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A simple one-pot procedure for the direct conversion of alcohols into azides using TsIm

Mohammad Navid Soltani Rad,[a,*] Somayeh Behrouz[b] and Ali Khalafi-Nezhad[b]

[a]*Department of Chemistry, Faculty of Basic Sciences, Shiraz University of Technology, Shiraz 71555-313, Iran*
[b]*Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran*

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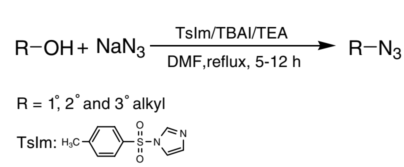
Abstract—A facile and efficient method for one-pot conversion of alcohols into azides using *N*-(*p*-toluenesulfonyl)imidazole (TsIm) is described. In this method, alcohols are refluxed with a mixture of NaN_3, TsIm and triethylamine in the presence of catalytic amounts of tetra-*n*-butylammonium iodide (TBAI) in DMF affording the corresponding alkyl azides in good yields. This methodology is highly efficient for various structurally diverse alcohols with selectivity for ROH: $1° > 2° > 3°$.

Alkyl azides[1] are versatile substrates in organic synthesis and have been used extensively for the introduction of primary amino groups and the construction of *N*-heterocycles.[2] The most common routes to aliphatic azides involve nucleophilic substitution of alkyl halides or sulfonates with inorganic azides or addition of hydrazoic acid (HN_3) to alkenes.[3] Direct synthesis of azides from the corresponding alcohols would be a highly advantageous and attractive strategy. There are a few methods established for accessing alkyl azides from alcohols using Mitsunobu reactions.[4] These methods use hydrazoic acid as the azide source for alkyl, benzylic, and allylic alcohols. However, the use of highly toxic and explosive hydrazoic acid limits the applicability of this method. Alternatives to HN_3 include diphenyl phosphorazidate (DPPA)[5] or zinc azide/bis-pyridine complex[6] as the azide source. Other methods for direct conversion of alcohols to azides include; $NaN_3/BF_3–Et_2O$[7] and $HN_3/TiCl_4$.[8] Thompson and co-workers established a procedure using diphenyl phosphorazidate (DPPA)/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[9] for conversion of diverse alcohols to azides. Modifications using bis-(2,4-dichlorophenyl)chlorophosphate/NaN_3/4-(dimethylamino)pyridine (DMAP)[10] and bis(*p*-nitrophenyl)phosphorazidate/DBU[11] have been reported. The one-pot synthesis of allyl azides from allyl alcohols using NaN_3/triphosgene has also been described.[12] Alkyl azides were prepared from alcohols with $CBr_4/Ph_3P/NaN_3$ and exemplified by syntheses of azidonucleosides[13a] and mappicin.[13b] In contrast to Mitsunobu conditions, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was used instead of diethyl azodicarboxylate (DEAD) for conversion of alcohols to azides.[14]

The aforementioned methods are effective for the conversion of alcohols to azides, but they have several drawbacks including the use of highly toxic and explosive HN_3[3,4,8] and expensive DEAD,[4] the limitation of various reactions to allylic, benzylic and tertiary alcohols,[7,8,12] ineffectiveness with some alcohols,[9–11] tedious work-up as well as cumbersome separation from generated $Ph_3P{=}O$ and unreacted Ph_3P.[4–6,13,14] In order to reduce the above problems and also in our efforts towards azidation of acyclic nucleosides, we report *N*-(*p*-toluenesulfonyl)imidazole (TsIm) as a highly efficient, cheap and stable reagent for conversion of alcohols to azides in the presence of NaN_3, triethylamine (TEA) and catalytic amounts of tetra-*n*-butylammonium iodide (TBAI) in DMF (Scheme 1).



Scheme 1.

Keywords: Azide; Alcohol; *N*-(*p*-Toluenesulfonyl)imidazole (TsIm); Triethylamine (TEA); Tetrabutylammonium iodide (TBAI).
* Corresponding author. Tel.: +98 711 7261392; fax: +98 711 7354523; e-mail addresses: soltani@sutech.ac.ir; nsoltanirad@gmail.com

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Table 1. Effect of various solvents on the conversion of *N*-(2-hydroxyethyl)phthalimide into the corresponding azide

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	12	30
2	DMF	5	91
3	DMF[a]	24	10
4	THF	48	NR[c]
5	MeCN	18	20
6	HMPA	18	20
7	Toluene	48	NR
8	Acetone/H_2O[d]	24	Trace
9	H_2O	48	NR

[a] Anhydrous DMF.
[b] Isolated yield.
[c] No reaction.
[d] (1:1) Ratio.

