LIGAND FREE Pd CATALYZED CYCLIZATION-INFLUENCE OF STERIC HINDRANCE

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ABSTRACT

Synthesis of sultams was performed using ligand free palladium catalyst following Heck cyclization. The diverse synthesized intermediates in this strategy includes halogenated sulfonyl chloride, alkyl/aryl sulfonamides, *N*-alkylation using halogenated alkenyl reagents followed by improved Heck cyclization with Pd(OAc)₂/DIPA in 1-methyl-pyrrolidin-2-one/toluene. In this way, isomeric six membered sultams with endocyclic & exocyclic double bonds (benzothiazine) and seven membered (thiazipene) were obtained. Endocyclic double bond isomer was dominates in respect of yield over the exocyclic double bond isomer. The isolated amounts of endocyclic sultams and thiazipene were almost equal in amounts. The intermediates and final products were characterized using IR, ¹H-NMR, ¹³C-NMR and EI-MS techniques.

Key words; cyclic sultams, 1,2-benzothiazine, ligand free Heck reaction

1. INTRODUCTION

Synthesis of new organic compounds is a highly cherished sector of chemistry. After the first Kolbe's synthesis developed for construction of the carbon-carbon (C-C) bond, literature provides references like, Grignard-, aldol- and pericyclic type of reactions. Formation of C-C bond through cleavage of C-H bond *via* metal-catalyzed reaction has been developed as the most attractive research area for organic, as well as, organometallic chemists in synthesis of homo/heterocyclic compounds¹⁻⁴. The inestimable significance of these transition metal-catalyzed synthetic transformations has been disclosed by Stille⁵, Negishi⁶, Suzuki-Miyaura⁷, Hiyama⁸ and palladium-catalyzed Heck cross-couplings [9] using organohalides and other surrogates in synthetic chemistry^{10,11}. The traditional Heck reaction drives through: i) a suitable amount of homogenous/heterogeneous palladium (0/II) catalyst, ii) a ligand, usually phosphine and iii) a suitable base. These catalyst systems afford different drawbacks including air/moisture sensitivity and extra cost¹². Therefore, there is always room for developing new catalyst systems which will be more advantageous with respect to operation and cost.

Among heterocycles, the benzothiazines¹³ are important molecules to serve as anti-cancer¹⁴⁻¹⁶, analgesic¹⁷, anti-microbial¹⁸, anti-viral¹⁹, anti-inflammatory²⁰⁻²², anti-pyretic²³, anti-diabetic²⁴, anti-hypertensive²⁵, antioxidant²⁶, herbicidal²⁷, and fungicidal²⁸, agents. On the other hand, these are reported to exhibit the high vaso-relaxant potency²⁹ as Potassium Channel Openers (KCOs). The rapid demand for the synthesis of libraries of these types of medicinal compounds with high throughput activities led us towards the synthesis of sultams. Since the time Braun *et al* synthesized first benzothiazine, thousands of its derivatives have been synthesized and checked for their biological activities³⁰⁻³³. Initially, the most famous and long-time applied methodology for the synthesis of benzothiazine and thiazepine derivatives involved Gabriel-Colman rearrangement³⁴. The most recent attempts applied for preparation of these heterocyclic molecules are now using palladium as catalyst^{35,36} accompanied with a bulky neutral ligand such as triphenylphosphine.

The aforementioned literature together with our already existing program to synthesize new non-steroidal anti-inflammatory drugs (NSAIDs)³⁷⁻⁴¹ and their crystallographic studies^{42,43}, cultivated our interest to develop a new methodology. The present communication is an outcome of this effort whereby we are reporting a convenient, straightforward and ligand-free palladium catalyzed arylation targeted towards synthesis of six-membered sultams only.

2. EXPERIMENTAL

The reactions sensitive to air/moisture were carried out under appropriate conditions. The raw materials were purchased from Merck, BDH, Alfa Aesar or Fluka and used without purification. Standard methods were applied to purify all the solvents and reagents, where applicable. Merck manufactured TLC plates were used to monitor the progress of reactions. ¹H-NMR and

¹³C-NMR spectra were recorded on a varian AM 400 instrument. Chemical shifts are reported in ppm referenced to the residual solvent signal. IR spectra were recorded on a Perkin Elmer 1600-FT spectrometer. Melting points were recorded on Electrothermal (Griffin 1090) melting point apparatus and are reported as uncorrected.

