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A novel approach for the synthesis of α-aminonitriles using Mitsunobu's reagent under solvent-free conditions

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Dedicated to my Doctoral mentor, Dr. Suprabhat Ray on the occasion of his 70th Birthday

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ABSTRACT

A highly efficient, one-pot, three-component, solvent-free protocol for the synthesis of α-aminonitriles starting from their corresponding carbonyl compounds, amines, using Mitsunobu's reagent has been developed. Diversity of α-aminonitriles has been synthesized in good to excellent yields (80–99%) using various kinds of aldehydes/ketones and a variety of amines.

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α-Aminonitriles constitute a major class of naturally occurring compounds of great interest displaying remarkable biological activities[1] such as anticancer, antibacterial, antifungal, antibiotic, and antiviral etc. and also serve as efficient precursors for the synthesis of natural and unnatural α-amino acids.[2] They have also been widely used as the essential building blocks of peptides and proteins synthesis.[3] Their tremendous synthetic utility has further been explored as versatile synthon for the syntheses of amides, diamines, and various kinds of structurally diverse nitrogen and sulfur heterocycles[4] such as imidazoles, thiadiazoles etc. Furthermore, their synthetic utility has also been explored through the carbanion induced nucleophilic attack of α-carbon atom with a variety of electrophiles which offers many other interesting synthetic transformations of importance in synthetic organic chemistry.[5] Among the traditional methods reported for their syntheses, Strecker reaction, the nucleophilic addition of cyanide ion to imines, is of great importance in modern organic chemistry as it offers one of the most direct and viable method for the syntheses of α-aminonitriles.[6] The cyanide sources used during the course of this reaction are mainly HCN, KCN, TMSCN, $(EtO)_2P(O)CN$, Et_2AlCN, Bu_3SnCN, MeCOCN, acetone cyanohydrin, or acyl cyanides, ethyl cyanoformate, *bis*(dialkyl)aminocyanoboranes, $K_4[Fe(CN)_6]$ etc.[7] majority of which are hazardous, toxic, and involve harsh reaction conditions. Among the aforementioned reagents, TMSCN is relatively a safer and more efficient cyanide source and has been frequently employed during the Strecker's synthesis. In recent years, in order to search for novel and efficient protocols for the syntheses of α-aminonitriles, a broad spectrum of various kinds of metal complexes, Lewis acids, solid supported acids, bases, and organic catalysts which include $NiCl_2$, $RuCl_3$, $RuI_3.H_2O$, $GdCl_3$, $InCl_3$, $BiCl_3$, InI_3, I_2, $TiCl_3$, H_2PdCl_4, Al_2O_3, Fe_3O_4, $Cu(OTf)_3$, $Sc(OTf)_3$, $Ga(OTf)_3$, $Zr(HSO_4)_4$, $La(NO_3)_3{\cdot}6H_2O$, $GdCl_3{\cdot}6H_2O$, $H_4CoW_{12}O_{40}{\cdot}3H_2O$, $Fe(Cp)_2PF_6$, $H_4SiW_{12}O_{40}/Al_2O_3$, $[Bmim]BF_4$, H_2SO_4/silica-gel, vanadyltriflate, xanthansulfuric acid, amberlyst-15, montmorillonite, lithium perchlorate, zinc halides, silica-supported heteropolyacids, guanidine hydrochloride, cellulose, sulfamic acid, nanocrystalline magnesium oxide, trimethylsilyltrifluoromethane sulfonate etc. have been developed to promote this reaction.[8,9] Although, majority of these catalytic systems were found to be effective in carrying out this transformation, most of these systems are associated with several drawbacks such as low reactivity, requirement of large amount of catalysts, cost, toxic and moisture sensitive nature, harsh reaction conditions, tedious work-up, longer reaction times, generation of toxic byproducts, and few of them also involve two or more steps. The majority of these catalysts are only efficient for the synthesis of α-aminonitriles from active

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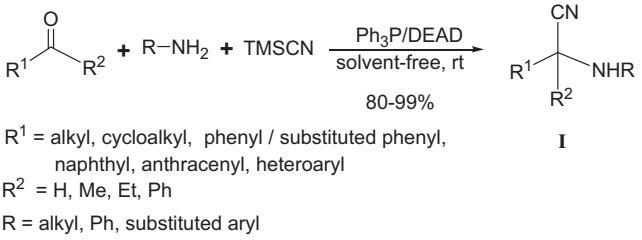


Scheme 1.

aldehydes and are not suitable for ketone substrates. Therefore, there is continued interest in developing new, efficient, and safer protocols employing mild reaction conditions.

