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Dehydration of Chiral α-Amides to Chiral α-Nitriles Under the Appel Reaction Conditions

Shekharappa[1] · L. Roopesh Kumar[1] · C. Srinivasulu[1] · Vommina V. Sureshbabu[1]

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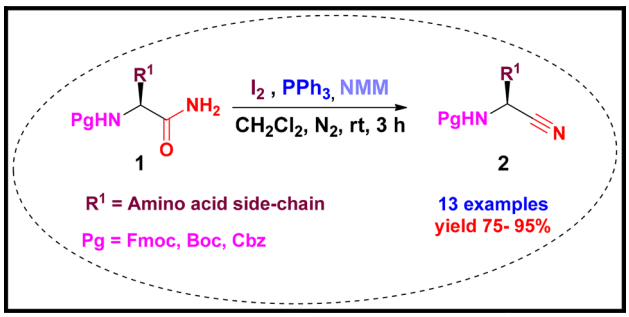
Abstract

An efficient synthesis of N^{α}-protected amino nitriles from N^{α}-protected amino acid amides employing Ph_3P, I_2 and NMM was described. Various amino acid amides, protected by Fmoc, Z and Boc were conveniently converted to nitriles in high yields. Side chain protected amino acid amides were well-tolerated and a good yield of products was obtained. The protocol serves as one of the mild, among a few available, methods for the racemization-free conversion of N^{α}-protected amino acid amides to corresponding nitriles with neither harsh condition nor catalyst.

Graphic Abstract

N^{α}-protected amino acid amides were efficiently transformed to N^{α}-protected amino acid nitriles employing I_2, PPh_3, and NMM under mild reaction conditions. Fmoc, Boc and Cbz-protected amino acid amides were converted into their corresponding nitriles groups. Side chain protected amino acid amides also underwent facile conversion to their corresponding nitriles with good yields.



Keywords α-Amide · α-Nitrile · *N*-Methylmorpholine · Molecular iodine · Triphenylphosphine

Introduction

Many attempts to synthesize nitriles are being made as these are intermediates in the production of polyamides, pharmaceuticals, dyes and numerous fine chemicals (Fatiadi et al. 1983; Miller and Marson 2001). And also, nitrile group serves as an important intermediate in organic synthesis for various functional group transformations (Caddick et al. 2000; Munoz et al. 2011; Yamaguchi and Mizuno 2014; Wanga 2015) and has often been utilized as a versatile precursor to synthesize various heterocyclic compounds (Aureggi and Sedelmeier 2007; Bosch and Vilarrasa 2007;

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✉ Vommina V. Sureshbabu
sureshbabuvommina@rediffmail.com; hariccb@hotmail.com

[1] Peptide Research Laboratory, Department of Studies in Chemistry, Bangalore University, Jnana Bharathi, Bangalore, Karnataka 560056, India

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Nishiwaki et al. 2011; Heller et al. 2002) (Fig. 1). Many compounds having nitrile group possess a broad spectrum of biological activities (Tarleton et al. 2012).

The most common way to synthesize nitriles is by dehydration of primary amides. This involves the use of acidic dehydrating reagents viz., P_2O_5 (Reisener and Horning 1963), $POCl_3$ (Rickborn and Jensen 1962), $SOCl_2$ (Krynitsky and Carhart 1963), and $TiCl_4$ (Lehnert 1971). In an attempt, sophisticated reagents, such as the combination of ethyl dichlorophosphate and diazabicyclo[5.4.0]undec-7-ene (DBU), were also used for the dehydration of amides (Kuo et al. 2007). Amide dehydration catalyzed by iron complexes (Zhou et al. 2009a, b), tetrabutylammonium fluoride (Zhou et al. 2009a, b) and cyclopropenone (Rai and Yadav 2013) can be found in literature. In addition, iron complex bearing an *N*-heterocyclic carbene ligand with hydrosilane at 100 °C has been used for this purpose (Elangovan et al. 2015). Recently, primary amides were converted to nitriles using visible light, with reaction duration 16–30 h (Yadav et al. 2014). Aminoalane reagent (Wojtkielewicz et al. 2015) and XtalFluor-E (Keita et al. 2015) as dehydrating reagents have been employed to access nitriles from amides. In addition, pivaloyl chloride-pyridine system (Narasaiah and Nagaiah 2004), Burgess (Claremon and Philips 1988) and similar type reagent (Rappai et al. 2011), (benzotriazol-1-yloxy)trispyrrolidinolphosphoniumhexafluorophosphate (PyBOP) DIEA system (Bose and Narasaiah 2001), trifluoroacetic anhydride (TFAA)-pyridine system (Sureshbabu et al. 2007, 2009a, b), triphenylphosphine (PPh_3)-carbon tetrachloride system (Kim et al. 1990), triphenylphosphine-*N*-chlorosuccinimide system (Iranpoor et al. 2002), cyanuric chloride (Maetz and Rodriguez 1997) have been employed for this functional group transformation. There are reports for the conversion of N^{α}-protected amino acid amides into N^{α}-protected aminonitriles, which are often used intermediates for the syntheses of various peptidomimetics (Sureshbabu et al. 2007, 2009a, b ; Santhosh et al. 2017).

