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A Convenient Tin-Free Procedure for Radical Carboazidation and Azidation

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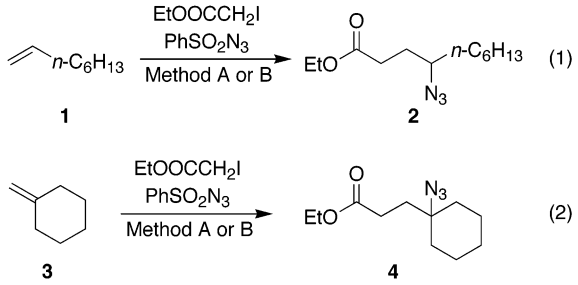
Abstract: The radical carboazidation of alkenes has been achieved in water with triethylborane as initiator. This efficient process is complete in 1 h at room temperature in an open system. These new tin-free carboazidation conditions are environmentally friendly and allow running reactions with an excess of either the alkene or the radical precursor. They are also suitable for simple radical azidation of alkyl iodides as well as for more complex cascade reactions involving annulation processes.

We recently reported a useful radical carboazidation of alkenes and its application toward concise synthesis of the core of different alkaloids.[1,2] This efficient procedure uses hexabutylditin as the chain transfer reagent. Organotin reagents are widely used in radical chemistry, especially because they are known to sustain efficiently radical chains.[3] However, their toxicity and the difficulties encountered to remove traces of tin byproducts greatly limit their use for preparative purposes. The development of tin-free conditions for the carboazidation reaction is therefore strongly needed.[4] Furthermore, several total syntheses of natural compounds under investigation in our laboratories are based on the carboazidation of structurally complex alkenes. Since these alkenes are produced through multistep syntheses, we became very concerned about the need to use them in a 2-fold excess to achieve carboazidation in high yield. Ideally, the new conditions should work equally well with an excess of either the radical precursor or the alkene.

Radical azidation with ethanesulfonyl azide and dilauroyl peroxide (DLP) was the first system developed for tin-free azidation.[5,6] These reaction conditions proved to be problematic for carboazidation reactions. Indeed, large amounts of DLP as initiator are necessary for the reaction to proceed to completion and side products resulting from the decomposition of DLP considerably complicate the purification of the final products. Recently, Oshima demonstrated that the system triethylborane/oxygen is a general and efficient method for radical initiation[7,8] that is particularly suitable to run atom transfer reactions.[9,10] Since radical carboazidations are occurring via an initial transfer of iodine atom or xanthate group, the triethylborane method became an obvious choice for us. Furthermore, Oshima reported excellent results by running reactions in aqueous media.[11]

We started our investigations by testing this initiation system on the carboazidation of alkenes **1** and **3** leading to azides **2** and **4** (Scheme 1, eqs 1 and 2). The results are summarized in Table 1. The ditin-mediated reactions (method A) have already been reported and proceed in good yield (entries 1 and 4).[2] The triethylborane-induced reactions (method B) gave slightly higher yields with water as solvent (entries 2 and 5). Running the reaction in a 2.3:1 mixture of ethanol/water or in pure ethanol gave very similar yields (entries 3 and 6).

SCHEME 1. Tin-Mediated and Triethylborane-Induced Carboazidations[a]



[a] Reagents and conditions: (method A) alkene (2 equiv), $EtOOCCH_2I$ (1 equiv), $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), DTBHN (6 mol %), N_2, C_6H_6, 80 °C, 4 h; (method B) alkene (2 equiv), $EtOOCCH_2I$ (1 equiv), $PhSO_2N_3$ (3 equiv), Et_3B (2.5 equiv), air, H_2O or EtOH/H_2O 2.3:1, 25 °C, 75 min. DTBHN = di-*tert*-butylhyponitrite.

TABLE 1. Carboazidations According to Scheme 1

entry	alkene	method	solvent	azide, yield
1	**1**	A	benzene	**2**, 79%
2	**1**	B	H_2O	**2**, 85% (71%[a])
3	**1**	B	EtOH/H_2O	**2**, 81% (78%,[b] 70%[a])
4	**3**	A	benzene	**4**, 89%
5	**3**	B	H_2O	**4**, 90% (79%[a])
6	**3**	B	EtOH/H_2O	**4**, 88% (77%[a])

[a] Yield based on the alkene; reaction performed with alkene (1 equiv), $EtOOCCH_2I$ (1.2 equiv), and Et_3B (3 equiv). [b] In pure EtOH.

