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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Anusaya S. Chavan, Arun S. Kharat, Manisha R. Bhosle & Ramrao A. Mane (2017): A convenient Baker yeast accelerated, one-pot synthesis of pentasubstituted thiopyridines, Synthetic Communications, DOI: 10.1080/00397911.2017.1350982

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1350982

A convenient Baker yeast accelerated, one-pot synthesis of pentasubstituted thiopyridines

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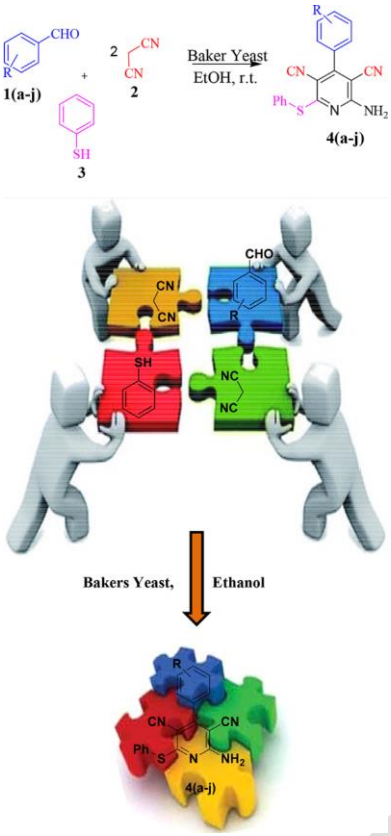
Full experimental details and ^{1}H, ^{13}C NMR and HRMS spectra of other products in the supplementary content of this article web page are available.

ABSTRACT

Here we report a novel Baker yeast catalysed one pot cyclocondensation, carried at room temperature in ethanol for obtaining high yields of polyfunctionalised pyridines, 2-amino-4-aryl-

3,5-dicyano-6-phenylthio-pyridines. The developed protocol obeys certain green principles and is scalable and cost effective.

GRAPHICAL ABSTRACT



KEYWORDS: 2-amino-4-aryl-3,5-dicyano-6-phenylthio-pyridines, Baker yeast, multicomponent reaction, one pot

Introduction

Heterocycles exhibit significant diverse medicinal properties. Among the nitrogen heterocycles,[1] functionalised pyridines, isolated from nature and syntheses are found to display wide range of therapeutic activities.[2–11] They are systematically reviewed by Khan et al.[12]</link> It has also been reported that pentasubstituted pyridines are found to have medicinal properties

like inhibiting mitogen activated protein kinase- (MAPK-), activating protein kinase 2 (PK-2), targeting for tumour necrosis factor R- (TNFR-) mediated diseases,[2] modulating androgen receptor function,[3] serving as potassium channel openers with applications in treating urinary incontinence,[4] inhibiting IKK2 with a potential for treating hepatitis B virus (HBV) infection,[5] and acting as anti-bacterial,[6] anti-cancer,[7] antibiofilm, and anti-infective agents.[8] Recently, these compounds have been recognized as potential targets for the development of new drugs for the treatment of Parkinson's, hypoxia, asthma, kidney, epilepsy, and Creutzfeldt–Jacob diseases.[9a–c] Some of these pyridine compounds are found to be active inhibitors of the adenosine receptors and, therefore, can be used for treating these diseases.[10] They are also inhibitors of cholinesterases and may be used for treating neurodegenerative diseases.[11]

Considering the various applications in the field of medicinal and supramolecular chemistry, attempts are found to be directed on designing and development of novel methodologies for synthesis of polyfunctionalised pyridines. First time Evdokimov et al.[13] have reported one pot cyclocondensation of aldehydes, thiophenol, and malononitrile, using Et_3N or DABCO as a catalyst and obtained 20–48% yield of 2-amino-3,5-dicyano-6-sulphanyl pyridines along with by-products (enaminonitriles). These are the main limitations of this method.

