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Stereoselective synthesis of oxazolidine, hexahydropyrrolo [2,1-*b*] oxazole, and tetrahydro-2*H*-oxazolo [3,2-*c*] thiazole grafted macrocycles through intramolecular 1,3-dipolar cycloaddition reaction

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ABSTRACT

A facile one-pot synthesis of oxazolidine, hexahydropyrrolooxazole and tetrahydro-2*H*-oxazolothiazole grafted macrocycles through intramolecular 1,3-dipolar cycloaddition reaction (1,3-DC reaction) is reported. X-ray diffraction studies and 2D NOESY experiments of the cycloadducts proved the stereo- and regiochemistry of the cycloaddition.

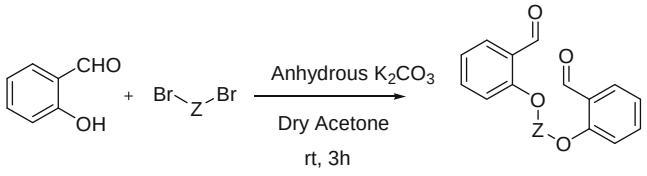
The design and synthesis of new class of macrocycles with novel shapes and heterocyclic moiety continue to be the topics of current interest,[1–3] because they can act as a ligand in asymmetric catalysis[4] and as a host molecule for the incorporation of guest molecule or ions.[5–7] New structural variants of cyclophanes are continued to be designed in search of unraveling novel stereochemical and spectral aspects associated with such molecules.1,3-DC reaction is a powerful method for the construction of five-membered heterocyclic ring system.[8] In particular, the chemistry of azomethine ylides has gained significance in recent years as it serves as an expedient route for the construction of pyrrolidine ring system.[9] Recently, our research group reported the synthesis of complex pyrrolidine, chromeno[4,3-*d*]pyrroles, pyrrolo[1,2-*c*]thiazole, and pyrrolizidine derivatives through 1,3-DC reactions,[10–12] which are found to possess significant biological activities.[13,14] In the present work synthesis of novel macrocyclic oxazolidines has been accomplished through intramolecular 1,3-DC reaction.

The literature survey revealed that there are only a few reports for the construction of oxazolidines and 1-oxapyrrolizidine[15] using carbonyl group as dipolarophiles. In continuation of our research in the field of 1,3-DC reaction, herein we report for the first time, the synthesis of oxazolidines grafted macrocycles through intramolecular [3+2] cycloaddition reaction in which aldehyde acts as a dipolarophile.

The substrates chosen for our study **1a–d** have been synthesized from salicylaldehyde in good yields[16] as shown in Scheme 1. The dialdehyde so prepared was reacted with sarcosine/L-proline/thiazolidine-4-carboxylic acid. One of the aldehydes generated the 1,3-dipole, azomethine ylide which underwent neat intramolecular regioselective cycloaddition with the other aldehyde group as dipolarophile to yield novel macrocyclic oxazolidines in good yield.

Scheme 2 represents the one-pot reaction of dialdehyde **1a–d** with sarcosine **2** in dry acetonitrile resulting in the formation of macrocyclic cis-fused oxazolidine **3a–d** in good yield.[17] The reaction was found to form only cis product as determined by spectroscopic techniques (Scheme 2).

The structures of the products (**3a–d**) were confirmed by elemental analysis as well as ^{1}H NMR, ^{13}C NMR, DEPT 135, NOESY, and mass spectral analysis. The ^{1}H NMR spectrum of **3a** exhibited a



1a-d

a) Z = -$(CH_2)_4$- , **b)** Z = -$(CH_2)_2$-, **C)** Z = *o*-xylyl, **d)** Z = *m-xylyl*

Scheme 1. Preparation of dialdehyde **1a–d** from salicylaldehyde.

