A Practical and Cost-Efficient, One-Pot Conversion of Aldehydes into Nitriles Mediated by 'Activated DMSO'

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Received 20 April 2011

Abstract: Participation of 'activated DMSO' in the one-pot transformation of aldehydes to nitriles has been described by reacting aldehydes with NH_2OH ·HCl in DMSO in the absence of any added base or catalyst. The method is applicable to access a wide range of aromatic, heterocyclic, and aliphatic nitriles, in which only water is a byproduct. A straightforward and practical procedure is demonstrated on a multigram scale.

Key words: activated DMSO, nitriles, aldehydes, dehydration, catalyst

The nitrile group is a key component in numerous natural products, and nitriles are also significant synthetic intermediates for pharmaceuticals, material sciences, agricultural chemicals, and dyes.¹ Accordingly, the formation of nitriles from the analogous aldehydes has become an important functional-group transformation in organic chemistry.² The most widely used method is based on the dehydration of aldoximes, and although various protocols already exist, new variants continue to appear.³ The use of ammonia combined with an appropriate oxidant is also a useful method for the transformation of aldehydes to their corresponding nitriles.⁴ Direct conversion of aldehydes into nitriles without isolation of nitrogen-containing intermediates is a topic of current interest. Consequently, a number of reagents have emerged for this purpose.⁵⁻¹⁰ However, many of these suffer from disadvantages such as inconvenient preparation of the reagents,⁶ limited substrate scope,⁷ or use of expensive metals.⁸ Further, some of the methods involve hazardous oxidants such as SeO₂⁹ and environmental pollutants like molybdenum and tungsten.10

Dimethylsulfoxide (DMSO) is a highly polar aprotic solvent with low toxicity. The combination of DMSO with an electrophilic species to form 'activated DMSO'¹¹ has been widely exploited for the oxidation of alcohols to their respective carbonyl compounds.¹² However, the use of an 'activated DMSO' for the synthesis of nitriles from aldehydes is less explored. In continuation of our studies directed toward the development of efficient one-pot reactions for nitrile synthesis from aldehydes,¹³ described herein is a straightforward and practical procedure involving 'activated DMSO' in which only water is a byproduct.

Inspired by the report from Li and co-workers that DMSO could be activated by HCl,¹⁴ we decided to explore the potential of this reaction in generating nitriles from aldehydes. We reasoned that the reaction of aldehydes with NH₂OH·HCl in DMSO could generate aldoximes in the absence of an added base, and the HCl associated with hydroxylamine would concurrently activate DMSO. The 'activated DMSO' would subsequently facilitate the dehydration of aldoximes. We were interested to find that when a DMSO solution of 4-bromobenzaldehyde (1.0 equiv) and NH₂OH·HCl (1.1 equiv) was heated at 90 °C, complete consumption of starting material occurred to provide 4-bromobenzonitrile (2a) in 99% yield (entry 1, Table 1). The above conditions were most suitable for the transformation as the reaction time was considerably longer while performing it at 70 °C (entry 2, Table 1). Similarly, aldoxime 1a was the major product while performing the reaction at room temperature (entry 3, Table 1). When triethylamine (1.5 equiv) was introduced to the reaction mixture, aldoxime was isolated as the sole product (entry 4, Table 1). Interestingly, no solvents other than DMSO promoted the one-pot transformation of 4bromobenzaldehyde to nitrile 2a, and instead produced the intermediate **1a** in moderate to good yields in the absence of an added base (entries 5-10, Table 1). Furthermore, when the reaction was performed in dioxane containing DMSO (5 equiv) at reflux (entry 11, Table 1), an incomplete reaction was observed after five hours giving a mixture of 2a (73%) and 1a (23%). Under similar conditions in DMSO, introduction of water (5 equiv) as well led to nitrile in 98% yield (entry 12, Table 1). Though the rate of reaction was noticeably diminished, the formation of nitrile in the presence of added water demonstrates the tolerance of this method to moisture, and also accounts for a clean reaction despite the fact that water is liberated in the reaction.

The high efficiency of DMSO-mediated one-pot transformation of aldehydes to nitriles was maintained to the same extent with structurally diverse aldehydes (Table 2). The reaction was complete in less than two hours for all substrates tested, and the nitriles were isolated in excellent yields.¹⁵ As described in Table 2, electronic disparity of the aromatic substituents did not diminish the efficiency and selectivity. Protection of a hydroxy group or an amino group on substrates was not necessary to achieve optimum conversion (entries 2 and 3, Table 2). A substrate possess-

SYNLETT 2011, No. 15, pp 2223–2227 Advanced online publication: 12.08.2011 DOI: 10.1055/s-0030-1261181; Art ID: D12411ST © Georg Thieme Verlag Stuttgart · New York

