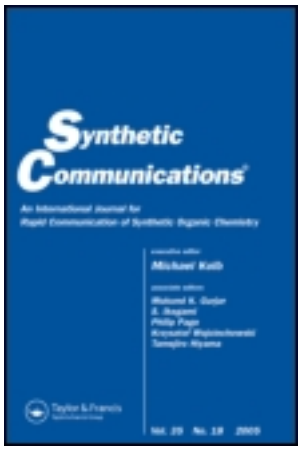

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A RAPID AND FACILE CONVERSION OF PRIMARY AMIDES AND ALDOXIMES TO NITRILES AND KETOXIMES TO AMIDES WITH TRIPHENYLPHOSPHINE AND *N*-CHLOROSUCCINIMIDE

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ABSTRACT

Primary amides and aldoximes are easily converted to their corresponding nitriles using a mixture of triphenylphosphine and *N*-chlorosuccinimide in dichloromethane at room temperature. The reaction of aldoximes occurs almost immediately and primary amides in 0.5 h by this method. By this procedure secondary amides are produced by Beckmann rearrangement of ketoximes.

Key Words: Amide; Aldoxime; Nitrile; Triphenylphosphine; *N*-chlorosuccinimide

Nitriles are important intermediates for fine chemicals such as medicines, agricultural chemicals and dyes. One of the most general methods for synthesis of nitriles is the nucleophilic substitution reaction of alkyl halides with inorganic cyanides. However, due to violent poisons of cyanide, the

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conversion of primary amides and aldoximes into nitriles has gained important synthetic application for this transformation. Several methods have been used for dehydration of aldoximes to nitriles.[1–9] However, many of these methods are deficient in some respect such as tedious work-up, vigorous reaction conditions, unsatisfactory yields and use of great excess of reagents. Reagents such as triethylamine/sulfur dioxide[10] and sulfuryl chloride fluoride[11] allow the rapid and mild dehydration of aldehyde oximes but the preparation of the reagents is inconvenient (at $-78^{\circ}C$). Dehydration with zeolite (CsX) suffers from high temperatures ($350^{\circ}C$)[12] and reagents like phosgene,[13] diphosgene[14] and triphosgene[15] are hazardous to use. Also, the use of Envirocat EPZG^{R} has long reaction times for this transformation.[16] Some methods have also been reported for the conversion of amides into nitriles. Recent developed procedures for this reaction include Vilsmeier reagent,[17] cyanuric chloride/DMF,[18] triethoxydiiodophosphorane[19] and trifluoroacetic anhydride.[20] However, these reagents still have some disadvantages regarding difficulty in handling or unsatisfactory yields. Also, the Beckmann rearrangement has been of tremendous interest to all practicing organic chemists as the reaction effects a nitrogen insertion into a carbon framework.[21] The conventional Beckmann rearrangement usually requires the use of excess amounts of strongly Bronsted acid such as conc. H_2SO_4 or polyphosphoric acid (PPA) which cause serious problems such as product decomposition and formation of large amount of inorganic salts caused by neutralization. To circumvent these problems, during recent years, different solid catalysts such as metal oxides,[22] metal phosphates,[23] supported boria,[24] zeolite,[25] aluminosilicate[26,27] including clay are being used. However, most of these reactions are vapor phase reactions or are carried out at very high temperatures ($523\,K^{\circ}$). Therefore, there is still a need for research to introduce more convenient and generally applicable methods for these important synthetic transformations. In continuation of our previous work on preparation of nitriles,[28] and introducing new applications for Ph_3P,[29a,b] we wish to report a rapid and facile method for dehydration of primary amides and aldoximes to their corresponding nitriles and Beckmann rearrangement of ketoximes to secondary amides by use of triphenylphosphine/*N*-chlorosuccinimide, (PPh_3/NCS), as efficient reagent under mild reaction conditions.

First, we studied the reaction of phenylacetamide with Ph_3P in the presence of various electrophilic halogen sources such as *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and also 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO).[30] The results are shown in Table 1.

Results of Table 1 show that the use of Ph_3P/NCS as source of electrophilic halogen is more efficient than using Ph_3P/NBS and Ph_3P/TABCO.

Table 1.

$$BnCNH_2 \xrightarrow[CH_2Cl_2]{\text{r.t.0.5 h}} BnCN$$

Entry	Reagent	Molar Ratio (Amide : PPh_3 : NXS)	Yield (%)[a]
1	PPh_3/NCS	1 : 1.2 : 1.2	71
2	PPh_3/NCS	1 : 1.5 : 1.2	73
3	PPh_3/NCS	1 : 1.2 : 1.5	74
4	PPh_3/NCS	1 : 1.6 : 1.6	91
5	PPh_3/NBS	1 : 1.2 : 1.2	51
6	PPh_3/NBS	1 : 1.6 : 1.2	71
7	PPh_3/TABCO[b]	1 : 1.2 : 1.2	34
8	PPh_3/TABCO	1 : 1.6 : 1.2	54

[a]By NMR analysis.
[b]2,4,4,6-Tetrabromo-2,5-cyclohexadienone was prepared according to the literature.[30]

The reaction of phenyl acetamide with PPh_3/NCS occurs at room temperature in CH_2Cl_2 and produces benzyl nitrile in excellent yield (Table 1, Entry 4), however, the same reaction with Ph_3P/NBS and Ph_3P/TABCO produce phenyl acetamide in only 51 and 34% yields, respectively. We therefore extended this procedure for dehydration of other primary amides and also aldoximes (Table 2).

