Acceleration of Azidation by Microwave Irradiation

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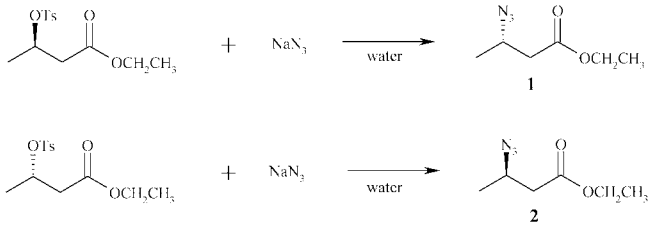
Azides are versatile intermediates in organic synthesis, since they can be used for the preparation of a variety of amines or amino compounds that show interesting biological activities.[1-5] As simpler, milder and more efficient methods for the reduction of azides to amines have been developed,[5,6] azides have recently been drawing much attention in synthetic organic chemistry. In the context of our recent studies, it has also been shown that β-amino acids can be prepared from indium-mediated reduction of the corresponding azides that are transformed chemically from microbial polymer polyhydroxyalkanoates (PHAs).[7] In connection with our ongoing research project for the synthesis of biologically active modified peptides containing β-amino acids,[8] we require a simple and fast preparation of azides which can serve for reductive process resulting in amines or amino compounds.

We describe use of microwave to promote a reaction of tosylates with azide ion. Many reactions have been accelerated by the use of microwave,[9] but application to azide introduction represents a particular useful transformation. Although considered a good nucleophile, azides often react very slowly with many halides and other alkylating agents. Such reactions cannot usually be heated since the product azides frequently decompose or have the hazardous nature in general.[1] Thus the microwave assisted process will be of interest to many chemists who work with azides.

In this paper, we report a novel, simple and efficient method for the preparation of azides using a microwave technique[9] which has been employed to reduce pollution at the source and to increase atom economy.[10]

Synthesis of optically active ethyl 3-azidobutyrates. Ethyl (*S*)-(+)-3-azidobutyrate (**1**) and ethyl (*R*)-(−)-3-azidobutyrate (**2**) were prepared by stirring of the corresponding tosylates with sodium azide at room temperature for 12 h (Scheme 1).[7] It should be noted that no conventional heating under reflux was employed in order to effect this reaction with the desired configuration at the chiral center. Transposition of this procedure to a domestic microwave oven led to a huge reduction of the reaction time (5 min) in similar yield with desired configurations (Table 1). The very rapid rise of temperature of reactants via microwave irradiation favors some reaction pathways over others and thus leads to selectivity and hence cleaner products.[9d]



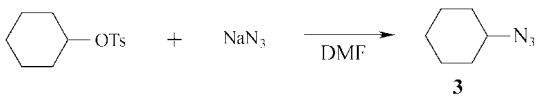
Scheme 1

Table 1. Results on the preparation of optically active ethyl 3-azidobutyrates (**1** and **2**)

Product	Conventional method			Microwave irradiation		
	Time	Yield	$[\alpha]_D$[a]	Time	Yield	$[\alpha]_D$[a]
1	12 h	76%	+41°	5 min	78%	+42°
2	12 h	78%	-35°	5 min	82%	-35°

[a](*c* 1, $CHCl_3$).

Synthesis of alkyl azides. Cyclohexyl azide (**3**) was prepared by the heating of the corresponding tosylate with sodium azide in *N*,*N*-dimethylformamide (DMF) at 90 °C for 12 h (Scheme 2).[7] Transposition of this procedure to a domestic microwave oven led to a huge reduction of the reaction time (3 min) in a similar yield (91%) (Table 2). A simple conical flask with a loose cover was used as a reaction vessel, and no stirrer was used since the reactants



Scheme 2

Table 2. Results on the preparation of alkyl azides **3** and **4**

Product	Conventional heating			Microwave irradiation		
	Time[a]	Temp.	Yield	Time[a]	Temp.[b]	Yield
3	12 h	90 °C	91%	5 min	90 °C	92%
4	12 h	90 °C	92%	5 min	90 °C	94%

[a]The progress of reaction was monitored by the thin layer chromatography every minute. [b]The approximate temperature of the reaction mixture was determined by using a thermometer immediately after the microwave irradiation was stopped, and the temperature of the reaction mixture was controlled by a beaker of water as a heat sink.[9d]

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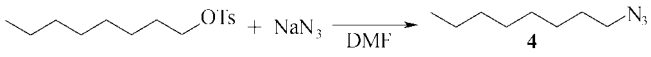

Scheme 3

are energized directly due to the characteristic heating properties of microwave. Since DMF has a reasonably high boiling point (153 °C) and a substantial dipole resulting in absorption of microwave, it was used as the reaction medium as in conventional heating. Octyl azide (**4**) was also prepared in DMF by both conventional heating and microwave irradiation (Scheme 3), and the results are summarized in Table 2.

In summary, we have developed a novel, simple and efficient method for the small- scale preparation of azides for laboratory use in which tosylates were treated with sodium azide in water or DMF under microwave irradiation to afford the corresponding azides **1-4** in quantitative yields. The results obtained with azides demonstrated the generality of the reaction. This methodology is expected to be applicable to the simple and efficient preparation of amines or amino compounds from the corresponding alcohols or hydroxy compounds via rapid microwave assisted synthesis of azides. Currently, we are in the process of using this method for the preparation of β-amino acids from diverse members of microbial polyester PHAs[11] as a chiral pool, the results of which will be reported in due course.

