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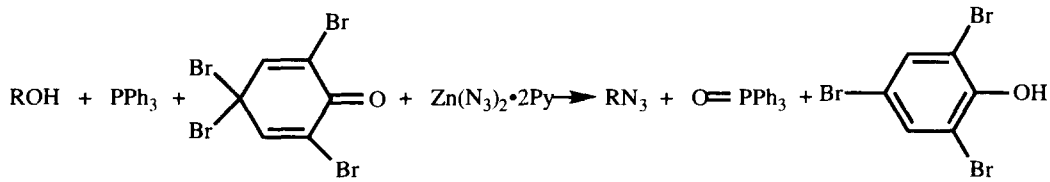
An Efficient Method for Converting Alcohols to Azides with 2,4,4,6-Tetrabromo-2,5-cyclohexadienone/PPh_3/$Zn(N_3)_2$•2Py

Akiko Saito, Kazumi Saito, Akira Tanaka,* and †Takayuki Oritani

Division of Environmental Bioremediation, Graduate School of Agriculture, and †Department of Applied Biological Chemistry, Faculty of Agriculture, Tohoku University, 1-1 Tsutsumidori-amamiyamachi, Aoba-ku, Sendai 981, Japan

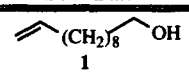
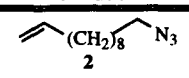
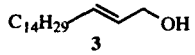
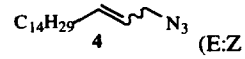
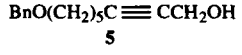
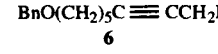
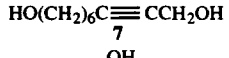
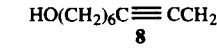
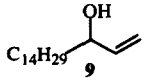
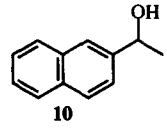
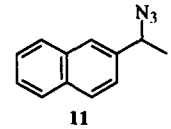
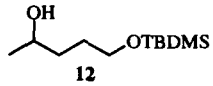
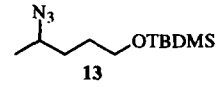
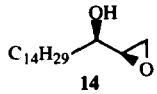
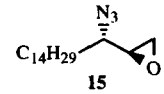
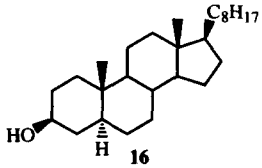
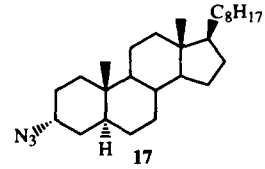
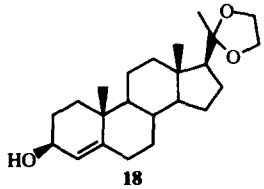
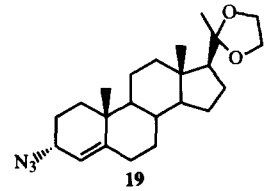
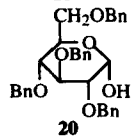
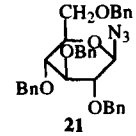
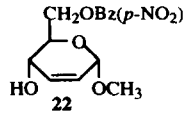
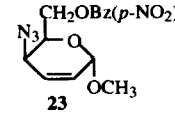
Abstract:Treatment of the salt generated from 2,4,4,6-tetrabromo-2,5-cyclohexadienone and PPh_3 in a mixed solvent of CH_3CN/toluene with primary and secondary alcohols in the presence of $Zn(N_3)_2$•2Py led to azides in excellent yields with inversion of configuration. Addition of hexamethylphosphorictriamide considerably accelerated the reaction.

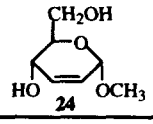
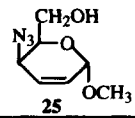
Alkylazides are extremely versatile intermediates for the preparation of amino group-containing compounds. Among the known numerous methods for accessing alkylazides,[1] the Mitsunobu reaction that converts alcohols directly to the corresponding azides is most attractive in that the reaction can be conducted under mild and neutral conditions, and generally leads to excellent yields of products.[2,3] In a previous paper, we described a mild and efficient method for converting alcohols and THP ethers to bromides with 2,4,4,6-tetrabromo-2,5-cyclohexadienone/ PPh_3 couple.[4] In the course of our work on applying this reagent system to other functional group preparations, we found that a combination of this reagent and $Zn(N_3)_2$•2Py was quite effective for azide formation from alcohols. This communication deals with the scope and limitation for this newly developed azidation method.



