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Synthesis of 3,4-Diylidine and N-Substituted Pyrrolidines and its Anti-Microbial Activity

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ABSTRACT

The synthesis of Nitrogen containing heterocycles particularly substituted pyrrolidines constitutes very important moieties of many biologically active molecules[1] including natural and non-natural substances. The synthesis of functionalized pyrrolidines continues to attract interest, both for their synthetic challenges,[2] and also their value in synthetic chemistry[3] and their diverse biological properties.[4] The present work includes the synthesis of substituted pyrrolidines from alkyl dihalide and primary amines by simple and efficient cyclocondensation process. This methodology gives varies of substitution pattern on 2,3-position of the pyrrolidines[5] Scheme 1. This strategy improved greener synthetic methodology and worked out as a simple and straightforward one-pot approach for the synthesis nitrogen containing heterocycle as pyrrolidines.

Keywords: Pyrrolidine, Heterocyclic compound, Dihalide.

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INTRODUCTION

The radical and cycloaddition[6] strategies have been widely used to access synthesis of substituted pyrrolidine, effective metal-mediated[7] and organocatalytic[8] ring closing strategies have been developed in recent years. Although the manipulation of pre-existing nitrogen heterocycles has been a very successful strategy to access functionalized pyrrolidin(on)es,[9] particularly starting from pyroglutamic acid[10] it has also been found that approaches based upon ring closure using radical,[11] cycloaddition,[12] Dieckman[13] and aldol[14] processes are also highly effective. It is very unusual to see amongst these cyclisation strategies, sequences which proceed via closure on nitrogen, but it had been reported some time ago that ring closure onto a nitrogen bearing a good leaving group provided rapid and direct access to pyrrolidines,[15] although interestingly this strategy has not been widely adopted; a similar strategy has recently been used to access pyrazoles[16] by ring closure. In our approach the synthesis of 3,4-diylidine substituted pyrrolidines from 1,4-dibromobutane- 2,3-dione and aromatic amines as well as the aliphatic amine by simple and efficient cyclocondensation in presence of Cesium carbonate as base in water and diglyme solvent. This methodology gives varies of substitution pattern on 2,3 positions of the pyrrolines[5] by using required primary amine Scheme 1. This strategy improved greener synthetic methodology and worked out as a simple and straightforward one-pot approach for the synthesis nitrogen containing heterocycle as substituted pyrrolidines.

MATERIALS AND METHOD

All the Chemicals used in the synthesis of the compounds were obtained from Merck, Sigma-Aldrich and were of analytical grade. Purity of the compounds was checked by Thin Layer Chromatography using silica gel as stationary phase and combination of Ethyl acetate:Petrol as mobile phase. The IR, NMR, Mass spectra of the synthesized compounds were recorded for the characterization from the University of Mumbai and Indian Institute of Technology (IIT) Mumbai and TIFR Mumbai. All the synthesized compounds were screened for their antimicrobial activities by drug diffusion method by preparing the discs of the drug.

