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Synthesis of Antimicrobial, Amino Pyrano [2, 3-c] Pyrazolone Carbonitrile Derivatives by Thiourea Catalyzed Hetero-Cyclization Reaction

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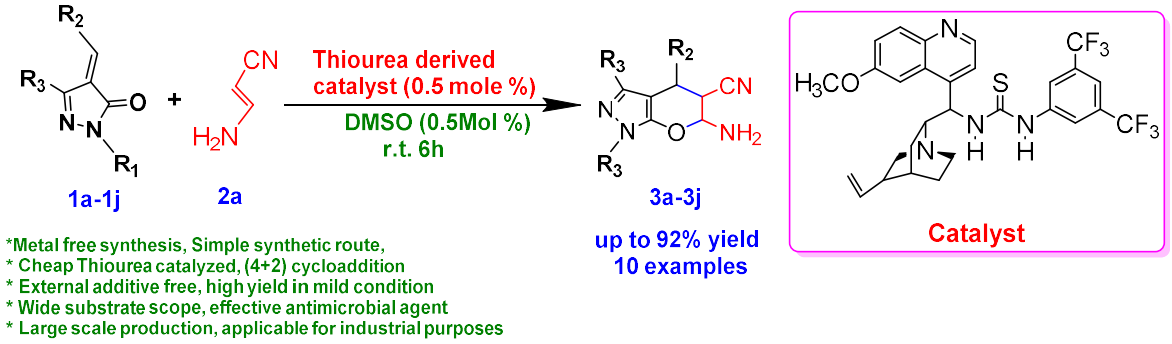
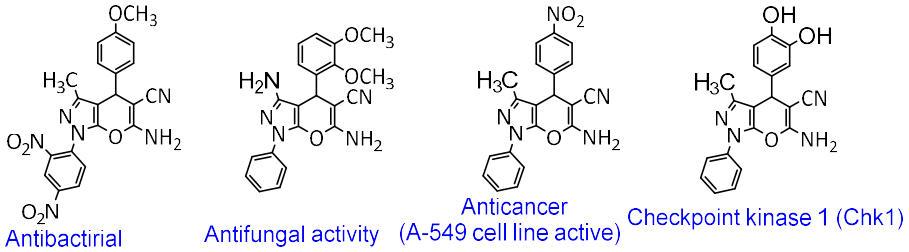
Abstract: ***Hetero Diels-Alder reaction for direct [4+2] cycloaddition between vinyl pyrazolone and conjugate amino alkene carbonitrile, catalyzed by thiourea derivatives in DMSO at room temperature gives pyrano[2, 3-c] pyrazolone derivatives. The newly synthesized compounds show antimicrobial activity against Gram positive bacteria (S. aureus and B. subtilis), Gram negative bacteria (P. aeruginosa and E. coli) and antifungal activity against fungi (A. niger).***



Keywords: Pyrano [2, 3-c] pyrazole, thiourea derivatives, Hetero cycloaddition reaction, Antimicrobial agent

