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A practical one-pot synthesis of azides directly from alcohols

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Abstract. Alkyl/benzyl azides can be readily synthesized in excellent yields from their corresponding alcohols by stirring a solution of sodium azide in DMSO with a thoroughly ground equimolecular mixture of triphenylphosphine, iodine and imidazole.

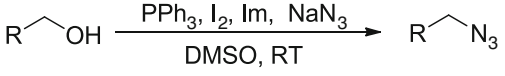
Keywords. Alcohol; azide; triphenylphosphine; iodine; imidazole; chemoselective.

1. Introduction

Azide is one of the most versatile functional groups in organic synthesis owing to the fact that it is the most convenient source of amines, which are very common in natural products as well as pharmaceutical heterocycles.[1] Additionally, the stability of azides under physiological conditions and their inimitable reactivity patterns make them one of the most sought-after functionalities in click chemistry[2] as well as in bioconjugation *via* Straudinger ligation.[3] Therefore, the development of efficient protocols for the synthesis of azide using easily available, yet efficient reagent systems is of immense importance. In spite of the availability of a wide range of indirect methods, the most common being the substitution of alkyl halides with inorganic azides, direct methods for the said transformation are only a few. The most familiar and versatile one is the Mitsunobu displacement,[4] where hydrazoic acid is used as azide source in the presence of diethyl azadicarboxylate (DEAD) and triphenylphosphine as hydroxyl group activator. As hydrazoic acid is considered a health hazard, a few modifications of the Mitsunobu displacement reaction have surfaced, which include the use of diphenyl phosphorazidate (DPPA),[5] *bis*(*p*-nitrophenyl)phosphorazidate,[6] zinc azide/*bis*-pyridine complex,[7] *bis*(2,4-dichlorophenyl) phosphate/NaN_3,[8] N-(*p*−toluenesulphonyl)imidazole/NaN_3/Et_3N/TBAI.[9] In a bid to replace expensive DEAD from Mitsunobu reagent, Hendrickson and Hussoin[10] reported the use of triphenylphosphonium anhydride trifluoromethanesulphonate, which has the advantage of recyclability by treating with trifluoromethanesulphonic anhydride (Tf_2O). But the method suffers from a serious disadvantage of generation of olefins from secondary alcohols.[11] An efficient alternative to DEAD was reported by Lee *et al.*[12] in the form of CBr_4, where synthesis of azides by Mitsunobu type displacement reaction was carried out using PPh_3/CBr_4/NaN_3. But, our experience with this procedure showed that the separation of unreacted triphenylphosphine from the products is always very tedious. Here, we report a practical procedure for the conversion of alcohols to azide in DMSO using NaN_3, PPh_3, I_2 and imidazole at room temperature (scheme 1).

2. Experimental

All reagents were commercially available and used without further purification. Most of the aldehydes were purchased from Sigma Aldrich. The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer. For column chromatography, we employed Merck silica gel 60–120 mesh. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on an AMX-400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the compounds were performed on a Perkin–Elmer-2400 CHN/S analyzer.



Scheme 1. Conversion of alcohol to azide.

*For correspondence

2.1 *Typical procedure for synthesis of azide from alcohol*

A mixture of stearyl alcohol (0.810 g, 3 mmol), triphenylphosphine (0.943 g, 3.6 mmol) and iodine (0.914 g, 3.6 mmol) was ground with a pestle in a mortar for 10 min, when exothermic reaction took place to make a paste. Then a solution of sodium azide (0.780 g, 12 mmol) in DMSO was added and stirred for 30 min. Upon completion of the reaction, ice-cooled solution of sodium thiosulphate (50 mL) was added and extracted with diethyl ether (3×30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to get the crude product, which was purified by column chromatography using 5% ethyl acetate in hexane as eluent to get the product in 85% (0.752 g, 2.55 mmol) yields.

2.2 *Spectroscopic data of the new compounds*

2.2a *1-(1-Azidoethyl)-3-bromobenzene*: Colourless liquid; IR (KBr): ν 3018, 2402, 2110, 1527, 1487, 1434, 1215, 1076, 1016, 930, 764, 671, 506 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8 Hz, 2H), 7.12(d, J = 8 Hz, 2H), 4.23 (s, 2H); ^{13}CNMR (100 Hz, $CDCl_3$): δ 134.37, 131.99, 129.81, 122.34, 54.08; ESI-MS: m/z 234.0 (M+ Na), 236.0 (M+ Na).