To obtain optimized reaction conditions, we chose the reaction of *N*-(2-hydroxyethyl)phthalimide with excess NaN_3 (3 equiv), freshly prepared TsIm[15] (1.5 equiv) and a catalytic amount of TBAI as a reaction model; the effect of various solvents on reaction times and yields was studied. The results are depicted in Table 1.

As Table 1 indicates, DMF (Table 1, entry 2) was the most efficient solvent hence it was the solvent of choice. Using anhydrous DMF afforded a low yield of the corresponding azide. The role of base in the reaction was critical for activation of the alcohols to react with TsIm. In this case, we evaluated the potency of various organic and inorganic bases on reaction times and yields of the model reaction (Table 2). The results in Table 2 demonstrate that among the examined bases TEA (Table 2, entry 7) was the most appropriate for activation of *N*-(2-hydroxyethyl)phthalimide.

We also investigated the role of phase transfer catalysts (PTC) on the reaction (Table 3). In the absence of PTC no reaction occurred even when reflux was prolonged up to 48 h. Other PTCs (Table 3, entries 2–4, 6 and 7) were not as effective as TBAI (Table 3, entry 5). Moreover, the use of an equal mixture of TBAI and TBAB (Table 3, entry 8) was less efficient. Using further amounts of TBAI and other PTCs had negligible effects on the reaction.

Table 2. Effect of various bases on the conversion of *N*-(2-hydroxyethyl)phthalimide into the corresponding azide

Entry	Base	Time (h)	Yield[a] (%)
1	DBU	48	Trace
2	DABCO	24	20
3	DMAP	24	20
4	MgO	48	Trace
5	Cs_2CO_3	18	35
6	K_2CO_3	48	NR[b]
7	TEA	5	91
8	NaH	12	45

[a] Isolated yield.
[b] No reaction.

Table 3. Effect of various PTCs on the conversion of *N*-(2-hydroxyethyl)phthalimide into the corresponding azide

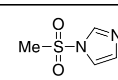
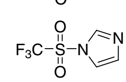
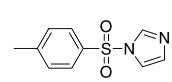
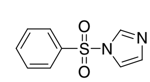
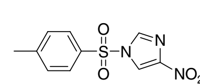
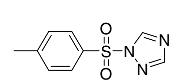
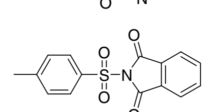
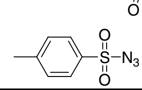
Entry	PTC	Time (h)	Yield[b] (%)
1	None	48	NR[c]
2	TBAF	18	25
3	TBAC	12	43
4	TBAB	12	50
5	TBAI	5	91
6	$(n\text{-}Bu_4N)HSO_4$[a]	24	15
7	$(n\text{-}Bu_4N)N_3$	22	33
8	TBAI/TBAB	12	70

[a] Two equivalents of TEA was used.
[b] Isolated yield.
[c] No reaction.

The optimized amount of TsIm was found to be 1.5–2.0 equiv per equivalent of alcohol. We also examined other TsIm analogues (Table 4).

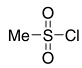
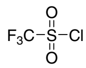
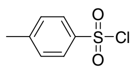
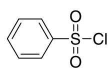
As the data in Table 4 indicates, a higher yield of azide and short reaction time were obtained with TsIm (Table 4, entry 3) in comparison with other sulfonyl analogues. Replacing the tolyl in TsIm with methyl, trifluromethyl and phenyl gave no improvement in reaction yield (Table 4, entries 1, 2 and 4). Furthermore, changing the imidazole residue to other azole derivatives did not affect the reaction efficiency (Table 4, entries 5 and 6). *N*-Tosyl phthalimide and tosyl azide[2a] (Table 4, entries 7 and 8) were inactive for the conversion of *N*-(2-hydroxyethyl)phthalimide to the corresponding azide even after reflux for 48 h.