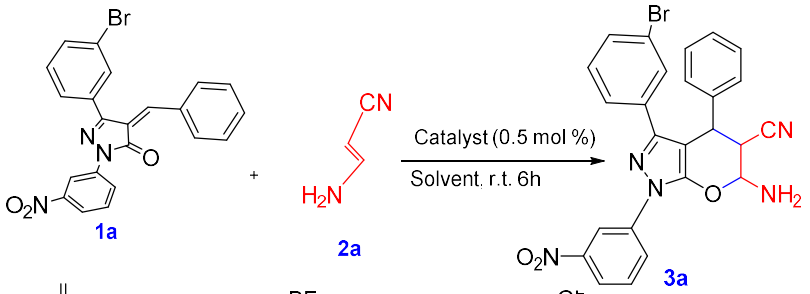
1. Introduction

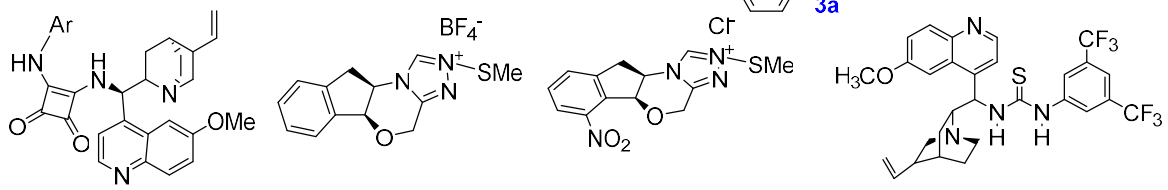
Pyrano [2, 3-C] pyrazoles are biologically active, highly important structural motifs. When we focused on their synthesis, it is observed that vinyl pyrazolone can undergo cyclization with electron deficient, multifunctional groups can be developed [1, 2, 3]. The hetero Diel-Alder reaction [4], Rauhut-Currier cycloaddition reaction [5], are reported for synthesis of such motifs. Pan group in 2023 develops a strategy for synthesis of Pyrano [2, 3-c] pyrazole through reverse electron demand [6]. Such derivatives are very effective human Chk1 kinase inhibitors [7], having good anticancer activity [8]. The substituted dihydropyrans are synthesized by thiourea catalyzed hetero-Michael cycloaddition reaction [9]. Du group synthesized multifunctional Pyrano [2, 3-C] pyrazoles [10]. Using [4+2] Cycloaddition reaction Albrecht group synthesized tetrahydropyridine derivatives [11]. Hong group reported the hemi cyclization, organocatalyzed reaction for synthesize nitro olefin derivatives of pyrano-pyrazolones [12]. These are good antimicrobial [13], NMDA receptors [14], and antitubercular [15]. In recent years tetrahydro pyrano pyrazoles are synthesized by using different pyrazolone derivatives [16-21]. Herein our interest is to introduce cyclo-addition reaction between vinyl pyrazolones and amino alkene carbonitriles.



2. Screening Catalyst and Solvent

When 0.5 mol % catalyst **I** at rt in toluene solvent was stirred for 6h it gives low yield of pyrano-pyrazole derivative obtained (up to 40%) (Table 1, entry 1). Catalyst**II** and **III** also gives poor yield in ethyl acetate (Table 1, entry 2, 3). Our study starts with catalyst **IV**with DCE, DCM, and toluene as solvents but yield was not satisfactory (Table 1, entry 4, 5, 6). Then we tried catalyst lV in DMSO solvent, it gives high yield (85%) and dr (10:1) with 95% ee, thus thiourea derivative was selected as suitable catalyst in DMSO as a solvent.





I II III IV

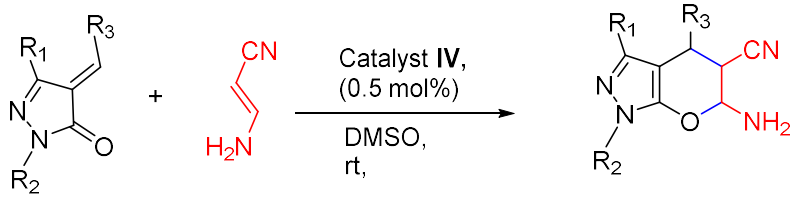
Entry	Catalyst	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	I	Toluene	40	03:1	60
2	II	EtOAc	35	05:1	40
3	III	EtOAc	39	02:1	55
4	IV	DCE	40	05:1	72
5	IV	DCM	47	06:1	65
6	IV	Toluene	59	07:1	90
7	IV	DMSO	85	10:1	95

[a]0.10 mmol 1a and 0.12 mmol 2a in 0.2 mL solvent stirred at rt. [b] Yield isolated by silica gel column chromatography. [c] Determined by ^{1}H NMR. [d] Diastereomer determined by HPLC.

3. General procedure for synthesis of pyrano-pyrazolone derivatives:

After getting suitable solvent and catalyst, proceeding forward for scope of substituted vinyl Pyrazolones and amino derivatives of alkene nitrile (table-2). When substituted vinyl Pyrazolones (0.1 mmol) and alkene derivative (0.1 mmol), catalyst lV, (0.5 mol%), were stirred in DMSO (1.0 mL) at room temperature for relevant time. The reaction mixture is monitored by TLC, after completing of reaction, the reaction mixture is flashed in column chromatography having Ether: Methyl acetate (5:2, v/v ratio) solvent, to get corresponding product (3a-3j).

