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

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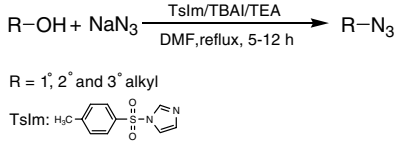
Abstract—A facile and efficient method for one-pot conversion of alcohols into azides using *N*-(*p*-toluenesulfonyl)imidazole (TsIm) is described. In this method, alcohols are refluxed with a mixture of NaN_3, TsIm and triethylamine in the presence of catalytic amounts of tetra-*n*-butylammonium iodide (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).
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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

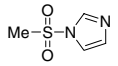
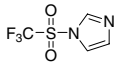
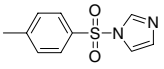
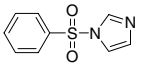
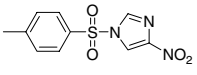
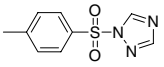
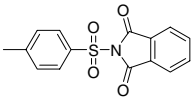
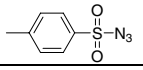
Entry	PTC	Time (h)	Yield[b] (%)
1	None	48	NR[c]
2	TBAF	18	25
3	TBAC	12	43
4	TBAB	12	50
5	TBAI	5	91
6	$(n\text{-}Bu_4N)HSO_4$[a]	24	15
7	$(n\text{-}Bu_4N)N_3$	22	33
8	TBAI/TBAB	12	70

[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.