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One pot synthesis of 2-amino-4-(substituted-phenyl)-6-naphtho[2,1-*b*]furan-2-yl-nicotinonitrile derivatives by using bismuth nitrate pentahydrate as efficient catalyst

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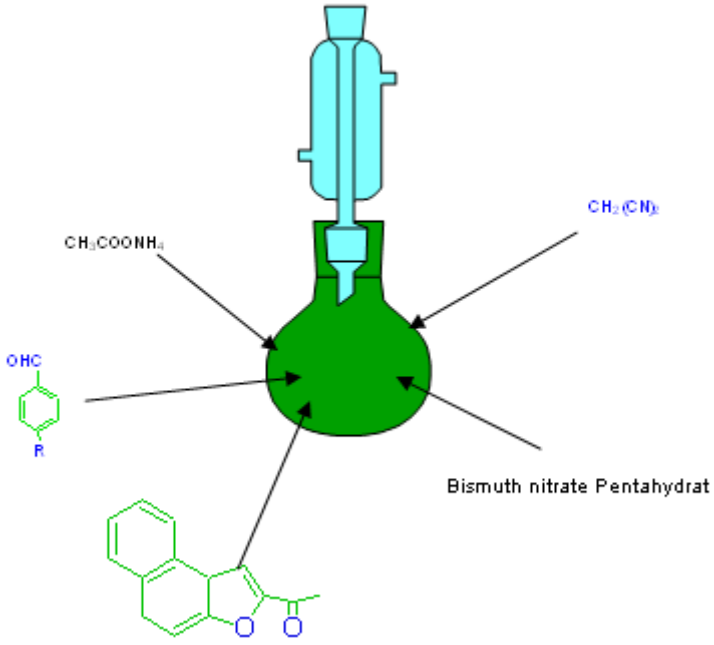
ABSTRACT



A series of 2-amino-4-(substituted-phenyl)-6-naphtho[2,1-b]furan-2-yl-nicotinonitrile derivatives have been prepared by one-pot condensation from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate by using Bismuth nitrate Pentahydrate as the efficient catalyst. This method has the advantage of short routine, high yields and being environmentally-friendly.

Keywords: Pyridine derivatives, one-pot synthesis, Bismuth nitrate Pentahydrate

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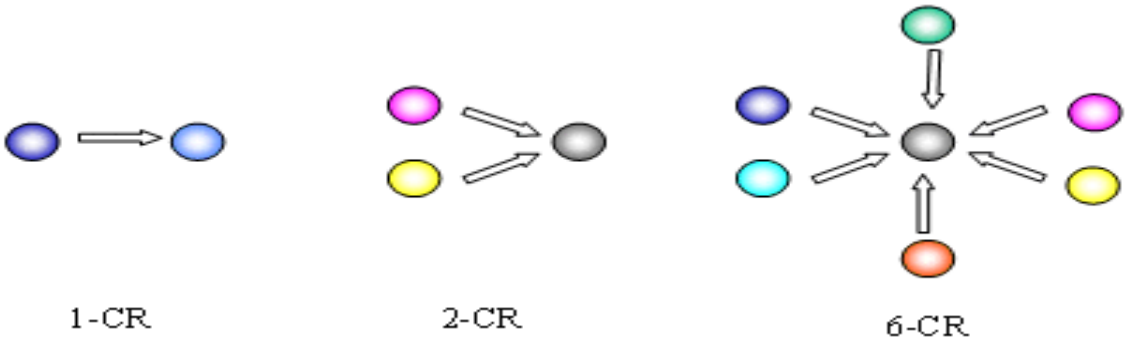
INTRODUCTION

Multicomponent Reactions

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria,

which all finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs[1].



Furan and pyridine derivatives

Furan moieties are common substructures in numerous natural products[2]. Naphthofuran derivatives have been isolated from various natural sources like Fusarium oxy-sporum[3], Gossypium barbadense[4], etc and are well known for various biological activities like antitumour[5], antifertility[6], mutagenic[7], growth inhibitory[8] and oestrogenic[9]. In addition, Many natural occurring and synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties[10].1 Among them, 2-amino-3-cyanopyridines have been identified as IKK-βinhibitors.2 Besides, they are important and useful intermediates in preparing variety of heterocyclic compounds[11].3 Therefore, the synthesis of 2-amino-3-cyanopyridine derivatives continues to attract much interest in organic chemistry. It has been reported that the 2-amino-6-aryl-3-cyano-4-piperidinylpyridine core structure can be constructed using a one-pot coupling reaction of methyl ketone, malononitrile and ammonium acetate in conventional heating mode[12-13]. Nevertheless, the protocol gives comparatively lower yields and longer reaction time. These problems have encouraged the search for other methods, especially alternating catalytic amounts of various solid acids with stoichiometric amounts of corrosive Brönsted acids.[14-15]

MATERIALS AND METHODS

General Procedures. Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds were checked by TLC, FT-IR spectra were taken in a Perkin Elmer 157 infrared spectrophotometer. ^{1}H NMR spectra (300 MHz) were recorded on a Brucker supercon FT-NMR instrument using TMS as internal standard (chemical shifts in ppm).

