Use of PyBOP as a Convenient Activator for the Synthesis of Nitriles from Primary Amides†

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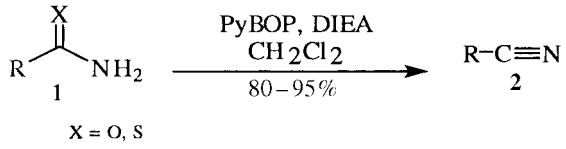
Abstract: Various types of primary carboxamides were reacted with benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) and *N*-ethyldiisopropylamine to obtain the corresponding nitriles in high yields.

Key words: nitriles, amides, *N*-ethyldiisopropylamine, PyBOP, transformation, dehydration

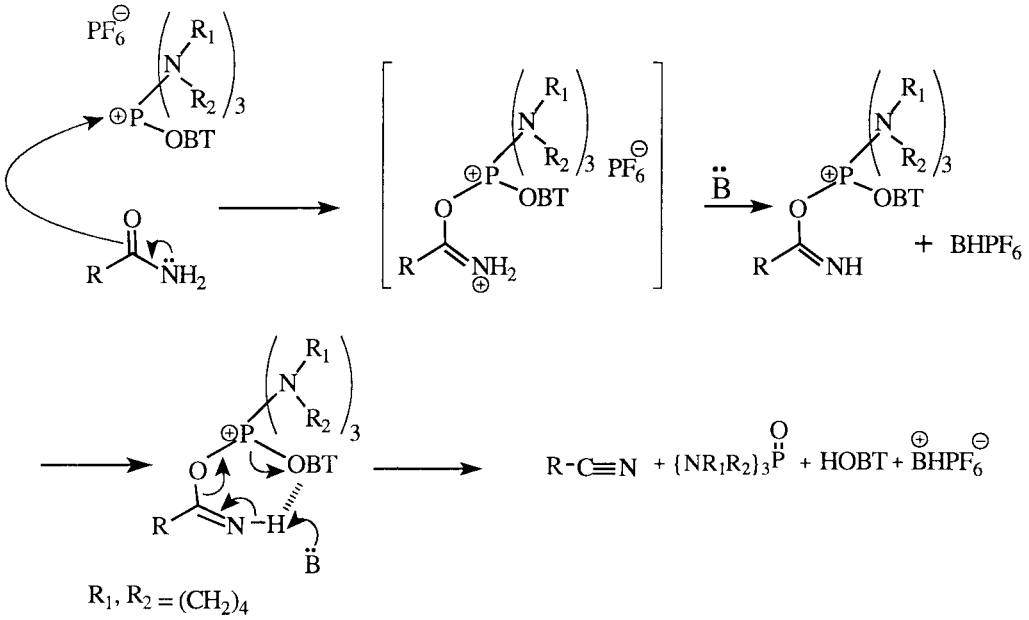
There is considerable interest in organic synthesis to exploit new reagents which make it possible for selective functional group transformations with high selectivities on a preparative scale under mild conditions. PyBOP [benzotriazol-1-yloxytris(pyrrolidinol)phosphonium hexafluorophosphate] may be one of the candidates which has been widely used for the low racemization-free coupling of peptides,[1] but has also been used in convenient synthesis of esters from carboxylic acids and alcohols avoiding the formation of toxic byproduct.[2]

Nitriles are of particular interest as intermediates in preparative organic synthesis due to their conversion into carboxylic acids, aldehydes, amides, amines, and ketones.[3] In recent reports, it was shown that nitriles could be converted to thiazole derivatives as inhibitors of superoxide,[4] transformed to 1,2-diarylimidazoles as potent anti-inflammatory agents[5] or could be used as a starting material for triazolo[1,5-*c*]pyrimidines with potential anti-asthma activity.[6] They are usually prepared by nucleophilic substitution[7a] with CN or by regenerating CN via oxidation,[7b] rearrangement[7c] or elimination. In view of their potential utility in organic synthesis,[8] a plethora of reagents for the preparation of nitriles by dehydration of carboxamides using phosphorous pentoxide,[9a] titanium tetrachloride,[9b] thionyl chloride,[9c] trifluoroacetic anhydride,[9d] have been documented in the literature.

More recently, alkylating and dehydrating reagents have been disclosed that permit the reaction to proceed under mild,[10] neutral conditions[11] and at low temperature[12] or in liquid triphasic systems.[13] However, many of these methods suffer from certain limitations such as the need for isolation of an unstable intermediate and subsequent treatment with a strong base,[14a] long reaction time (up to 12 h reflux temperature in case of formic acid),[14b] limited to

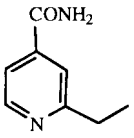
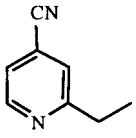
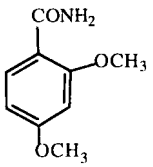
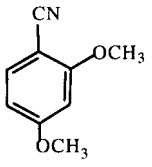
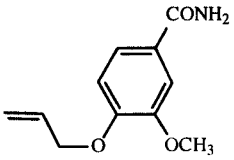
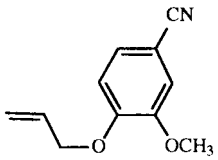
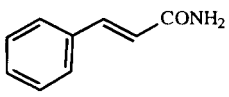
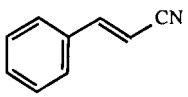
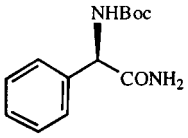
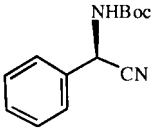
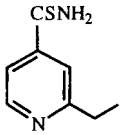
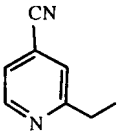
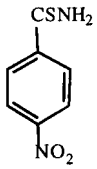
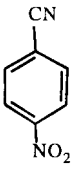
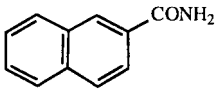
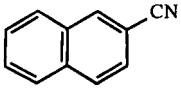
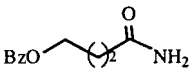
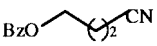