The optimum conditions for this reaction were explored with various solvents and azide reagents. THF was one of the usable solvents in this reaction. The most effective solvent system was a mixture of CH_3CN and toluene. Use of CH_3CN or toluene alone resulted in a deep coloration of the solution. Among the various azidation agents tested including $Ti(Oi\text{-}Pr)_2(N_3)_2$[5,6] and NaN_3/18-crown-6, $Zn(N_3)_2$•2Py[7,8] was the best reagent. A combination of this reagent and a mixed solvent of CH_3CN/toluene led to azides in excellent yields and with reasonable reaction rates (Table 1).[9,10,11] Furthermore, addition of HMPA to this mixture was found to considerably accelerate the reaction (entry 2). In all cases investigated, the reactions proceeded very smoothly.[12] In the cases of allylic alcohols **3** and **9**, however, rearrangement or olefin isomerization occurred to afford a mixture of geometric isomers (entries 4, 5, 8), which experimental results might suggest the Lewis acidic property of $Zn(N_3)_2$•2Py. An excellent feature of this method is that the reactions proceed with considerably faster rates compared to those of the Mitsunobu-type azidation reaction. Thus, when sugar derivative **22** was subjected to the Mitsunobu conditions (PPh_3/diethyl azodicarboxylate/NaN_3 in toluene), it took three hours at ambient temperature for completion of the reaction (62% yield), while the time taken in our explored reagent system was only 5 min at 0°C (entry 15). Another remarkable characteristic is the marked difference in reaction rates between saturated and unsaturated (allylic and acetylenic) alcohols, allowing only allylic and propargylic positions to be azidated in the presence of saturated alcohols (entries 7, 16). Inversion of configuration in this reaction is evident

Table 1[a]

Entry	Substrate	Solvent[b]	Time	Yield(%)	Product
1	 **1**	A	3 hr	quant.	 **2**
2		B	45 min	quant.	
3		C	3 hr	quant.	
4	 **3**	A	5 min	98	 **4** (E:Z = 2:1)[c]
5		C	10 min	88	(E:Z = 2:1)[c]
6	 **5**	A	5 min	92	 **6**
7	 **7**	C	5 min	97	 **8**
8	 **9**	A	5 min	87	**4** (E:Z = 2:1)[c]
9	 **10**	A	30 min	98	 **11**
10	 **12**	B	24 hr	93	 **13**
11	 **14**	B	3 hr	75	 **15**
12	 **16**	B	12 hr	94	 **17**
13	 **18**	B	5 min	quant.	 **19**
14	 **20**	A	2 hr	quant.	 **21**
15	 **22**	A	5 min	72	 **23**

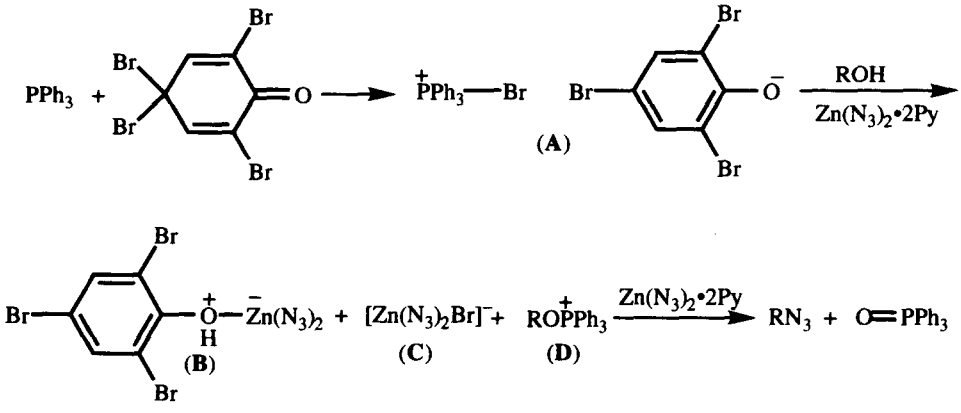
16	 24	C	1.5 hr	60	 25

a) All reactions were performed in 0.5 mmol scale using 2,4,4,6-tetrabromo-2,5-cyclohexadienone (3 eq.), PPh_3 (3 eq.) and $Zn(N_3)_2$•2Py (6 eq.) at room temperature or at 0°C in the cases of allylic and acetylenic substrates (entries 4, 5, 6, 7, 8, 13, 15). b) A: CH_3CN-toluene B: CH_3CN-toluene-HMPA C: THF c) Determined by ^{1}H-NMR.

from the results obtained in the steroid cases (entries 12, 13).

