An Efficient One-Step Method for the Conversion of β-(Dimethylamino)styrenes into Arylacetonitriles

Alexey M. Starosotnikov,* Alexander V. Lobach, Svyatoslav A. Shevelev

N. D. Zelinsky Institute of Organic Chemistry, Leninsky pr. 47, Moscow 119991, Russia
Fax +7(095)135 5328; E-mail: ams@fromru.com

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Abstract: A new simple and efficient one-step method for the preparation of arylacetonitriles by reaction of β-(dimethylamino)styrenes with hydroxylamine hydrochloride in formic acid solution is described.

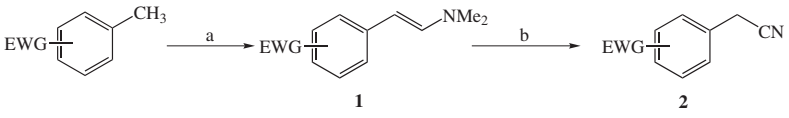
Key words: acetals, arylacetonitriles, β-(dimethylamino)styrenes, hydrolyses, nitriles

Arylacetic acid derivatives and in particular arylacetonitriles are widely used as useful precursors in the synthesis of heterocyclic compounds because of the active methylene fragment (especially with electron-withdrawing substituents in the aromatic ring), as well as the cyano group which is able to undergo reactions with nucleophiles[1] and dipolar cycloaddition reactions.[2] One of the classical methods for the synthesis of arylacetonitriles is the reaction of (halomethyl)benzenes[3,4] or benzyl tosylates[4,5] with the cyanide ion. A not less important method for the preparation of arylacetonitriles is the dehydration of the corresponding arylacetaldoximes[3,4,6,7] or primary amides.[3–5] In addition, a one-step method for the conversion of β-(*N,N*-dimethylamino)styrenes to arylacetonitriles is described,[8] which involves treatment of initial enamines with hydroxylamine-*O*-sulfonic acid (HASA) in aqueous media.

We have now found a new efficient one-step method for the synthesis of arylacetonitriles based on β-(*N,N*-dimethylamino)styrenes **1** containing electron-withdrawing substituents in the benzene ring (Scheme 1). Substrates **1** are easily obtained by the reaction of the corresponding substituted toluenes with *N,N*-dimethylformamide dimethyl acetal (DMA DMF) in DMF with heating (**1a**[9] and **1b**[10]) or in toluene at 20 °C (**1c**[11]).

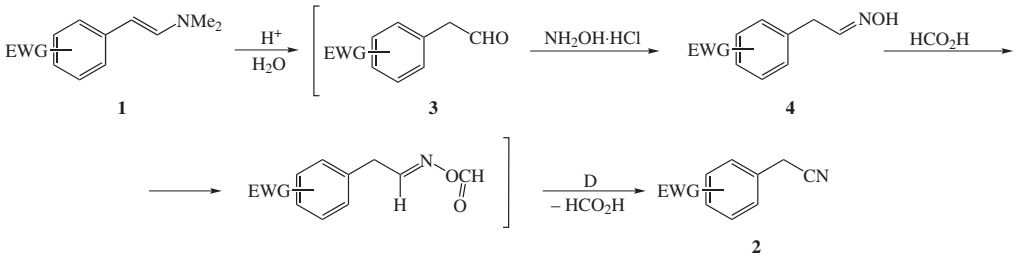
Compound **1d** was prepared analogously. Further transformations of enamines **1** to nitriles **2** (Scheme 1) were carried out in boiling formic acid solution in the presence of 30% mol excess of $NH_2OH·HCl$ (Table 1). The system $NH_2OH·HCl–HCO_2H$ has already been used before for the preparation of aromatic and aliphatic nitriles from the corresponding aldehydes.[12] The products **2a–d** obtained are listed in Table 1.

The most probable mechanism for the formation of **2** from **1** (Scheme 2) includes the hydrolysis of the enamine **1** to form aldehyde **3** (formic acid containing 2–5% of water was used), which reacts with hydroxylamine to the corresponding oxime **4**. Under the reaction conditions, **4** is then converted to arylacetonitrile **2**. The reaction time does not depend on the enamine structure and the nature of its substituents.