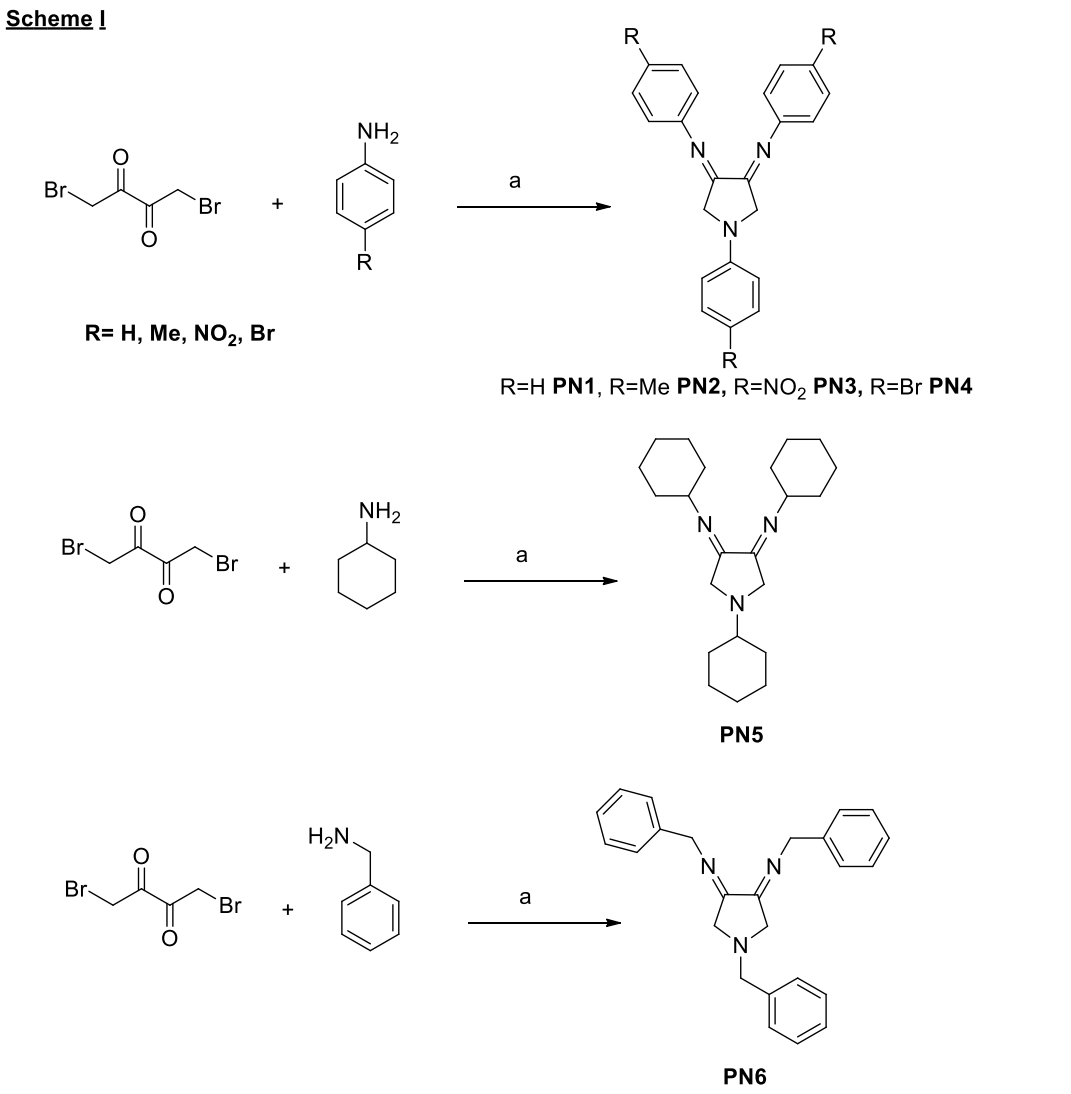

Figure 1: Nucleophilic condensation

RESULTS AND DISCUSSION

General Procedure

When dihalide (1,4-Dibromobutane-2,3-dione) (1eq.) was added to a well stirred mixture of primary amine (Aromatic and Aliphatic) (3 eq.) and Cs_2CO_3 (2 eq.) in water:diglyme (1:1) as solvent. The reaction mixture was reflux for 5 to 10hrs and reaction progress was monitored by TLC. Reaction mixture was pour in to water and product was extracted by ethyl acetate and dried over brine and anhydrous Na_2SO_4, concentration of the organic layer gave the crude product, which was purified by Column chromatography (eluting with ethyl acetate: petrol) to afford the product as substituted pyrrolidines.

Synthesis of N,N'-(1-phenylpyrrolidine-3,4-diylidene)dianiline, PN1(scheme 1)

A mixture of 1,4-Dibromobutane-2,3-dione 1.0g (4.1 mmol), distilled aniline 1.2g (12.3 mmol) and cesium carbonate 1.6g (8.2 mmol) in water:diglyme was refluxed for 5hrs and the reaction progress was monitored by TLC. After completion of reaction the product PN1 was obtained by chromatography purification.

PN1compound, Yield = (890mg, 67% as pale yellow colored) **IR (KBr):** 1620 cm^{-1} (N=C), 2979 cm^{-1} (C-H), 1230 cm^{-1} (C-N), 1450-1600 cm^{-1}, 3070 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 3.4 (s, 4H, C_2 and C_5 -CH_2), δ 6.8, δ 6.9, δ 7.0, δ 7.3, δ 7.5 (m, 15ArH). **^{13}C NMR :** δ 54, δ 111, δ 119, δ 121, δ 128, δ 129, δ 130, δ 147, δ 152, δ 159. **Mass m/z = $C_{22}H_{19}N_3^+$,** HRMS (ESI+) 325.1476.

