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Selective one-pot multicomponent synthesis and anti-tubercular evaluation of 5-(aryl/cyclohexylsulfanyl)-2-alkoxy-4,6-diarylnicotinonitriles

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ABSTRACT

A new set of highly substituted pyridine derivatives has been synthesized by a product selective four component reaction of aryl aldehyde, malononitrile and 2-aryl/cyclohexylsulfanyl-1-aryl-1-ethanones in presence of sodium hydroxide in methyl/ethyl alcohol. Among the compounds, 4,6-bis(4-chlorophenyl)-5-[(4-chlorophenyl)sulfanyl]-2-methoxynicotinonitrile (**4n**) inhibited *Mycobacterium tuberculosis* (MTB) with minimum inhibitory concentration (MIC) of 3.1 μM and was more potent than ethambutol and pyrazinamide.

Tuberculosis (TB) is an ancient infectious disease of global influence, re-emerged with multi-drug resistant strains (MDR-TB) and acquired immune deficiency syndrome (AIDS). According to World Health Organization (WHO), one third of the world's populations are infected with *Mycobacterium tuberculosis* (MTB) and it is predicted that more new TB cases will occur worldwide.[1,2] Furthermore, it has been more than 40 years since a new drug for TB was discovered. Therefore, it is an imperative need to develop novel anti-tubercular drugs that can be equally effective against MTB and MDR-TB, and shorten the duration of therapy. The anti-tubercular activity of pyridine containing compounds is being investigated from early days. In our earlier works, we have reported various 4-pyridinecarboxylic acid hydrazides, some of which were found to be most potent with a minimum inhibitory concentration (MIC) of 0.49 μM against MTB and isoniazide-resistant MTB.[3] We have also reported various pyridylthiourea compounds endowed with high activity toward MDR-TB.[4] In continuation of work on pyridine derivatives, herewith we are reporting the synthesis of novel poly substituted pyridines by product selective one-pot multicomponent synthesis and their anti-tubercular activities.

The reaction of malononitrile and arylaldehyde with ketone having active methylene group is interesting as the course of this multicomponent reaction is normally decided by different factors, mainly the solvent polarity. The product may be either an oxygen heterocycle or a nitrogen heterocycle or even a carbocyclic system. It has been shown that the reaction of $RCOCH_2R'$ in presence of Vilsmeier's reagent followed by malononitrile treatment gives a 3-cyanopyridine derivative.[5] A 1,3-diketone reacts with arylaldehyde and malononitrile in the presence of quaternary ammonium salt giving a tetrahydrobenzopyran derivative.[6] Similar reaction with a β-ketoester has been shown to yield two products, a pyran derivative and a piperidone derivative.[7] A microwave initiated reaction of the above type in presence of ionic liquid has found to yield only pyran system selectively with excellent yield.[8] 6-Methoxytetralone undergoes condensation with malononitrile and aromatic aldehyde in presence of sodium methoxide to give a pyridine derivative. It is to be noted that the methoxy group has been incorporated as a substituent in the pyridyl ring.[9,10] However, when piperidine or sodium hydroxide is used in DMF, instead of sodium methoxide in methanol, the pyran ring is generated. It is interesting to note that this multicomponent reaction leads to carbocyclic rings also. Thus when the reaction was carried out in the presence of triethylamine and alumina, a benzene ring with cyano and amino substituents is created.[11] Formation of pyran[12,13] as well as pyridine ring system[12,14] from this approach seems to be facile - the solvent, base used and the other conditions determining the outcome of the reaction.

Having realized that the multicomponent reaction of malononitrile, arylaldehyde and appropriate ketone leads to a variety of products, it has been planned to carry out one such reaction with a ketone with arylthio group in the α-position of the ketone. The identified

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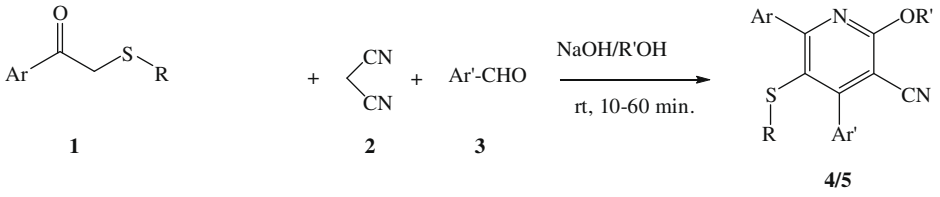
substrates, 2-aryl/cyclcohexylsulfanyl-1-aryl-1-ethanones **1**, have been prepared from substituted phenacyl bromides and aryl/cyclohexylthiols. All the compounds of the series **1**, except 1-(4-chlorophenyl)-2-[(4-methoxyphenyl)sulfanyl]-1-ethanone, have been reported in the literature.[15–22]