2.2b *Stearyl azide*: Colourless liquid; IR (KBr): ν 2103, 2870-2950 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.2 Hz, 3H), 1.25 (m, 30H), 1.58 (m, 2H), 3.25 (t, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.53, 23.13, 27.14, 29.27, 29.61, 29.82, 29.93, 30.00, 30.08, 30.12, 30.14, 32.37, 51.86; MS: *m/z* 318.2 [M^+].

2.2c *4-Azido-2-methylpentan-2-ol*: Colourless liquid; IR (KBr): ν 3025, 2402, 2110, 1898, 1725, 1600, 1527, 1434, 1381, 1222, 1122, 1043, 930, 758, 678, 545, 446 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) : δ 3.69 (m, 1H), 1.97 (s, 1H, -OH), 1.6 (dd, J = 14.8, 10 Hz, 2H), 1.49 (dd, J = 14.8, 3.2 Hz, 2H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}CNMR (100 Hz, $CDCl_3$): δ 70.15, 54.51, 48.20, 30.15, 29.80, 20.43; ESI-MS: m/z 166.1 (M+ Na).

2.2d *4-Azidobutan-2-ol*: Colourless liquid; IR (KBr): ν 3608, 3429, 3025, 2965, 2402, 2342, 2103, 1725, 1606, 1507, 1447, 1387, 1222, 1122, 1049, 923, 764, 671 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) : δ 3.88 (m, 1H), 3.35 (m, 1H), 1.87 (s, 1H, -OH), 1.65 (m, 2H), 1.17 (d, J = 6 Hz, 3 H); ^{13}CNMR (100 Hz, $CDCl_3$): δ 65.59, 48.56, 37.59, 23.74; ESI-MS: m/z 137.0 (M+ Na).

2.2e *1-(1-Azido-1-phenylmethyl)-4-chlorobenzene*: Colourless liquid; IR (KBr): ν 3018, 2925, 2625, 2667, 2408, 2103, 1507, 1434, 1215, 1096, 1023, 930, 764, 671 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.29–7.16 (m, 9H), 5.61(s,1H); ^{13}CNMR (100 Hz, $CDCl_3$): δ 139.11, 138.15, 133.91, 128.87, 128.85, 128.70, 128.32, 127.37, 67.81; ESI-MS: m/z 266.1 (M+ Na), 268.1 (M+ Na).

2.2f *Citronellyl azide*: Colourless oil; IR (KBr): ν 3018, 2925, 2402, 2097, 1520, 1460, 1387, 1215, 1029, 930, 758, 671 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 5.01 (t, J = 6.4 Hz, 1H), 3.22 (m, 2H), 1.77 (q, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.38–1.08 (m,7H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}CNMR (100 Hz, $CDCl_3$): δ 131.50, 124.41, 49.50, 36.84, 35.62, 29.95, 25.71, 25.36, 19.22, 17.65; ESI-MS: m/z 204.1 (M+ Na).

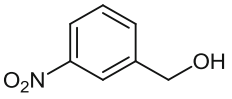
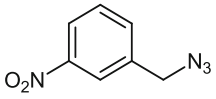
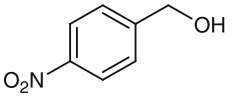
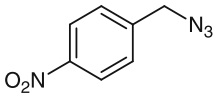
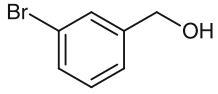
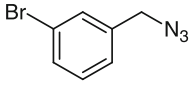
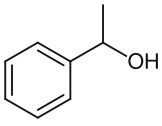
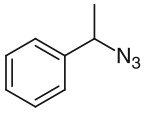
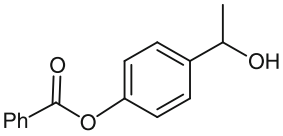
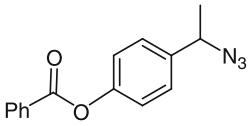
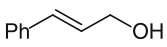
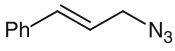
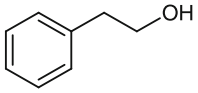
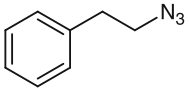
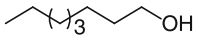
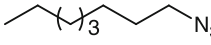
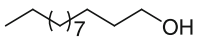
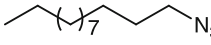
2.2g *1-Azido-4-tert-Butyldimethylsilyloxybutane*: Colourless liquid; IR (KBr): ν 3343, 3012, 2402, 2103, 1977, 1904, 1825, 1725, 1600, 1434, 1374, 1215, 1116, 1043, 930, 758, 545, 543 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.58 (t, J = 6 Hz, 2H), 3.24 (t, J = 6.8 Hz, 2H), 1.64- 1.20 (m, 6H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}CNMR (100 Hz, $CDCl_3$) : δ 62.44, 51.37, 29.84, 25.91, 25.50, −5.34; ESI-MS: m/z 252.0 (M+ Na).