In recent years, Mitsunobu's reagent (i.e. equimolar mixture of triphenyl phosphine and diethyl azadicarboxylate) is a most popular reagent in synthetic organic chemistry and has been employed in a variety of synthetic transformations.[10] We have also reported the synthesis of carbamates, dithiocarbamates, carbonates, xanthates, *S*-alkyl carbamates, trithiocarbonates, *S,S*-dialkyl carbonates, carbazates, dithiocarbazates, and substituted ureas from a variety of starting materials employing Mitsunobu's reagent.[11] In the present Letter, we wish to report an efficient and novel protocol for the synthesis of α-aminonitriles involving the reaction of the corresponding carbonyl compounds, amines, and TMSCN using Mitsunobu's reagent under solvent-free conditions.[12] To the best of our knowledge this is the first report for the synthesis of α-aminonitriles employing Mitsunobu's reagent.

In order to carry out this synthetic protocol, a reaction of equimolar amount of aniline with benzaldehyde, trimethysilylcyanide, using Mitsunobu's reagent was tried in various organic solvents such as CH_2Cl_2, THF, diethylether, CH_3CN, DMF, nitromethane, methanol at room temperature and the corresponding α-aminonitrile product was indeed obtained. The characterization of the product was confirmed through the various spectroscopic and analytical techniques and was further confirmed through the data of reported authentic sample. This reaction was further optimized employing various kinds of reaction conditions and the different molar amounts of the Mitsunobu's reagent wherein it was realized that best yields (99%) of the desired α-aminonitrile could be achieved using at least one equivalent of the reagent along with the equimolar amount of aldehyde, and amine without using a solvent (Scheme 1). It was further realized that the desired α-aminonitrile could be achieved through the reaction of benzaldehyde with aniline using TMSCN without using Mitsunobu's reagent under solvent-free conditions, wherein the reaction takes longer time (4 h) and afforded lower yield (92%). A reaction of acetophenone, tried with aniline using TMSCN and Mitsunobu's reagent, afforded high-yield of the desired α-aminonitrile under solvent-free conditions at room temperature (Table 1). However, when this reaction was repeated without using Mitsunobu's reagent even for a longer time (4 h), the corresponding α-aminonitrile could not be achieved. This would clearly suggest that α-aminonitriles from ketones could not be achieved without using Mitsunobu's reagent and thus further confirm that Mitsunobu's reagent facilitates the formation of corresponding imine. Furthermore, this reaction was tried employing Mitsunobu's reagent without using TMSCN, the corresponding imine was obtained, while without using Mitsunobu's reagent the formation of imine could not be realized. This would clearly explain the role of Mitsunobu's reagent in the in situ generation of corresponding imine specifically from ketones.

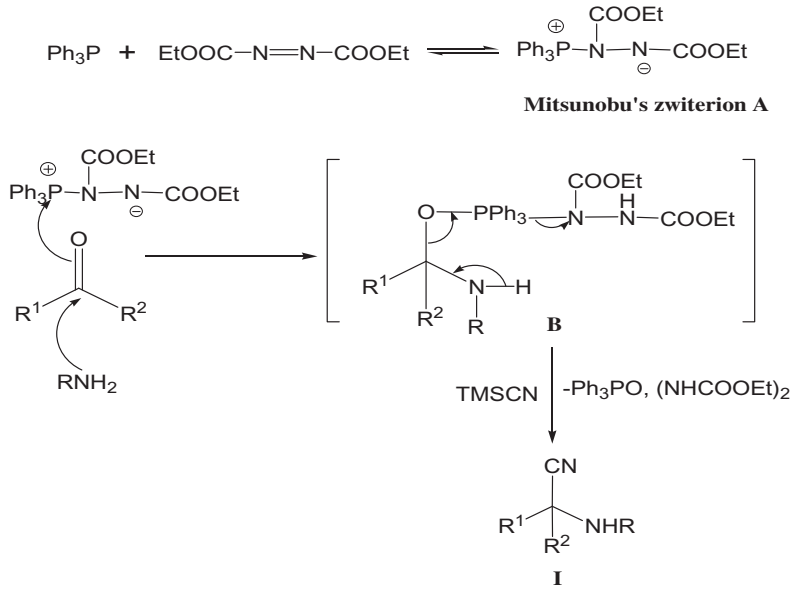
Encouraged by our above mentioned experiment, the synthetic utility and scope of this reaction were further explored employing various kinds of aliphatic/aromatic substituted aldehydes/ketones bearing electron releasing and electron withdrawing functionalities using at least 1 equiv of Mitsunobu's reagent and one equivalent of primary aliphatic/aromatic amines having electron releasing and electron withdrawing functional groups. Best yields of the products were obtained when the electron releasing group was introduced at the *p*-position of aryl-substituted aldehydes/ketones and amines, respectively. It must be emphasized here that only primary aliphatic/aromatic/cyclic/heterocyclic amines would give the resultant imine which on subsequent nucleophilic attack of cyanide ion afforded the corresponding product. Thus, various

