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Synthesis of Highly Substituted Pyrrolidines via Double Michael Addition Reaction and its Anti-Microbial Activity

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ABSTRACT

The synthesis of Nitrogen base heterocycles particularly highly substituted pyrrolidines are very important skeleton of many biologically active molecules[1] including natural and non-natural substances. The synthesis of functionalized pyrrolidines persists to attract interest, both for their synthetic challenges,[2] and also their value in synthetic chemistry[3] and their diverse biological activity.[4] The present work includes the synthesis of highly substituted pyrrolidines through double Michael addition reaction of acetylene carboxylate with substituted malonate and amine in one pot results into the cyclisation. This methodology gives substitution pattern on 2, 2, 3,3,5-position of the pyrrolidines Scheme 1 and 3. This strategy is very simple and efficient to have highly substituted nitrogen containing heterocycle as pyrrolidines.

Keywords: Pyrrolidine, Heterocyclic compound, amino acid.

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INTRODUCTION

The radical and cycloaddition[5] strategies have been broadly used to have synthesis of substituted pyrrolidine, activated metal-mediated[6] and organocatalytic[7] ring closing strategies have been reported in the recent years. There are many examples of pre-existing nitrogen heterocycles has been a very successful way to functionalized pyrrolidin(on)es,[8] particularly starting from pyroglutamic acid[9] it has also been reported that approaches based upon ring closure using radical,[10] cycloaddition,[11] Dieckman[12] and aldol[13] 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,[14] although interestingly this strategy has not been widely adopted; a similar strategy has recently been used to access pyrazoles[15] by ring closure.

In our approach ethanolamine was converted into tosylated ethanolamine **2a** by treating excess of tosyl chloride, which on nucleophilic substitution with diethylmalonate in presence of carbonate base results into the compound **3a** as alkylated malonate[16]. The compound **3a** having tosylated amine with activated proton undergoes the Michael Addition reaction with methylacetylene carboxylate in ethanol-water[17] give the product **4a** which further undergoes intra molecular Michael addition reaction leads to cyclization to the highly functionalized pyrrolidines **5a**, the yield increase when carbonate base was added separately in DCM as solvent (scheme 1). It was also proved that alkylated malonate **3a** on condensation with formaldehyde in presence of carbonate base gives cyclized product as pyrrolidine **6a** (scheme 2).

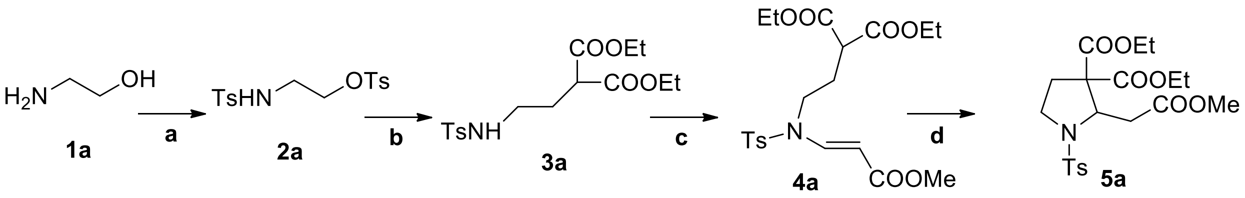
The same strategy was employed to amino as serine (scheme 3), where in serine methyl ester was prepared by stirring serine in methanol and HCl, and the same was protected by Boc- anhydride[18] to give as **9a**, subsequently it was treated with tosyl chloride and hydroxyl group become more labile towards substitution with iodide as nucleophile, which on alkylation with diethylmalonate to gives compound **12a** as the desired one for the double Michael addition reaction to give as highly substituted pyrrolidines **13a** and **14a** (scheme 3) with methylacetylenecarboxylate and dimethyl acetylenecarboxylate respectively. In the same course of reaction as cyclisation through the double Michael addition reaction the deprotection of Boc[19] also take place.

This methodology gives varies of substitution pattern on 2,3,5 positions of the pyrrolidines and simple and straightforward one-pot approach as through double Michael addition reaction.