Synthesis of 2-bromo-*N*-methyl(or *N*-2,3-dimethyl-phenyl)-benzenesulfonamide (4,5)

Et₃N (0.23 g, 2.29 mmol) was added to the solution of 2-bromobenzenesulfonyl chloride⁴⁴ (0.25 g, 1 mmol) and methylamine hydrochloride (or *N*-2,3-dimethylphenyl) (1.35 mmol) in dichloromethane (DCM) under ice, drop wise. After the completion of addition the mixture was stirred at room temperature for 10 hrs and quenched with saturated NH₄Cl solution. The organic layer was separated and aqueous layer was extracted with AcOEt. The combined organic layer was evaporated under vacuum after drying over anhydrous Na₂SO₄ to obtained yellow oil

2-Bromo-*N*-methylbenzenesulfonamide (4)

Yield; 96.89 %, IR (neat) $\nu_{\max}$: 3319, 1314, 1160 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃) δ : 8.18 (1H, d, aromatic), 7.78 (1H, d, aromatic), 7.42 (2H, m, aromatic), 5.15 (1H, s, NH), 2.58 (3H, d, CH₃), ¹³C-NMR: (400 MHz), (CDCl₃) δ : 142.65, 140.40, 138.28, 137.85, 133.78, 126.24, 29.72,

2-Bromo-*N*-(2,3-dimethyl-phenyl)-benzenesulfonamide (5)

Light brown solid, Yield: 74.4 %, MP: 131-132 °C, IR (KBr) $\nu_{\max}$: 3319, 1314, 1160 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃) δ : 7.92 (1H, d, aromatic), 7.68 (1H, d, aromatic), 7.31 (2H, dd, aromatic), 6.89 (1H, d, aromatic), 6.81 (1H, t, aromatic), 6.69 (1H, d, aromatic), 3.07 (1H, m, NH), 2.19 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃) δ : 138.88, 135.11, 134.30, 133.83, 133.66, 132.01, 128.50, 127.81, 125.83, 122.08, 119.81, 14.21, 8.65.

General procedure for the synthesis of allyl derivatives (6-11)

A solution of 2-bromo-*N*-methyl/2,3DMA-benzenesulfonamide (0.8 mmol) in DMF (5 ml) was added to the *n*-hexane washed suspension of sodium hydride (0.06 g of 60 %, 1.6 mmol) in DMF (2 ml). The solution was allowed to stir for half an hour at room temperature. Then unsubstituted allylbromide (0.99 mmol) was added to the above solution and allowed to stir at room temperature for 2-3 hrs. The progress of the reaction was observed by TLC. The mixture was poured on ice and pH was adjusted at 3-4. Precipitates obtained were further purified on column chromatography and dried over anhydrous Na₂SO₄ for spectral studies.

***N*-Allyl-2-bromo-*N*-methyl-benzenesulfonamide (6)**

Light Yellow oil, Yield: 78 %, IR (neat) $\nu_{\max}$: 1329, 1153 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃) δ : 7.98 (1H, d, aromatic), 7.65 (1H, d, aromatic), 7.38 (2H, m, aromatic), 5.76 (1H, m, CH), 5.24 (2H, dd, =CH₂), 5.24 (2H, d, CH₂), 2.68 (3H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃) δ : 143.26, 139.86, 139.05, 136.97, 135.78, 133.93, 123.43, 122.90, 54.57, 35.88

2-Bromo-*N*-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide (7)

Light Yellow oil, Yield: 79.8 %, IR (neat) $\nu_{\max}$: 1332, 1158 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃) δ : 8.17 (1H, d, aromatic), 7.72 (1H, d, aromatic), 7.42

(2H, dd, aromatic), 5.18 (1H, t, CH), 3.82 (2H, d, CH₂), 2.79 (3H, s, NCH₃), 1.61 (3H, s, CH₃), 1.52 (3H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 138.85, 137.67, 135.63, 133.34, 132.27, 120.43, 118.78, 47.30, 33.75, 25.78, 17.70

2-Bromo-N-methyl-N-(3-phenyl-allyl) benzenesulfonamide (8)