Synthesis of N,N'-(1-(p-tolyl)pyrrolidine-3,4-diylidene)bis(4-methylaniline), PN2

A mixture of 1,4-Dibromobutane-2,3-dione 1.0g (4.1 mmol), p-toluidine 1.3g (12.3 mmol) and cesium carbonate 1.6g (8.2 mmol) in water:diglyme was refluxed for 5hrs and the reaction progress was monitored by TLC. After completion of reaction the product **PN2** was obtained by chromatography purification.

PN2 compound, Yield = (1.1g, 73% as pale yellow colored) **IR (KBr):** 1624 cm^{-1} (N=C), 2985 cm^{-1} (C-H), 1200 cm^{-1} (C-N), 1400-1600 cm^{-1}, 3050 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 2.4, (s, 9H, $3CH_3$), δ 3.4 (s, 4H, C_2 and C_5 -CH_2), δ 6.7, δ 7.1, δ 7.3, δ 7.4 (d, J 7.4Hz, 12ArH). **^{13}C NMR:** δ 22, δ 54, δ 113, δ 122, δ 130, δ 131, δ 137, δ 144, δ 148, δ 159. **Mass m/z = $C_{25}H_{25}N_3^+$,** HRMS (ESI^+) 367.1174.

Synthesis of N, N'-(1-(4-nitrophenyl)pyrrolidine-3,4-diylidene)bis(4-nitroaniline), PN3

A mixture of 1,4-Dibromobutane-2,3-dione 1.0g (4.1 mmol), p-Nitroaniline 1.7g (12.3 mmol) and cesium carbonate 1.6g (8.2 mmol) in water:diglyme was refluxed for 5hrs and the reaction progress was monitored by TLC. After completion of reaction the product **PN3** was obtained by chromatography purification.

PN3 compound, Yield = (800mg, 42% as yellow semisolid) **IR (KBr):** 1640 cm^{-1} (N=C), 2980 cm^{-1} (C-H), 1210 cm^{-1} (C-N), 1390, 1560 cm^{-1} (-NO_2), 1400-1600 cm^{-1}, 3050 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 3.4 (s, 4H, C_2 and C_5 -CH_2), δ 6.9, δ 7.0, δ 8.0, δ 8.1 (d, J=7.3Hz, 12ArH). **^{13}C NMR :** δ 54, δ 112, δ 123, δ 125, δ 126, δ 138, δ 147, δ 154, δ 159. **Mass m/z = $C_{22}H_{16}N_6O_6^+$,** HRMS (ESI^+) 460.1072.

Synthesis of N, N'-(1-(4-bromophenyl)pyrrolidine-3,4-diylidene)bis(4-bromoaniline), PN4

A mixture of 1,4-Dibromobutane-2,3-dione 1.0g (4.1 mmol), p-Bromoaniline 2.1g (12.3 mmol) and cesium carbonate 1.6g (8.2 mmol) in water:diglyme was refluxed for 5hrs and the reaction progress was monitored by TLC. After completion of reaction the product **PN4** was obtained by chromatography purification.

PN4 compound, Yield = (1.3g, 57% as semisolid) **IR (KBr):** 1644 cm^{-1} (N=C), 2985 cm^{-1} (C-H), 1215 cm^{-1} (C-N), 1400-1600 cm^{-1}, 3075 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 3.4 (s, 4H, C_2 and C_5 -CH_2), δ 6.7, δ 7.3, δ 7.4, δ 7.7 (d, J=7.5Hz, 12ArH). **^{13}C NMR :** δ 54, δ 116, δ 117, δ 122, δ 123, δ 132, δ 133, δ 146, δ 151, δ 159. **Mass m/z = $C_{22}H_{16}Br_3N_3^+$,** HRMS (ESI^+) 562.1132.

Synthesis of N,N'-(1-cyclohexylpyrrolidine-3,4-diylidene) dicyclohexanamine, PN5

A mixture of 1,4-Dibromobutane-2,3-dione 1.0g (4.1 mmol), p-Bromoaniline 1.2g (12.3 mmol) and cesium carbonate 1.6g (8.2 mmol) in water:diglyme was refluxed for 5hrs and the reaction progress was monitored by TLC. After completion of reaction the product **PN5** was obtained by chromatography purification.

