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A Simple One-Pot Procedure for the Direct Conversion of Alcohols to Azides via Phosphate Activation

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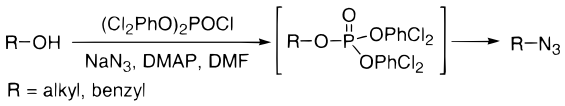
ABSTRACT



A one-pot procedure was developed to prepare efficiently alkyl azides from alkanols using bis(2,4-dichlorophenyl) phosphate activation. 4-(Dimethylamino)pyridine was used as a base, and phosphorylpyridinium azide is believed to be the activating agent under this condition.

Conversion of an alcohol to its corresponding azide is an important functional group transformation in organic synthesis.[1] Although there are a variety of indirect methods reported in the literature, few direct azidation methods are known. Among the known direct methods, Mitsunobu displacement[2] using hydrazoic acid as the azide source[3] proved to be the most efficient in transforming alkyl, benzylic, and allylic hydroxyls into their corresponding azides. However, the use of highly toxic hydrazoic acid limits the applicability of this method. Alternatives to hydrazoic acid include diphenyl phosphorazidate (DPPA)[4] and zinc azide/bis-pyridine complex.[5] Under these conditions, a substrate alcohol is mixed with diethyl azadicarboxylate and triphenyl phosphine prior to the addition of the azide reagent, a procedure that often leads to racemization and olefin formation. A more recent method reported by Thompson et al. for direct conversion of alcohols to azides uses DPPA and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry toluene,[6] where DBU acts as a base to help convert the alcohol to the corresponding phosphate intermediate and then, without isolation, the phosphate is displaced by the azide ion. However, few simple alkanols have been successfully converted to their corresponding azides using such direct methods.

In our efforts to synthesize anticancer prodrugs of phosphoramide mustard and FUDR, we needed to convert the hydroxyl groups in compounds **1**, **2**, and **3** to their corresponding azides. Hydrazoic acid-assisted Mitsunobu reaction successfully converted compound **1** to its corresponding azide in 93% yield, while *Thompson*'s procedure using DPPA/DBU in toluene failed. The latter procedure also failed to convert alkanol **2** and benzylic diol **3** to the desired azide products even upon heating to 45 °C; only the corresponding phosphates **4** and **5** were isolated. This prompted us to develop new direct procedures for the preparation of alkyl azides from such simple and less reactive alcohols. In this Letter, we wish to report a convenient one-pot procedure using bis(2,4-dichlorophenyl) phosphate as a good leaving group to activate hydroxyl groups for the direct conversion

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(3) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1977**, *60*, 417−425.

(4) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977−1980.

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(6) Thompson, A. S.; Humphrey, G. R.; Demarco, A. M.; Mathre, D. J.; Grabowski, J. J. *J. Org. Chem.* **1993**, *58*, 5886−5888.

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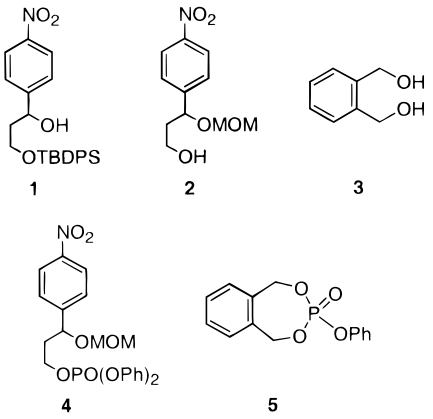
of simple alkanols or less reactive benzyl alcohols to their corresponding azides.

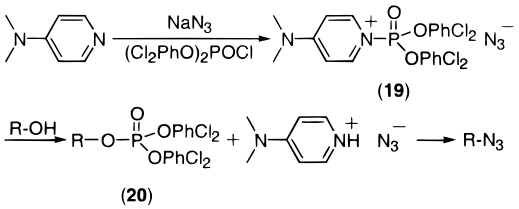


The failure of Thompson's direct azidation procedure to convert compounds **1**, **2**, and **3** to their corresponding azides and the isolation of phosphate intermediates **4** and **5** suggest that diphenyl phosphate was not a good enough leaving group to activate, for S_N2 displacement, hydroxyl groups of simple alkanols or less reactive benzyl alcohols with strong electron-withdrawing substituents on the phenyl ring. This was also shown as a limitation of Thompson's procedure in the original report.[6] We reasoned that introduction of electron-withdrawing substituents on the phenyl ring would make it a better leaving group and the resulting phosphate could be sufficiently reactive for displacement by azide ion. Thus, we replaced diphenyl chlorophosphate, the common activating agent used in the indirect methods, with bis(2,4-dichlorophenyl) chlorophosphate. To avoid the isolation of phosphate intermediates and the preparation of phosphorazidate,[7] we decided to perform the activation and azide displacement using the following one-pot procedure.[8] To a solution of substrate alcohol (1 mmol) in anhydrous DMF (5 mL) were added at room temperature with stirring NaN_3 (4 equiv) and DMAP (1.2 equiv) followed by bis(2,4-dichlorophenyl) chlorophosphate (1.05 equiv). Stirring was continued for 2 h or until the starting material disappeared as monitored by TLC. The reaction usually works well at room temperature. If TLC showed incomplete conversion after 2 h, the temperature could be raised to 45 °C to complete the reaction. For workup, ethyl ether (100 mL) and brine (30 mL) were added to the reaction mixture. The organic phase was separated, washed with aqueous NaOH (20%) and brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude product was purified by flash column chromatography (ethyl ether:hexane) to afford the desired azide product.