Table 1 Screening Optimal Conditions

| Br | CHO N | H ₂ OH·HCI | Br 1a | ∼ _N _OH + I | Br 2a |
|-------|-------------------|-----------------------|--------------|------------------------------|---------------------------------------|
| Entry | Solvent | Time (h) | Temp (°C) | Yield o (%) | f 1a Yield of 2a (%) |
| 1 | DMSO | 1 | 90 | 0 | 99 |
| 2 | DMSO | 5 | 70 | 0 | 99 |
| 3 | DMSO | 9 | 25 | 78 | 17 |
| 4 | DMSO ^a | 1 | 100 | 99 | 0 |
| 5 | dioxane | 6 | reflux | 95 | 0 |
| 6 | MeOH | 5 | reflux | 98 | 0 |
| 7 | MeCN | 5 | reflux | 91 | 0 |
| 8 | EDC | 5 | reflux | 34 ^b | 0 |
| 9 | DMF | 5 | 100 | 96 | 0 |
| 10 | THF | 5 | reflux | 93 | 0 |
| 11 | dioxanec | 5 | reflux | 23 | 73 |
| 12 | DMSO ^d | 8 | 90 | 0 | 98 |

^a Reaction was performed in the presence of Et_3N (1.5 equiv).

^b Starting material was recovered.

^c Reaction was performed in the presence of DMSO (5 equiv).

 $^{\rm d}$ Reaction was performed in the presence of H_2O (5 equiv).

ing two aldehyde groups exclusively produced mononitrile while reacting with NH₂OH·HCl (1.1 equiv) in DMSO (entry 8, Table 2). A boronic acid functionality (entry 5, Table 2) as well as a carboxylate group (entry 9, Table 2) were tolerated under the reaction conditions. Further, various heteroaromatics turned out to be compatible with the new reaction conditions to yield the respective nitriles in excellent yields (entries 10–15, Table 2).

Not only were aromatic/heteroaromatic aldoximes efficiently converted into respective cyano compounds but aliphatic aldoximes could also be employed as a good substrate with comparable selectivity to afford the corresponding aliphatic nitriles (entries 16–22, Table 2). It is notable that fairly acid-sensitive molecules such as *N*-Boc-4-piperidine carboxaldehyde (entry 19, Table 2) and azetidine carboxaldehyde (entry 20, Table 2) reacted smoothly under the reaction conditions to provide the corresponding nitriles in quantitative yields. Although the acidity of HCl in DMSO is weaker than in water,¹⁶ these reactions were performed at 70 °C as a precautionary measure.

To illustrate the preparative utility of the method, our procedure was performed on a multigram scale (Scheme 1). A synthesis on 84 grams of material gave 2f in 96% yield, and the product was isolated in pure form simply by aqueous workup. Likewise, 32.3 g (94%) of 5-cyanoindazole (21) was produced in pure form by reacting 5-formylinda-

Synlett 2011, No. 15, 2223–2227 $\,$ © Thieme Stuttgart \cdot New York

zole (35 g) with NH₂OH·HCl in DMSO. However, in both these cases, a slight excess of NH₂OH·HCl (1.3 equiv) was used to achieve optimum conversion (Scheme 1).

Table 2 DMSO-Mediated Synthesis of Nitriles from Aldehydes

| Entry | Substrate | Product | Yield (%) ^a |
|-------|----------------------|---|---------------------------|
| 1 | Br | Br | 99 |
| 2 | Br CHO | 2a Br HO | 98 |
| 3 | CI CHO | $2\mathbf{b}$ $CI \qquad CN$ $H_2N \qquad CN$ | 98 |
| 4 | | $\dot{C}l$ 2c F F CN NO_2 | 97 |
| 5 | HO ^B CHO | 2d HO _B CN | 95 |
| 6 | CHO F | 2e F F | 96 ^{b,c} |
| 7 | O ₂ N CHO | 2f O ₂ N | 97 |
| 8 | онс | 2g OHC CN | 98 |
| 9 | MeOOC | ZII MeOOCC | 99 |
| 10 | OHC | | 96 |
| 11 | Br CHO | 2j Br N | 98 |

| Table 2 | DMSO-Mediated | Synthesis | of Nitriles | from . | Aldehydes |
|-----------|---------------|-----------|-------------|--------|-----------|
| (continue | d) | | | | |

| R-CH | O NH ₂ OH·HCl (1.1 equiv) | NH ₂ OH·HCI (1.1 equiv) | | | |
|-------|--------------------------------------|--|---------------------------|--|--|
| Entry | DMSO, 90 °C, 1–2 h Substrate | 2a-v Product | Yield (%) ^a | | |
| 12 | OHC | NC | 94 ^{c,d} | | |
| 13 | CHO | 2l | 97 | | |
| 14 | Br | 2m | 98 | | |
| 15 | СНО | 2n | 98 | | |
| 16 | СНО | 20 CN | 95 | | |
| 17 | СНО | 2p CN | 94 | | |
| 18 | СНО | 2q CN | 96 | | |
| 19 | Boc N CHO | 2r | 95° | | |
| 20 | Ph Ph Ph | $\begin{array}{c} 2s \\ \stackrel{Ph}{} N \\ \stackrel{Ph}{} CN \end{array}$ | 92 ^e | | |
| 21 | O ₂ N CHO | 2t | 97 | | |
| 22 | Сретсно | 2u | 93° | | |

^a Isolated yields.