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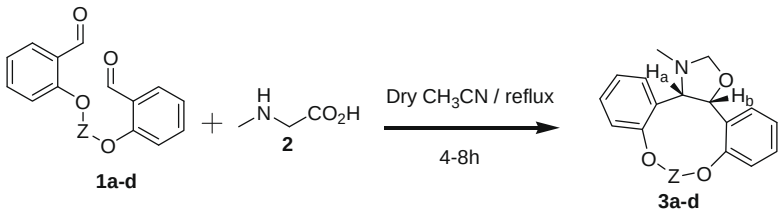
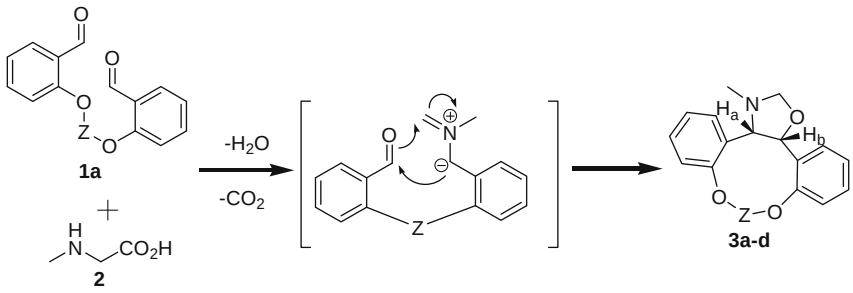
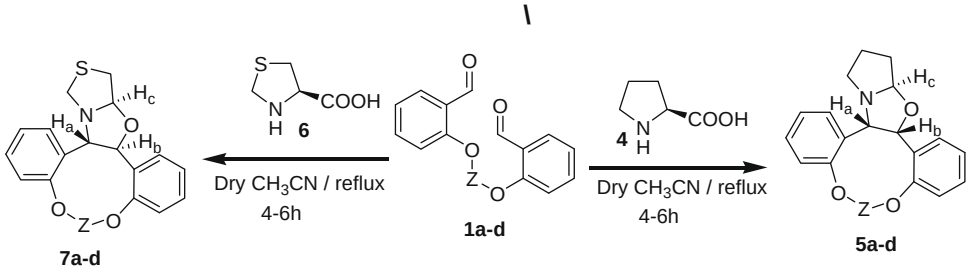


a) Z = -$(CH_2)_4$- , b) Z = -$(CH_2)_2$-, C) Z = *o*-xylyl, d) Z = *m-xylyl*

Scheme 2. Synthesis of oxazolidine grafted macrocycles.



Scheme 3. Possible mechanism for regioselectivity.



a) Z = -$(CH_2)_4$- , b) Z = -$(CH_2)_2$-, C) Z = *o*-xylyl, d) Z = *m-xylyl*

Scheme 4. Synthesis of pyrrolooxazole/oxazolothiazole grafted macrocycles.

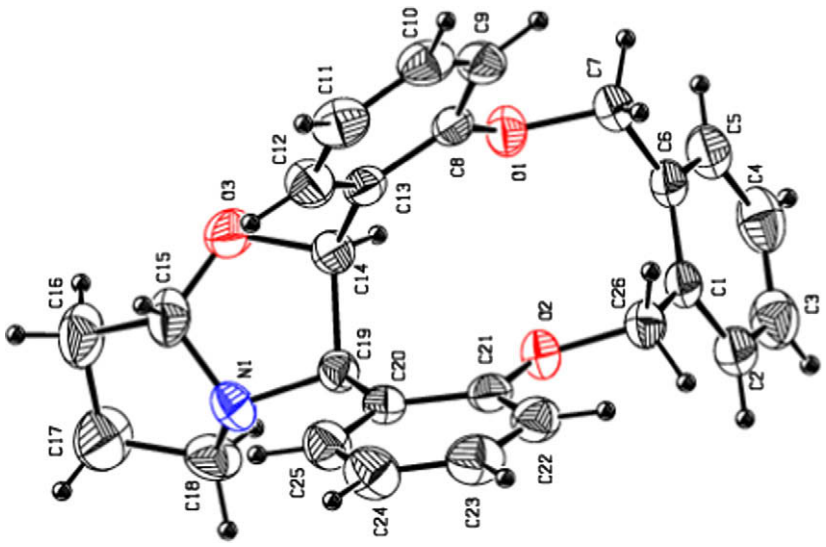


Figure 1. ORTEP diagram of **5c**.