An equimolar mixture of ketone **1**, malononitrile **2**, arylaldehyde **3** and sodium hydroxide, was stirred at room temperature in the presence of in ethanol/methanol. The reaction proceeds smoothly taking 10–60 min for completion as revealed by TLC studies. Only one product was obtained quantitatively in all the cases. The product after column purification, has been characterized as a highly substituted pyridine derivative, 5-[aryl/cyclohexylsulfanyl]-2-alkoxy-4,6-diarylnicotinonitrile **4/5**[23] vide infra (Scheme 1). The compounds **4a–p** have arylthio group in the 5-position, while compounds **5a–n** have cyclohexylthio group in that position.

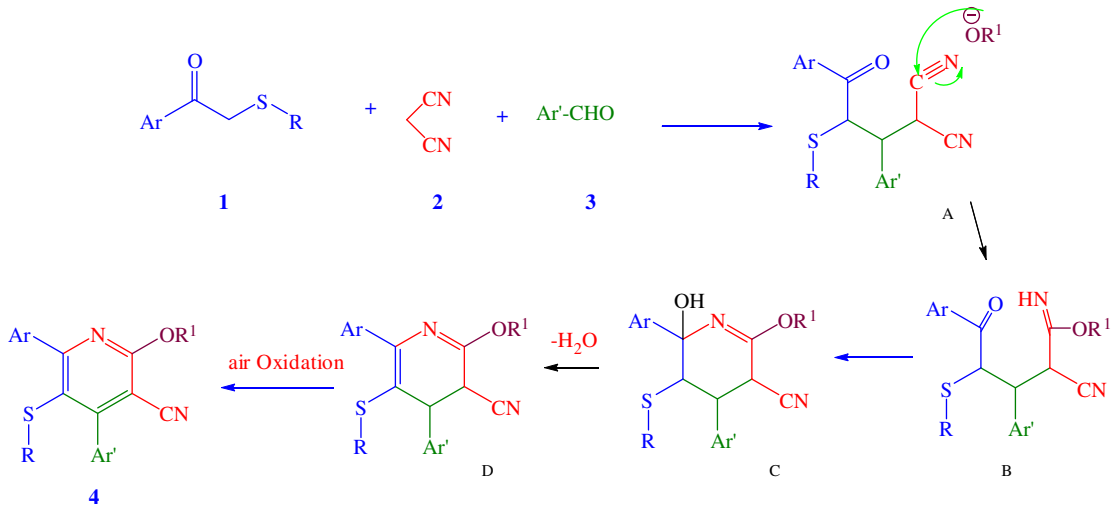
The ^{1}H NMR spectrum of **4m** has three pairs of doublets in the aromatic region, each accounting for two hydrogens, indicating the presence of three *para* substituted aryl rings. Singlets at 3.00 and 4.10 ppm, the former accounting for six hydrogens of the *N*,*N*-dimethylamino group and the latter probably for a methoxy group as it accounts for three hydrogens, are the other signals present. The ^{13}C NMR spectrum also has signals for *N*,*N*-dimethylamino group and methoxy group. Apart from the carbons identified to be those due to the three aryl rings, the presence of six other quaternary carbons (DEPT 135) are noticed in the spectrum. The H,H-COSY spectrum helps to identify the coupling pairs in the three aryl systems. The signals at 6.55 and 6.97 ppm are due to the *p*-*N*,*N*-dimethylaminophenyl ring hydrogens. The doublets at 6.67 and 7.19 and 7.33 and 7.54 ppm are the other partners. The HMBC spectrum helps to identify the *ipso* carbons to *N*,*N*-dimethylamino and methoxy groups, 150.9 and 163.8 ppm, respectively. The carbon at 150.9 ppm gives a contour with the hydrogens at 6.97 ppm confirming the latter hydrogens to be that of the *N*,*N*-dimethylaminophenyl ring. The C,H-COSY spectrum is useful to identify the carbon at 111.1 ppm to be that *ortho* to *N*,*N*-dimethylamino group. The spectral features hence support the proposed structure for **4/5**.