Typical procedure 2-Amino-4-(4-hydroxyphenyl)-6-naphtho[2,1-*b*]furan-2-ylnicotinonitrile 4d

A mixture of 2-acetylnaphtho[2,1-*b*]furan **3** (2.21g, 0.01 mole) and the 4-hydroxybenzaldehyde (1.22g, 0.01 mole) in ethanol (30 ml) was treated with malanonitrile (0.66g, 0.01 mole), a pinch Bismuth nitrate Pentahydrate and ammonium acetate (6.18g, 0.08 mole). The mixture was refluxed for completion of the reaction by monitoring TLC. After cooling to room temperature, the reaction mixture was poured into crushed ice and the separated solid was filtered and recrystallised from ethanol. Similarly, the compounds **4** (b-g) were synthesized from **3** by reacting with appropriate aromatic aldehydes.

Table – IR and NMR Spectral data of 4(a-g)

Compounds	IR (KBr) cm^{-1}			^{1}H NMR δ in ppm
	-OH	$-NH_2$	-CN	
4a	-	3240	2188	δ 6.6 (s, 2H,-NH_2), δ 7. 2-8.5 (m, 12H, ArH)
4b	-	3250	2190	δ 6.5 (s, 2H,-NH_2), δ 7. 3-8.6 (m, 12H, ArH)
4c	-	3252	2195	δ 6.7 (s, 2H,-NH_2), δ 7.5-8.5 (m, 13H, ArH)
4d	3344	3216	2201	δ 6.8 (s, 2H,- NH_2), δ 7.3 - 8.0 (m, 12H, ArH and 1H, OH))
4e	-	3290	2188	δ 3.90 (s, 3H, OCH_3), δ 6.4 (bs, 2H,- NH_2), δ 7.5 - 8.2 (m, 12H, ArH)
4f	-	3260	2188	δ 3.90 (s, 3H, OCH_3), δ 6.6 (bs, 2H,- NH_2), δ 7.5 - 8.2 (m, 12H, ArH)

RESULTS AND DISCUSSION

When a mixture of aromatic aldehyde, methyl ketone, malononitrile ammonium acetate and bismuth nitrate pentahydrate was refluxed on water bath (Scheme 1), the reactions were almost completed in 2-3 hours. The reaction mixtures were then washed with a small amount of ethanol. The crude products were purified by recrystallization from 95% ethanol to afford products with good yields (80-86%). The main results for the synthesis of these compounds are given in Table 1. It is seen that this procedure has the advantage of short routine, good yields, convenient workup and being environmentally friendly.

Scheme 1. One-pot synthesis of 2-Amino-4-(4-hydroxyphenyl)-6-naphtho[2,1-*b*]furan-2-ylnicotinonitrile

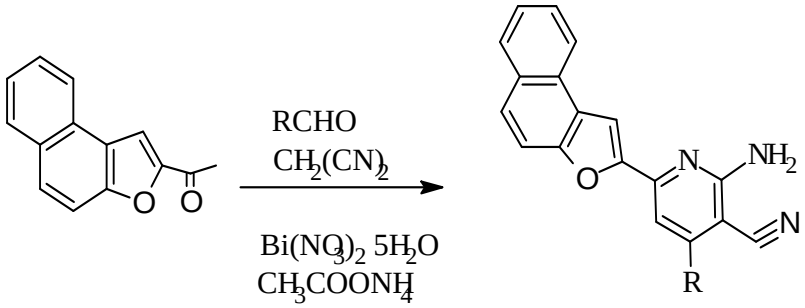


Table 1 Synthesis of 2-Amino-4-(4-hydroxyphenyl)-6-naphtho[2,1-*b*]furan-2-ylnicotinonitrile by using catalyst.

Entry	R	Time (hours)	Yield (%)	Mp(°C)
2a	3-NO_2 C_6H_4	3	80	168
2b	4-Cl C_6H_4	2.5	82	175
2c	C_6H_5	3	85	189
2d	4-OH C_6H_4	3	80	183
2e	3-OCH_3 C_6H_4	2.5	86	173
2f	4-$OCH_3C_6H_4$	3	84	195
2g	4-OH 3-OCH_3 C_6H_3	3	81	168

CONCLUSION

We have synthesized a series of 2-amino-3-cyanopyridine derivatives by one-pot method by using catalyst thus providing a facile, rapid, efficient and environmentally friendly method.

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