singlet at δ 2.30 corresponding to *N*-methyl proton. There were two well-separated doublets at δ 4.68 (J = 3.6 Hz) and 5.01 (J = 3.6 Hz) corresponding to benzylic proton Ha and Hb, respectively, which clearly showed the stereo- and regiochemistry of the cycloaddition reaction. If the other possible regioisomer had been formed, the ^{1}H NMR spectrum would have shown a singlet for proton Ha. The stereochemistry of cycloadducts **3a–d** were deduced on the basis of 2D NOESY experiments. The strong contour connecting Ha and Hb in 2D NOESY proved that both are cis to each other. Interestingly, the oxazolidine methylene protons exhibited doublets at δ 4.65 (J = 2.4 Hz) and 5.24 (J = 2.4 Hz). This downfield shift was supported by well known anisotropic effect reported by Orsini et al.[15a]

The ^{13}C NMR spectrum of **3a** showed the benzylic –CH– signals at 97.7 and 80.1 ppm and methine carbon at 68.5 ppm. Furthermore, the presence of molecular ion peak at *m/z* 326.13 (M^++1) in the mass spectrum of **3a** confirmed the structure of the cycloadduct. Scheme 3 explains the regioselectivity observed in the above reaction wherein the electron-rich benzylic carbanion (HOMO) interacts with the electron-deficient carbonyl carbon (LUMO) to give the observed products[18](Scheme 3).

We have found acetonitrile (65–90%) to be the best solvent for the reaction compared to DMSO (15–40%, incomplete), methanol (20%, incomplete), toluene, and benzene (no reaction).

We have extended the methodology for the synthesis of hexahydropyrrolooxazole/tetrahydrooxazolothiazole grafted macrocycles by reacting dialdehydes **1a–d** with L-proline/thiazolidine-4-carboxylic acid. The azomethine ylides generated from one of the dialdehydes in the reaction reacted with the other aldehyde carbonyl group as dipolarophile to yield hexahydropyrrolo [2,1-*b*] oxazole[19] **5a–d** and tetrahydro-2*H*-oxazolo [3,2-*c*] thiazole[20] grafted macrocycles (**7a**–**d**) (Scheme 4).

The ^{1}H NMR spectrum of **5a** showed two well-separated doublets at δ 4.74 (J = 4.8 Hz) and 5.25 (J = 4.8 Hz) corresponding to benzylic proton Ha and Hb, respectively, which clearly showed the stereo- and regiochemistry of the cycloaddition reaction. The stereochemistry of cycloadducts **5a–d** was also deduced on the basis of 2D NOESY experiments. Furthermore, the presence of molecular ion peak at *m/z* 352.20 (M^++1) in the mass spectrum, confirmed the structure of the cycloadduct **5a**.

Finally, the regio- and stereochemical outcome of the cycloaddition reaction was confirmed by single crystal X-ray analysis[21] of the cycloadduct **5c** (Fig. 1).

In the case of tetrahydrooxazolothiazole, the Ha and Hb protons are observed to be in trans geometry as evident from single crystal X-ray analysis.

All these characteristic features delineate the fact that the cycloaddition reactions proceeded in a highly regio- and stereospecific manner affording in all the cases a single isomer.

In conclusion, for the first time we have developed a simple, one-pot and high-yielding protocol for the synthesis of heterophanes containing oxazolidine, pyrrolooxazole, and oxazolothiazole grafted cyclophanes with aldehyde as a dipolarophile through intramolecular 1,3-dipolar cycloaddition methodology.