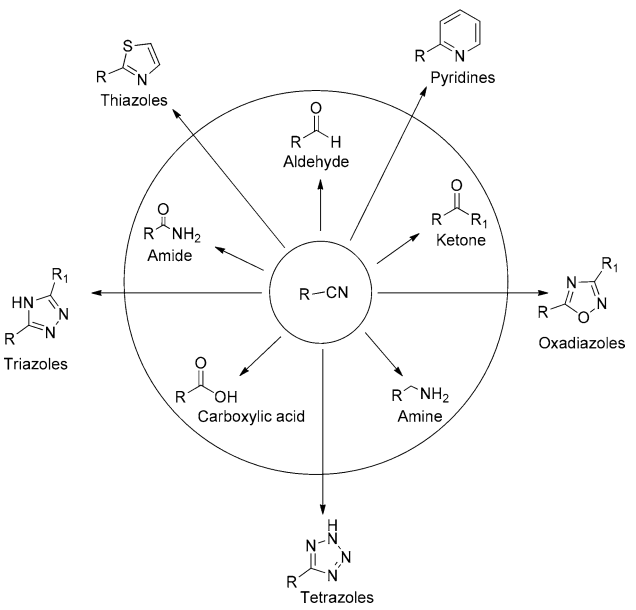


Fig. 1 Selected examples of various functional group transformations and heterocycles from nitrile

Till date, Burgess reagent (Claremon and Philips 1988), $(COCl)_2$–Et_3N (Nakajima and Ubukata 1997), cyanuric chloride (Maetz and Rodriguez 1997) and TFAA–pyridine system (Sureshbabu et al. 2007, 2009a, b) are the prominent ones exclusively employed for dehydration of N^{α}-protected amino acid amides. However, not much demonstration has come out of these reagents. Though all the aforementioned protocols were able to transform primary amide to nitriles, they are, by one or other, suffer from drawbacks. Most of the methods require long duration with high reflux temperatures and catalysts. Problems involving storage, handling and waste generation and tedious work up warrants an improved protocol for the conversion. Especially, most of these reagents are inconvenient to use in amino acid chemistry, as they apply base-sensitive or acid-sensitive protecting groups, like Fmoc and Boc, respectively. Despite several protocols that are available, there is a continuous search for the mild protocols as nitriles are of great practical importance. Besides, on quick literature search, it was found that not many protocols were reported to obtain N^{α}-protected aminonitriles from corresponding amides. In an attempt to develop a mild and simple protocol to achieve this conversion, we found that combination of PPh_3, I_2 and a base could serve as one. The combination was efficiently used to convert formamides to isonitriles at mild conditions and with the minimum reaction duration (Wang et al. 2015). And also, it is noteworthy that the combination of PPh_3 and I_2 (and $CBrCl_3$) along with base was effectively used for the synthesis of nitriles from primary amides (Wang and Ganesan 2000; Jasema et al. 2014), however, exclusive application of this combination is not yet demonstrated for the racemization free synthesis of N^{α}-protected amino nitrile from the corresponding amides involving common, yet sensitive functional groups. We envisaged exploiting this combination for the conversion of amide functional groups to nitrile. Reaction when carried out using N^{α}-protected amino acid amides, the conversion of amide to corresponding nitriles was completed in 3 h at room temperature. The yields obtained were surprisingly better, up to 95%. With our interest in developing a new, mild protocol for the synthesis of N^{α}-protected amino nitrile, herein we report a protocol to synthesize N^{α}-protected aminonitriles from N^{α}-protected amino acid amides employing the combination of PPh_3, I_2 and NMM.