As shown in Table 1, all the alkanols we examined were converted to their corresponding azides[9] in satisfactory yields between 76 and 92% with the less reactive benzyl alcohol **1** giving the lowest yield of the desired azide **11**. In the case of symmetrical benzylic diol **3,** where the same 1.05 equiv of bis(2,4-dichlorophenyl) chlorophosphate was used, the major product isolated was the monoazidated product **13** (82%) with the corresponding bisazidated compound as the minor product (9.2%). This unexpected selectivity suggests that our one-pot procedure might be used to selectively convert diols to azido alcohols without going through the typical protection−deprotection steps.

Mechanistically, we believe the reaction takes place in three discrete steps as illustrated in Scheme 1. (i) DMAP

Scheme 1



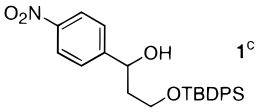
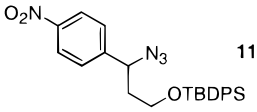
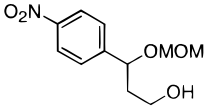
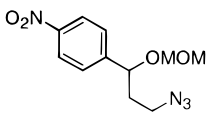
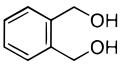
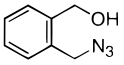
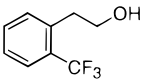
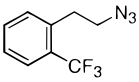
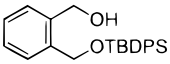
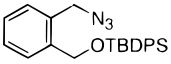
reacts with bis(2,4-dichlorophenyl) chlorophosphate in the presence of sodium azide to form bis(2,4-dichlorophenyl)-phosphoryl 4-(dimethylamino)pyridinium azide **(19)**. (ii) The phosphoryl pyridinium azide **(19)** then reacts with the substrate alcohol to form the activated bis(2,4-dichlorophenyl) phosphate **(20)**. (iii) The bis(2,4-dichlorophenyl)-phosphoryl group in **20** is displaced by azide ion to produce the desired azide. In this mechanism, the activating reagent is bis(2,4-dichlorophenyl)phosphoryl 4-(dimethylamino)-pyridinium azide **(19)**. To confirm this, we performed the following experiments. First, we mixed an equimolar mixture of bis(2,4-dichlorophenyl) chlorophosphate and sodium azide in DMF at room temperature and monitored the reaction using IR spectroscopy. We observed a complete shift of the azide signal from 2010 to 2174 cm^{-1} in about 30 min. When DMAP was added into the mixture, the azide absorption at 2174 cm^{-1} disappeared quickly and a new peak appeared at 2133 cm^{-1}. This result suggested that bis(2,4-dichlorophenyl) chlorophosphate reacted with sodium azide to form the bis-(2,4-dichlorophenyl) phosphorazidate and the phosphorazidate was then converted quickly to bis(2,4-dichlorophenyl)-phosphoryl 4-(dimethylamino)pyridinium azide **(19)** upon the

(7) Shioriri, T.; Yamada, S. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 206−207.

(8) **Caution**: Azides especially bisazidated products are potentially explosive and should be handled with care. The procedure should be performed in a well-ventilated hood.