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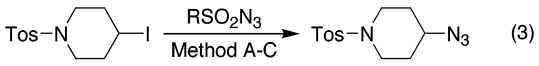
SCHEME 2. Azidation of an *N*-Protected Iodopiperidine[a]



5 **6**

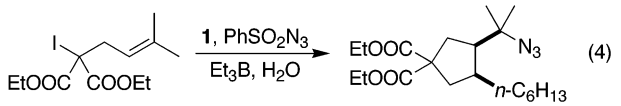
[a] Reagents and conditions: (method A) **5** (1 equiv), $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), DTBHN (6 mol %), N_2, C_6H_6, 80 °C, 4 h, 89%; (method B) **5** (1 equiv), $PhSO_2N_3$ (3 equiv), Et_3B (3 equiv), air, CH_2Cl_2, 25 °C, 75 min, 80%; (method C) **5** (1 equiv), $EtSO_2N_3$ (3 equiv), DLP (0.6 equiv), ClC_6H_5/heptane, reflux, 12 h, 81%. DTBHN = di-*tert*-butylhyponitrite.

In contrast to Oshima's results for atom transfer reactions,[12] the nature of the solvent does not affect effectively the yields, even if slightly better results were obtained when water was used as solvent. Carboazidation with an excess of ethyl 2-iodoacetate was also examined (entries 2, 3, 5, and 6, yield in hyphens). For this procedure, 1.2 equiv of radical precursor was loaded and 3 equiv of triethylborane was added to reach reaction completion. Despite a minor decrease in yield, these conditions nicely extend the scope of our carboazidation process by providing the opportunity to choose a procedure adapted to a defined synthetic strategy (excess of alkene versus excess of iodide).[13] Interestingly, the triethylborane procedure does not only allow us to avoid the use of tin and benzene but it also permits us to reduce considerably the reaction time and to suppress the heating as well as the work under an inert atmosphere. Nevertheless, an excess of triethylborane should be added since the reaction is not a chain process in contrast to our initial expectations.[14,15]

The simple azidation of *N*-tosyl-4-iodopiperidine (**5**) was investigated next (Scheme 2, eq 3). The reaction was conducted according to method B in water and then in ethanol/water 2.3:1 but unreacted **5** was always recovered along with azide **6** in low yield. These disappointing results are caused by the low solubility of **5** in both water and ethanol. Gratifyingly, running the reaction in methylene chloride gave **6** in 80% yield. This demonstrates again the convenience and the efficiency of the newly developed procedure since **6** was synthesized with similar yields using the DLP-induced azidation (method C, 81%) and the ditin-mediated reaction (method A, 89%).[6]

To test further the utility of this tin-free procedure, a tandem radical annulation−azidation was examined. The one-pot radical addition of the iodomalonate **7** to 1-octene followed by successive cyclization and azidation gave the tertiary azide **8** in 72% yield as a 4:1 inseparable mixture of diastereomers (Scheme 3, eq 4).[16] The cis stereochemistry was assigned to the major isomer on the basis of a literature precedent.[17]

SCHEME 3. Tin-Free Tandem Radical Annulation−Azidation[a]



7 **8** (72%, cis/trans 4:1)

[a] Reagents and conditions: **7** (1 equiv), **1** (2 equiv), $PhSO_2N_3$ (3 equiv), Et_3B (2.5 equiv), air, H_2O, 25 °C, 75 min.

In conclusion, we report here an efficient and convenient procedure that allows the running of simple azidation as well as carboazidation and more complex tandem reactions. Compared to previously reported methods, this procedure allows work under tin-free conditions and benzene is advantageously replaced by water. When required (for instance for solubility reasons), other solvents are fully compatible with these reaction conditions. Finally, the reaction is run in an open system within 1 h at room temperature. These improvements are expected to render radical azidation processes more suitable for preparative purposes. Applications in the total synthesis of nitrogen-containing biologically active compounds are currently being investigated, encouraged by the possibility of using an excess of either the radical precursor or the alkene.