Results and Discussions

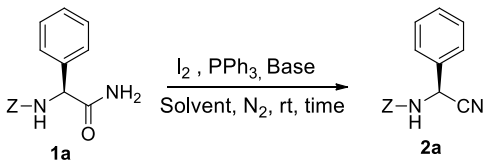
In order to ascertain the feasibility of our envisaged preparation of nitriles using PPh_3 and I_2, Z-Phg-NH_2 (**1a**) was chosen as a model substrate. We began our investigation based on the work by Wang et al., and Narasaiah group (Wang et al. 2015; Narasaiah et al. 2006). In the latter, nitriles were obtained from aldoximes with PPh_3 and I_2 without a base. Initially, solvent THF was chosen as N^{α}-protected amino acid amides were neatly soluble in it. We began our screening with with PPh_3 (1.0 equiv.) and I_2 (1.0 equiv.) in the absence of base and the conversion did not take place, indicated by thin layer chromatography (TLC) (Table 1, **Entry 1**). Speculating that adding base could yield the conversion was also failed undeservedly as only meagre conversion was observed (Table 1, **Entries 2 and 3**). On changing to DCM, it was still the same; no nitrile was formed without a base (Table 1, **Entry 4**). On addition of 1.0 equiv. of base, to our delight, nitrile was formed, proving base was an indispensable factor for the conversion (Table 1, **Entry 5**). Once the reagents necessary for the preparation of nitriles were found, we further investigated on the stoichiometric amount of reactants that are required for the conversion. After a small series of examination, it was found that the absence or inadequate amount of any one of the reagent or with a reaction time less than 3 h led to decrease in the yield (Table 1, **Entries 6–8**). Reaction when carried out for 3 h, significant increase in yield was observed and further increase in reaction duration did not improve the yield (Table 1, **Entry 9).** Moreover, increasing molar ratios of PPh_3 and I_2 had led to decrease in the yield (Table 1, **Entry 10**). Reactions with DMF and EtOAc in two separate experiments did not give noticeable conversion (Table 1, **Entries 11 and 12**).

Chiral RP-HPLC analysis of compounds Z-(L)Phg-CN (**2a**) and Z-(D)Phg-CN (**2a***) gave single peak in the chromatogram i.e., at $t\mathbf{R_1} = 20.133$ and $t\mathbf{R_2} = 17.797$ respectively (see supporting information), confirming the products are racemization free (for chiral RP-HPLC chromatograms of the compounds **2d** and **2g** see supporting information). Eventually, we arrived at the optimized conditions-PPh_3 (1.5 equiv.), I_2 (1.5 equiv.) and NMM (3.0 equiv.) with the reaction time of 3 h having dry DCM as a solvent (Table 1, **Entry 13**). Generality and scope of the protocol were demonstrated, during which, it was found that Cbz-protected amino acid amides showed maximum compatibility by giving maximum yields up to 95% (Scheme 1, **Entries 2a–c**) Nevertheless, Boc and Fmoc-protected amino acid amides gave a satisfactory yield, up to 90% and 76% respectively (Scheme 1, **Entries 2d–m**). As an extension and to demonstrate the tolerance, the protocol was applied to side chain protected N^{α}-protected amino acid amides and they also underwent facile conversion to nitriles and good yield of products were isolated (Scheme 1, **Entries 2f, 2l and 2m**).

All the compounds were well characterized by mass, ^1H and ^{13}C NMR analysis and were correspondent with the structures of the compounds. Infrared spectroscopy showed medium-weak peaks at around 2239–2250 cm^{-1}, confirming nitrile functional group. RP-HPLC analysis of the compounds using chiral column resulted in single peaks, which confirmed the racemization- free synthesis of the title compounds.

Recent literature reports suggest that PPh_3-I_2 system proved to be a versatile combination as it has been continuously exploited in various organic syntheses viz., amidation (Wangngae et al. 2015); N-alkylation of purine, pyrimidine and azole derivatives (Rad and Soleimani 2016); allylic amines (Chavan et al. 2014), substituted guanidines and 2-iminoimidazolin-4-ones (Wangngae et al. 2017); and 2,3-disubstituted-3H-quinazolin-4-ones (Phakhodee et al. 2017). Based on these literature precedents, reaction mechanism of the present work was proposed (Scheme 2). The familiar reaction proceeds by the formation of Appel's salt **A**, to which nucleophilic addition of oxygen of the carbonyl group of the amide forms the intermediate **B**, which subsequently yields nitrile on reacting with the base.