(9) ^1H NMR (200 MHz, $CDCl_3$) data for the azide products listed in Table 1: δ ppm **11**: 8.14 (d, J = 8.4 Hz, 2H), 7.60−7.52 (m, 4H), 7.39−7.29 (m, 8H), 4.83 (t, J = 5.8 Hz, 1H), 3.80−3.69 (m, 1H), 3.58−3.50 (m, 1H), 1.94−1.80 (m, 2H), 1.10 (s, 9H); **12**: 8.22 (dd, J = 1.8, 6.8 Hz, 2H), 7.52 (dd, J = 0.3, 6.9 Hz, 2H), 4.83 (dd, J = 4.5, 9.0 Hz, 1H), 4.60 (d, J = 6.9 Hz, 1H), 0.4.51 (d, J = 1.2, 6.8 Hz, 1H), 3.51−3.40 (m, 2H), 3.37 (s, 3H), 2.07−2.02 (m, 1H), 1.93−1.89 (m, 1H); **13**: 7.40−7.32 (m, 4H), 4.69 (d, J = 5.9 Hz, 2H), 4.45 (s, 2H), 2.52 (t, J = 5.9 Hz, 1H); **14**: 7.68 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.1 Hz, 1H), 7.38 (t, J = 7.9 Hz, 2H), 3.53 (t, J = 7.3 Hz, 2H), 3.10 (t, J = 7.3 Hz, 2H); **15**: 7.69 (d, J = 7.7 Hz, 4H), 7.50−7.32 (m, 10H), 4.80 (s, 2H), 4.34 (s, 2H), 1.09 (s, 9H); **16**: 7.73−7.69 (m, 4H), 7.48−7.42 (m, 6H), 3.79 (t, J = 5.9 Hz, 2H), 3.49 (t, J = 6.8 Hz, 2H), 1.85 (p, J = 6.3 Hz, 2H), 1.10 (s, 9H); **17**: 7.78−7.73 (m, 4H), 7.49−7.43 (m, 6H), 3.75 (t, J = 6.1 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H), 1.69−1.55 (m, 6H), 1.14 (s, 9H); **18**: 7.75−7.70 (m, 4H), 7.46−7.42 (m, 6H), 3.72 (t, J = 6.2 Hz, 2H), 3.28 (t, J = 6.9 Hz, 2H), 1.64−1.58 (m, 4H), 1.43−1.37 (m, 6H), 1.11 (s, 9H).

Table 1. Conversion of Alcohols to Azides[a]

alcohol		azide		yield (%)[b]	azide IR (cm^{-1})
	**1**[c]		**11**	76	2093
	**2**		**12**	88	2070
	**3**		**13**	82[d]	2092
	**6**		**14**	92[e]	2103
	**7**		**15**	80	2093
$TBDPSO(CH_2)_3OH$	**8**	$TBDPSO(CH_2)_3N_3$	**16**	84	2091
$TBDPSO(CH_2)_5OH$	**9**	$TBDPSO(CH_2)_5N_3$	**17**	80	2092
$TBDPSO(CH_2)_7OH$	**10**	$TBDPSO(CH_2)_7N_3$	**18**	87	2092

[a] Reaction conditions: bis(2,4-dichlorophenyl) chlorophosphate (1.05 eq), sodium azide (4 eq), DMAP (1.2 eq), DMF, rt. [b] Racemic starting material was used to obtain a racemic product mixture of **11**. [d] Bisazidated product was also isolated in 9.2% yield. [e] The reaction mixture had to be warmed up to 45 °C to obtain the best product yield.

addition of DMAP. In our second experiment, we added sodium azide to an equimolar mixture of bis(2,4-dichlophenyl) chlorophosphate and DMAP and found that the azide signal at 2133 cm^{-1} appeared immediately upon the addition of sodium azide. In our one-pot procedure, the same azide signal at 2133 cm^{-1} was initially observed when all reagents were mixed with substrate alcohol and slowly disappeared as a new product signal appeared (Table 1). Apparently, when all three reagents are mixed together with or without substrate alcohol present, the bis(2,4-dichlorophenyl)phosphoryl 4-(dimethylamino)pyridinium azide **(19)** is formed quickly without going through the bis(2,4-dichlorophenyl) phosphorazidate intermediate, suggesting that pyridinolysis of bis(2,4-dichlorophenyl) chlorophosphate is faster than the reaction of bis(2,4-dichlorophenyl) chlorophosphate with sodium azide or the substrate alcohol.[10] These results are consistent with bis(2,4-dichlorophenyl)phosphoryl 4-(dimethlyamino)pyridinium azide **(19)** being the actual activating agent in this reaction. Subsequently, we found that the best method was adding bis(2,4-dichlorophenyl) chlorophosphate to the reaction mixture last in order to obtain the desired product in good yields.

It should also be noted that even though chloride ions were present in each of the reactions, no chloride displacement byproduct was isolated and that the desired azide product was obtained in satisfactory isolated yield (Table 1). These results suggest that the azide ion is the major, if not the only, nucleophile participating in the S_N2 displacement reactions.

In summary, we developed a simple one-pot procedure for the direct conversion of alcohols to the corresponding azides, demonstrating the usefulness of phosphate chemistry[11] in organic functional group transformation. Our method is mild and convenient and should be complementary to Thompson's procedure of direct azidation to convert alcohols to their corresponding azides. Furthermore, this one-pot procedure might be adapted to introduce nucleophiles other than azides.[12]

Acknowledgment. We gratefully acknowledge the financial support of Grant DAMD 17-98-1-8544 from the U.S. Army Department of Defense Prostate Cancer Research Program and a research grant from the State of New Jersey Commission on Cancer Research.

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(11) The mechanism of phosphoryl transfer from phosphate monoesters and diesters has been the subject of many recent investigations. See: Thatcher, G. R. J.; Luger, R. K. *Adv. Phys. Org. Chem.* **1989**, *25*, 99−103 and references therein.

(12) For example, sodium cyanide might be used in place of sodium azide to convert alcohols to the corresponding chain extended nitriles in a similar "one-pot" procedure.