The mechanism of this reaction is not clear. However, when compound **1** was submitted to azidation in 1,2-dichloroethane, we obtained the following interesting experimental results. Thus, changing the molar ratio of $Zn(N_3)_2$•2Py to the bromotriphenylphosphonium salt led to different reaction patterns. The use of 0.5 molar equivalent of the azide reagent to the salt resulted in the predominant formation of the corresponding bromide. When an equimolar amount of the azidation agent was employed, the reaction did not proceed at all. Utilization of two-fold excess of the reagent provided azide **2** in 65% yield, although the reaction was very slow (2 days). Based on these observations, coupled with some information from the previously reported bromination experiment,[4] we propose the reaction pathway illustrated in Scheme 1. The salt (**A**), generated from PPh_3 and 2,4,4,6-tetrabromo-2,5-cyclohexadienone would react with alcohols in the presence of the azidation reagent to afford an alkoxytriphenylphosphonium ion (**D**) and a Lewis acid/base complex (**B**), together with a bromide ion-containing species (**C**). The formation of **C** would retard the bromination resulting from the nucleophilic attack on **D** by the free bromide ion. Finally, the reaction between **D** and excess $Zn(N_3)_2$•2Py would lead to alkylazides and triphenylphosphine oxide.

In conclusion, it was demonstrated that a combined system consisting of 2,4,4,6-tetrabromo-2,5-cyclohexadienone, PPh_3 and $Zn(N_3)_2$•2Py in a mixed solvent of $CHCN_3$/toluene was a mild and efficient reagent for accessing azides from alcohols. Further application of the salt generated from 2,4,4,6-tetrabromo-2,5-cyclohexadienone and PPh_3 to other functional group preparations is now under investigation.



Scheme 1

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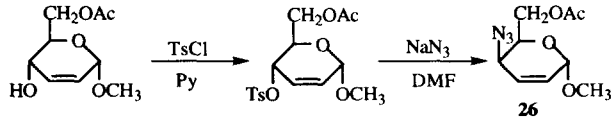
7 Agrell, I.; *Acta Chem. Scand.*, **1970**, 24, 1247-1261.
8 Viaud, M. C.; Rollin, P.; *Synthesis*, **1990**, 130-132.
9 Data for compound **17**: mp 62-63°C. $[\alpha]_D^{22}$+16.4 (c 0.39, $CHCl_3$){lit.,[8] $[\alpha]_D$+19 ($CHCl_3$)}.
10 Compounds **15** and **19** were identical with the samples obtained by submitting **14** and **18** to the Mitsunobu reaction.
11 Acetylation of azide **25** with Ac_2O/pyridine led to the same compound **26** as that obtained by the following transformation.



26

12 A typical experimental procedure is as follows: To an ice-cooled mixture of PPh_3 (393 mg, 1.5 mmol) in CH_3CN (1.5 ml) was added portionwise 2,4,4,6-tetrabromo-2,5-cyclohexadienone (615 mg, 1.5 mmol). After complete disappearance of the yellow color, toluene (15 ml) was added slowly, whereupon the solution exhibited a milky turbidity. Addition of $Zn(N_3)_2$•2Py (797 mg, 3 mmol) followed by acetylenic alcohol **5** (116 mg, 0.5 mmol) resulted in a two-phase solution and after 5 min, the reaction was quenched with sat. aq. $NaHCO_3$. Extraction with ether in the usual way and purification of the crude product by preparative TLC (SiO_2) gave azide **6** (118 mg, 92%) . IR(film) ν_{max} cm^{-1}: 3550, 3030, 2930, 2850, 2120, 1450, 1360, 1340, 1240, 1110, 1100, 730, 700. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 7.38-7.28 (5H, m), 4.52 (2H, s), 3.90 (2H, t, J = 2.0 Hz), 3.50 (2H, t, J = 6.6 Hz), 2.31-2.26 (2H, m), 1.70-1.48 (6H, m). HREIMS (m/z): Calcd. for $C_{15}H_{18}ON$ (M^+–H–N_2), 228.1388. Found, 228.1381.

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