Table 1 Optimization of reaction conditions



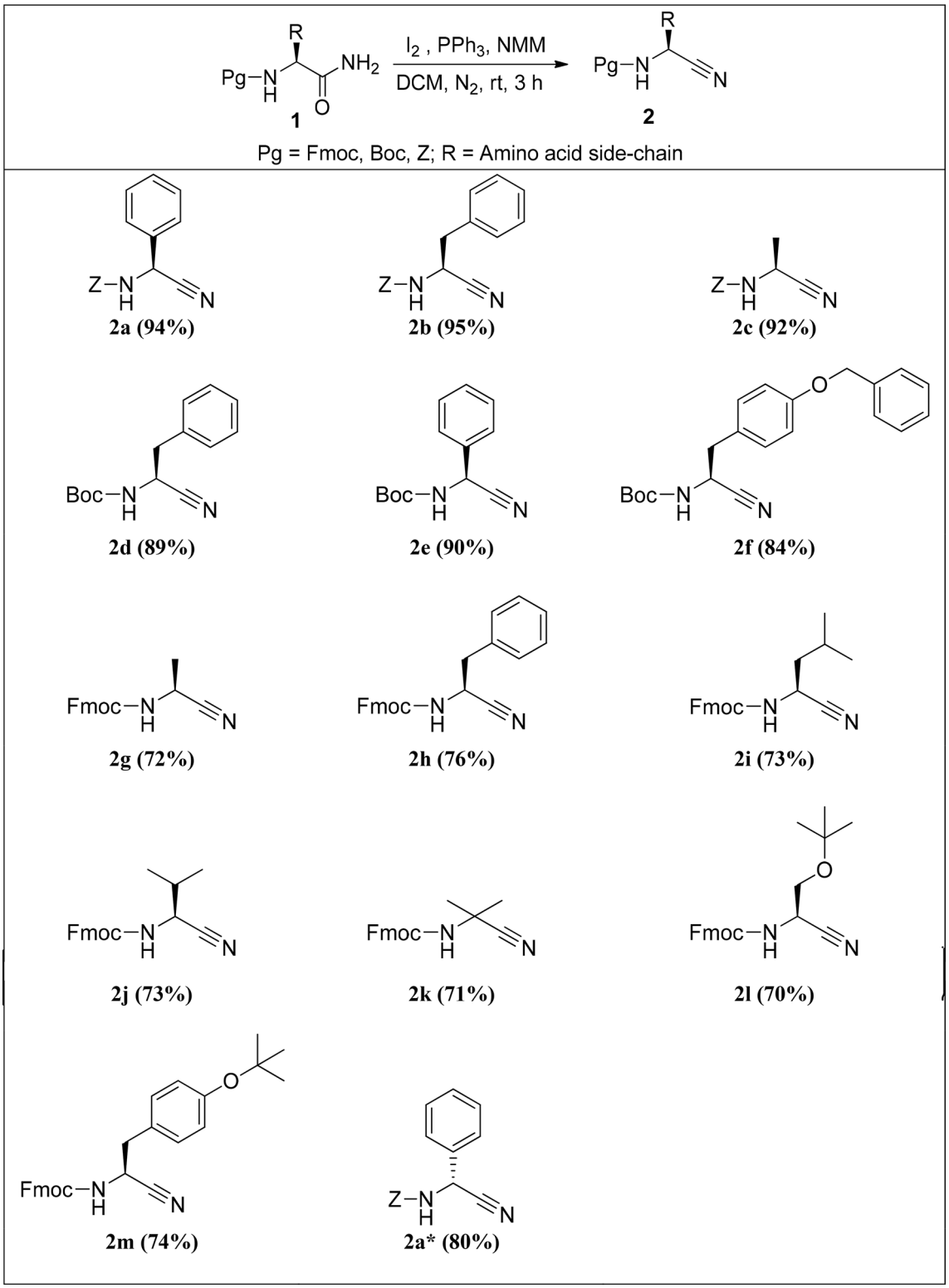
Entry[a]	Solvent	Base (equiv.)	PPh3:I2 (equiv.)	Time (h)	Yield[b] (%)
1	THF	–	1:1	12	–
2	THF	Et_3N (2.0)	1:1	12	Trace[c]
3	THF	Et_3N (2.0)	1.5:1.5	12	Trace[c]
4	DCM	–	1:1	6	–
5	DCM	Et_3N (1.0)	1:1	6[d]	36
6	DCM	Et_3N (2.0)	1:1	6[d]	55
7	DCM	Et_3N (2.0)	1.5:1.5	3[d]	74
8	DCM	Et_3N (3.0)	1.5:1.5	3	75
9	DCM	Et_3N (3.0)	1.5:1.5	3[d]	75
10	DCM	Et_3N (3.0)	2.0:2.0	3	80
11	DMF	Et_3N (3.0)	1.5:1.5	3	Trace[c]
12	EtOAc	Et_3N (3.0)	1.5:1.5	3	Trace[c]
13	DCM	NMM (3.0)	1.5:1.5	3	95