Experimental Section

General Techniques. The 2 M solution of Et_3B in dry EtOH was freshly prepared and kept under N_2. EtOH was distilled from magnesium ethoxide under N_2. Other reagents were obtained from commercial sources and used as received. Flash column chromatography (FC): SdS silica gel (0.063−0.200 mm); EtOAc and hexane as eluents. Thin-layer chromatography (TLC): Macherey-Nagel SIL G-25 UV_{254} precoated TLC plates; detection either with UV or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (3 mL) in H_2O (300 mL) and subsequent heating. NMR spectroscopy: chemical shifts δ in ppm relative to $CHCl_3$ for ^1H (δ = 7.26 ppm) and $CDCl_3$ for ^{13}C (δ = 77.0 ppm).

Caution: Since sulfonyl azides are capable of exploding, it is strongly recommended to apply standard safety rules and to use a safety shield.

General Procedure. A 2 M solution of Et_3B in dry EtOH was added at room temperature over 1 h by using a syringe pump to an open-air vigorously stirred mixture of radical precursor, alkene, and $PhSO_2N_3$ in solvent (*important*: the needle should be immersed into the reaction mixture to avoid direct contact of Et_3B drops with air). The reaction was stirred for 15 min more and hexane (5 mL) was added. After separation, the aqueous layer was extracted with Et_2O and the combined organic phases were washed with brine and dried over Na_2SO_4. The crude product was purified by FC (hexane/EtOAc).

Ethyl 4-Azidodecanoate (2). (a) **2** was prepared according to the general procedure given above from ethyl 2-iodoacetate (214 mg, 1.0 mmol), 1-octene (0.31 mL, 2.0 mmol), $PhSO_2N_3$ (550 mg, 3.0 mmol), and Et_3B (1.25 mL, 2.5 mmol) in water (2.0 mL). Two successive FC (hexane/EtOAc 95:5) gave **2** (205 mg, 85%) as a colorless oil. Physical and spectral data were in accordance with literature data.[2] ^1H NMR (360 MHz, $CDCl_3$) δ 4.15 (q, J = 7.3 Hz, 2H), 3.35−3.27 (m, 1H), 2.50−2.31 (m, 2H), 1.95−1.81 (m, 1H), 1.80−1.64 (m, 1H), 1.62−1.21 (m, 10H), 1.26 (*t*, J = 7.3

(12) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776.

(13) The use of dithiocarbonates as radical precursors for the Et_3B-induced azidation was also examined. Surprisingly, their conversion into azides proved to be less efficient than under the previously reported tin-mediated conditions. For example, azide **2** was isolated in 51%, using method B starting from ethoxythiocarbonylsulfanyl acetate.

(14) A chain reaction was proposed for the bromination of tributylborane with benzenesulfonyl bromide: (a) Davies, A. G.; Roberts, B. P. *Acc. Chem. Res.* **1972**, *5*, 387. (b) Davies, A. G.; Roberts, B. P.; Sanderson, B. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 626.

(15) For a detailed discussion of the mechanism of the carboazidation process, see ref 2.

(16) The iodomalonate **7** has to be freshly prepared to obtain reproducible yields.

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Hz, 3H), 0.89 (*t*, J = 6.8 Hz, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) 173.0, 62.2, 60.5, 34.4, 31.6, 30.9, 29.5, 29.0, 26.0, 22.5, 14.2, 14.0.

(b) **2** was prepared according to the general procedure given above from 1-octene (112 mg, 1.0 mmol), ethyl 2-iodoacetate (257 mg, 1.2 mmol), $PhSO_2N_3$ (550 mg, 3.0 mmol), and Et_3B (1.50 mL, 3.0 mmol) in water (2.0 mL). Two successive FC (hexane/EtOAc 95:5) gave **2** (172 mg, 71%).