Scheme 1



Scheme 2

Table 1 Conversion of Primary Amides to Nitriles with PyBOP

Entry	Amide **1**	Nitrile **2**[a]	Yield (%)[b]
a			95
b			89
c			87
d			85
e			83
f	$TrO(CH_2)_4CONH_2$	$TrO(CH_2)_4CN$	80
g			90
h			86
i			88
j			82

[a] All products were characterized by comparison of their mp, IR and ^1H NMR spectra with those of the authentic samples.
[b] Isolated Yields.

only arylamides[14c] and tedious workup procedures.[14d] In this context, there is still the need to devise a method using readily available and safe reagents. This has led us to investigate a new methodology, which is able to carry out the rapid conversion of carboxamides to nitriles in high yields. As part of our ongoing program on the synthesis and development of new methodologies in organic synthesis,[15] we herein report a new, simple and efficient procedure for effecting this transformation by using (PyBOP) and *N*-ethyldiisopropylamine (DIEA) in CH_2Cl_2 at 40 °C in high yields. To the best of our knowledge, the generality and applicability of PyBOP in the preparation of nitriles from primary amides is not known.

The synthetic utility of this reagent for functional group conversion is shown in Scheme 1 and several experimental results are illustrated in the Table. The synthesis of aliphatic and aromatic nitriles by the use of PyBOP and DIPEA proceeds smoothly under mild conditions in apolar solvents such as dichloromethane, or in dipolar aprotic solvents such as DMF or DMSO. Different workup procedures can be used depending on the solvent and nature of the product. The method is compatible with a variety of protecting groups and even very acid labile protecting groups, such as the triphenylmethyl group or the base labile ester group, are not affected during the reaction. Furthermore, the reagent was successfully utilized for the preparation of nitriles from thioamides.

The mechanism by which these reactions proceed is particularly intriguing, and we could find no literature precedence for nitrile formation from amides using PyBOP. A proposed reaction mechanism is depicted in Scheme 2. All the reactions were carried out at 1−5 mmol scale. The efficacy of the reaction was also studied by subjecting substrates in entries **a** and **b** in 15 mmol scale under similar conditions. However, it appears that there is no significant improvement in the rate of reaction by changing experimental parameters. Neither racemization of the α-bearing carbon[16] nor β-elimination of the nitrile groups were observed. Furthermore, it appears that electron-withdrawing or -donating groups do not significantly affect the rate of reaction.

In summary, the good yield, simple workup and the fairly neutral conditions of this method could therefore potentially be used to synthesize nitriles of complicated molecules containing multiple protected functional groups.

Nitriles 2 from Primary Amides 2; General Procedure

PyBOP (1.145 g, 2.2 mmol) was added to a stirred ice-cooled solution (or suspension) of the amide **1** (2.0 mmol) in anhyd CH_2Cl_2 (10 mL) and anhyd *N*,*N*-diisopropylethylamine (569 mg, 4.4 mmol) under N_2. The reaction mixture was slowly heated to 40 °C for a period of 5−8 h until the amide was consumed (TLC analysis). The mixture was quenched with H_2O (2 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and the solvent was removed in vacuo to afford the crude product, which was purified by column chromatography (EtOAc/hexane, 1:9 v/v) on silica gel to give pure nitrile **2** in 80−95% yields (Table).

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(16) Physical and spectral data of compounds **2a−c**:
2a
IR (neat): ν = 3050−2830, 2230, 1600, 1550, 1490, 1400 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 8.65 (d, 1 H, *J* = 5 Hz), 7.31−7.29 (m, 2 H), 2.95−2.79 (q, 2 H, *J* = 8.5 Hz), 1.35−1.27 (t, 3 H, *J* = 8.5 Hz).
MS: *m*/*z* = 132 (M^+).
2b
IR (KBr): ν = 2240, 1600, 1260, 830 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$): δ = 7.42 (d, 1H, J = 8.4 Hz), 6.52−6.39 (m, 2 H), 3.86 (s, 3 H), 3.82 (s, 3 H).
MS: *m*/*z* = 163 (M^+), 138, 103, 31.
2c
Mp 58−60 °C.
IR (KBr): ν = 2239 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 4.64 (dd, $J_{vicinal}$ = 5.4, $J_{4\text{-bond}}$ = 1.2 Hz, 2 H, allylic H), 5.33 (ddd, J_{cis} = 10.6, J_{gem} = 3.0, $J_{4\text{-bond}}$ = 1.2 Hz, 1 H, terminal vinylic H), 5.42 (ddd, J_{trans} = 17.2, J_{gem} = 3.0, $J_{4\text{-bond}}$ 1.2 Hz, 1 H, terminal vinylic H), 6.02 (m, 1 H, internal vinylic H), 6.90 (d, J_{ortho} = 8.4 Hz, 1 H, Ar-H), 7.09 (d, J_{meta} = 2.0 Hz, 1 H, Ar-H), 7.25 (dd, J_{ortho} = 8.4, J_{meta} = 2.0 Hz, 1 H, Ar-H).
The optical rotation of the product **2e** indicated that no racemization had occurred during the transformation process; this was confirmed by comparison with the amine hydrochloride salt; $[\alpha]_D$ +30.0 (*c* = 1.0, H_2O); Lit.[17] $[\alpha]_D$ +33.0 (*c* = 1.001, H_2O).

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