Improved Synthesis of 2-Amino-3-cyanopyridines in Solvent Free Conditions under Microwave Irradiation†

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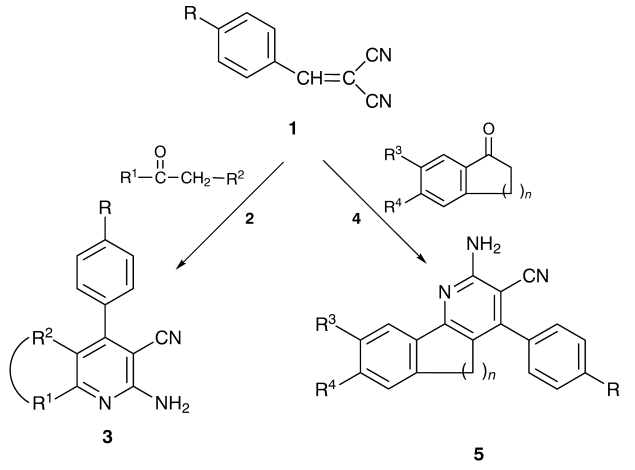
A simple and efficient method is developed for the rapid synthesis of 2-amino-3-cyanopyridines **3**–**5** from arylidenemalanonitriles **1** and ketones **2** or **4** in presence of ammonium acetate without solvent/containing traces of solvent under microwave irradiation: reaction times are considerably reduced with improved yields as compared to those obtained under classical heating.

Organic synthesis under microwave irradiation is now widely used.[1–3] Dry media techniques by microwave heating have attracted much attention[4–6] and offers several advantages: solvents are often expensive, toxic, difficult to remove in case of aprotic dipolar solvents with high boiling points, and are agents that pollute the environment. Liquid–liquid extraction is avoided for the isolation of the reaction products. The absence of solvent also reduces the risk of hazardous explosions when the reaction takes place in a closed vessel in the microwave oven.

The preparation of 2-amino-3-cyanopyridines continues to be the subject of numerous papers as these are versatile intermediates for the synthesis of variety of heterocyclic compounds.[7–9] Many of the standard procedures[10–12] require either longer reaction times or in some cases lead to mixtures of products and proceed in low yields.

Keeping in view the importance of 2-amino-3-cyanopyridines and recent trends of phasing out the use of organic solvents and devising environmentally-friendly techniques, we report the synthesis of 2-amino-3-cyanopyridines **3**–**5** from arylidenemalanonitriles **1** and ketones **2** or **4** in the presence of ammonium acetate using microwaves without solvent or containing traces of solvent.

In the classical approach, the synthesis of **3** or **5** requires 5–8 h refluxing in benzene. In contrast, the same reaction when performed under microwave irradiation required 3–5 min and improvement in yields was also observed. The work-up is simply reduced to treatment with ethanol, which on standing gave 2-amino-3-cyanopyridines as crystalline products.



3a R = H, R^1 = Ph, R^2 = H
3b R = OMe, R^1 = Ph, R^2 = H
3c R = H, R^1 + R^2 = -$[CH_2]_4$-
3d R = OMe, R^1 + R^2 = -$[CH_2]_4$-
5a R = R^3 = R^4 = H, *n* = 2
5b R = OMe, R^3 = R^4 = H, *n* = 2
5c R = H, R^3 = OEt, R^4 = OMe, *n* = 1
5d R = OMe, R^3 = OEt, R^4 = OMe, *n* = 1

Scheme 1

The amount of ammonium acetate and power output was adjusted to get the maximum yield of the products **3** or **5**. By carrying out reactions with different amounts of ammonium acetate at different power outputs, it has been found that 8 mmol of the ammonium acetate furnished the maximum yield for 1 mmol of the reactants, when irradiated at a power output of 275 W. Furthermore, it has been found that if *o*-dichlorobenzene (0.5 ml) was added to the reactants (3 mmol), the yields increase considerably *e.g.* in **5b** it increases from 50 to 78%. The addition of