2.2h *1-Azido-4-tetrahydropyranyloxybutane*: Colourless liquid; IR (KBr): ν 3018, 2945, 2402, 2103, 1520, 1460, 1215, 1029, 930, 764, 671 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.49 (t, J = 4.4 Hz, 1H), 3.79–3.66 (m, 2H), 3.43–3.30 (m, 2H), 3.23 (t, J = 6.4 Hz, 2H), 1.75–1.42 (m, 10H); ^{13}CNMR (100 Hz, $CDCl_3$): δ 98.87, 66.79, 62.35, 51.32, 30.68, 26.89, 25.93, 25.42, 19.59; ESI-MS: m/z 222.2 (M+ Na).

3. Results and discussion

Our recent interest in the catalytic application of iodine[13] opened up the idea that if triphenylphosphine and iodine is mixed together, the resulting phosphonium salt can act as an excellent hydroxy group activator. Since iodine is a cheap solid reagent and operational friendly, we envisaged that the use of iodine would facilitate further simplification of the protocol. Moreover, unreacted triphenylphosphine should sit with the triphenylphosphine oxide as iodotriphenylphosphonium iodide, thereby making the purification process

Table 1. Conversion of alcohol to azide.[a]

Entry	Substrate	Product	Time (min)	% yield[c]	Ref.
1	$C_6H_4CH_2OH$	$C_6H_4CH_2N_3$	30	94	17
2	*p*-OH $C_6H_4CH_2$ OH	*p*-OH $C_6H_4CH_2$ N_3	30	87	
3	*p*-Cl $C_6H_4CH_2$ OH	*p*-Cl $C_6H_4CH_2$ N_3	30	92	18
4	*p*-MeO $C_6H_4CH_2$ OH	*p*-MeO $C_6H_4CH_2$ N_3	30	72	19
5			30	82	20
6			30	85	20
7			45	93	21
8			45	86	22
9			45	70	22
10			45[b]	88	23
11			30	93	17
12			30	86	17
13			30	89	17
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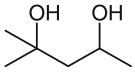
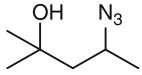
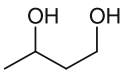
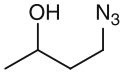
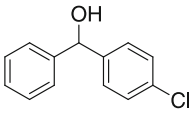
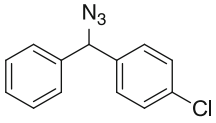
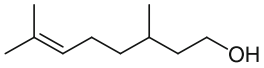
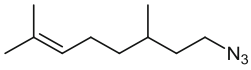
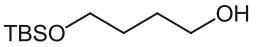
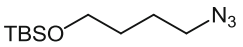
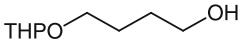
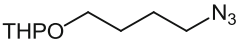
15	t-BuOH	No product	8h	–	
16			45	91	
17			30	75	
18			55	93	
19	Cyclohexanol	Cyclohexyl azide	45	82	19
20			45[b]	91	
21			30	92	
22			30	89	
23	3β-Cholesterol	3β-Azido-cholest-5-ene	45[b]	83	24