Table 1
Effect of Mitsunobu's reagent in the formation of α-aminonitriles **I**

R	R^1	R^2	Time	Mitsunobu's reagent	Yield (%)
Ph	Ph	H	20 min	Used (1 Molar)	98
Ph	Ph	H	4 h	Not used	92
Ph	Ph	Me	25 min	Used (1 Molar)	98
Ph	Ph	Me	4 h	Not used	Nil

Table 2
Synthesis of various kinds of α-aminonitriles of general formula **I**

Entry	R	R^1	R^2	Time (min.)	Yield (%)	Reference
1	Ph	Ph	H	20	98	[8d]
2	Ph	4Cl-Ph	H	20	97	[8m]
3	Ph	4-NO_2Ph	H	25	94	[8i]
4	Ph	4-BrPh	H	25	94	[9i]
5	Ph	3,4-Dichloro-Ph	H	25	95	[9i]
6	Ph	4-F-Ph	H	30	91	[9b]
7	Ph	4-CH_3Ph	H	25	90	[9a]
8	Ph	4-MeOPh	H	30	91	[9a]
9	Ph	Py	H	25	89	[8i]
10	Ph	C_9H_{19}-	H	60	80	[8p]
11	Ph	C_2H_5-	H	60	89	[7f]
12	4-Me-Ph	Ph	H	20	95	[8m]
13	4-MeO-Ph	Ph	H	20	96	[8p]
14	Ph	Ph	Me	25	98	[9b]
15	4-MeO-Ph	Ph	Me	25	99	[8n]
16	4-ClPh	Ph	Me	25	92	[8n]
17	$PhCH_2$	Ph	H	20	95	[9b]
18	Ph	1-Naphthyl	H	25	93	[8o]
19	Ph	9-Anthracenyl	H	30	91	[8q]
20	Ph	Cyclopropyl	H	25	90	[8o]
21	$PhCH_2$	Ph	Me	25	93	[9b]
22	Ph	$R_1 = R_2$ = Cyclopentanone		25	94	[8n]
23	Ph	$R_1 = R_2$ = Cyclohexanone		25	98	[8n]
24	Ph	$R_1 = R_2$ = Cycloheptanone		30	96	[9a]
25	Ph	Ph	CH_2CH_3	25	92	[9b]
26	$PhCH_2$	Ph	CH_2CH_3	25	88	[9b]
27	Ph	Ph	Ph	30	85	[9b]
28	Ph	Naph	Me	30	84	[9b]
29	Ph	$(CH_3)_2CH$	CH_3	40	82	[9b]
30	Ph	PhCH=CH	H	40	80	[9b]
31	*n*-C_4H_9	Ph	H	30	81	[8i]
32	*n*-C_4H_9	4-Me-Ph	H	30	83	
33	$PhCH_2$	Cyclohexyl	H	30	81	
34	Ph	Cyclohexyl	H	30	80	
35	Ph	*n*-C_4H_9	*n*-C_4H_9	40	86	[8q]
36	Ph	Naph	Ph	45	83	[8q]
37	Ph	4-NO_2Ph	CH_3	50	81	[9b]
38	Ph	3-Me-2-thiophenyl	Me	50	83	[8o]
39	4MeO-Ph	3-Pyridyl	Me	40	87	[8n]
40	4MeO-Ph	3,4-Methylenedioxy-Ph	Me	45	82	[8n]



Scheme 2. Proposed mechanism of formation.

kinds of α-aminonitriles from a variety of carbonyl compounds (aldehydes and ketones) have been synthesized employing Mitsunobu's reagent and their structural confirmation was correlated with the reported authentic data as depicted in Table 2.