Table 4. Comparison of TsIm reactivity with analogues in the conversion of *N*-(2-hydroxyethyl)phthalimide into the corresponding azide

Entry	Reagent	Time (h)	Yield[a] (%)
1		24	20
2		24	32
3		5	91
4		12	60
5		12	54
6		12	48
7		48	NR[b]
8		48	NR

[a] Isolated yield.
[b] No reaction.

Table 5. Effect of various sulfonyl chlorides in the conversion of *N*-(2-hydroxyethyl)phthalimide into the corresponding azide

Entry	Sulfonyl chloride	Time (h)	Yield[a] (%)
1		24	31
2		24	38
3		24	27
4		24	22

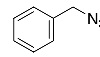
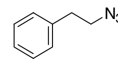
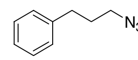
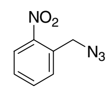
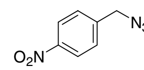
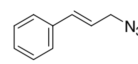
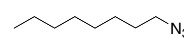
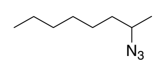
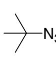
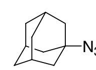
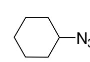
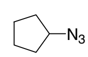
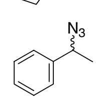
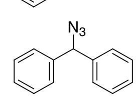
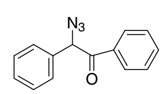
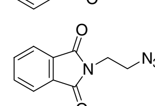
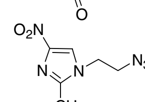
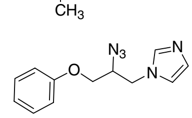
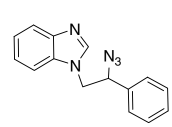
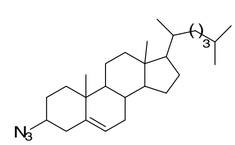
[a] Isolated yield.

Various sulfonyl chlorides were examined instead of TsIm (Table 5). Lower yields of azide were obtained when sulfonyl chlorides were used for sulfonylation of (2-hydroxyethyl)phthalimide instead of TsIm. This probably results from the fact that the highly reactive sulfonyl chlorides have less selectivity for reaction with alcohols.

To evaluate the general applicability and versatility of the method, the optimized conditions were applied to various structurally diverse alcohols (Table 6). As the results in Table 6 indicate, various alcohols including: primary, secondary and tertiary were successfully converted into the corresponding azides in good yields. The generality of the method was confirmed with respect to allylic (Table 6, entry 6), benzylic (Table 6, entries 1, 4, 5, 13–15 and 19), aliphatic (Table 6, entries 7–9), alicyclic (Table 6, entries 10–12 and 20) and other alcohols containing *N*-heterocycles (Table 6, entries 16–19 and 21). Furthermore, the conversion of complex or naturally occurring alcohols into their corresponding azides is feasible using this method (Table 6, entries 20 and 21). For example, 5′-trityl-thymidine was converted into its azide (Table 6, entry 21) which can be transformed into AZT (Zidovudine)[4d,16] after detritylation.

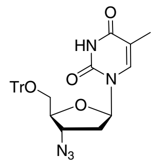
Mechanistically, we suggest that firstly reaction of base-activated alcohol with TsIm affords an alkyl tosylate. Subsequently, the azide ion reacts with the alkyl tosylate to give the alkyl azide via nucleophilic substitution. Two roles for TBAI can be considered: (1) by anion exchange more azide anions enter as (n-Bu_4N)N_3; (2) some tosylate can be exchanged by iodide which is a better leaving group than tosylate for nucleophilic substitution. Indeed, iodide ions considerably catalyze the reaction (Table 3). We also examined other sources of iodide including: LiI, NaI and KI for the conversion of *N*-(2-hydroxyethyl)phthalimide to the corresponding azide. The azide was obtained in 25%, 31% and 32% yields, respectively. This experiment manifested the significance of the tetrabutylammonium cation and iodide anion simultaneously. Using our method for the conversion of optically pure *R*-(+)-1-phenylethanol into its corresponding azide (Table 6, entry 13) was followed with a reduction in optical purity (64% ee). This can be explained as a result of partial inversion and retention of

Table 6. One-pot conversion of alcohols to azides using TsIm/TBAB/TEA in refluxing DMF