EWG = 4-NO_2 (**a**); 2,4-$(NO_2)_2$ (**b**); 2,4,6-$(NO_2)_3$ (**c**); 2,6-$(NO_2)_2$-4-CO_2Me (**d**).

Scheme 1 *Reagents and conditions*: a) DMA DMF, DMF or toluene; b) $NH_2OH·HCl$, HCO_2H, 100 °C.



Scheme 2

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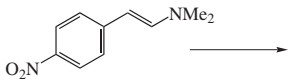
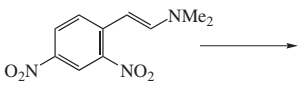
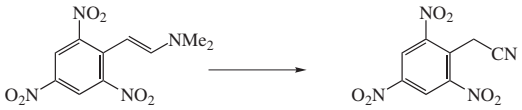
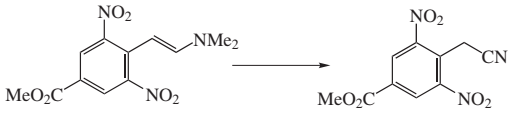
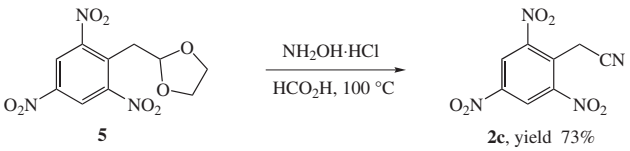
Table 1 Nitriles **2** from Enamines **1**

Enamine (**1**) ⟶ Nitrile (**2**)	Product	Yield (%)	Mp (°C)		^{1}H NMR, δ (*J* = Hz)
			Found	Reported	
	**2a**	49	107–109	108–113[17]	4.2 (s, 2 H, CH_2), 7.75 (d, 2 H_{arom}, *J* = 9.3), 8.25 (d, 2 H_{arom-}, *J* = 9.3)
	**2b**	57	85–86	89[18]	4.5 (s, 2 H, CH_2), 8.05 (d, 1 H_{arom}, *J* = 8.9), 8.6 (d, 1 H_{arom}, *J* = 8.9), 8.85 (s, 1 H_{arom})
	**2c**[a]	76	160–162	–	4.35 (s, 2 H, CH_2), 9.1 (s, 2 H_{arom})
	**2d**[a]	92	67–68	–	4.0 (s, 3 H, CH_3), 4.3 (s, 2 H, CH_2), 8.8 (s, 2 H_{arom})

[a] Satisfactory microanalyses obtained: C ± 0.13, H ± 0.16.

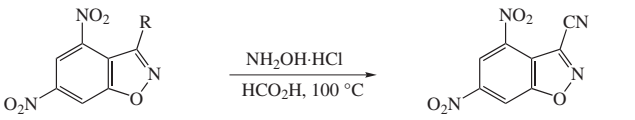
The formation of arylacetonitriles **2** from the enamines **1** under the action of HASA was considered[8] not to proceed via the corresponding aldehydes despite the fact that the process is carried out in water in the presence of a strong acid (HASA) and the initial hydrolysis of the enamine can not be excluded. However, we believe that aldehydes **3** serve as intermediates in our case (see Scheme 2). This assumption is proved by the fact that the reaction conditions are suitable not only for the conversion of β-(dimethylamino)styrenes to arylacetonitriles. We also found that some other aldehyde derivatives (acetals, imines) form nitriles under these conditions as well. Thus 2-(2,4,6-trinitrophenyl)methyl-1,3-dioxolane (**5**)[11] forms nitrile **2c** under the same conditions (Scheme 3).



5 **2c**, yield 73%

Scheme 3

The heteroaromatic nitrile, 4,6-dinitrobenzo[*d*]isoxazole-3-carbonitrile (**7**), can be obtained under these conditions from *O*-methyloxime **6a** as well as from the cyclic acetal **6b**, which were synthesized before,[13] without separation of the corresponding aldehyde (Scheme 4).