To overcome the limitations/lacunas, associated with this protocol and taking inspiration from their pharmacological applications, several researchers have tried to provide alternative, cost-effective synthetic protocols[12],[14–20] for these pyridines. These alternative protocols include the incorporation of catalysts *viz*. nano crystalline magnesium oxide,[14] silica nanoparticles,[15] KF/alumina,[16] basic ionic liquid [bmIm]OH,[17] $ZnCl_2$,[18] pipridine/microwave,[19] DBU,[20] Cd(II) metal–organic frameworks (MOFs),[12] Zn(II), refluxed in basic alumina,[21a] molecular sieves,[21b] CaO nanoparticles,[21c] and boric acid in aqueous medium.[21d] Recently, alcoholic KOH

has also been employed for the synthesis of highly functionalized pyridine derivatives and obtained moderate yields.[12] However it has been found that all these protocols are accompanying with one or other kind of drawbacks such as low yields, longer reaction time, and toxic or expensive catalysts. Till the quest is continued to develop a safer, cost-effective, high yielding and environmental benign method for the titled products. The literature revels that till this day nobody has attempted use of biocatalysts, particularly whole cell Baker yeast in accelerating one pot multicomponent cyclocondensation of aldehydes, malononitrile and thiophenol for obtaining the titled products.

Prompted by the above observations and in continuation of our earlier interest in biocatalysis[22–26] here in the present work, an alternative baker yeast catalysed protocol has been developed by optimising the reaction conditions for getting enhanced yields of the titled products using scalable conditions.

Results and Discussion

One-pot multi component cyclocondensation protocol has been developed for 2-amino 4-aryl-3,5-dicyano-6-phenyl thio-pyridines (**4a-j**) by carrying cyclocondensation of aryl aldehydes, (**1a-j**) malononitrile (**2**) and thiophenol (**3**) in ethanol in presence of using activated baker yeast (Scheme 1).

In order to set the best experimental conditions, the cyclocondensation of 4-chlorobenzaldehyde (**1a**), malononitrile (**2**) and thiophenol (**3**) has been practiced as a standard model reaction (Scheme 2).

To screen the suitable medium, we carried the model reaction in different solvents *viz*; water, ethanol, methanol, acetonitrile, *N*,*N*-dimethyl formamide and dichloromethane in the

presence of Baker yeast under identical conditions. The performance of these solvents is recorded in **Table 1**. It seems that aprotic organic solvents viz. DCM, and acetonitrile when used to carry model reaction yield of the titled pyridine is moderate. Protic solvents viz, methanol, H_2O, and EtOH are found to be relatively accelerating rates and hence yield of the product. Ethanol was found to be better solvent and gave high yield of 2-amino 4-aryl-3,5-dicyano-6-phenylthio-pyridine (**4a**). Hence, ethanol was selected as a solvent for this cyclocondensation.

To optimize the amount of Baker yeast, required for accelerating the cyclocondensation the above standard reaction was performed in ethanol at r.t. by varying amount of baker yeast from o to 1 gm for 9.4 mmol of benzaldehyde, 18.8 mmol of malononitrile and 9.4 mmol of thiophenol. It was found that when 1gm baker yeast was incorporated, while carrying the above cyclocondensation it gave better yield of (**4a**) within 40 min at r.t.

Then employing the above optimized conditions, cyclocondensation of various aryl aldehydes (**1b-j**), malononitrile (**2**) and thiophenol (**3**) using baker yeast at room temperature has been carried and obtained substituted 2-amino 4-aryl 3,5-dicyano-6-phenyl thio- pyridines (**4b-j**) with better to excellent yields (**Table 2**, Scheme 1).

Under optimised condition when standard reaction was performed in the absence of Baker yeast, keeping stirring more than 24 h at r.t. there was negligible conversion of reactants to product (**4a**). Hence it seems that baker yeast is displaying its role as a catalyst. Baker yeast is whole cell source of various enzymes. The enzymes having strong nucleophilic and electrophilic active amino residues may be participating in the interactions with carbonyl of aldehydes, active methylene of malononitrile and mercapto of thiophenol, enhancing electrophilic character of methylene of malononitrile and nucleophilic character of mercapto of thiophenol, respectively. Such participating amino acid residue could be histidine, serine and aspartate anion present in a bank of

enzymes of baker yeast like lipase etc. These factors are probably responsible for the cyclocondensation at room temperature in successive steps generating the desired polyfunctionalised pyridines rapidly. The plausible mechanism of the cyclocondensation is depicted in Scheme 2.

Conclusions

An efficient, cost effective and environmentally friendly protocol has been developed for the synthesis of 2-amino-4-aryl 3,5-dicyano-6-phenyl thio-pyridines (**4a-j**) for the first time by employing very cheaper, easily available natural catalyst, baker yeast. The method offered several advantages such as operational simplicity, easy work-up procedure, shorter reaction time and high yields of the products (82–93%). This protocol is user-friendly and could be an attractive tool for the synthesis of highly functionalized bioactive 2-amino-4-aryl 3,5-dicyano-6-phenyl thio-pyridines.