[a]Reactions were carried out under nitrogen atmosphere

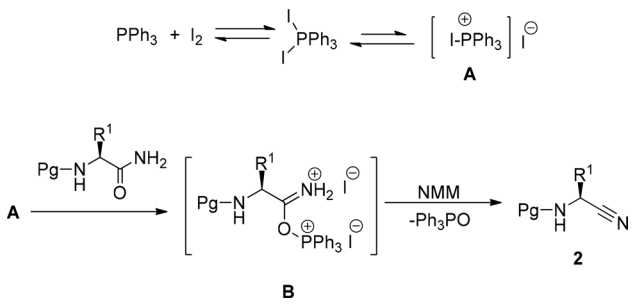
[b]Isolated yield after aqueous workup and column chromatography

[c]Indicated by the TLC

[d]Yield remained same for 12 h of reaction time



Scheme 1 Synthesis of N^{α}-protected amino nitriles from N^{α}-protected amino acid amides



Scheme 2 Plausible reaction mechanism

Conclusion

Amino acid nitriles, important intermediates in building various peptidomimetics, were accessed from simple, straight forward protocol employing Ph_3P, I_2 and NMM was reported. Various Boc, Z, and Fmoc protected amino acid amides underwent racemization-free conversion to nitriles. Side chain protected amino acid amides were also converted to the products in good yields, which reflected the widened application and compatibility of the combination of the reagents.

Materials and Methods

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich Company. Infrared spectra were recorded on the Bruker ATR instrument, ^1H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz (and 500 MHz) respectively, with $CDCl_3$ as an internal standard. Mass spectra were recorded using high resolution mass spectrometer (HRMS) Q-Tof mass spectrometer. All the reactions were monitored using TLC with precoated silica gel plates purchased from Merck. Column Chromatography was performed with Merck silica gel (100–200) at normal atmospheric pressure and The RP-HPLC analysis was carried out using the Agilent instrument (method: gradient 0.1% TFA water–acetonitrile (0–100%) in 30 min; VWD at $\lambda = 254$ nm; flow rate: 1.0 mL/min; column: Phenomenox made lux, cellulose—, pore size—5 µm, diameter × length = 4.6 × 150 mm).

Experimental Procedure

To the N^{α}-protected amino acid amide (1.0 equiv.) in dry DCM at rt were added PPh_3 (1.5 equiv.) followed by molecular iodine in portions (1.5 equiv.). After 5 min, NMM (3.0 equiv.) was added in drop wise to the reaction mixture, and allowed to stir until the completion of the reaction (by TLC). The reaction mixture was diluted with DCM, and the organic layer was washed with saturated $Na_2S_2O_5$ solution, water, brine solution and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and resulting crude compound was purified by column chromatography (80:20 hexane:EtOAc).

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Compliance with Ethical Standards

Conflict of interest The authors declare that this article content has no conflicts of interest.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent The article does not contain any studies in patients by any of the authors.