Table 2. Scope of Unsaturated Pyrazolone derivatives



1 2 3

Entry[a]	Compound	R_1	R_2	R_3	Yield[b] (%)	ee[c] (%)	dr[d]
1	3a	3-BrC_6H_4	3-$NO_2C_6H_4$	Ph	92	98	20:1
2	3b	4-ClC_6H_4	Ethyl	H	90	99	12:1
3	3c	4-MeC_6H_4	Me	4-$(CF_3)C_6H_4$	50	69	10:1
4	3d	4-$(CF_3)C_6H_4$	Ethyl	Ph	50	55	05:1
5	3e	1-naphthyl	Me	H	90	65	06:1
6	3f	3-BrC_6H_4	Me	2-Ethyl-Ph	80	98	20:1
7	3g	4-BrC_6H_4	Ethyl	CF_3	90	97	12:1
8	3h	4-MeC_6H_4	Me	4-$(CF_3)C_6H_4$	60	60	10:1
9	3i	2, 4-$Me_2C_6H_4$	Ethyl	Ph	90	51	15:1
10	3j	1-naphthyl	Me	H	92	69	06:1

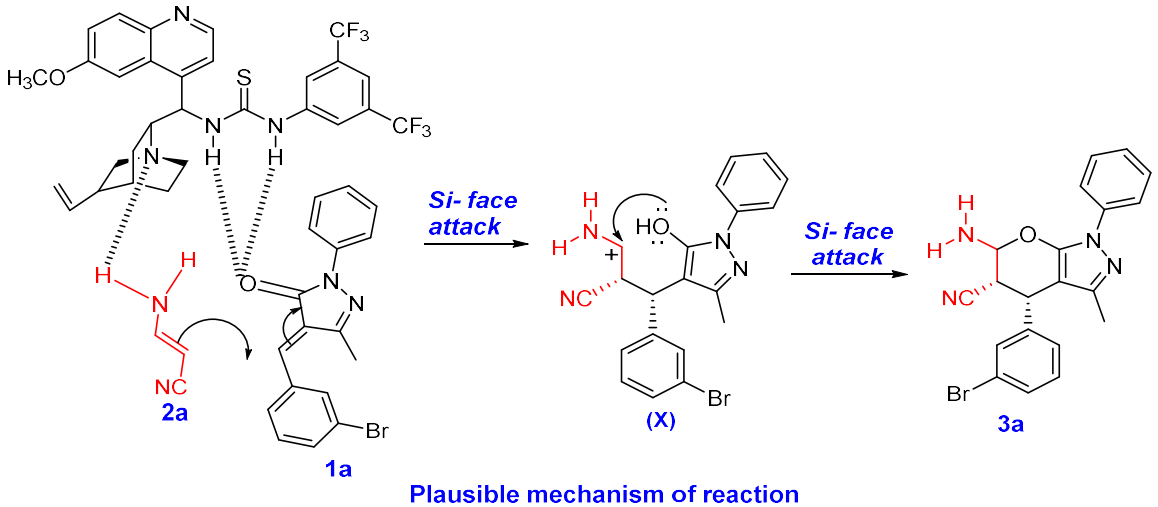
[a]0.10 mmol **(1)** and 0.1 mmol **(2)** in 0.2 mL DMSO stirred at rt. [b] Yield isolated by silica gel column chromatography. [c] Determined by ^{1}H NMR. [d] Diastereomer determined by HPLC.