Experimental

General

All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance 300 spectrometer operating at 300MHz using DMSO-d6 solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm.^{13}C NMR spectra were recorded on Bruker Avance 75MHz on Jeol. The purity of each compound was checked by TLC using silica-gel, 60F_{254} aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

General experimental procedure for the synthesis of 2-amino-4-aryl-3,5-dicyano-6-phenyl thio-pyridines (4a-j)

Baker yeast (1 gm) was added in ethanol (15mL) and mass was sonicated at 35 KHz at rt for 30minutes . To this then aryl aldehydes (9.4 mmol), Malanonitrile (18.8 mmol), Thiophenol (9.4 mmol), were added. Then the reaction mass was stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography using ethyl acetate: pet ether (2:8) as eluent. After 45min ., ethyl acetate (30 mL) was added to the reaction mass. Then the reaction mixture was filtered through the bed of celite (1 g). From the filtrate, the solvents were removed under reduced pressure and the crude solid product isolated was crystallized from ethanol. The melting points and the yields of the derivatives are recorded in **Table 2**. Melting points and spectral data of the 2-amino-4-aryl 3,5-dicyano-6-phenyl-thio- pyridines (**4a-j**) are in good agreement with those reported in the literature.[21]

2-Amino-4-(4-chlorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (**4f**)

^{1}H NMR (300 MHz , $CDCl_3$) δ ppm: 5.53 (s, 2H, NH2), 7.26 (s, 2H, Ar-H), 7.42–7.58 (m, 5H, Ar-H); ^{13}C NMR (75 MHz , $CDCl_3$) δ ppm = 87.39, 115.23, 114.80, 127.22, 129.69, 129.59, 130.10, 130.24, 131.73, 136.01, 137.66, 157.34, 159.47, 169.58; HRMS (ESI^+): Anal. Calcd. for $C_{19}H_{11}ClN_4S$ $[M + H]^+$:363·0426; Found: 363·0464.

Acknowledgments

The authors are thankful to Professor D. B. Ingle for his invaluable discussions and guidance. The authors are also thankful to SAIF, Central Drug Research Institute (CDRI), Lucknow for spectral analysis.

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Table 1. Screening of reaction media for the synthesis of compound (**4a**).

Entry	Solvent	Yield (%)
1	Ethanol	93
2	DCM	69
3	MeOH: H_2O	68
4	MeOH	72
5	CH_3CN	65
6	H_2O	57

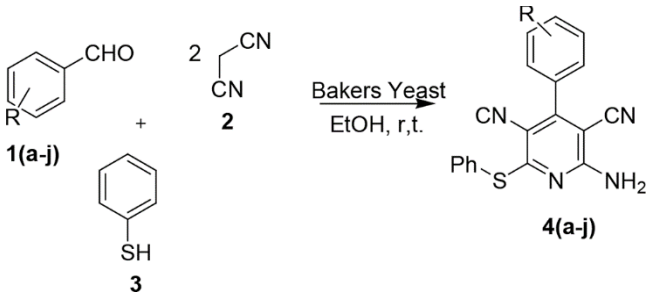
Reaction conditions: benzaldehyde (9.4 mmol), Malanonitrile (18.8 mmol), Thiophenol (9.4 mmol), Backer yeast (1 g), solvent (15 ml) and stirred for 40 min . at r.t.

Table 2. Physical data of 2-amino 4-aryl 3,5-dicyano 6-phenyl thio- pyridines.

Entry	Compounds	R	Yield (%)[b]	M.P. (°C)[c]
1	4a	-H	93	216–218
2	4b	2-NO_2	92	288–290
3	4c	4-F	90	235–236
4	4d	4-OMe	93	272–274
5	4e	4-OH	85	265–266
6	4f	4-Cl	87	230–232
7	4g	4-NMe_2	82	168–170
8	4h	4-Br	84	212–213
9	4i	3,4-$(OMe)_2$	90	226–228
10	4j	4-Me	82	208–210

[a]Reaction conditions:, benzaldehydes (9.4 mmol), Malanonitrile (18.8 mmol), Thiophenol (9.4 mmol), Backer yeast (1 g), ethanol (15 mL), at r.t. for 40 min . [b]Isolated yields. [c]Melting points are in good agreement with those reported in the literature.[21]

Scheme 1. Synthesis of 2-amino 4-aryl 3,5-dicyano-6-phenyl thio-pyridines (4a-j).



Scheme 2. Plausible mechanism for the formation of polyfunctionalised pyridines.