The mechanism for the formation of **4/5** in the above reaction is given in Scheme 2**.** It can be seen that only one product in good yield is obtained, even though there are other possible product formations. The reason for the preferential formation of pyridine derivative rather than pyran derivative can be accounted by the fact that the initial enolisation of **A**, which is essential to attack cyano group internally to give pyran derivative, seems to be slow. The alkoxide/alcohol present in the reaction medium is nucleophilic enough to attack the cyano group, paved the way for a pyridine nucleus.

The antimycobacterial activity of the synthesized pyridines (**4/5**) have been screened for their in vitro activity against *M. tuberculosis* H_{37}Rv (MTB) by agar dilution method for the determination of MIC in triplicates. The minimum inhibitory concentration (MIC)



Scheme 1. Synthesis of poly substituted pyridines **4/5**.



Scheme 2. The mechanism for the formation of **4/5**.

Table 1
Physical constants and anti-TB activities of poly substituted pyridines

Compd	Ar	R	Ar′	R[1]	Yield (%)	Mp (°C)	MIC (μM)
4a	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	C_6H_5	Et	92	—[a]	13.1
4b	*p*-Cl–C_6H_4	*p*-CH_3–C_6H_4	C_6H_5	Et	93	248–249	54.8
4c	*p*-Cl–C_6H_4	*p*-CH_3–C_6H_4	*p*-$N(CH_3)_2C_6H_4$	Et	90	238–239	>50.0
4d	*p*-Cl–C_6H_4	C_6H_5	*p*-$N(CH_3)_2C_6H_4$	Et	87	241–242	>51.4
4e	*p*-Cl–C_6H_4	*p*-CH_3–C_6H_4	*p*-Cl–C_6H_4	Et	92	158–159	25.5
4f	*p*-Cl–C_6H_4	C_6H_5	*p*-Cl–C_6H_4	Et	90	143–144	26.2
4g	*p*-OCH_3–C_6H_4	*p*-Cl–C_6H_4	*p*-$N(CH_3)_2C_6H_4$	Et	88	136–137	24.2
4h	*p*-Cl–C_6H_4	*p*-CH_3–C_6H_4	*p*-OCH_3–C_6H_4	Et	85	98–99	51.3
4i	*p*-Cl–C_6H_4	*p*-OCH_3–C_6H_4	*p*-$N(CH_3)_2C_6H_4$	Et	87	80–81	48.5
4j	*p*-Br–C_6H_4	*p*-Cl–C_6H_4	*p*-$N(CH_3)_2C_6H_4$	Et	82	110–111	5.6
4k	C_6H_5	*p*-Cl–C_6H_4	*p*-$N(CH_3)_2C_6H_4$	Me	90	114–115	26.5
4l	C_6H_5	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	Me	90	124–125	27.0
4m	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	*p*-$N(CH_3)_2C_6H_4$	Me	91	103–104	12.4
4n	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	Me	92	225–226	3.1
4o	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	*p*-OCH_3–C_6H_4	Me	92	144–145	25.4
4p	*p*-Cl–C_6H_4	*p*-Cl–C_6H_4	C_6H_5	Me	89	93–94	27.1
5a	C_6H_5	C_6H_{11}	C_6H_5	Et	94	—[a]	25.0
5b	*p*-Cl–C_6H_4	C_6H_{11}	C_6H_5	Et	92	152–153	27.8
5c	*p*-NO_2–C_6H_4	C_6H_{11}	C_6H_5	Et	95	84–85	6.8
5d	*p*-NO_2–C_6H_4	C_6H_{11}	*p*-$N(CH_3)_2C_6H_4$	Et	98	171–172	12.5
5e	*p*-Cl–C_6H_4	C_6H_{11}	*p*-$N(CH_3)_2C_6H_4$	Et	99	151–152	25.4
5f	*p*-Cl–C_6H_4	C_6H_{11}	*p*-Cl–C_6H_4	Et	94	161–162	6.5
5g	*p*-CH_3–C_6H_4	C_6H_{11}	*p*-$N(CH_3)_2C_6H_4$	Et	90	149–150	26.5
5h	*p*-Cl–C_6H_4	C_6H_{11}	*p*-CH_3–C_6H_4	Et	88	155–156	27.0
5i	*p*-Cl–C_6H_4	C_6H_{11}	*p*-Cl–C_6H_4	Me	96	144–145	13.3
5j	*p*-Cl–C_6H_4	C_6H_{11}	*p*-$N(CH_3)_2C_6H_4$	Me	99	172–173	13.1
5k	*p*-Cl–C_6H_4	C_6H_{11}	*p*-OCH_3–C_6H_4	Me	99	140–141	26.9
5l	*p*-Cl–C_6H_4	C_6H_{11}	*p*-CH_3–C_6H_4	Me	99	142–143	28.0
5m	*p*-Cl–C_6H_4	C_6H_{11}	C_6H_5	Me	99	143–144	57.6
5n	*p*-Cl–C_6H_4	C_6H_{11}	*o*-Cl–C_6H_4	Me	99	255–256	13.3
Isoniazid							0.4
Ethambutol							7.6
Pyrazinamide							50.8

