A Practical Procedure for the Synthesis of Alkyl Azides at Ambient Temperature in Dimethyl Sulfoxide in High Purity and Yield

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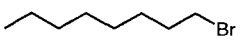
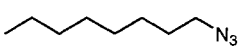
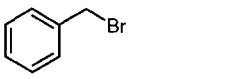
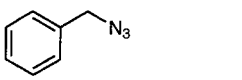
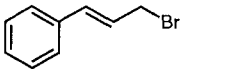
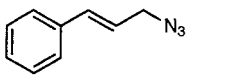
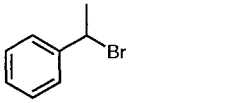
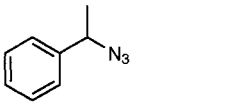
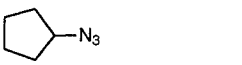
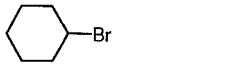
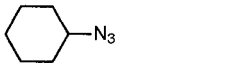
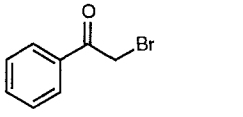
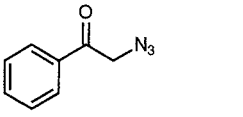
Described is the often neglected, but very efficient, procedure for the preparation of primary and secondary alkyl and cycloalkyl azides in excellent purity and high yields. At ambient temperature conditions, the alkyl azides were readily obtained from alkyl bromides by the nucleophilic substitution of bromide with 1.1 equivalents of sodium azide in dimethyl sulfoxide (DMSO). This facile and practical procedure provides highly pure products and eliminates the hazards associated with distillation of alkyl azides.

As part of our successful program on the reduction of functional groups utilizing the novel lithium aminoborohydride ($LiABH_3$) reagents,[1] we directed our efforts toward the synthesis and reduction of alkyl azides.[2] Alkyl azides are useful organic intermediates[3] for the preparation of various nitrogen containing functional groups, some of which are important in medicinal chemistry.[4]

The literature reports a plethora of procedures for the synthesis of alkyl azides.[5] One of the most common methods for the synthesis of primary and secondary alkyl azides is the nucleophilic substitution of bromide with sodium azide[6] or lithium azide[7] from the corresponding alkyl bromide in various solvents. However, these methodologies all suffer from either complex procedures, long reaction times, high heating temperatures, and low yields. In addition, the greatest difficulty in purification of the product when the reaction is incomplete is that some alkyl azides decompose rapidly with danger of explosion[8] when one attempts distilling.[9] Furthermore, alkyl azides, generally, have boiling temperatures adjacent to the corresponding alkyl bromides.[10] Thus, we decided to initiate a systematic study of the versatility of the nucleophilic substitution of bromide utilizing NaN_3 in DMSO at ambient temperature. Herein, we discuss the successful preparation, in high yield, of various primary and secondary alkyl and cycloalkyl azides in excellent purity and which avoids the hazards associated with distillation of alkyl azides.

After preparing several solutions of reagent-grade DMSO with varying amounts of NaN_3 and vigorously stirring for 24 hours at 25 °C, our studies indicated that the maximum concentration for complete dissolution of

Table. Alkyl Azides Prepared from Alkyl Bromides and 1.1 equiv of NaN_3 in DMSO at Ambient Temperature

