

Communications

A Novel and Efficient Synthesis of Nitriles from Aldehydes under Solvent-free Microwave Irradiation Conditions

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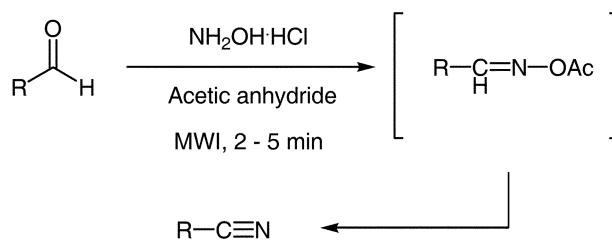
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Nitriles are of importance as very useful starting materials for the synthesis of a variety of biologically important heterocyclic compounds.¹ The direct transformation of aldehydes into the corresponding nitriles is one of the most fundamental and important reactions in organic transformations.² Thus considerable efforts have been directed towards developing efficient methods for the conversion of aldehydes into corresponding nitriles. Among the numerous methods to prepare nitriles, the dehydration of aldoximes has been served as one of the most useful method. Conventional methods for the dehydration of aldoximes include the use of reagent systems such as alumina/methanesulfonyl chloride,³ graphite/methanesulfonyl chloride,⁴ aluminium chloride/potassium iodide,⁵ NaI/MeCN,⁶ alumina/PCl₅,⁷ and [RuCl₂(*p*-cymene)]₂/molecular sieves.⁸ However, above mentioned methods suffered from serious disadvantages which include harsh reaction conditions, long reaction times, low yields, use of exotic reagents and organic solvents.

Recently microwave irradiation technique has been utilized as a powerful tool for the various organic transformations.⁹ The main benefits of performing reactions in microwave irradiation conditions are the significant enhancement of the reaction rates, yields, and selectivity. In particular, the microwave irradiation conditions proved to be highly effective to promote condensation reactions.¹⁰ Thus, a couple of methods for the conversion of aldehydes to nitriles were recently reported utilizing microwave irradiation technique. For examples, microwave promoted dehydration of aldoximes have been achieved by use of chemical reagents such as peroxymonosulfate/alumina,¹¹ sodium hydrogen sulphate/SiO₂,¹² and HY-Zeolite.¹³ However, these methods invariably utilized acidic or basic inorganic reagents and solid supports. In practice, the microwave induced methods utilizing solid supports often encountered with low reproducibility due to the heterogeneous nature of reaction conditions. Furthermore, regardless of conventional or microwave irradiation conditions, only few are applicable to produce nitriles from aldehydes without use of inorganic salts or solid supports.

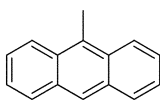
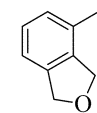
Although many methods exist for the conversion of aldehydes into the corresponding nitriles, there has been no

previous report on the use of microwave irradiation mediated method conducted in neat reaction conditions for the direct preparation of nitriles from aldehydes. Therefore it is highly desirable to develop practically applicable protocol for the conversion of aldehydes to nitriles using microwave



Scheme 1

Table 1. Nitriles prepared from aldehydes under solvent-free microwave irradiation conditions

Entry	R	Time (sec)	Yield (%) ^a
1	C ₆ H ₅ -	300	88
2	<i>p</i> -MeC ₆ H ₄ -	180	92
3	<i>p</i> -MeOC ₆ H ₄ -	150	98
4	<i>p</i> -ClC ₆ H ₄ -	210	96
5	<i>p</i> -FC ₆ H ₄ -	210	85
6	2,4-Cl ₂ C ₆ H ₃ -	210	85
7	<i>p</i> -NO ₂ C ₆ H ₄ -	150	95
8	CH ₃ (CH ₂) ₃ CH ₂ -	210	78
9	CH ₃ (CH ₂) ₅ CH ₂ -	210	77
10	C ₆ H ₅ CH=CH-	120	94
11	3-Pyridyl	120	98
12	2-Thiophene	180	88
13		120	93
14		210	89

^aIsolated yields.

irradiation in the homogeneous neat solvent-free media.

During the course of our research projects on development of environmentally friendlier synthetic methods for synthesis of heterocyclic compounds, we required a facile method for the preparation of nitriles. After tested various reagent systems, we found that the acetic anhydride highly promotes the conversion of aldoxime intermediates into nitriles under microwave irradiation conditions. Acetic anhydride represents one of the most easily available and safe reagent in organic chemistry. Although acetic anhydride was occasionally utilized as a dehydration agent in some of organic transformations,¹⁴ its use in the direct conversion of aldehydes into corresponding nitriles has been unprecedented. Herein, we wish to disclose a new and eco-friendly preparative route to nitriles through direct treatment of aldehydes with hydroxylamine and acetic anhydride under solvent-free microwave irradiation conditions. The reactions were carried out by treating neat aldehydes with 4.0 equiv of acetic anhydride and hydroxylamine hydrochloride under microwave irradiation using domestic microwave oven (Scheme 1). Closer inspection of the reaction conditions revealed that the use of four equivalents of acetic anhydride was necessary to obtain high yields and diminution of side-products. As shown in the Table 1, the reaction could be easily applied to structurally diverse aldehydes to give the corresponding nitriles in excellent yields. This protocol was compatible with reactive substituents such as alkoxy, and alkenyl compounds. The variation of electron donating and withdrawing substituents to the aromatic rings have no significant effects on the reaction rates and yields. In case of enolizable aliphatic aldehydes provided less satisfactory yields of aliphatic nitriles (entries **8-9**). The present method probably proceed *via* initial formation of *O*-acetylaldoxime intermediates, formed *in situ* by the reaction of aldoxime intermediates with acetic anhydride, followed by its decomposition under microwave irradiation conditions. In general procedure, aldehydes (1.0 mmol), hydroxylamine hydrochloride (2.0 mmol) and acetic anhydride (4.0 mmol) were mixed thoroughly on a vortex mixer. The reaction mixture was placed in an alumina bath inside a domestic microwave oven (Samsung RE-21C, 850W) and irradiated 4-10 times for a

period of 30 sec with 20 sec intervals. After completion of the reaction, the product mixture was dissolved in dichloromethane (25 mL) washed with water (50 mL), and dried over magnesium sulfate. After removal of the solvent the residue was purified by column chromatography (silica gel, dichloromethane : hexane = 1 : 1) to give the corresponding nitrile.

In conclusion we have developed a new and efficient method for the direct conversion of aldehydes into nitriles under microwave promoted neat solvent-free reaction conditions. The advantages of the present method in terms of facile manipulation, fast reaction rates, and formation of cleaner products under neat reaction conditions should make this protocol as a valuable alternative to the existing methods.

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