4. Result and discussion

It is observed that both aliphatic and aromatic substituted pyrazolones results excellent yield with diastereomeric and enantiomeric selectivity. Reaction applied for various groups like as NO_2, Cl, CF_3, CN, (table-2 entry-1, 2, 7), shows good result. When reactions of different, Pyrazolones are applied in our laboratory, good yield of the spiro pyrazolones with some aliphatic residue obtained. Remarkably presence of p-(trifluoromethyl) phenyl groupgives very poor yield of spiro

Pyrazolones (Table-2, entry-3, 4, 8,), presence of methyl and naphthyl, ethyl phenyl derivatives on pyrazolones gives premier results (Table-2, entry-1, 5, 6, 9, 10). In this experiment relative configurations are obtained by 1H NMR spectral analysis, X-ray diffraction. Confirmational analysis is carried out by using Monte Carlo-MMFF94 (Titan 1.0.5, Wave function), 5 kcal/mol window is optimized. Frequency for harmonic vibration is calculated same level for confirmation of their stability (any imaginary frequency is not observed).

A plausible mechanism for proposed above reaction with catalyst **IV** has bifunctional moiety. The carbonyl group of pyrazolone **1a** is activated by thiourea moiety by *Re* face attackand (E)-3-aminacrylonitrile **2a** byquinuclidine moiety. The vinylogous Michael addition between amino acrylonitrile **2a** and benzylidene group of **1a** occurs from *Si* face attack, the intermediate **(X)** is formed. Finally, oxo-cyclization Michael reaction gives product **3a**.



Plausible mechanism of reaction

5. Experimental

5.1 Instruments

IR spectra, Perkin-Emer (500), Bruker-advance 400 NMR spectrometer (For ^{1}H, 400 M Hz &For ^{13}C, 100 M Hz) were used, the chemical shifts are relative to the resonance of the denatured solvent as the internal standard ($CDCl_3$, δ = 7.27 ppm for ^{1}H NMR, δ =77.10 ppm for carbon NMR). JSCO P-2000 polarimeter and HRMS were used for measurement of optical rotation. Reactions are monitored by TLC on silica gel coated plates.

Table 3: Antimicrobial examinations**:**

S.N.	Compound	Gram-positive *S. aureus*	Gram-positive *B. subtilis*	Gram-Negative *P. aeruginosa*	Gram-Negative *E. coli*	Fungi *A. Niger*
1	3a	18	18	16	18	10
2	3b	10	10	12	8	-
3	3c	-	9	9	6	10
4	3d	19	7	22	9	
5	3e	5	-	-	10	22
6	3f	16	14	9	20	20
7	3g	10	-	13	-	10
8	3h	8	-	15	9	9
9	3i	20	20	12	-	6
10	3j	-	15	20	9	17
X	Amphotericin. B	9	10	-	-	26.8
Y	Ciprofloxacin	-	-	30.2	25.8	-
Z	Amoxicillin	25.6	28.3	-	-	-

5.2 Methodology

Screening of antimicrobial activity, disc diffusion method is used [22]. Newly synthesized compounds are screened for antibacterial activity against Gram positive bacteria (*S. aureus and B. subtilis*), Gram negative bacteria (*P. aeruginosa and E. coli*) [23], and antifungal activity against fungi (*A. niger*) [24], all microbial species were isolated from infected part of host plant i.e., Potato dextrose sugar. Single spore isolation technique is used for purification of fungal culture. Synthesized Pyrazolone derivatives were dissolved in DMSO having concentration 1mg/ml. Sterilized Whatman filter paper no.1, were saturated with 15 µl of above solution. Culture plates were inoculated and incubated at 25^{0}C for 48 hrs. After observation of plates, diameter of inhibition zones was measured and tabulated.

5.2.1 Antibacterial activity: The compounds 3a, 3i, shows potent activity against *S. aureus* and *B. subtilis* having inhibition zone 18, and 20mm compared to reference drug

Amoxicillin of 25.6 and 28.3mm. Whereas 3d, 3fshows potency against *S. aureus* and 3f, 3j shows potency against *B. subtilis*. The compounds 3d, 3j, shows potent activity against *P. aeruginosa,* having inhibition zone 22, and 20nm compared to reference drug Ciprofloxacin of 30.2mm. whereas 3a, 3f shows potency against *E. coli* with inhibition zone 18, 20mm compare to reference drug Ciprofloxacin of 25.8mm.

