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STRAIGHTFORWARD CONVERSION OF ALCOHOLS INTO NITRILES

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The reaction of various alcohols with cyanogen bromide, triphenylphosphine, and a base afforded the corresponding nitrile in satisfactory yields.

Keywords: Alcohol; cyanogen bromide; nitrile; nucleophilic substitution

INTRODUCTION

One carbon elongation of alkyl chains through the conversion of alcohols into nitriles is a key transformation in organic synthesis.[1] Several methods have been developed for this purpose. The classical two-step procedure requires the initial conversion of the hydroxyl group into a leaving group (e.g., halide or sulfonate), followed by nucleophilic displacement of the latter with cyanide ions.[2] This reaction sometimes requires higher temperature with secondary and tertiary alcohols, and elimination often competes with substitution. The direct one-pot cyanation of alcohols has also been reported in the literature using the Mitsunobu reaction (including analogous variants)[3] or the PPh_3/DDQ/nBu_4NCN[4]–mediated conversion. In addition, Masutani et al. recently described direct cyanation of primary alcohols using a new type of oxidation–reduction process.[5]

RESULTS AND DISCUSSION

In the present article, we report an alternative one-pot procedure for the transformation of alcohols into nitriles. Our approach involves the utilization of triphenylphosphine in combination with cyanogen bromide and a base. The in situ formation of a $Ph_3P(Br)(CN)$ complex is expected to induce smooth cyanation by first activating the alcoholic group followed by nucleophilic displacement by the cyanide ion (Scheme 1). Complexes as $R_3P(X)(CN)$ have already been synthesized and thoroughly characterized (including x-ray structure) by Godfrey et al.[6]

First, experiments were conducted with 1-naphtalenemethanol as substrate. However, treatment of the latter at room temperature with triphenylphosphine

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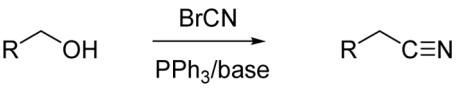
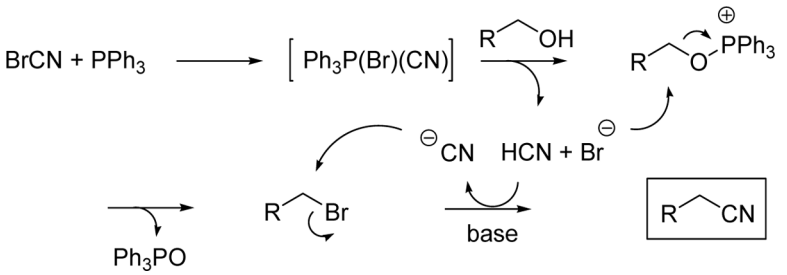


Scheme 1. General transformation of alcohols into nitriles.

and cyanogen bromide in dichloromethane only afforded the corresponding bromide, which was obtained in nearly quantitative yield. The reaction thus failed to give the expected nitrile. Nevertheless, when the same reaction was conducted in the presence of triethylamine, we obtained the corresponding 1-naphtylacetonitrile in good yield. The key intermediate in the alcohol to nitrile transformation thus seems to be the halogenated derivative, which, in the presence of a base, undergoes further reaction with cyanide anions. Optimization of the procedure by varying the base [e.g., diisopropylethyl amine (DIPEA), K_2CO_3, $CsCO_3$, NaH, lutidine, tetramethylguanidine (TMG)] led to the selection of diazabicyclo-undecene (DBU), which provided the best results in terms of overall yields.