Pale Yellow oil, Yield: 67 %, IR (neat) ν_{max} : 1331, 1158 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 8.04-7.59 (9H, aromatic), 6.43 (1H, d, =CH ³J = 19.5), 5.98 (1H, m, =CH ³J = 19.5 Hz), 3.94 (2H, d, CH₂), 2.18 (3H, s, NCH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 162.62, 138.65, 136.68, 136.16, 135.72, 134.49, 133.79, 132.39, 131.77, 128.85, 128.51, 126.20, 123.95, 120.34, 52.30, 33.56,

N-Allyl-2-bromo-N-(2,3-dimethyl-phenyl)-benzenesulfonamide (9)

Brown solid, Yield: 78.3 %, MP: 112-113 °C, IR (KBr) ν_{max} : 1334, 1158 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.68 (2H, d, aromatic), 7.26 (2H, m, aromatic), 7.01 (1H, d, aromatic), 6.87 (1H, t, aromatic), 6.63 (1H, d, aromatic), 5.81 (1H, m, =CH), 4.94 (2H, d, =CH₂), 4.34 (2H, d, CH₂), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 139.46, 138.08, 136.53, 135.56, 133.16, 132.88, 129.59, 128.38, 127.37, 125.50, 120.05, 119.26, 56.14, 29.70, 22.67, 20.54, 14.97.

2-Bromo-N-(2,3-dimethyl-phenyl)-N-(3-methyl-but-2-enyl) benzene sulfonamide (10)

Brown viscous liquid, Yield: 98 %, IR (neat) ν_{max} : 1341, 1159 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.74 (2H, q, aromatic), 7.29 (2H, m, aromatic), 7.01 (1H, d, aromatic), 6.89 (1H, t, aromatic), 6.69 (1H, d, aromatic), 5.21 (1H, t, =CH), 4.48 (1H, q, CH₂), 4.31 (1H, q, CH₂), 2.20 (3H, s, CH₃), 2.08 (3H, s, CH₃), 1.58 (3H, s, =CCH₃), 1.32 (3H, s, =CCH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 141.21, 138.70, 138.62, 137.95, 135.94, 133.62, 133.20, 130.17, 128.73, 127.72, 125.84, 120.43, 119.34, 51.30, 26.10, 20.92, 18.34, 17.84, 15.31.

2-Bromo-N-(2,3-dimethyl-phenyl)-N-(3-phenyl-allyl)-benzene sulfonamide (11)

Brown viscous solid, Yield: 63 %, IR (KBr) ν_{max} : 1331, 1158 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 8.14-7.52 (12H, aromatic), 6.49 (1H, d, =CH ³J = 19.5), 5.79 (1H, m, =CH ³J = 19.5 Hz), 4.02 (2H, d, CH₂), 1.17 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 143.11, 141.51, 139.71, 138.73, 138.01, 136.04, 135.81, 133.67, 133.12, 131.25, 130.67, 129.61, 128.37, 127.02, 126.10, 125.64, 120.49, 120.92, 119.34, 118.34, 52.15, 18.24, 15.81.

Synthesis of cyclization products

N-un/substituted Allyl-2-bromo-N-methyl-2,3-DMA-benzenesulfonamide (0.482 mmol), catalytic amount of Pd(OAc)₂ (0.0048 mmol) and DIPA/Et₃N (0.482 mmol) was added to the 1-methyl-2-pyrrolidinone/toluene in round bottom flask (25 ml) under N₂. The mixture was subjected to heat for 24 hrs at 100-120 °C with stirring. The different products were separated with prep-HPLC technique using mixture of 20 % AcOEt in n-hexane as mobile phase.

2,4-Dimethyl-2H-1,2-benzothiazine 1,1-dioxide (12)

Light Yellow oil, Yield: 38.2 %, IR (neat) ν_{max} : 1334, 1176 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.82 (1H, d, aromatic), 7.59 (1H, t, aromatic), 7.42 (2H, dd, aromatic), 6.25 (1H, s, CH), 3.24 (3H, s, NCH₃), 2.13 (3H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 134.20, 132.06, 131.05, 129.79, 127.35, 124.50, 121.59, 113.57, 34.40, 16.21,

2-Methyl-4-methylidene-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (13)

Light Yellow oil, Yield: 2.3 %, IR (neat) ν_{max} : 1338, 1179 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.92 (1H, d, aromatic), 7.44 (2H, dd, aromatic), 7.33 (1H, t, aromatic), 5.45 (2H, s, CH₂), 4.03 (2H, t, CH₂), 2.51 (3H, s, NCH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 147.69, 139.16, 133.98, 133.09, 131.12, 129.87, 129.19, 99.35, 49.29, 34.56