Acknowledgments

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17. *General procedure for macrocyclic oxazolidines* (**3a–d**): A mixture of dialdehyde **(1a–d)** (1 mmol) and sarcosine (1 mmol) were refluxed in dry acetonitrile (30 mL) for about 6–8 h under N_2 atm. After completion of the reaction as indicated by TLC, acetonitrile was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane/EtOAc (8:2) as eluent.*Oxazolidine grafted macrocycle* **3a**: Isolated yield: 70%. White crystals, mp 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90–1.97 (m, 4H); 2.30 (s, 3H); 3.80–3.89 (m, 2H); 4.03–4.09 (m, 2H); 4.65 (d, J = 2.4 Hz, 1H); 4.68 (d, J = 3.6 Hz, 1H); 5.01 (d, J = 3.6 Hz, 1H); 5.24 (d, J = 2.4 Hz, 1H); 6.75 (d, J = 8.1 Hz, 2H); 6.87 (t, J = 7.5 Hz, 2H); 7.11–7.15 (m, 2H); 7.39–7.46 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.1, 26.2, 41.5, 67.5, 67.6, 68.1, 79.5, 88.7, 109.9, 110.1, 119.0, 119.3, 125.9, 126.8, 127.1, 127.3, 129.5, 129.6, 155.3, 155.4 ppm. ESI Mass *m/z*: 326.13 (M^++1). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.72; H, 7.26; N, 4.42.
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19. *General procedure for macrocyclic hexahydropyrrolooxazoles* (**5a–d**): A mixture of dialdehyde (**1a–d**) (1 mmol) and L-proline (1 mmol) was refluxed in dry acetonitrile (30 mL) for about 4–6 h under N_2 atm. After completion of the reaction as indicated by TLC, acetonitrile was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane/EtOAc (8:2) as eluent.*Hexahydropyrrolooxazole grafted macrocycle* **5a**: Isolated yield: 88%. Light brown crystals, mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86–1.96 (m, 6H); 2.10–2.18 (m, 2H); 2.76–2.79 (m, 1H); 3.01–3.05 (m, 1H); 3.74–3.82 (m, 2H); 4.05–4.10 (m, 2H); 4.74 (d, J = 4.8 Hz, 1H); 5.25 (d, J = 4.8 Hz, 1H); 5.30–5.33 (m, 1H); 6.69 (t, J = 7.8 Hz, 2H); 6.84 (t, J = 7.5 Hz, 2H); 7.09 (t, J = 7.8 Hz, 2H); 7.44–7.56 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 26.0, 28.6, 30.8, 53.9, 67.2, 67.5, 68.5, 80.1, 97.7, 110.2, 110.6, 119.1, 119.3, 126.2, 126.7, 126.9, 127.3, 129.8, 130.8, 154.6, 154.7 ppm. ESI Mass *m/z*: 352.20 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.31; H, 7.30; N, 3.90.
20. *General procedure for macrocyclic tetrahydro-2H-oxazolo[3,2-c]thiazole cycloadducts* (**7a–d**): A mixture of dialdehyde **(1a–d)** (1 mmol) and thiazolidine-4-carboxylic acid **6** (1 mmol) was refluxed in dry acetonitrile (30 mL) for about 4-6 h under N_2 atm. After completion of the reaction as indicated by TLC, acetonitrile was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane/EtOAc (8:2) as eluent.*Tetrahydro-2H-oxazolo[3,2-c]thiazole grafted macrocycle* **7a**: Isolated yield: 89%. White crystals, mp 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90–1.96 (m, 4H); 3.05–3.11 (m, 1H); 3.17–3.21 (m, 1H); 3.77–3.82 (m, 1H); 3.89–4.08 (m, 4H); 4.16–4.19 (m, 1H); 4.49 (d, J = 9 Hz, 1H); 5.38–5.39 (m, 1H); 5.87 (d, J = 9 Hz, 1H); 6.69–6.87 (m, 4H); 7.07–7.18 (m, 3H); 7.39–7.43 (m, 1H); ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 26.8, 39.2, 57.1, 68.0, 68.4, 68.6, 77.9, 96.9, 112.6, 112.8, 119.8, 120.1, 125.2, 125.8, 127.9, 128.3, 128.4, 130.6. 156.2, 156.4 ppm.ESI Mass *m/z*: 370.24 (M^+ +1). Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.38; H, 6.17; N, 3.89.
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