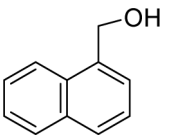
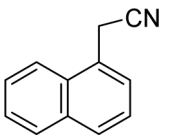
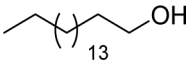
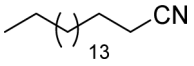
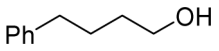
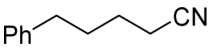
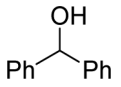
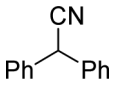
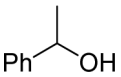
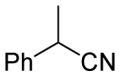
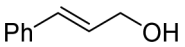
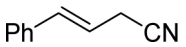
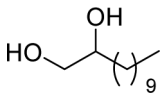
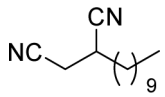
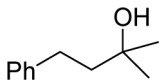
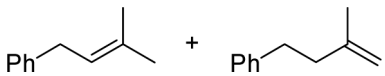
A postulated reaction mechanism is illustrated in Scheme 2. We suggest that, in the first step, the $Ph_3P(Br)(CN)$ complex is produced in situ. The phosphonium salt then undergoes reaction with the hydroxyl group of the substrate, giving rise to a leaving group. The activated alcohol is then displaced by Br^- (with concomitant release of Ph_3PO), and the resulting halide is subsequently substituted by CN^-. The cyanide ion is produced in situ by the base-mediated deprotonation of the newly released HCN. In this procedure, cyanogen bromide plays a triple role: (i) activator of the phosphine, (ii) brominating reagent, and (iii) masked source of nucleophilic cyanide anion.

The scope and limitation of this novel reaction was assessed using a variety of alcoholic subtrates. Results are summarized in Table 1. The overall yields are moderate to good depending on the substitution of the starting alcohol. Primary alcoholic substrates such as heptadecan-1-ol (entry 2), 4-phenyl-1-butanol (entry 3), and cinnamyl alcohol (entry 6) afforded the expected nitriles in satisfactory yields. It is noteworthy that in the latter case, only one product was observed, despite the propensity of allylic systems to participate in S_N' pathways. The process is also efficient with a primary benzylic alcohol (e.g., 1-naphtalenemethanol, entry 1) because 1-naphtylacetonitrile was obtained in 69% yield. However, less yields of isolated products were obtained when working with secondary alcoholic substrates. Indeed, the conversion of diphenylmethanol (entry 4) or 1-phenylethanol (entry 5) only yielded the corresponding nitriles in 28 and 25% yields, respectively. Surprisingly, in the case of a 1,2-diol (entry 7),



Scheme 2. Postulated mechanism of the conversion of alcohols into nitriles.

Table 1. Examples of cyanation of alcohols

Entry	Alcohol	Product(s)	Yield (%)[a]
1			69
2			52
3			66
4			28
5			25
6			44
7			45
8			55

[a]Isolated yield after purification by silica-gel chromatography.

double substitution was obtained, leading to the corresponding bis-nitrile derivative in 45% yield. We were never able to isolate the mono-substituted derivative even when working with less than stoichiometric amounts of reagents. Our attempt to extend the reaction to a tertiary alcohol was unsuccessful; we obtained only a mixture of dehydrated products (entry 8). The isolated yields of products indicate the following order of reactivity for the starting alcohols: primary $\sim$ benzylic $\sim$ allylic $\gg$ secondary $\ggg$ tertiary.

CONCLUSION

In conclusion, we report here a new and efficient process for the one-pot conversion of alcohols into nitriles. The method involves the use of triphenylphosphine together with cyanogen bromide and an appropriate base. The procedure is simple and provides straightforward access to nitriles.

EXPERIMENTAL

Typical Procedure for the Cyanation of 1-Naphthalenemethanol

Under nitrogen, PPh_3 (709 mg, 1 equiv.) diluted with 1 mL of anhydrous CH_2Cl_2 was added to BrCN (302 mg, 1.05 equiv.), followed by 1-naphthalenemethanol

(433 mg, 2.71 mmol, 1 equiv.) in 4 mL of anhydrous CH_2Cl_2. The reaction was monitored by thin-layer chromatography (TLC; C_6H_{12}/CH_2Cl_2, 3:2) to follow the formation of the halogenated intermediate (typically 1 h). The flask was then placed an ice bath, and DBU (415 μL, 1.05 equiv.) was introduced. The mixture was further stirred at room temperature for 2 h. Solvents were then evaporated under vacuum, and the resulting brownish oil was chromatographed on silica (C_6H_{12}/CH_2Cl_2, 3:2) to give 1-naphtylacetonitrile as a colorless oil (329 mg, 69% yield).

Data

^{1}H NMR ($CDCl_3$): δ 4.5 (s, 2H), 7.5 (m, 1H), 7.6 (m, 3H), 7.9 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 21.6, 117.6, 122.3, 125.4, 125.7, 126.3, 126.4, 127.0, 128.9, 129.0, 130.7, 133.6. IR (neat): 3051, 2252, 1599, 1511, 1397, 792, 774 cm^{-1}.

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