5.2.2 Antifungal activity: The compounds 3e, 3fshows strong activity against *A. niger*, with inhibition zone of 22, 20mm compared to the reference drug Amphotericin. B of 26.8mm.

6. Characterization of products:

1) **6-amino-3-(4-bromophenyl)-1-(4-nitrophenyl)-4-phenyl-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3a):** White solid, m.p. 165–167 °C, 92% yield, [α]25 D –20.1 (c 0.5, $CHCl_3$), 98% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.66 (s, 1 H), 4.73 (br. s, 2 H), 7.25–7.38 (m, 6 H), 7.46 (t, J = 8.1 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100MHz, $CDCl_3$): 12.8, 37.5, 63.6, 98.5, 119.3, 121.3, 126.9, 127.9, 127.8, 128.7, 129.2, 137.5, 142.1, 143.5, 146.7, 158.3. HRMS (ESI) m/z calc'd for $C_{20}H_{15}BrN_4O$ [M–H]–: 327.1252, found 327.1255.
2) **6-amino-3-(4-chlorophenyl)-1-ethyl-1, 4, 5, 6-tetrahydropyrano[2, 3-c] pyrazole-5-carbonitrile (3b):** White solid, m.p. 163–166 °C, 90% yield, [α]25 D –10.3 (c 0.5, $CHCl_3$), 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.88 (s, 3 H), 4.67 (s, 1 H), 4.78 (br. s, 2 H), 7.25–7.39 (m, 6 H), 7.49 (t, J = 8.0 Hz, 2 H), 7.66 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100MHz, $CDCl_3$): 12.9, 37.6, 63.7, 98.6, 119.5, 121.2, 126.5, 127.6, 127.6, 128.6, 129.3, 137.3, 142.2, 143.6, 146.3, 158.5
3) **6-amino-1-methyl-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3c):** White solid, m.p. 153–154 ^{0}C, 50% yield, [α]25 D –6.4 (c 0.5, $CHCl_3$), 69% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (s, 3 H), 4.91 (s, 2 H), 5.27 (s, 1 H), 7.18–7.26 (m, 3 H), 7.30 (t, J = 7.6 Hz, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.64 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ12.6, 33.8, 61.8, 98.0, 118.9, 121.1, 126.7, 127.5, 128.7, 129.2, 129.8, 130.5, 133.2, 137.4, 139.1, 143.9, 146.1, 158.9.
4) **6-amino-1-ethyl-4-phenyl-3-(4-(trifluoromethyl)phenyl)-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3d):** White solid, m.p. 165–167 °C, 50% yield, [α]25 D +6.4 (c 0.5, $CHCl_3$), 55% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.64 (s, 1 H), 4.72 (br. s, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 7.2 Hz, 1 H), 7.44–7.49 (m, 4 H), 7.64 (d, J = 7.6 Hz, 2 H). 13C NMR (100.6 MHz, CDCl3): 12.9, 37.0, 63.3, 97.8, 118.8, 121.2, 121.6, 126.9, 129.3, 129.6, 132.0, 137.4, 141.1, 143.8, 146.2, 158.2.
5) **6-amino-1-methyl-3-(naphthalen-1-yl)-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3e):** White solid, m.p. 184–187 °C, 90% yield, [α]25 D –4.0 (c 0.25, CHCl3), 65% ee. ^{1}H NMR (400 MHz, DMSO-d6): 1.80 (s, 3 H), 4.97 (s, 1 H), 7.33 (t, J = 7.2 Hz, 1 H), 7.36 (s, 2 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 7.6 Hz, 3 H), 8.15 (s, 2 H). ^{13}C NMR (100MHz, DMSO-d6): 12.5, 36.1, 57.0, 97.5, 119.7, 120.0, 122.1, 122.2, 126.2, 129.2, 130.2, 134.6, 137.3, 143.9, 145.0, 145.9, 147.9, 159.6.