[a] Viscous liquid.

is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values of **4/5** along with the standard drugs for comparison are furnished in Table 1. Twenty nine compounds have been screened and the compounds showed in vitro activity against MTB with MIC ranging from 3.1 to 57.6 μM. Four compounds (**4j, 4n, 5c**, and **5f**) inhibited MTB with MIC of less than 10 μM. When compared to one of the first line anti-TB drug ethambutol (MIC 7.6 μM), four compounds, **4j, 4n, 5c**, and **5f** were found to be more potent and compound **4n** was found to be 2.4 times more active than ethambutol. When compared to pyrazinamide (MIC 50.8 μM), all the compounds, except **4b–d, 4h**, and **5m**, were found to be more potent, though all the compounds were less potent than another anti-Tb drug isoniazid. Compound 4,6-bis(4-chlorophenyl)-5-[(4-chlorophenyl) sulfanyl]-2-methoxynicotinonitrile (**4n**) inhibited MTB with MIC of 3.1 μM and was 2.4 times and 16.1 times more potent than ethambutol and pyrazinamide, respectively.

Between **5i** and **5n**, where the groups at R, Ar, and R′ are all constant and the structural change is effected only in Ar′, the activity is found to increase with electron releasing ability of the *para*-substituent. Among 5-phenyl sulfanyl derivatives (**4a**–**p**), introduction of chlorine atom in the *para* position of the phenylsulfanyl ring increases potency compared to the unsubstituted, but the introduction of a methyl or methoxy substituent has no statistically significant effect. In between methoxy and ethoxy groups at 2-position, in general, the ethoxy derivatives showed better activity in many instances (**5b** vs **5m**, **5e** vs **5j**, **4a** vs **4p**).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.025.

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23. *General procedure for the synthesis of the 6-aryl-5-[aryl/cyclohexylsulfanyl]-2-alkoxy-4-arylnicotinonitriles* (**4**/**5**): A mixture of malononitrile **2** (0.002 mol), sodium hydroxide (0.002 mol), *p*-substituted benzaldehyde **3** (0.002 mol), and 2-(aryl/cyclohexylsulfanyl)-1-aryl-1-ethanone **1** (0.002 mol) in ethanol/methanol, added in that order, was stirred for 15–60 min at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, the solidified compound was filtered and the crude mixture was purified by column chromatography using petroleum ether–ethyl acetate mixture as eluent. The product **4**/**5** was recrystallised from dichloromethane. Spectroscopic data for representative compound is given below.
6-(4-Chlorophenyl)-5-[(4-chlorophenyl)sulfanyl]-4-[4-(dimethylamino)phenyl]-2-methoxynicotinonitrile (**4m**): (Table 1, entry 13) yellow solid (dichloromethane); yield 98%; mp 103–104 °C; time 15 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 6H), 4.10 (s, 3H), 6.55 (d, J = 8.1 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.1, 54.8, 96.9, 111.1, 114.9, 120.9, 122.6, 127.9, 128.6, 129.5, 130.2, 130.8, 131.8, 135.2, 135.6, 137.8, 150.9, 162.5, 163.6, 163.8. Anal. Calcd for $C_{27}H_{21}Cl_2N_3OS$: C, 64.03; H, 4.18; N, 8.30. Found: C, 64.15; H, 4.27; N, 8.44.