2-Methyl-2,3-dihydro-1,2-benzothiazepine 1,1-dioxide (14)

Light Yellow oil, Yield: 37.3 %, IR (neat) ν_{max} : 1341, 1169 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.96 (1H, d, aromatic), 7.43 (2H, dd, aromatic), 7.29 (1H, t, aromatic), 6.46 (1H, d, CH), 5.82 (1H, dd, CH), 4.23 (2H, t, CH₂), 2.59 (3H, s, NCH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 138.67, 133.76, 132.96, 130.28, 129.45, 128.90, 127.43, 121.49, 52.90, 35.46,

2-(2,3-Dimethyl-phenyl)-4-methyl-2H-benzo[e][1,2]thiazine 1,1-dioxide (15)

Light Brown powder, Yield: 38.12 %, MP: 98-100 °C, IR (KBr) ν_{max} : 1331, 1155 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.92 (1H, d, aromatic), 7.61 (1H, t, aromatic), 7.48 (2H, dd, aromatic), 7.28 (1H, t, aromatic), 7.12 (2H, m, aromatic), 6.47 (1H, s, =CH), 2.23 (3H, s, CH₃), 2.08 (3H, s, CH₃), 1.49 (3H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 139.56, 138.59, 136.97, 136.40, 134.48, 133.97, 133.04, 132.06, 131.84, 130.91, 129.72, 128.21, 127.63, 56.55, 21.13, 16.28, 14.68.

2-(2,3-Dimethylphenyl)-4-methylidene-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (16)

Light brown powder, Yield: 5.6 %, MP: 115-116 °C, IR (KBr) ν_{max} : 1337, 1155 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.83 (1H, d, aromatic), 7.59 (1H, t, aromatic), 7.42 (2H, dd, aromatic), 7.22 (1H, t, aromatic), 7.13 (2H, m, aromatic), 5.16 (2H, s, CH₂), 5.06 (1H, d, =CH₂), 4.24 (1H, d, =CH₂), 2.13 (3H, s, CH₃), 2.21 (3H, s, CH₃), 2.12 (3H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 138.80, 136.63, 133.97, 132.04, 130.90, 130.45, 129.79, 127.79, 127.37, 126.98, 126.28, 124.25, 122.27, 114.32, 20.49, 16.27, 14.67.

6-(2,3-Dimethyl-phenyl)-6,7-dihydro-5-thia-6-aza-benzocycloheptene 5,5-dioxide (17)

Light Brown solid, Yield: 33.41 %, MP: 87-88 °C, IR (KBr) ν_{max} : 1339, 1157 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.87 (1H, d, aromatic), 7.58 (1H, t, aromatic), 7.51 (2H, dd, aromatic), 6.93 (1H, t, aromatic), 6.54 (1H, d, =CH-), 6.29 (2H, dd, aromatic), 6.09 (1H, m, =CH-), 4.21 (2H, d, CH₂), 2.12 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 138.81, 136.63, 134.79, 133.54, 132.26, 130.09, 129.18, 128.85, 127.38, 126.42, 125.15, 123.78, 114.42, 55.05, 20.68, 14.97, 14.45.

2-Methyl-4-(propan-2-yl)-2H-1,2-benzothiazine 1,1-dioxide (18)

Light Yellow oil, Yield: 23.9 %, IR (neat) ν_{max} : 1334, 1156 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.81 (1H, d, aromatic), 7.55 (2H, dd, aromatic), 7.48 (1H, m, aromatic), 6.21 (1H, s, CH), 3.24 (3H, s, NCH₃), 3.06 (1H, m, CH), 1.17 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 132.26, 131.82, 129.34, 127.56, 125.40, 123.67, 122.71, 117.50, 34.51, 27.05, 22.14,

2,5,5-Trimethyl-2,5-dihydro-1,2-benzothiazepine 1,1-dioxide (19)

Light Yellow oil, Yield: 23.9 %, IR (neat) ν_{max} : 1328, 1164 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.76-7.41 (4H, aromatic), 4.23 (1H, d, CH), 4.98 (1H, d, CH), 2.51 (3H, s, NCH₃), 1.48 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 134.62, 133.62, 132.15, 131.53, 127.78, 124.23, 122.46, 119.65, 52.25, 41.76, 35.26,