Entry[ref.]	R–N_3[a]	ν[b] (cm^{-1})	Time (h)	Yield[c] (%)
1[7d,14,17a–c]		2097	7	86
2[6,14]		2097	6	93
3[14]		2098	8	92
4		2166	10	82
5[17b]		2106	8	90
6[6,7d]		2096	8	83
7[11,14,17a–d]		2100	6	88
8[11,14]		2167	10	62
9[17e]		2098	12	56
10[14]		2168	12	50
11[14,17c,d]		2090	9	79
12[17c]		2103	9	82
13[6,9,11,17c]		2106	8	75[d]
14[7d,14,7d]		2099	10	73
15[7d]		2156	11	67
16		2112	5	91
17		2102	6	90
18		2102	10	65
19		2187	12	54
20[9]		2114	12	41

(*continued on next page*)

Table 6 (*continued*)

Entry[ref.]	R–N_3[a]	ν[b] (cm^{-1})	Time (h)	Yield[c] (%)
21[16,4d]		2085	12	47

[a] All products were characterized by ^1H and ^{13}C NMR, IR, CHN and MS analysis.
[b] IR signal of azide in wavenumbers (cm^{-1}).
[c] Isolated yield.
[d] Also obtained from optically pure *R*-(+)-1-phenylethanol, $[\alpha]_D^{20}$ +45 (*c* 5, in MeOH) in 64% ee.

configuration at the same time. Finally, it is interesting to note that there was a remarkable tendency for TsIm to react with alcohols rather than nucleophiles present in the reaction mixture: no tosyl azide was observed through the course of reactions even in trace amounts.

In conclusion, a convenient method has been established for the one-pot conversion of alcohols into the corresponding azides using TsIm/TEA/TBAI (cat.) in refluxing DMF. This method has favorable generality and applicability for primary, secondary and tertiary alcohols with selectivity: 1° > 2° > 3°.

General procedure for the one-pot conversion of alcohols to azides: In a double-necked round bottom flask (100 mL) equipped with a condenser was added a mixture, consisting of alcohol (0.01 mol), TsIm (0.015 mol),[15] TEA (0.02 mol), NaN_3 (0.03 mol) and a catalytic amount of TBAI (0.1 g) in DMF (30 mL). The mixture was refluxed, and in most cases, darkening occurred. Reflux was continued until TLC monitoring indicated no further improvement in the conversion (Table 6). The solvent was evaporated under vacuum and the remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with *n*-hexane–EtOAc (15:1).[18]