6a, R = CH=NOCH$_3$
6b, R = 1,3-dioxolan-2-yl

7, yield 58% (from **6a**)
yield 72% (from **6b**)

Scheme 4

It should be noted that benzo[*d*]isoxazole-3-carbaldehydes are usually unstable and undergo deformylation with opening of the isoxazole ring.[14,15] That is why the transformation of aldehyde derivatives **6** to nitrile **7** shows the possibility of further functionalization of benzo[*d*]isoxazoles in position 3 without recourse to the preparation of the intermediate aldehyde.

In summary, a new general method for the synthesis of arylacetonitriles from β-(dimethylamino)styrenes was developed. It was shown also that other derivatives of aromatic and arylacetic aldehydes such as acetals and imines form the corresponding nitriles under the applied reaction conditions.

Mps were measured on a Boetius apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer in DMSO–CCl_4 (1:1) mixture as a solvent. Chemical shifts are reported in ppm downfield from TMS using the δ scale. All reactions were monitored by TLC using Silufol plates which were visualized with UV light. Organic solvents and reagents were purified by the standard literature procedures. For all new compounds satisfactory microanalyses were obtained. Compounds **1a**,[9] **1b**,[10] **1c**,[11] and 4-methyl-3,5-dinitrobenzoic acid[16] were prepared as described before.

Methyl 4-[(*E*)-2-(Dimethylamino)ethenyl]-3,5-dinitrobenzenecarboxylate (1d)

A mixture of 4-methyl-3,5-dinitrobenzoic acid (0.70 g, 3.1 mmol), DMA DMF (0.7 mL, 5.2 mmol) and toluene (10 mL) was refluxed for 8 h and then allowed to cool to r.t. The solvent was removed under reduced pressure and EtOH (10 mL) was added to the residue. The resulting precipitate was collected by filtration and recrystallized from EtOH to give **1d**; yield: 0.65 g (71%); mp 128–130 °C (EtOH).

^{1}H NMR: δ = 2.95 (s, 6 H, 2 CH_3), 3.9 (s, 3 H, OCH_3), 5.45 (d, 1 H, *J* = 13.1 Hz), 6.8 (d, 1 H, *J* = 13.1 Hz), 8.3 (s, 2 H_{arom}).

Anal. Calcd for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44. Found: C, 48.62; H, 4.59.

Arylacetonitriles 2 from β-(Dimethylamino)styrenes 1; General Procedure

A solution of the corresponding enamine (2 mmol) and $NH_2OH·HCl$ (181 mg, 2.6 mmol) in 95–98% formic acid (15 mL) was refluxed for 3 h and then allowed to cool to r.t. The mixture was diluted with ice-water (60 mL), the precipitate formed was collected by filtration and dried in air to give pure (NMR) nitrile. In the case of compound **2d**, the aqueous solution was extracted with EtOAc (3 × 25 mL), the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuum and the residue was purified by column chromatography (silica gel, $CHCl_3$) to give pure (NMR) product as yellow oil that solidified on standing (Table 1).

2-(2,4,6-Trinitrophenyl)acetonitrile (2c) from Acetal (5)

A solution of compound **5** (0.60 g, 2 mmol) and $NH_2OH·HCl$ (0.20 g, 2.8 mmol) in 95–98% formic acid (15 mL) was refluxed for 2 h and then allowed to cool to r.t. The mixture was diluted with ice-water (60 mL), the precipitate formed was filtered off and dried in air to give pure (NMR) nitrile **2c** (0.37 g, 73%). Mp and spectral characteristics of the product were identical to those listed in Table 1.

4,6-Dinitrobenzo[*d*]isoxazole-3-carbonitrile (7)

A solution of compound **6a** or **6b** (2 mmol) and $NH_2OH·HCl$ (0.2 g, 2.8 mmol) in 95–98% formic acid (15 mL) was refluxed for 15 h and then worked up as described above to give pure (NMR) nitrile **7**. The yields are shown in Scheme 4; mp 147–149 °C.

IR (KBr): 3100, 3080, 2264, 1608, 1560, 1544, 1356, 1340, 1248, 1068, 1016, 964, 932, 800, 744, 742, 692, 640 cm^{-1}.

^1H NMR: δ = 9.0 (s, 1 H_{arom}), 9.5 (s, 1 H_{arom}).

Anal. Calcd for $C_8H_2N_4O_5$: C, 41.04; H, 0.86. Found: C, 41.02; H, 0.82.

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