MATERIALS AND METHOD

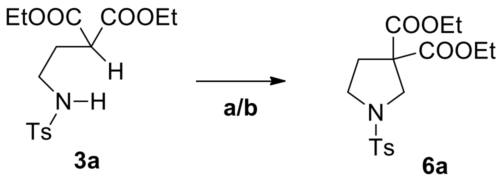
All the Chemicals used in the synthesis of the compounds were obtained from Merck, Sigma-Aldrich and were of analytical grade. Purity of the compounds was checked by Thin Layer Chromatography using silica gel as stationary phase and combination of Ethyl acetate: Petrol as mobile phase. The IR, NMR, Mass 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.

Scheme 1



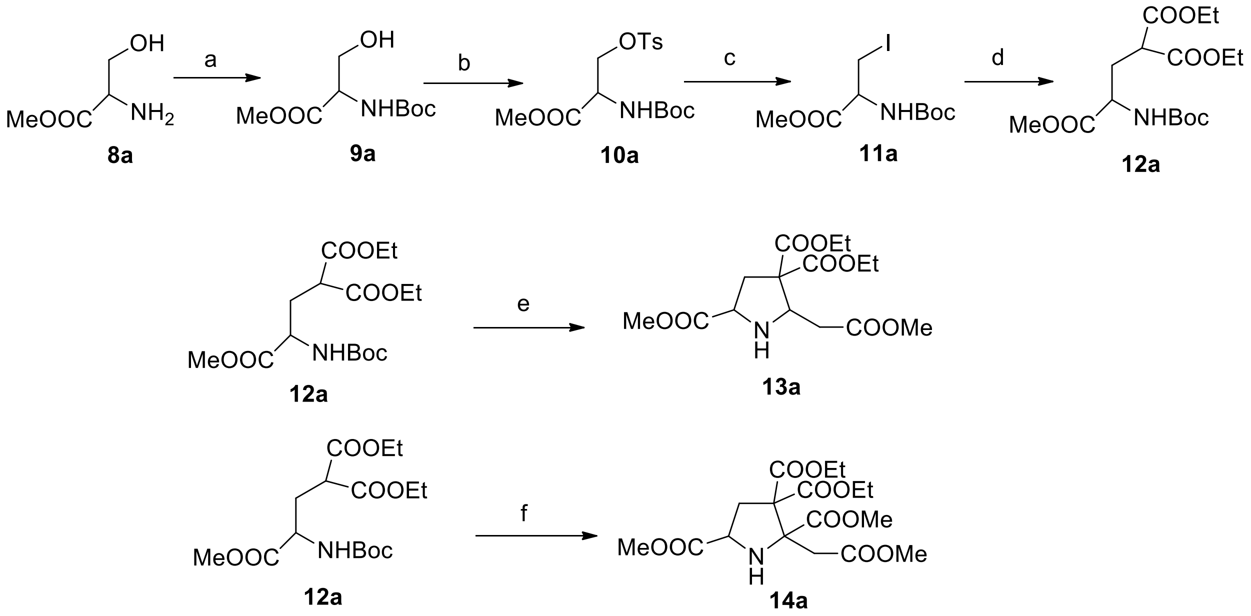
Reagent and Conditions:- a) TsCl, Et_3N, DCM, rt, 12hrs. 83% b) DEM, Dioxane, K_2CO_3, reflux 24hrs 69%. c) Methyl acetylenecarboxylate,Ethanol-Water, reflux, 12hrs, 45% d) K_2CO_3, DCM, reflux, 12hrs, 47%.

Scheme 2



Reagent and Conditions:- a) HCHO, K_2CO_3, DCM, rt, 2 days. 33%, b)HCHO, CS_2CO_3, DCM, rt, 2 days. 24%

Scheme 3



Reagent and Conditions:- a) Boc_2O in water 82% b) TsCl, Et_3N, DCM, rt, 12hrs. 53%. c) NaI in Acetone reflux 12-18hrs 67% d) DEM, K_2CO_3, DCM, reflux,12hrs, 58% e) Methyl acetylenecarboxylate, K_2CO_3, Ethanol-Water, reflux, 12hrs, 37% f) Dimethyl acetylenecarboxylate, K_2CO_3, Ethanol-Water, reflux, 12hrs, 30%.