[a]Substrate: PPh_3: I_2: Im: NaN_3 = 1: 1.2: 1.2: 4.
[b]The reaction was carried out at 45°C.
[c]Yield of the isolated pure product

easy. Surfing through the literature gave us some important clues on application of a triphenylphosphine and iodine reagent system for Mitsunobu cycloetherification,[14] conversion of aldoximes to nitrile,[15] alcohols to iodide,[16] etc. Henceforth, one-pot conversion from alcohol to azide through iodide seemed very much possible. Ordinarily, alcohol to iodide is accomplished with PPh_3/I_2/Imidazole reagent system in dry DMF and requires high temperature besides maintaining highly inert atmosphere. We presumed that iodophosphonium iodide should form even in the absence of any solvent if they are mixed thoroughly, which in turn should react with the alcohol to generate iodide. If that iodide is ground with NaN_3, it may lead to formation of azide. To verify our assumption, we ground a mixture of benzyl alcohol, triphenylphosphine, iodine and imidazole with a pestle in a mortar for 30 min, mixed with solid sodium azide and ground together for another half an hour. But reaction stopped in the iodination stage and did not give slightest amount of azide derivative. Therefore, we added dry DMF to the mixture and stirred for 5 h at 70°C under inert atmosphere to find that most of the starting material was converted to azide. When the same procedure was carried out with distilled DMF, product formation was found to be very sluggish. When the ground mixture of benzyl alcohol, triphenylphosphine, iodine and imidazole (Im) was stirred with a NaN_3 solution in DMSO, reaction took only half an hour at room temperature for complete conversion of benzyl alcohol to benzyl azide (scheme 1). The reaction was quenched by adding to ice-cold water and extracted with diethyl ether, to get the corresponding azide. As sodium azide is known as explosive, use of DMSO solution of sodium azide makes the protocol completely safe to handle. When the same reaction protocol was tried in other solvents such as acetonitrile, DMF, THF, and 1,2-dichloroethane at room temperature, the azide formation did not take place.

As this reaction does not require any sophistication and can be carried out at room temperature, we were excited to explore the application of our method for diverse alcohols (table 1). It was observed that both the primary and secondary aliphatic alcohols gave very good yields as well as an allylic alcohol. As for the benzylic alcohols (entry 1–9, 18), reaction worked excellently as evident from their isolated yields and +M or –M effect of substituents on the benzene ring (entry 2–7, 9) hardly played any role. Interestingly, the phenolic hydroxy group was not affected under this reaction condition as both the alcoholic hydroxyl groups (entries 2) gave good yields of their corresponding azides. Under these reaction conditions, functional groups like methoxy (entries 4), nitro (entry 5–6), benzoyl (entry 9), OTBS (entry 21) and OTHP (entry 22) were not affected and gave good to excellent yields.

It was found that benzylic alcohols are also highly reactive under this condition and yields were relatively less dependent on the substitution pattern on the phenyl rings. Under the optimized conditions, we next examined the reactivity of tert-butanol (entries 15), which did not give the product even after 8 h. Henceforth, we tried chemoselective conversion of 2-methyl-pent-2,4-diol (entry 16) with our protocol. The reaction gave exclusively 4-azido-2-methyl-pent-2-ol within 45 min leaving the tertiary alcohol intact. We tried similar reaction on butan-1,3-diol (entry 17) to study chemoselectivity between primary and secondary alcohol. It was found that one equivalent of reagent system converted the primary alcohol into azide selectively in preference to the secondary alcohol. The structure of the product was confirmed by DEPT-135 study, wherein the presence of the tertiary carbon at δ 64.7 ppm indicated its attachment to the hydroxy group.

Since the cationic cholesterol mimic 3β-amino-5-cholestene (3β-cholesterylamine) is known for its high affinity for phospholipid membranes[25] and its derivatives were also used to construct photoaffinity probes,[26] membrane trafficking,[27] and drug delivery[28] besides having antimicrobial activity,[29] synthesis of 3β-azido-chlest-5-ene directly from cholesterol constitutes a very efficient access to its amino derivatives. When we applied our method to synthesize 3β-azido-cholest-5-ene directly from cholesterol (entry 23), we got excellent yield (83%) of the desired product on heating at 45°C for 45 min.

4. Conclusion

In summary, we have developed a simple and efficient protocol for direct conversion of alcohol into azide avoiding the purification of the iodide. The use of DMSO as solvent has proven to be very effective for this conversion. The protocol showed extremely good chemoselectivity in favour of less substituted alcohols. Good to excellent yields, shorter reaction times and excellent reactivity towards primary, secondary as well as less reactive benzyl alcohols may prove our protocol very attractive to synthetic chemists.

Supporting information

Copy of the ^{1}HNMR and ^{13}CNMR spectra of the new compounds are available as supplementary data in the journal website (www.ias.ac.in/chemsci).

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