We propose that Mitsunobu's reagent plays a crucial role in facilitating this transformation through in situ generation of imine. Initially, the Mitsunobu zwitterion **A** formed through the reaction of triphenylphosphine with diethylazadicarboxylate, reacts with the mixture of a keto-compound and amine generating the intermediate **B**. The electronic rearrangement of intermediate **B** resulting in situ generated imine which on subsequent nucleophilic attack of cyanide ion afforded the corresponding α-aminonitrile **I** in a one-pot reaction (Scheme 2).

In conclusion, we have developed a simple and efficient method for the synthesis of α-aminonitriles starting from their corresponding carbonyl compounds, amines, and trimethylsilyl cyanide using Mitsunobu's reagent under solvent-free conditions. Mitsunobu's reagent a cheap, easy to handle, and mild reagent has been used during the course of this reaction to generate the corresponding imines from a variety of aldehydes and ketones, afforded the desired α-aminonitriles in high yields (80–99%).

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12. *Typical experimental procedure: Synthesis of α-aminonitriles from carbonyl compounds:*A mixture of aldehyde (1 mmol), amine (1 mmol), Mitsunobu's reagent (1 mmol), and trimethylsilylcyanide (1.2 mmol) was added at room temperature and stirring was continued until the reaction was complete (monitored by TLC). After completion of the reaction, the reaction mixture was extracted with ethylacetate, dried over anhydrous Na_2SO_4, and concentrated. Purification of the crude product by chromatography on silica gel (60–120 mesh) with petroleum ether–EtOAc (5:1) as eluent gave the pure product.
Data of selected compounds
2-Anilino-2-phenyl acetonitrile (Entry 1):
Light yellow solid; mp = 85–86 °C; IR (CHCl3): ν = 3368, 3055, 2233, 1602, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.03 (d, 1H, J = 9 Hz), 5.41 (d, 1H, J = 9 Hz), 6.76 (d, 2H, J = 9 Hz), 6.90 (t, 1H, J = 6 Hz), 7.30 (t, 2H, J = 9 Hz), 7.44 (m, 3H), 7.59 (m, 2H) ppm; ^{13}C NMR (75 MHz, CDCl3): δ = 49.8, 114.0, 118.1, 119.9, 127.0, 128.3, 129.4, 129.8, 133.6, 144.6 ppm; MS (ESI): m/z = 208.2 (M^+); Anal. Cald for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45%. Found: C, 80.80; H, 5.76; N, 13.47%.
2-Anilino-2-(4-chloro phenyl) acetonitrile (Entry 2)
White solid; mp 96–98 °C; IR (CHCl3): ν = 3365, 3055, 2235, 1603, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.02 (d, 1H, J = 6 Hz), 5.41 (d, 1H, J = 9 Hz), 6.75 (d, 2H, J = 9 Hz), 6.92 (t, 1H, J = 6 Hz), 7.28 (m, 2H), 7.42 (d, 2H, J = 9 Hz), 7.53 (d, 2H, J = 6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.5, 114.2, 117.8, 120.4, 128.4, 129.2, 129.6, 132.8, 135.4, 144.3 ppm; MS (ESI): m/z = 242.1 (M^+); Anal. Cald for $C_{14}H_{11}C_lN_2$: C, 69.28; H, 4.57; N, 11.54%; Found: C, 69.19; H, 4.63; N, 11.56%.
2-Anilino-2-(4-nitro phenyl) acetonitrile (Entry 3)
Gummy; IR (CHCl3): ν = 3381, 3063, 2225, 1601, 1550, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.08 (d, 1H, J = 9 Hz), 5.57 (d, 1H, J = 9 Hz), 6.68 (d, 2H, J = 9 Hz), 6.78 (t, 1H, J = 8 Hz), 7.29 (t, 2H, J = 9 Hz), 7.8 (d, 2H, J = 9 Hz), 8.1 (d, 2H, J = 9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.8, 115.3, 118.0, 127.0, 127.7, 127.8, 128.6, 129.0, 133.8, 144.1, 145.0 ppm; MS (ESI): m/z = 276.2 (M^++Na); Anal. Cald for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59%; Found: C, 66.46; H, 4.40; N, 16.51%.