PN5 compound, Yield = (900mg, 64% as colorless liquid) **IR (KBr):** 1630 cm^{-1} (N=C), 2985, 2964 cm^{-1} (C-H), 1215 cm^{-1} (C-N). **^{1}H NMR:** δ 1.1- δ 1.2 (CH_2), δ 1.4- δ 1.5 (CH_2), δ 1.4-1.6 (CH_2), δ 1.5-1.7 (CH_2), δ 1.7-1.9 (CH_2), δ 2.4 (s, 4H, C_2 and C_5 -CH_2), δ 2.6 (CH), δ 4.9 (CH). **^{13}C NMR:** δ 24, δ 25, δ 26, δ 32, δ 33, δ 51, δ 56, δ 71, δ 158. **Mass m/z = $C_{22}H_{37}N_3^+$,** HRMS (ESI^+) 343.1592.

Synthesis of N, N'-(1-benzylpyrrolidine-3,4-diylidene)bis(1-phenylmethanamine), PN6

A mixture of 1,4-Dibromobutane-2,3-dione 1.0g (4.1 mmol), p-toluidine 1.3g (12.3 mmol) and cesium carbonate 1.6g (8.2 mmol) in water:diglyme was refluxed for 5hrs and the reaction progress was monitored by TLC. After completion of reaction the product **PN6** was obtained by chromatography purification.

PN6 compound, Yield = (1.3g, 80% as pale yellow colored) **IR (KBr):** 1622 cm^{-1} (N=C), 2980 cm^{-1} (C-H), 1220 cm^{-1} (C-N), 1400-1600 cm^{-1}, 3060 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 2.4 (s, 4H, C_2 and C_5 -CH_2), δ 2.7 ($2CH_2N$), δ 3.7 (CH_2N), δ 7.2-7.5 (m, 15ArH). **^{13}C NMR :** δ 53, δ **6**4, δ 126, δ 127, δ 128, δ 129, δ 130, δ 132, δ 139, δ 158. **Mass m/z = $C_{25}H_{25}N_3^+$,** HRMS (ESI^+) 367.1204.

Antimicrobial Activity

The all synthesized substituted pyrrolidines including PN1, PN2, PN3, PN4, PN5, PN6 were tested for their antimicrobial activities[17] by drug diffusion method by preparing the discs of the drug. The activity was tested with *Staphylococcus aureus* (Gram positive), *Salmonella typhi* and *Escherichia coli* (Gram negative) bacterial strains taking Streptomycin, Ciprofloxacin and Cloxacillin as standard drugs. Further all antimicrobially active compounds were tested to find their minimal inhibitory concentration (MIC); using (50 µg/ml), (100µg/ml), (150µg/ml), (200µg/ml) concentrations.

Table 1: Antibacterial activity of compounds PN1, PN2, PN3, PN4, PN5, PN6.

Compd No.	Zone of inhibition in mm											
	E. coli				***S. typhi***				***S. aureus***			
	50 µg	**100 µg**	**150 µg**	**200 µg**	**50 µg**	**100 µg**	**150 µg**	**200 µg**	**50 µg**	**100 µg**	**150 µg**	**200 µg**
PN1	13	16	18	22	10	12	15	16	09	12	16	18
PN2	14	15	17	19	11	12	16	18	10	14	17	18
PN3	15	17	20	27	10	12	14	19	12	13	17	19
PN4	14	18	20	28	11	14	17	20	11	13	16	19
PN5	12	14	17	22	10	13	15	18	10	13	15	19
PN6	13	17	19	24	10	14	16	19	10	13	14	17

Disc size: 6.35 mm; standard: streptomycin; control: DMSO; duration: 24 h. resistant (< 11 mm), intermediate (14 mm), sensitive (>15 mm).

CONCLUSION

This is the efficient one pot greener synthesis of the substituted pyrrolidines and the antibacterial screening data concluded that the all compounds **PN1-PN6** showed activity against gram negative microorganisms as well as gram positive organisms. The compounds having the nitro- and bromo- as substituent showed little more activity as compared to the other. The zones of inhibition were found to at 28 mm, 20 mm and 19 mm as the highest inhibition zone against *E. coli, S.typhi and S. aureus* with concentration 200 µg.

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