Entry	Alkyl Bromide	Product	Reaction Time (h)	Isolated Yield (%)[a]	IR[b] (neat) ν_{as} (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
1			4	99	2095.3	0.88 (3H, t, J = 6.87), 1.28–1.39 (10H, m), 1.60 (2H, p, J = 6.94), 3.35 (2H, t, J = 6.94)	14.08, 22.65, 26.75, 28.86, 29.16, 31.78, 51.51
2			1	98	2094.4	4.35 (2H, s), 7.26–7.45 (5H, m)	54.84, 128.29, 128.37, 128.90, 135.42
3			1	98	2095.5	3.94–3.97 (2H, dd, J = 6.57, J = 0.77), 6.20–6.32 (1H, dt, J = 15.77, J = 6.57), 6.64 (1H, d, J = 15.77), 7.26–7.45 (5H, m)	53.08, 122.45, 126.71, 128.26, 128.74, 134.60, 136.05
4			1	98	2102.2	1.56 (3H, d, J = 6.80), 4.64 (1H, q, J = 6.80), 7.32–7.46 (5H, m)	21.64, 61.16, 126.45, 128.20, 128.84, 140.94
5			9	98	2099.0	1.59–1.83 (8H, m), 3.93–3.97 (1H, m)	23.52, 32.11, 62.97
6			360 1.5[c]	80[d] 82[d]	2087.4	1.22–1.33 (10H, m), 3.27–3.36 (1H, m)	24.26, 25.30, 31.64, 59.93
7			1	complex mixture	–	–	–

[a] Purity confirmed by ^1H and ^{13}C NMR and capillary GC.
[b] Asymmetric stretching frequencies for C-N_3.
[c] Heated at 70–75 °C.
[d] GC analyses, prior to removal of solvent, indicated a mixture of 88% azidocyclohexane and 12% cyclohexene.

NaN_3 in DMSO was 0.5 M.[11] Thus a standard stock solution of 0.5 M NaN_3 in DMSO for subsequent use was prepared. For our preliminary studies, all the reactions were monitored by periodically taking aliquots and analyzing them by capillary GC. To ensure the essentially quantitative transformation of the alkyl bromides to the corresponding alkyl azides at ambient temperature, only 1.1 equiv of NaN_3 was satisfactory. The data obtained is shown in the Table.

The results summarized in the Table for the nucleophilic transformation of alkyl bromides to the corresponding alkyl azides demonstrates that this methodology is of general applicability at ambient temperature. Notably (3-bromoprop-1-enyl)benzene provided, exclusively, the S_N2 product (3-azidoprop-1-enyl)benzene[12] (98%) in 1 h while the S_N2' product was not detected by high field NMR and GC (Entry 3). By gently heating at 70–75 °C for 1.5 h, bromocyclohexane afforded a mixture of azidocyclohexane and cyclohexene (88:12). The generated cyclohexene was readily removed by reduced pressure (20 Torr) to afford cleanly the azidocyclohexane in 82% yield (Entry 6). In contrast, it was reported that the reaction of bromocyclohexane with 6 equiv of NaN_3 and heating at 120 °C for 15 h provided the azidocyclohexane after cautious distillation of the crude mixture.[13]

In all the reactions, the purity of the isolated product was confirmed by high field ^1H and ^{13}C NMR, GC, and FT-IR. Without any further purification, these highly pure alkyl azides were utilized as substrates for $LiABH_3$ reductions.[14]

In summary, we have described the ambient temperature preparative method of alkyl azides from alkyl bromides by nucleophilic substitution of bromide with sodium azide in DMSO. This efficient procedure affords primary and secondary alkyl and cycloalkyl azides in high yield and excellent purity, thus avoiding the hazards associated with distillation of alkyl azides.

General Procedure:

A stock solution of 0.5 M NaN_3 in DMSO was prepared by stirring the solution for 24 hours at 25 °C. To a 100 mL round-bottom flask equipped with a magnetic stir bar, was added a 0.5 M solution of NaN_3 (0.715 g, 11 mmol) in DMSO (22 mL) at 25 °C. To this solution was added the alkyl halide (10 mmol), and the mixture was stirred until all the starting material had been consumed, as observed by GC analyses. The reaction was quenched with H_2O (50 mL) [slightly exothermic] and stirred until it cooled to r.t. The mixture was extracted with Et_2O (3 × 30 mL); the Et_2O extracts were washed with H_2O (2 × 50 mL) and once with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed in vacuo (20 Torr) to afford the pure alkyl azides (Table).

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