Experimental Section

Flash column chromatography was performed on silica gel 60 (230-400 mesh, Merck) and all chromatographic separations were monitored by TLC analyses, performed using glass plates precoated with 0.25-mm, 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Optical rotations were measured on a JASCO DIP-181 Digital Polarimeter. IR spectra were recorded on a Bomen MB154 FTIR (KBr pellets or neat). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 500-MHz FTNMR spectrometer in $CDCl_3$, DMSO-d_6, or D_2O solution, and chemical shifts were recorded in ppm units using $SiMe_4$ as an internal standard. Mass spectra were measured on a Varian MAT 371 Mass Spectrometer at 70 eV.

Preparation of Ethyl (*S*)-(+)-3-azidobutyrate (**1**).

Conventional method[7]: Reaction mixture of tosylate (854 mg, 2.98 mmol), hexadecyltributylphosphonium bromide (150 mg, 0.30 mmol) and sodium azide (387 mg, 5.96 mmol) in water (2.5 mL) was vigorously stirred at room temperature. After 12 h, ether (20 mL) was added and the organic layer was collected and dried over sodium sulfate. Evaporation under reduced pressure gave 355 mg (76%) of the title compound as a light-yellow oil: $[\alpha]_D$ +41° (*c* 1, $CHCl_3$); IR (neat) 2982, 2936, 2122, 1742, 1377, 1295, 1254, 1185, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (q, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.34 (d, *J* = 6.5 Hz, 3H, $CH_3CH(N_3)$), 3.95-4.04 (m, 1H, CHN_3), 4.18 (q, *J* = 7.0 Hz, 2H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 14.17, 19.51, 41.17, 54.34, 60.87, 170.56; CIMS, *m/z* 157 (M^+), 155, 149, 131, 115, 91 (base), 88, 84, 73, 70, 69, 60, 57, 56, 55, 49.

Microwave method: Reaction mixture of tosylate (854 mg, 2.98 mmol), hexadecyltributylphosphonium bromide (150 mg, 0.298 mmol) and sodium azide (387 mg, 5.96 mmol) in water (5 mL) was irradiated in a domestic microwave oven at an output of 1000 watts for 5 min. The progress of azidation was monitored by TLC analysis every minute. Water (100 mL) was placed in another vessel and irradiated simultaneously. After cooling to room temperature, ether (20 mL) was added and the organic layer was collected and dried over sodium sulfate. Evaporation under reduced pressure gave 365 mg (78%) of the title compound as a light-yellow oil: $[\alpha]_D$ +42° (*c* 1, $CHCl_3$); IR (neat) 2982, 2936, 2122, 1745, 1377, 1295, 1254, 1185, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (q, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1,34 (d, *J* = 6.5 Hz, 3H, $CH_3CH(N_3)$), 3.95-4.04 (m, 1H, CHN_3), 4.18 (q, *J* = 7.0 Hz, 2H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.5, 41.2, 54.3, 60.9, 170.6; CIMS, *m/z* 157 (M^+), 155, 149, 131, 115, 91 (base), 88, 84, 73, 70, 69, 60, 57, 56, 55, 49.

Preparation of Ethyl (*R*)-(-)-3-azidobutyrate (**2**) Same as **1** except for the opposite sign of the specific rotation: $[\alpha]_D$ -35° (*c* 1, $CHCl_3$).

Preparation of Cyclohexyl azide (**3**).

Conventional method[7]: Reaction mixture of tosylate (765 mg, 3.00 mmol) and sodium azide (390 mg, 6.00 mmol) in DMF (5.0 mL) was heated at 90 °C for 12 h. After cooling to room temperature, ether (20 mL) was added and the organic layer was washed with water, collected and dried over sodium sulfate. Evaporation under reduced pressure and flash column chromatography gave 341 mg (91%) of the title compound as a light-yellow oil.

Microwave method: Reaction mixture of tosylate (765 mg, 3.00 mmol) and sodium azide (390 mg, 6.00 mmol) in DMF (5.0 mL) was irradiated in a domestic microwave oven at an output of 1000 watts for 5 min. The progress of azidation was monitored by TLC analysis every minute. Water (100 mL) was placed in another vessel and irradiated simultaneously. After cooling to room temperature, ether (20 mL) was added and the organic layer was collected, washed with water and dried over sodium sulfate. Evaporation under reduced pressure and flash column chromatography gave 345 mg (92%) of the title compound as a light-yellow oil: IR (neat) 3116, 2306, 2097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15-1.45 (m, 5H), 1.60-1.65 (m, 1H), 1.70-1.82 (m, 2H), 1.85-1.95 (m, 2H), 3.34 (m, 1H, N_3CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 24.3, 25.3, 31.6, 59.9; CIMS, *m/z* 125 (M^+), 68, 55, 49 (base), 54, 40, 26.

Preparation of Octyl azide (4): IR (nujol) 2955, 2900, 2845, 2310, 2090, 1465, 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.1 Hz, 3H, CH_3), 1.12-1.82 (m, 12H), 3.49 (t, *J* = 6.5 Hz, 2H, CH_2N_3); ^{13}C NMR ($CDCl_3$) δ 28.6, 29.9, 31.2, 51.2; CIMS, *m/e* 155 (M^+), 113, 85, 71, 57, 43 (base), 41, 29.

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