RESULTS AND DISCUSSION

General Procedure:

Synthesis of 3a, 12a

In a stirring solution of tosylated (2a) or halide (11a) (1eq.) in DCM was added diethyl malonate (1.2 eq.) and K_2CO_3 (2 eq.), the reaction mixture was reflux for 12hrs 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 Michel adduct (3a, 12a).

Synthesis of 4a (Scheme 1)

A mixture of tosylated anime **3a** 1.0g (2.80 mmol) and methyl acetylenecarboxylate 352mg (4.20) mmol) in 10ml ethanol-water was refluxed for 12hrs, the reaction progress was monitored by TLC. After completion of reaction the product **4a** was obtained by chromatography purification.

4a compound, Yield = (550mg, 45%) **IR (KBr):** 2980 cm^{-1} (C-H), 1734 cm^{-1} (CO), 1210 cm^{-1} (C-O), 1450-1600 cm^{-1}, 3080 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 1.1 CH_3, δ 1.9 CH_2, δ 2.3 CH_3Ar, δ 3.2 CH_2, δ 3.3 CH, δ 3.8 O-CH_3, δ 4.1 O-CH_2, δ 4.8 CH, δ 6.8 CH, δ 7.4, 7.7 ArH. **^{13}C NMR :** δ

14, δ 21, δ 23, δ 49, δ 50, δ 61, δ 113, δ 128, δ 129, δ 133, δ 137, δ 149, δ 167, δ 169. **Mass m/z = $C_{20}H_{27}NO_8S^+$,** HRMS (ESI+) 441.1576.

Synthesis of 5a (Scheme 1)

The mixture of adduct **4a** 200mg (0.45 mmol) and anhydrous K_2CO_3 125mg (0.90 mmol) in 4ml DCM was refluxed for 12hrs and the reaction progress was monitored by TLC. After completion of reaction the product **5a** was obtained by chromatography purification.

5a compound, Yield = (94mg, 47%) **IR (KBr):** 2980 cm^{-1}(C-H), 1730-1750 cm^{-1} (CO), 1210 cm^{-1} (C-O), 3080 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 1.1 CH_3, δ 2.2, 2.4 CH_2, δ 2.3 CH_3Ar, δ 2.7, 2.8 CH_2, δ 3.7 O-CH_3, δ 4.1 O-CH_2, δ 4.6 CH, δ 7.4, 7.7 ArH. **^{13}C NMR :** δ 14, δ 20, δ 21, δ 32, δ 51, δ 52, δ 54, δ 62, δ 128, δ 129, δ 137, δ 143, δ 172, δ 173. **Mass m/z = $C_{20}H_{27}NO_8S^+$,** HRMS (ESI+) 441.1466.

Synthesis of 6a (Scheme 2)

A mixture of **3a** 100mg (0.28 mmol), formaldehyde 50mg (1.4 mmol) and anhydrous Cesium Carbonate 280mg (0.84mmol) or anhydrous K_2CO_3 115mg (0.84 mmol) in 3ml dry Dichloromethane was refluxed for 2 days and the reaction progress was monitored by TLC. After completion of reaction the product 6**a** was obtained by chromatography purification.

6a compound, Yield = (24mg, 24%) **IR (KBr):** 2980 cm^{-1}(C-H), 1735-1750 cm^{-1} (CO), 1210 cm^{-1} (C-O), 3080 cm^{-1} Aromatic ring. **^{1}H NMR :** δ 1.2 CH_3, δ 2.2 CH_2, δ 2.3 CH_3Ar, δ 3.3 CH_2, δ 3.9 CH_2, δ 4.2 O-CH_2, δ 7.4, 7.7 ArH. **^{13}C NMR :** δ 14, δ 21, δ 23, δ 46, δ 51, δ 54, δ 61, δ 128, δ 129, δ 138, δ 144, δ 171. **Mass m/z = $C_{17}H_{23}NO_6S^+$,** HRMS (ESI+) 369.1357.

Synthesis of 12a (Scheme 3)

A mixture of compound **11a** 1.2g (3.64 mmol) prepared by series of reaction as shown in (scheme 3), diethylmalonate 0.7ml (4.37 mmol) and anhydrous K_2CO_3 1.0g (7.28 mmol) in 10ml dry dichloromethane was refluxed for 12hrs and the reaction progress was monitored by TLC. After completion of reaction the product **12a** was obtained by chromatography purification.

