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A New Conversion of Primary Nitro Compounds into Nitriles

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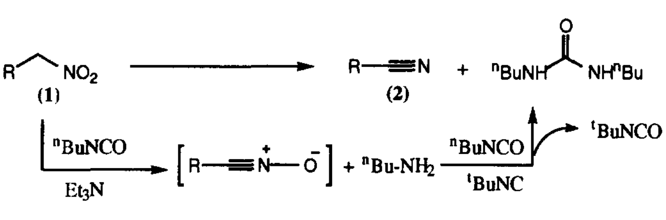
Abstract : The reaction of primary nitro compounds with isocyanides and isocyanates in the presence of a base leads to a new preparation of nitriles. The reaction probably proceeds through the in situ formation of a nitrile oxide followed by a fast oxygen transfer with the isocyanide. Combined with the Knovenagel addition of nitromethane to cyclic ketone, this reaction brings a highly effective regioselective formation of cyclic α-β unsaturated nitriles. © 1997 Published by Elsevier Science Ltd.

Nitro compounds are widely used in organic synthesis. Easy hydrogen abstraction to form nitronate salts provides a mean for efficient formation of carbon-carbon σ bonds through Michael or aldol type addition; furthermore several nitro group transformation leading to hydrocarbons, amines or ketone derivatives[1] are reported in the litterature. The conversion into nitriles allows a complete change in substrate reactivity and has been achieved with different chemical systems involving electrophilic phosphorus derivatives ($ClP(OEt)_2$[2], P_2I_4[3], PCl_3[4]), sulfur compounds (SO_2[5],$Me_3SiSSSiMe_3$[6], CS_2[7]), silyl derivatives ($ISiMe_3$[8]) or radical chemistry[9].

Our interest in isonitrile chemistry has led us to study the behaviour of nitro compounds with isonitriles under electrophilic activation. The use of an isocyanate as electrophile leads to a new one pot formation of nitriles from primary nitro compounds.

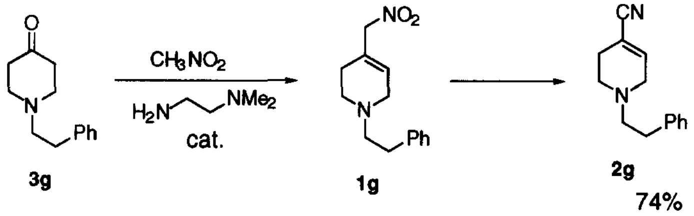
Isocyanates are known to react with nitro compounds under basic conditions forming nitrile oxides as reactive intermediates[10]. The reduction of nitrile oxides to nitriles with isocyanides, first reported by Finzi and Arbaniso[11], shows poor yields and important formation of nitrile oxide dimerisation product. Selecting a highly hindered and stable nitrile oxide, Barrett and Hiberty suppress furoxan formation and obtain a high yield in the oxidation of isocyanide [12]. However the synthetic potential of their study is rather limited and cannot be applied to a general conversion of primary nitro compounds into nitriles. A slow generation of nitrile oxide in the presence of isocyanide could also be expected to prevent fast dimerisation of unhindered nitrile oxides. Indeed we observed that, when generated in situ, nitrile oxides are smoothly reduced by isocyanides to give moderate to high yields of nitriles.

When a toluene solution of nitro compound (**1**) is thus heated for a few hours at 70°C with t-butylisocyanide (1,2 eq.), n-butylisocyanate (3 eq.) and triethylamine (1 eq.), the nitrile (**2**) is recovered after evaporation of the solvent and chromatography (scheme 1, Table 1). The low boiling point materials (t-butylisocyanide, n-butyl- and t-butylisocyanate) are easily removed during the evaporation step and the crude after evaporation is mainly a mixture of the nitrile (**2**) and N,N'-di-n-butyl urea (scheme 1). The absence of N-n-butyl N'-t-butyl urea in the reaction products is certainly due to prefered attack of nitronates and n-butylamine formed on the n-butylisocyanate rather than on the t-butylisocyanate.



Scheme 1

An interesting application of this reaction is found with cyclic allylic nitro compounds. The latter are obtained by a Knoevenagel reaction between nitromethane and cyclic ketones under basic catalysis in almost quantitative yields[13]. The following transformation of compound **1g** into nitrile **2g** has been performed directly on the crude just after evaporation of excess nitromethane in 74% yield from the starting ketone **3g** (scheme 2).



Scheme 2

This Knovenagel reaction exhibits furthermore a very high regioselectivity when α-substituted cyclic ketones are concerned[7]. Under the reaction conditions, only the kinetic, less substituted, nitro olefin is formed, allowing the synthesis of compounds **1c** and **1d** without any regioisomers. This selectivity emphasizes the potential of this two step procedure in comparison with methods based on cyanohydrin formation. For instance, the one pot conversion of ketones into nitriles by ZnI_2-TMSCN / $POCl_3$-Pyridine system gives poor selectivity when cyclic unsymmetrical ketones are concerned [14].

As expected, an unactivated nitro compound is less reactive and needs a longer reaction time, though with limited effect on the yield. The Michael adduct **1f** of nitromethane with chalcone, is thus transformed to nitrile **2f** in a 86% yield.

Formation of nitrile **2d** illustrates the efficiency of the oxygen transfer with isocyanides; In the absence of isocyanide the nitro compound is cleanly converted in isoxazole **3d** via intramolecular cycloaddition involving the nitrile oxide and the allylic residue. When 1,2 molar equivalents of isocyanide are present in the reaction medium the intermolecular oxygen transfer competes with the cycloaddition giving nitrile with a moderate 51% yield. Raising the amount of isocyanide to 2,2 molar equivalents gives the nitrile in a 74% yield with limited formation of isoxazole (table 1).

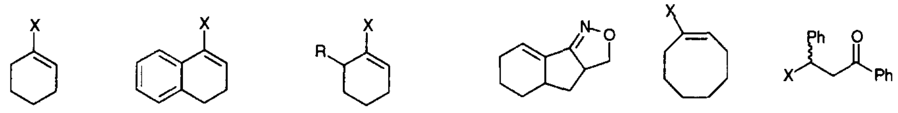
Table 1. Nitrile Conversion of Nitrocompounds (Temp. 80°C).

Starting Materials	Products (yields %)	Time (hours)
1a**	**2a** (58)	2
1b**	**2b** (82)	2
1c**	**2c** (57)	3
1d*	**3d** (75)	2
1d**	**2d** (51) **3d** (30)	3
1d***	**2d** (74) **3d** (15)	2
1e**	**2e** (81)	2
1f**	**2f** (86)	70

* Addition of 3 eq. BuNCO, 1 eq. NEt_3 to a 0,4 M solution of **1** in toluene

** Addition of 1,2 eq. tBuNC, 3 eq. BuNCO, 1 eq NEt_3 to a 0,4 M solution of **1** in toluene.

*** Addition of 2,2 eq. tBuNC, 3 eq. BuNCO, 1 eq NEt_3 to a 0,7 M solution of **1** in toluene.



1a : X = CH_2NO_2
2a : X = CN

1b : X = CH_2NO_2
2b : X = CN

1c : R = Me ; X = CH_2NO_2
2c : R = Me ; X = CN

1d : R = Allyl ; X = CH_2NO_2
2d : R = Allyl ; X = CN

3d

1e : X = CH_2NO_2
2e : X = CN

1f : X = CH_2NO_2
2f : X = CN

Structure for Table 1

In conclusion, this work discloses a new multicomponent reaction involving isocyanides and primary nitro compounds, the latter being efficiently transformed into nitriles. Further synthetic applications of these reactions are under study in our research group.

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