As shown in this table, aldoximes and primary amides easily convert to their corresponding nitriles. The reaction of aldoximes occurs almost immediately and amides react in 0.5 h with this reagent. In comparison with the reaction of Ph_3P/CCl_4 in CH_3CN with aldoximes and primary amides,[9d] the present reaction using Ph_3P/NCS requires shorter reaction time. In addition, the use of Ph_3P/CCl_4 in acetonitrile for this conversion suffers from the use of excess Ph_3P (four equimolar).

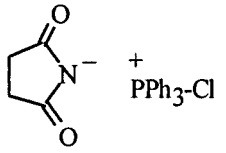
The Beckmann reaction of ketoximes with Ph_3P/NCS occurs also at room temperature almost immediately and their corresponding secondary amides are obtained in high yields (Table 2).

Dehydration reactions of aldoximes and primary amides with Ph_3P/NCS can occur through their reaction with (1) to produce the intermediates (2) and (3), respectively. These intermediates can then convert to nitrile by the formation of triphenyl phosphine oxide.

Table 2. Treatment of Amides and Oximes with PPh_3/NCS at Room Temperature[a]

Entry	Substrate	Molar Ratio[b]	Product[c]	Yield (%)[d]
1	$CH_3CH_2CONH_2$	1 : 1.4 : 1.4	CH_3CH_2CN	90[e]
2	$BnCONH_2$	1 : 1.6 : 1.6	BnCN	70 (90)[f]
3	$PhCONH_2$	1 : 1.5 : 1.5	PhCN	75[e]
4	PhCH=NOH	1 : 1.5 : 1.5	PhCN	97[e]
5	*p*-ClC_6H_4CH=NOH	1 : 1.2 : 1.2	*p*-ClC_6H_4CN	84
6	*o*-ClC_6H_4CH=NOH	1 : 1.3 : 1.3	*o*-ClC_6H_4CN	92
7	*p*-BrC_6H_4CH=NOH	1 : 1.4 : 1.4	*p*-BrC_6H_4CN	94
8	*p*-$O_2NC_6H_4CH$=NOH	1 : 1.3 : 1.3	*p*-$O_2NC_6H_4CN$	91
9	*o*-$O_2NC_6H_4CH$=NOH	1 : 1.2 : 1.2	*o*-$O_2NC_6H_4CN$	95
10	*p*-$CH_3C_6H_4CH$=NOH	1 : 1.4 : 1.4	*p*-$CH_3C_6H_4CN$	77
11	Ph_2C=NOH	1 : 1.3 : 1.3	PhCONHPh	82
12	$Ph(CH_3)C$=NOH	1 : 1.3 : 1.3	$CH_3CONHPh$	75 (95)[f]

[a]The reaction time for oximes is immediately and for amides is 0.5 h.
[b]The molar ratio of oxime or amide : PPh_3 : NCS.
[c]All the products are known compounds.[9a,16,32]
[d]Isolated yield.
[e]Yield is based on GC analysis using *n*-heptane as internal standard.
[f]Yield is based on NMR analysis using toluene or anisole as internal standard.



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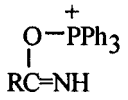

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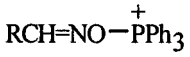
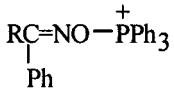


(3)

The reaction of (1) with ketoximes can form the intermediate (4). Beckmann rearrangement of (4) with loses of Ph_3PO produce (5), which can be attacked by a molecule of water in the work-up procedure to form the rearranged product.



(4)

(5)

In conclusion, PPh_3/NCS is a mild and efficient reagent for the conversion of primary amides and aldoximes into nitriles. The use of this reagent provides also a very mild and efficient method for the conversion

of ketoximes into secondary amides. Simple work-up, availability of the reagents, high yields, short reaction times and occurrence of the reactions at room temperature could also be considered as advantages of the present method.

EXPERIMENTAL

All oximes were prepared from aldehydes or ketones according to the literature.[31] All products are known compounds and were characterized by comparison of their physical data with literature values. IR spectra were recorded on a Perkin Elmer 781 spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Advance DPX-250 spectrometer. Mass spectra were recorded on Shimadzu GCMS-QP 1000 EX instrument.

Typical Procedure

To a solution of PPh_3 (0.315 g, 1.2 mmol) and NCS (0.16 g, 1.2 mmol) in dichloromethane (5 mL) was added 2-nitrobenzaldehyde oxime (0.166 g, 1 mmol). The mixture was well stirred at room temperature. TLC monitoring showed the immediate completion of the reaction. After evaporation of the solvent, the crude product was purified by column chromatography using *n*-pentane/ethyl acetate as eluent to give 2-nitrobenzonitrile as pale yellow crystals, 0.14 g, 95% yield, m.p. 109–110°C, Lit.[16] 111°C.

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