References

Aureggi V, Sedelmeier G (2007) 1,3-Dipolar cycloaddition: click chemistry for the synthesis of 5-substituted tetrazoles from organoaluminum azides and nitriles. Angew Chem Int Ed 46:8440–8444

Bosch L, Vilarrasa J (2007) $Cu_2(OTf)_2$-Catalyzed and microwave-controlled preparation of tetrazoles from nitriles and organic azides under mild, safe conditions. Angew Chem Int Ed 46:3926–3930

Bose DS, Narasaiah AV (2001) Use of PyBOP as a convenient activator for the synthesis of nitriles from primary amides. Synthesis 3:373–375

Caddick S, Haynes KK, Judd DB, Williams MRV (2000) Convenient synthesis of protected primary amines from nitriles. Tetrahedron Lett 41:3513–3516

Chavan SP, Khairnar LB, Chavan PN (2014) Efficient and mild method for preparation of allylic amines from aziridine-2-alcohols using PPh_3/I_2/imidazole. Tetrahedron Lett 55:5905–5907

Claremon DA, Philips BT (1988) An efficient chemoselective synthesis of nitriles from primary amides. Tetrahedron Lett 29:2155–2158

Elangovan S, Quintero-Duque S, Dorcet V, Roisnel T, Norel L, Darcel C, Sortias JB (2015) Knolker type iron complexes bearing an N-heterocyclic carbene ligand: synthesis, characterization, and catalytic dehydration of primary amides. Organometallics 34:4521–4528

Fatiadi AJ (1983) Preparation and synthetic application of cyano compounds. In: Patai S, Rappaport Z (eds) Triple-bonded functional groups, vol 2. Wiley, Chichester, pp 1057–1303

Heller B, Sundermann B, Buschmann H, Drexler HJ, You J, Holzgrabe U, Heller E, Oehme G (2002) Photocatalyzed [2+2+2]-cycloaddition of nitriles with acetylene: an effective method for the synthesis of 2-pyridines under mild conditions. J Org Chem 67:4414–4422

Iranpoor N, Firouzabadi H, Aghapour G (2002) A rapid and facile conversion of primary amides and aldoximes to nitriles and ketoximes to amides with triphenylphosphine and N-chlorosuccinimide. Synth Commun 32:2535–2541

Jasema YA, Barkhada M, Khazalib MA, Butta HP, El-Khwassc NA, Alazani M, Hindawid B, Thiemann T (2014) Two ways of