Ethyl 3-(1-Azidocyclohexyl)propanoate (4). (a) **4** was prepared according to the general procedure given above from ethyl 2-iodoacetate (214 mg, 1.0 mmol), methylenecyclohexane (0.24 mL, 2.0 mmol), $PhSO_2N_3$ (550 mg, 3.0 mmol), and Et_3B (1.25 mL, 2.5 mmol) in water (2.0 mL). Two successive FC (hexane/EtOAc 95:5) gave a 82:18 mixture of **4** and $PhSO_2N_3$ containing **4** (202 mg, 90% according to ^{1}H NMR) as a colorless oil. Physical and spectral data were in accordance with literature data.[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, J = 7.2 Hz, 2H), 2.42−2.38 (m, 2H), 1.90−1.87 (m, 2H), 1.71−1.65 (m, 2H), 1.62−1.51 (m, 5H), 1.40−1.24 (m, 3H), 1.27 (*t*, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 63.3, 60.6, 34.7, 34.4, 28.6, 25.3, 22.0, 14.2.

(b) **4** was prepared according to the general procedure given above from methylenecyclohexane (96 mg, 1.0 mmol), ethyl 2-iodoacetate (257 mg, 1.2 mmol), $PhSO_2N_3$ (550 mg, 3.0 mmol), and Et_3B (1.50 mL, 3.0 mmol) in water (2.0 mL). Two successive FC (hexane/EtOAc 95:5) gave a 60:40 mixture of **4** and $PhSO_2N_3$ containing **4** (178 mg, 79% according to ^{1}H NMR).

4-Azido-1-[(4-methylphenyl)sulfonyl]piperidine (6). 6 was prepared according to the general procedure given above from **5** (365 mg, 1.0 mmol, prepared from 3-hydroxypiperidine according to a literature procedure),[6] $PhSO_2N_3$ (550 mg, 3.0 mmol), and Et_3B (1.5 mL, 3.0 mmol) in CH_2Cl_2 (2.0 mL). Water (5 mL) was added instead of hexane once 15 min of additional stirring was performed. After separation, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. FC (hexane/EtOAc 85:15) gave **6** (225 mg, 80%) as a white solid. Physical and spectral data were in accordance with literature data.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 3.55−3.46 (m, 1H), 3.31−3.21 (m, 2H), 2.94−2.85 (m, 2H), 2.44 (s, 3H), 1.99−1.90 (m, 2H), 1.78−1.68 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 132.9, 129.7, 127.6, 56.0, 43.3, 29.8, 21.5.

Diethyl 3-(1-Azido-1-methylethyl)-4-hexyl-1,1-cyclopentanedicarboxylate (8). 8 was prepared according to the General Procedure given above from **7** (354 mg, 1.0 mmol, prepared from diethyl malonate, 4-bromo-2-methylbut-2-ene, and NaH followed by iodine and NaH according to literature procedures),[18,19] 1-octene (0.31 mL, 2.0 mmol), $PhSO_2N_3$ (550 mg, 3.0 mmol), and Et_3B (1.25 mL, 2.5 mmol) in water (2.0 mL). Two successive FC (hexane/EtOAc 96:4) gave **8** (275 mg, 72%) as a colorless 4:1 mixture of two isomers (inversed-gated decoupling ^{13}C NMR).

8-major: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26−4.08 (m, 4H), 2.54−1.75 (m, 6H), 1.58−1.00 (m, 22H), 0.91−0.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 173.1, 172.6, 61.6, 61.4 ($2CH_2$), 57.8, 52.8, 40.7, 37.5, 33.4, 31.9, 29.4, 28.1, 28.0, 26.9, 25.6, 22.6, 14.1, 14.0 ($2CH_3$).

8-minor: ^{13}C NMR (100 MHz, $CDCl_3$) 172.4, 172.0, 63.4, 59.0, 53.8, 40.1, 39.4, 36.3, 36.2, 31.8, 29.3, 28.2, 25.4, 24.1, 22.6 characteristic signals.

Mixture of isomers **8**: IR (film) 2957, 2931, 2872, 2857, 2100, 1732, 1464, 1446, 1390, 1368, 1256, 1180, 1107 cm^{-1}. MS (ESI, MeOH/H_2O/HCOOH 70:25:5) *m*/*z* (%) 404 (MNa^+, 38), 354 (77), 340 (52), 339 (100), 265 (47), 191 (28). Anal. Calcd for $C_{20}H_{35}N_3O_4$ (381.51): C, 62.96; H, 9.25; N, 11.01. Found: C, 62.99; H, 9.23; N, 11.08.

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