^b Reaction was performed on 84g scale.

^c 1.3 Equiv of NH₂OH·HCl were used.

^d Reaction was performed on 35 g scale.

^e Reaction was performed at 70 °C.

To authenticate the role of DMSO and HCl in nitrile synthesis, the reaction was further probed by a sequential approach. Thus aldoxime 1a was reacted with DMSO at 90 °C in the presence of a catalytic amount of 4 M HCl in



Scheme 1 Multigram synthesis of nitriles in one pot

dioxane (entry 1, Table 3). The reaction was complete within 30 minutes to generate **2a** in 96% yield. Conversely, under similar conditions when HCl was omitted, we did not observe any reaction (entry 2, Table 3). Likewise, all other solvents failed to promote the dehydration of aldoxime indicating the requirement for DMSO in the process (entries 3–8, Table 3). These observations also prove that the process is not an acid-catalyzed dehydration, but is driven by 'activated DMSO' and the role of HCl is limited to that of a catalyst to activate DMSO.

Table 3 Screening the Role of DMSO and HCl

| Br 1a | N_OH | 4 M HCl in dioxa solvent | ne (cat.) Br | CN 2a |
|----------|---------|-----------------------------|-----------------|---------------------|
| Entry | Solvent | Time (h) | Temp (°C) | Yield (%) 1 |
| 1 | DMSO | 0.5 | 90 | 96 |
| 2 | DMSO | 5 | 90 | n.r. ^{a,b} |
| 3 | DMF | 5 | 100 | n.r. ^b |
| 4 | dioxane | 5 | reflux | n.r. ^b |
| 5 | MeOH | 5 | reflux | n.r. ^b |
| 6 | MeCN | 5 | reflux | n.r. ^b |
| 7 | DCE | 5 | reflux | n.r. ^b |
| 8 | THF | 5 | reflux | n.r. ^b |

^a Reaction was performed in the absence of HCl.

^b No reaction.

Although the activity of HCl could be diminished while in contact with nitrogen heterocycles, it was surprising that all the nitrogen heterocycles participated effectively in the reaction (entries 10–15, Table 2). We decided to look into this phenomenon. Consequently, **1a** was reacted with DMSO at 90 °C in the presence of pyridine hydrochloride (0.5 equiv). The reaction was complete within four hours to give **2a** in 98% yield as shown in Scheme 2. This experiment proves that the reaction is not influenced by the nature of substrates involved, and the completion of reaction



Scheme 2 Reaction of aldoxime with pyridinium chlororide in DMSO

with substoichiometric amount of PyrH⁺Cl⁻ indicates the catalytic role of HCl in the process.

These results support the mechanism described in Scheme 3. The interaction of HCl (associated with hydroxylamine hydrochloride) with DMSO yields an oxysulfonium salt 3. The intermediate 3 instantaneously reacts with aldoxime 1 to produce 4 via electrophilic addition. Subsequent expulsion of nitrile from 4 regenerates DMSO and HCl. The process is mechanistically related to oxidation of aldoximes to nitriles using bromodimethyl-sulfonium bromide.¹⁷



Scheme 3 Probable pathway of nitrile generation from aldehydes involving 'activated DMSO'

In conclusion, we have demonstrated a practical and cost efficient one-pot transformation of aldehydes to nitriles mediated by 'activated DMSO'. A variety of aromatic, heterocyclic, and aliphatic aldehydes are converted into respective nitriles, in which only water is a byproduct.¹⁸ The reaction tolerates a wide scope of functional groups, and the method is simple to conduct. As established by us, this protocol can be readily applied to multigram-scale processes with high efficiency and selectivity, making it an economical and a convenient process for the preparation of nitriles.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (18) General Procedure for Nitrile Synthesis from Aldehydes A mixture of aldehyde (1 equiv) and NH₂OH·HCl (1.1

equiv) in DMSO (3–5 volumes depending on homogeneity of mixture) was stirred at 90 °C for 1–2 h. When the reaction was completed as confirmed by TLC (5% EtOAc in hexane), the mixture was cooled and diluted with H₂O. The solid precipitated was collected by filtration, washed with H₂O, and dried under suction to afford the corresponding nitrile in excellent yield. Alternatively, the reaction mixture could be poured onto H₂O and extracted with Et₂O. The organic phase could be evaporated to afford the nitrile with good purity and yield. This method is suitable for the isolation of liquid and aliphatic nitriles.