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References and notes

1. (a) Sheradsky, T. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience: New York, 1971; p 331; (b) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley& Sons (Asia) pte. Ltd: Singapore, 2005.
2. (a) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240; (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368; (c) Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1–57; (d) Smith, P. A. S. *Org. React.* **1946**, *3*, 337–349.
3. Smith, P. A. S. In *Open Chain Nitrogen Compounds*; W.A. Benjamin: New York, 1966; Vol. II, p 211.
4. (a) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679–680; (b) Hughes, D. L. *Org. React.* **1992**, *42*, 358–359; (c) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1977**, *60*, 417–425; (d) Mitsunobu, O. *Synthesis* **1981**, 1–28; (e) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; (f) Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 3955–3958; (g) Mizuno, M.; Shior, T. *Chem. Commun.* **1997**, 2165–2166; (h) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190–192; (i) Bessodes, M.; Abushanab, E.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 5899–5902; (j) Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 4235–4238; (k) Lee, S.-H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139–2145.
5. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980.
6. Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130–132.
7. (a) Khuong-Huu, Q.; Pancrazi, A.; Kabore, I. *Tetrahedron* **1974**, *30*, 2579–2586; (b) Adam, G.; Andrieux, J.; Plat, M.; Viossat, B.; Rodier, N. *Bull. Soc. Chim. Fr.* **1984**, 101–108; (c) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1985**, *41*, 399–407; (d) Kumar, H. M. S.; Reddy, B. V. S.; Anjaneyulu, S.; Yadav, J. S. *Tetrahedron Lett.* **1998**, *39*, 7385–7388.
8. Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237–4244.
9. Thompson, A. S.; Humphrey, G. R.; Demarco, A. M.; Mathre, D. J.; Grabowski, J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
10. Yu, C.; Liu, B.; Hu, L. *Org. Lett.* **2000**, *2*, 1959–1961.
11. Mizuno, M.; Shioiri, T. *Chem. Commun.* **1997**, 2165–2166.
12. Jayanthi, A.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Synlett* **2004**, 979–982.
13. (a) Li, Z.-S.; Qiao, R.-P.; Yang, Z. J.; Zhang, L.-R.; Zhang, L. H. *Tetrahedron: Asymmetry* **2006**, *17*, 1056–1061; (b) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110–7113.
14. Iranpoor, N.; Firouzabadi, H.; Akhalaghinia, B.; Nowrouzi, N. *Tetrahedron Lett.* **2004**, *45*, 3291–3294.
15. *N*-(*p*-Toluenesulfonyl)imidazole (TsIm) is a cheap and stable reagent that was applied previously for selective tosylation of alcohols (see: Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045–1047) and carbohydrates (see: Teranishi, K. *Carbohydr. Res.* **2002**, *337*, 613–619; Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203; Byun, H.-S.; Zhong, N.; Bittman, R. *Org. Synth. Coll. Vol. 10*, p 690; *Vol. 77*, p 225). It was also used for polynucleotide synthesis (see: Berlin, Y. A.; Chakhmakhcheva, O. G.; Efimov, V. A.; Kolosov, M. N.; Korobko, V. G. *Tetrahedron Lett.* **1973**, 1353–1354) and esterification of FMOC-amino acids with hydroxyl functionalized solid supports (see: Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701–1704). Although, this reagent is commercially available, in our experience the use of freshly prepared TsIm is better. This reagent can be easily prepared (see: Stabb, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351–367; Stabb, H. A.; Wendel, K. *Chem. Ber.* **1960**, *93*, 2902–2915; and also see: Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203; Byun, H.-S.; Zhong, N.; Bittman, R. *Org. Synth. Coll. Vol. 10*, p 690; *Vol. 77*, p 225). We prepared this reagent very efficiently on a large scale using a solvent-free technique: In a well-dried mortar a mixture consisting of tosyl chloride (1 equiv) and imidazole (2.2 equiv) was ground vigorously at room temperature. The reaction started immediately and the

mixture melted and solidified after 2 min. The resulting white solid was dissolved in $CHCl_3$ and washed with several portions of water. The organic layer was dried (Na_2SO_4) and evaporated to afford white crystals which could be used without further purification.

16. Lin, T.-S.; Mancini, W. R. *J. Med. Chem.* **1983**, *26*, 544–548.
17. (a) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697–6700; (b) Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1998**, *39*, 2915–2918; (c) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413–414; (d) Ito, M.; Koyakumaru, K.-I.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 376–378; (e) Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237–4244.
18. Selected data for *N*-(2-azidoethyl)phthalimide and 1-(2-azido-ethyl)-2-methyl-4-nitro-1*H*-imidazole (Table 5, entries 16 and 17). *N-(2-azidoethyl)phthalimide*: White crystals; R_f (EtOAc–*n*-hexane) (1:1) 0.69; mp 44.6 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ_{ppm}: 3.46 (t, 2H, $J = 6.0$ Hz, N_3CH_2), 3.79 (t, 2H, $J = 6.0$ Hz, NCH_2), 7.55–7.6 (m, 2H, aryl), 7.72–7.79 (m, 2H, aryl); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm}: 36.84, 48.94, 123.42, 131.83, 134.17, 167.97; IR (KBr) ν cm^{-1}: 2112(N_3); MS [m/z (%)]: 216.06 (81.3); Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H 3.73; N 25.91. Found: C, 55.50; H 3.76; N 25.95. *1-(2-Azido-ethyl)-2-methyl-4-nitro-1H-imidazole*: Pale-yellow crystals; R_f (EtOAc–*n*-hexane) (1:1) 0.12; mp 72.3 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ_{ppm}: 2.39 (s, 3H, Me), 3.72 (t, 2H, $J = 5.5$ Hz, N_3CH_2), 4.07 (t, 2H, $J = 5.5$ Hz, NCH_2), 8.17 (s, 1H, C(5)-H, imidazole);^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm}: 13.02, 46.10, 50.79, 120.29, 145.26, 146.45; IR(KBr) ν cm^{-1}: 2102 (N_3); MS [m/z (%)]: 196.07 (61.4); Anal. Calcd for $C_6H_8N_6O_2$: C, 36.74; H 4.11; N 42.84. Found: C, 36.72; H 4.16; N 42.80.