6) **6-amino-3-(3-bromophenyl)-4-(2-ethylphenyl)-1-methyl-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3f)s:**yellow solid, m.p. 160–165 °C, 80% yield, [α]25 D –20.1 (c 0.5, $CHCl_3$), 98% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 4.66 (s, 1 H), 4.73 (br. s, 2 H), 7.25–7.38 (m, 6 H), 7.46 (t, J = 8.1 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.8, 37.5, 63.6, 98.5, 119.3, 121.3, 126.9, 127.9, 127.8, 128.7, 129.2, 137.5, 142.1, 143.5, 146.7, 158.3. HRMS (ESI) m/z calc'd for $C_{20}H_{15}BrN_4O$ [M–H]–: 327.1252, found 327.1255
7) **6-amino-3-(4-bromophenyl)-1-ethyl-4-(trifluoromethyl)-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3g):**pale yellow solid, m.p. 163–169 °C, 90% yield, [α]25 D –10.3 (c 0.5, $CHCl_3$), 97% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.88 (s, 3 H), 4.67 (s, 1 H), 4.78 (br. s, 2 H), 7.25–7.39 (m, 6 H), 7.49 (t, J = 8.0 Hz, 2 H), 7.66 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.9, 37.6, 63.7, 98.6, 119.5, 121.2, 126.5, 127.6, 127.6, 128.6, 129.3, 137.3, 142.2, 143.6, 146.3, 158.5.
8) **6-amino-1-methyl-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)-1, 4, 5, 6tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3h):**yellow solid, m.p. 153–154 ^{0}C, 60% yield, [α]25 D –6.4 (c 0.5, $CHCl_3$), 60% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (s, 3 H), 4.91 (s, 2 H), 5.27 (s, 1 H), 7.18–7.26 (m, 3 H), 7.30 (t, J = 7.6 Hz, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.64 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ12.6, 33.8, 61.8, 98.0, 117.9, 151.1, 126.6, 127.4, 128.6, 129.3, 129.7, 130.6, 133.6, 137.3, 139.4, 141.9, 142.1, 358.8.
9) **6-amino-3-(2, 4-dimethylphenyl)-1-ethyl-4-phenyl-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3i):** White solid, m.p. 165–167 °C, 90% yield, [α]25 D +6.4 (c 0.5, $CHCl_3$), 51% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3 H), 3.64 (s, 1 H), 4.72 (br. s, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 7.2 Hz, 1 H), 7.44–7.49 (m, 4 H), 7.64 (d, J = 7.6 Hz, 2 H). 13C NMR (100.6 MHz, CDCl3): 12.9, 37.1, 63.4, 97.5, 115.8, 221.5, 121.4, 126.4, 123.3, 129.3, 132.4, 134.4, 144.1, 143.4, 146.2, 154.1.
10) **6-amino-1-methyl-3-(naphthalen-1-yl)-1, 4, 5, 6-tetrahydropyrano[2, 3-c]pyrazole-5-carbonitrile (3j): s**White solid, m.p. 184–187 °C, 92% yield, [α]25 D –4.0 (c 0.25, CHCl3), 69% ee. ^{1}H NMR (400 MHz, DMSO-d6): 1.81 (s, 3 H), 4.37 (s, 1 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.36 (s, 2 H), 7.20 (t, J = 7.6 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 7.6 Hz, 3 H), 8.15 (s, 2 H). ^{13}C NMR (100MHz, DMSO-d6): 13.5, 33.1, 56.0, 91.5, 114.7, 121.0, 124.1, 121.2, 123.2, 124.2, 131.2, 133.6, 137.3, 142.9, 145.1, 145.4, 147.3, 157.1.

7. Conclusions

Here we have developed well planned procedure for solvent selective, catalyst selective, synthesis of antimicrobial pyrano-pyrazolone, by reaction of (1a) and (2a), catalyzed

by thiourea derived catalyst in DMSO. The products are obtained in considerable yield with outstanding di stereoselectivity and enantioselectivities, having good antibacterial activity against Gram positive bacteria (*S. aureus and B. subtilis*), Gram negative bacteria (*P. aeruginosa and E. coli*), and antifungal activity against fungi *A. niger.*

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