Table 1 Analytical and spectral data of compounds **5**

Compound	Mp (°C)	M^a	υ_{max}/cm^{-1}	$\delta_H{}^b$	*m/z* (%)
5a	169–170	$C_{20}H_{15}N_3$	3420, 3350, 3175, 2210	2.55–2.95 [m, 4 H, $(CH_2)_2$], 5.20–5.50 (br s, 2 H, NH_2) 7.00–7.80 (m, 9 H, aryl H)	297 (100)
5b	164–165	$C_{21}H_{17}N_3O$	3450, 3350, 3150, 2220	2.60–3.0 [m, 4 H, $(CH_2)_2$], 3.85–3.95 (s, 3 H, OCH_3), 5.25–5.35 (br s, 2 H, NH_2), 6.95–7.60 (m, 8 H, aryl H)	327 (100)
5c	215–216	$C_{22}H_{19}N_3O_2$	3450, 3310, 3180, 2210	1.50–1.57 (t, 3 H, $-CH_3$), 3.60–3.66 (s, 2 H, $-CH_2$), 3.90–3.98 (s, 3 H, OCH_3), 4.20–4.28 (q, 2 H, OCH_2), 5.25–5.32 (br s, 2 H, NH_2), 6.98–7.60 (m, 7 H, aryl H)	357 (100)
5d	208–209	$C_{23}H_{21}N_3O_3$	3430, 3330, 3150, 2200	1.50–1.60 (t, 3 H, CH_3), 3.60–3.65 (s, 2 H, CH_2), 3.90–4.0 (s, 6 H, $2 \times OCH_3$), 4.20–4.30 (q, 2 H, OCH_2), 5.30–5.38 (br s, 2 H, NH_2), 6.95–7.55 (m, 6 H, aryl H)	387 (100)

[a]All the compounds gave C, H and N analyses within ±0.5%. [b]The ^1H NMR spectra were recorded in $CDCl_3$.

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Table 2 Comparison of reaction times and yields for compounds **3** and **5** using microwave and classical methods

Compound	Reaction time			Yield (%)		
	Microwave (min)		Classical reflux with benzene (h)	Microwave		
	Without solvent	Trace solvent		Without solvent	Trace solvent	Classical
3a	4.0	3.0	5	52	72	49
3b	4.0	3.5	6	43	75	46
3c	4.5	3	5.5	58	78	69
3d	3.5	3.5	6	52	69	46
5a	4.0	4.0	5.5	51	70	52
5b	4.5	4.0	6	50	78	55
5c	4.0	3.5	6	42	72	46
5d	4.5	3.5	5.5	52	70	48

o-dichlorobenzene as an energy-transfer medium is to permit a higher temperature and better homogeneity in the reaction medium.

In order to study the possible existence of a specific microwave effect, we have carried out all the reactions using the conventional heating mode (oil bath) at the same final temperatures and reaction times as measured in the microwave experiments. In all cases no reactions were detected as determined by TLC. Lower yields were obtained with the conventional heating mode, even after 4 h of reaction, indicating that the effect of microwave irradiation is not purely thermal.

The title compounds were characterised on the basis of analytical, spectral data and by comparison with authentic samples prepared by known methods[12] (Table 1). The reaction pathway is shown in Scheme 1. The reaction times and yields using microwave and conventional methods have been compared (Table 2).

Experimental

Melting points were determined in open capillaries on a Toshniwal melting point apparatus and are uncorrected. The reactions were monitored by means of TLC, IR spectra (υ_{max} in cm^{-1}) were recorded on a Shimadzu-435 spectrophotometer using KBr discs and ^1H NMR spectra in $CDCl_3$ and $CDCl_3$–[$^2H_6$]DMSO on Varian EM-390 (90 MHz) or Bruker AM-250 (250 MHz) spectrometers. The compound $SiMe_4$ was used as an internal standard; the chemical shifts are expressed in δ downfield from $SiMe_4$. The mass spectra were performed on a Delsi/Nermag spectral 30 spectrometer. Reactions were carried out in a BMO-700 T domestic microwave oven manufactured by BPL multimode Sanyo utilities and Appliances Ltd., Bangalore operating at 2450 MHz at a maximum power of 650 W.

General procedure for the synthesis of 2-*amino*-3-*cyanopyridines*.—A mixture of arylidenemalanonitrile **1** (3 mmol), ketone **2** or **4** (3 mmol), ammonium acetate (24 mmol) and *o*-dichlorobenzene (0.5 ml) was placed in a borosil beaker (100 ml) and mixed thoroughly with the help of a glass rod. The mixture was then subjected to microwave irradiation for an optimized time (Table 2) at a power output of 275 W. After completion of the reaction (monitored by TLC), ethanol (4 ml) was added to the reaction mixture and kept at room temperature for 5–10 min, the crystalline product obtained was filtered, washed with ethanol and recrystallised from the appropriate solvent (benzene, light petroleum (bp 40–60 °C)–ethanol or tetrahydrofuran). The analytical and spectral data of **5a**–**5d** are given in Table 1 while **3a**–**3d** were characterised by their literature melting points.[12]

In conclusion, we have developed a simple, efficient and environmentally friendly method for the synthesis of 2-amino-3-cyanopyridines using an unmodified domestic microwave oven. Yields were enhanced by addition of a small amount of solvent, here *o*-dichlorobenzene.

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