12a compound, Yield = (760mg, 58%) **IR (KBr):** 3350 cm^{-1}, 2980 cm^{-1} (C-H), 1730-1750 cm^{-1} (CO), 1215 cm^{-1} (C-O). **^{1}H NMR :** δ 1.1 CH_3, δ 1.3 *t*-Bu, δ 2.6 CH_2, δ 3.3 CH, δ 3.6 OCH_3, δ 4.2 OCH_2, δ 4.5CH, δ 5.9 NH. **^{13}C NMR :** δ 14, δ 26, δ 28, δ 46, δ 54, δ 61, δ 79, δ 155, δ 169, δ 172. **Mass m/z = $C_{16}H_{27}NO_8^+$,** HRMS (ESI+) 361.1758.

Synthesis of 13a (Scheme 3)

A mixture of compound **12a** 100mg (0.28 mmol), methyl acetylenecarboxylate 35mg (0.42 mmol) and K_2CO_3 115mg (0.84 mmol) in solvent Ethanol:water was refluxed for 12hrs and the reaction progress was monitored by TLC. After completion of reaction the product **13a** was obtained by chromatography purification.

13a compound, Yield = (35mg, 37%) **IR (KBr):** 3450 cm^{-1} (NH), 2980, 2960 cm^{-1} (C-H), 1735, 1740, 1745 cm^{-1}, 1210 cm^{-1} (C-O). **^{1}H NMR :** δ 1.1(CH_3), δ 2.4 (CH_2), δ 2.5(NH), δ 2.6-2.8 (CH_2), δ 3.5 (CH), δ 3.7 (OCH_3), δ 4.1 (O-CH_2), δ 4.7 (CH). **^{13}C NMR :** δ 14, δ 23, δ 36, δ 49, δ 52, δ 53, δ 56, δ 62, δ 171, δ 174, δ 175. **Mass m/z = $C_{15}H_{23}NO_8^+$,** HRMS (ESI^+) 345.1478.

Synthesis of 14a (Scheme 3)

A mixture of compound **12a** 100mg (0.28 mmol), dimethyl acetylenecarboxylate 60mg (0.42 mmol) and K_2CO_3 115mg (0.84 mmol) in solvent Ethanol:water was refluxed for 12hrs and the reaction progress was monitored by TLC. After completion of reaction the product **14a** was obtained by chromatography purification.

14a compound, Yield = (33mg, 30%) **IR (KBr):** 3460 cm^{-1} (NH), 2980, 2960 cm^{-1} (C-H), 1735, 1740, 1745 cm^{-1}, 1220 cm^{-1} (C-O). **^{1}H NMR :** δ 1.2(CH_3), δ 2.4 (NH), δ 2.5, 2.6 (CH_2), δ 2.8-2.9 (CH_2), δ 3.5 (CH), δ 3.7 (OCH_3), δ 4.1 (O-CH_2). **^{13}C NMR :** δ 14, δ 20, δ 33, δ 50, δ 52, δ 53, δ 56, δ 63, δ 171, δ 173, δ 175. **Mass m/z = $C_{17}H_{25}NO_{10}^+$,** HRMS (ESI^+) 403.2576.

ANTIMICROBIAL ACTIVITY

The all synthesized substituted pyrrolidines including 5a, 6a, 13a and 14a were tested for their antimicrobial activities[20] 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
5a	13	18	20	23	14	15	22	23	12	18	20	22
6a	15	18	23	25	12	16	22	24	15	21	22	24
13a	16	20	22	28	14	16	21	26	18	20	21	30
14a	18	21	25	27	11	15	19	28	19	20	23	28

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

CONCLUSION

This methodology gives access to highly substituted pyrrolidines and the antibacterial screening data concluded that the compounds 5a, 6a, 13a and 14a showed activity against gram negative microorganisms as well as gram positive organisms. The compounds having the more substituent showed little more activity as compared to the other. The zones of inhibition were found to at 30 mm, 28 mm and 27 mm as the highest inhibition zone against *E. coli, S.typhi and S. aureus* with concentration 200µg.

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