preparing benzonitriles using $BrCCl_3$-PPh_3 as the reagent. J Chem Res 38:80–84
Keita M, Vandamme M, Paquin JF (2015) Synthesis of nitriles from aldoximes and primary amides using XtalFluor-E. Synthesis 47:3758–3766
Kim JN, Chung KH, Ryu EK (1990) Improved dehydration method of aldoximes to nitriles: use of acetonitrile to triphenylphosphine/carbon tetrachloride system. Synth Commun 20:2785–2788
Krynitsky JA, Carhart HW (1963) Org Synth Coll IV:436
Kuo CW, Zhu JL, Wu JD, Chu CM, Yao CF, Shia KS (2007) A convenient new procedure for converting primary amides into nitriles. Chem Commun. https://doi.org/10.1039/b614061k
Lehnert W (1971) Nitrile aus primären carbonsäureamiden mit $TiCl_4$/base bei 0 °C. Tetrahedron Lett 19:1501–1502
Maetz P, Rodriguez M (1997) A simple preparation of N-protected chiral α-aminonitriles from N-protected α-amino acid amides. Tetrahedron Lett 38:4221–4222
Miller JS, Marson JL (2001) Designer magnets containing cyanides and nitriles. Acc Chem Res 34:563–570
Munoz JM, Alcazar J, Hoz A, Diaz-Ortiz A (2011) Application of flow chemistry to the reduction of nitriles to aldehydes. Tetrahedron Lett 52:6058–6060
Nakajima N, Ubukata M (1997) Preparation of nitriles from primary amides under Swern oxidation conditions. Tetrahedron Lett 38:2099–2102
Narasaiah AV, Nagaiah K (2004) An efficient and improved method for the preparation of nitriles from primary amides and aldoximes. Adv Synth Catal 346:1271–1274
Narasaiah AV, Sreenu D, Nagaiah K (2006) Triphenylphosphine-iodine: an efficient reagent system for the synthesis of nitriles from aldoximes. Synth Commun 36:137–140
Nishiwaki N, Kobiro K, Hirao S, Sawayama J, Saigo K, Ise Y, Okajima Y, Ariga M (2011) Inverse electron-demand 1,3-dipolar cycloaddition of nitrile oxide with common nitriles leading to 3-functionalized 1,2,4-oxadiazoles. Org Biomol Chem 9:6750–6754
Phakhodee W, Wangngae S, Pattarawarapan M (2017) Approach to the synthesis of 2,3-disubstituted-3H-quinazolin-4-ones mediated by Ph_3P-I_2. J Org Chem 82:8058–8066
Rad NMS, Soleimani F (2016) One-pot protocol for N-alkylation of purine, pyrimidine and azole derivatives via alcohols using Ph3P/I2: simple route for carboacyclic nucleoside synthesis. Tetrahedron 72:4947–4953
Rai A, Yadav LDS (2013) Cyclopropenone-catalyzed direct conversion of aldoximes and primary amides into nitriles. Eur J Org Chem 2013:1889–1893
Rappai JP, Karthikeyan J, Prathapan S, Unnikrishnan PA (2011) Simple and efficient one-pot synthesis of nitriles from amides and oximes using in situ-generated Burgess-type reagent. Synth Commun 41:2601–2606
Reisener DB, Horning EC (1963) Chloroacetonitrile. Org Synth Coll IV:144
Rickborn B, Jensen FR (1962) α-Carbon isomerization in amide dehydrations. J Org Chem 27:4608–4610
Santhosh L, Nagamangala SR, Thimmalapura VM, Sureshbabu VV (2017) Synthesis of 1,5-disubstituted tetrazole via Ugi-azide reaction: an asymmetric induction approach. Chem Select 2:5497–5500
Sureshbabu VV, Venkataramanarao R, Naik SA, Chennakrishnareddy G (2007) Synthesis of tetrazole analogues of amino acids using Fmoc chemistry: isolation of amino free tetrazoles and their incorporation into peptides. Tetrahedron Lett 48:7038–7041
Sureshbabu VV, Naik SA, Hemantha HP, Narendra N, Das U, Row TNG (2009a) N-Urethane-protected amino alkyl isothiocyanates: synthesis, isolation, characterization, and application to the synthesis of thioureidopeptides. J Org Chem 74:5260–5266
Sureshbabu VV, Naik SA, Nagendra G (2009b) Synthesis of Boc-amino tetrazoles derived from α-amino acids. Synth Commun 39:395–406
Tarleton M, Gilbert J, Sakoff JA, McCluskey A (2012) Cytotoxic 2-phenyacrylnitriles, the importance of the cyanide moiety and discovery of potent broad spectrum cytotoxic agents. Eur J Med Chem 57:65–73
Wang H, Ganesan A (2000) Total synthesis of the fumiquinazoline alkaloids: solution-phase studies. J Org Chem 65:1022–1030
Wang X, Wang QG, LuO QL (2015) Synthesis of isonitriles from N-substituted formamides using triphenylphosphine and iodine. Synthesis 47:49–54
Wanga MX (2015) Enantioselective biotransformations of nitriles in organic synthesis. Acc Chem Res 48:602–611
Wangngae S, Duangkamol C, Pattarawarapan M, Phakhodee W (2015) Significance of reagent addition sequence in the amidation of carboxylic acids mediated by PPh_3 and I_2. RSC Adv 5:25789–25793
Wangngae S, Pattarawarapan M, Phakhodee W (2017) Ph_3P/I_2-mediated synthesis of N,N′,N″-substituted guanidines and 2-iminoimidazolin-4-ones from aryl isothiocyanates. J Org Chem 82:10331–10340
Wojtkielewicz A, Totowski Z, Morzycki JW (2015) One-step synthesis of nitriles from acids, esters and amides using DIBAL-H and ammonium chloride. Synlett 26:2288–2292
Yadav AK, Srivastav VP, Yadav LDS (2014) Visible-light-mediated efficient conversion of aldoximes and primary amides into nitriles. RSC Adv 4:4181–4186
Yamaguchi K, Mizuno N (2014) Supported metal hydroxides as efficient heterogeneous catalyst for green functional group transformations. J Jpn Pet Inst 57:251–260
Zhou S, Addis D, Das S, Junge K, Beller M (2009a) New catalytic properties of iron complexes: dehydration of amides to nitriles. Chem Commun. https://doi.org/10.1039/b910145d
Zhou S, Junge K, Addis D, Das S, Beller MA (2009b) General and convenient catalytic synthesis of nitriles from amides and silanes. Org Lett 11:2461–2464