McClure, C. K.; Kiessling, A. J.; Link, J. S. *Tetrahedron* **1998**, *54*, 7121. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838. Depature, M.; Diewok, J.; Grimaldi, J. Hatem, J. *Eur. J. Org. Chem.* **2000**, 275.

(4) During their study of Curtius-type rearrangement based on thermal decomposition of sulfonyl azides, traces of alkyl azides were detected: Abramovitch, R. A.; Holcomb, W. D. *Chem. Commun.* **1969**, 1298. Breslow, D. S.; Martin, F. S.; Newburg, N. R.; Renfrow, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 2273. For mechanistic investigations of radical addition to sulfonyl azides, see: Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1493. For an azidation reaction with TMS-azide initiated by single-electron transfer, see: Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406.

(5) Intramolecular addition to alkyl azide has been reported; after loss of nitrogen, it leads to the formation of aminyl radicals: Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521. Kizil, M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409.

(6) The use allyl and alkenyl ethyl sulfones for tin free radical allylation and alkenylation has been recently reported: Le Guyader, F.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410. Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 2864. Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943. For related procedures using trifluoromethyl sulfones, see: Xiang, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 11986. Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 4163.

(7) Ollivier, C.; Bark, T.; Renaud, P., submitted.

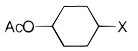
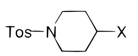
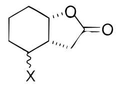
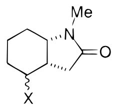
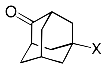
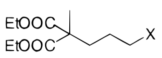
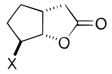
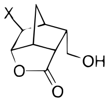
(8) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.

(9) The use of 1 equiv of DLP was in some cases necessary to reach 100% conversion; however, in most cases good conversions were observed with less than 0.5 equiv of DLP.

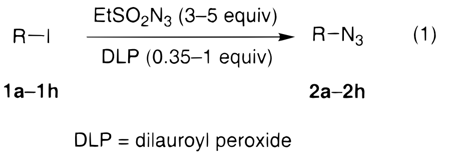
(10) The 2-alkoxy (or β-alkoxy) effect is well-known in radical reactions. Indeed, the nucleophilicity of alkyl radicals is strongly altered by the presence of a vicinal alkoxy substituent. Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 9190 and references therein.

10.1021/ja000673h CCC: $19.00

Table 1. Radical Azidation of Alkyl Iodides According to Eq 1

Entry	R–X	Method[a]	Yield [%]
1	 **1a**: X = I (*cis*/*trans* 59:41) **2a**: X = N_3 (*cis*/*trans* 54:46)	A	84
2	 **1b**: X = I **2b**: X = N_3	A	81
3	 **1c**: X = I (*exo*) **2c**: X = N_3 (*exo*/*endo* 74:26)	B	80
4	 **1d**: X = I (*exo*) **2d**: X = N_3 (*exo*/*endo* 80:20)	B	77
5	 **1e**: X = I **2e**: X = N_3	A	77 (87)[b]
6	 **1f**: X = I **2f**: X = N_3	B	24
7	 **1g**: X = I **2g**: X = N_3 (*exo*/*endo* 82:12)	B	60
8	 **1h**: X = I (*exo*) **2h**: X = N_3 (*exo*)	B	56

[a] Method A: 3 equiv of $EtSO_2N_3$ in refluxing chlorobenzene/heptane (1:1), DLP (0.35−1 equiv) as initiator; method B: 5 equiv of $EtSO_2N_3$ in chlorobenzene at 100 °C, DLP (0.35−1 equiv) as initiator. [b] Yield according to ^{1}H NMR.

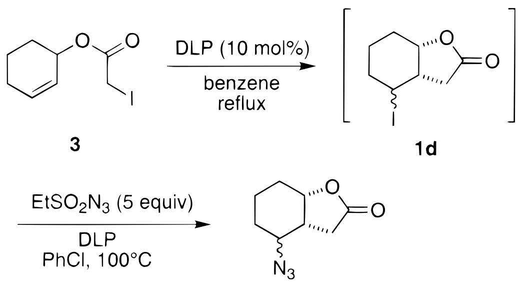


1a–1h **2a–2h**

DLP = dilauroyl peroxide

Interestingly, the azidation procedure can be combined with an iodine atom transfer carbon−carbon bond formation in a one-pot procedure. A typical example is depicted in Scheme 2. The α-iodoester **3** gave, upon treatment with DLP in benzene, the bicyclic iodide **1d**[7] that, after replacing benzene by chlorobenzene and treatment with ethanesulfonylazide (method A), gave the azide **2d** in 80% overall yield.

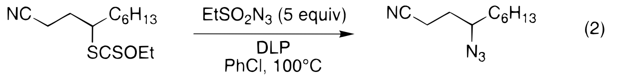
Scheme 2



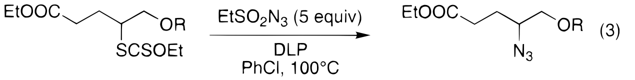
3 **1d**

DLP = dilauroyl peroxide **2d** (80%, *exo/endo* 74:26)

The use of dithiocarbonates as radical precursors was then investigated. For instance, when the dithiocarbonate **4** was treated with ethanesulfonylazide under method B, the azide **5** was obtained in 85% isolated yield (equation 2). 2-Alkoxylated radicals react also efficiently with ethanesulfonyl azide as shown by the conversion of **6a** and **6b** to **7a** and **7b**, respectively (equation 3). In a similar way, the anomeric dithiocarbonate **8** gave the anomeric azide **9** as a single α-anomer in 74% yield (equation 4).[12] Such anomeric azides are of considerable interest for the preparation of *N*-linked glycoconjugates. Interestingly, the α-isomers are more difficult to prepare by classical nucleophilic displacement with azide anion.[13]

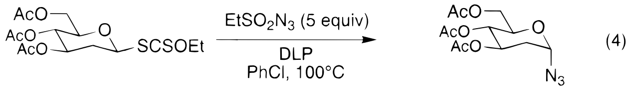


4 **5** 85%



6a (R = OEt)
7a (R = OAc)

6b (R = OEt, 67%)
7b (R = OAc, 72%)



8 **9** 74%

In conclusion, we have presented here a new radical approach to make alkyl azides that is complementary to the well-established electrophilic and nucleophilic azidation processes. The starting material can be either secondary or tertiary alkyl iodides as well as dithiocarbonates. This method is based on easily available and cheap reagent such as ethanesulfonylazide and dilauroyl peroxide (DLP). Moreover, one of the main drawbacks of many radical processes, that is, the use of tin derivatives, could be overcome by using an approach based on atom or group transfer reactions. The possibility of running a one-pot transformation involving carbon−carbon bond formation and azidation offers new opportunities in total synthesis

Acknowledgment. This work was funded by the *Fonds National Suisse de la Recherche Scientifique*.

Supporting Information Available: Detailed experimental procedures and spectral data for compounds **1**−**9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000673H

---

(11) A 0.5 M solution of the iodide **1h** in DMF was heated at 70 °C during 8 h in the presence of 2 equiv of NaN_3. The starting material was recovered in 69%. No trace of **2h** was detected by GC analysis.

(12) The stereochemistry is in accordance with related radical reactions involving anomeric radicals: Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed.* **1983**, *22*, 622.

(13) Soli, E. D.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 9724 and references therein.