2-(2,3-Dimethyl-phenyl)-4-(propan-2-yl)-2H-1,2-benzothiazine 1,1-dioxide (20)

Light brown paste, Yield: 29.46 %, IR (neat) ν_{max} : 1332, 1158 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.81 (1H, d, aromatic), 7.55 (2H, dd, aromatic), 7.48 (1H, m, aromatic), 6.21 (1H, s, CH), 3.24 (3H, s, NCH₃), 3.06 (1H, m, CH), 1.17 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 132.26, 131.82, 129.34, 127.56, 125.40, 123.67, 122.71, 117.50, 34.51, 27.05, 22.14

6-(2,3-Dimethyl-phenyl)-9,9-dimethyl-6,9-dihydro-5-thia-6-aza-benzocycloheptene 5,5-dioxide (21)

Light brown paste, Yield: 26.35 %, IR (neat) ν_{max} : 1342, 1168 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.76-7.41 (4H, m, aromatic), 4.23 (1H, d, CH), 4.98 (1H, d, CH), 2.51 (3H, s, NCH₃), 1.48 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 134.62, 133.62, 132.15, 131.53, 127.78, 124.23, 122.46, 119.65, 52.25, 41.76, 35.26,

4-Benzylidene-2-methyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (22)

Pale Yellow oil, Yield: 54 %, IR (neat) ν_{max} : 1325, 1157 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 7.86-7.43 (9H, aromatic), 6.23 (1H, s, =CH), 3.83 (2H, s, CH₂), 3.24 (3H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 132.51, 132.00, 131.83, 131.66, 129.28, 128.96, 128.44, 128.31, 127.21, 126.62, 125.47, 124.70, 124.42, 122.04, 51.92, 34.13

4-Benzylidene-2-(2,3-dimethyl-phenyl)-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (23)

Brown powder, Yield: 54 %, MP: 202-204 °C, IR (KBr) ν_{max} : 1329, 1154 cm⁻¹, ¹H-NMR: (400 MHz) (CDCl₃)δ: 8.02-7.21 (12H, aromatic), 6.08 (1H, s, =CH), 4.11 (2H, s, CH₂), 2.97 (6H, s, CH₃), ¹³C-NMR: (400 MHz) (CDCl₃)δ: 149.05, 147.24, 142.17, 139.03, 138.26, 137.41, 135.18, 134.76, 133.52, 131.68, 130.18, 129.29, 128.01, 127.31, 126.09, 125.85, 121.51, 120.06, 119.11, 117.34, 53.51, 19.91, 16.57.

3. RESULTS AND DISCUSSIONS

The present work covers the development of new research methodology headed for the synthesis of sultams. The cheap and readily available *o*-aminobenzenesulfonic acid (orphanilic acid) (**1**) was used as starting material (Scheme 1). Diazotization of (**1**) led to *o*-bromobenzenesulfonic acid which was treated with base NaOH to produce sodium *o*-bromobenzenesulfonate (**2**). The sulfonyl chloride (**3**) was isolated (50-60 %) following chlorination of (**2**) with PCl₅ in a neat fashion⁴⁴. The sulfonamide derivatives (**4**, **5**) were synthesized in encouraging yields by direct reaction of sulfonyl chloride (**3**) with methyl amine hydrochloride and 2,3-dimethylaniline (2,3-DMA), respectively. *N*-alkylation of the sulfonamides (**4**, **5**) was carried out with three allyl bromide reagents i.e. allylbromide, 3,3-dimethylallylbromide and *trans*-cinnamyl bromide to get the corresponding derivatives (**6-11**). The compounds were characterized by spectroscopic techniques and used in the next scheme without further purification.

Scheme 1: Synthesis of sulfonamides

The six allyl-containing benzenesulfonamides (**6-11**) were subjected to C-C cross-coupling by applying Pd(II) acetate under basic conditions (using di-isopropylamine) in either 1-methyl-2-pyrrolidinone or toluene as reaction medium. The attempt of cyclization was made without employing triphenylphosphine ligand which is mandatory for Heck cyclization. The pace of reaction was monitored by TLC. For first two reactions pyrrolidinone, while for rest of the four reactions toluene was employed as reaction medium for the sake of convenience in work-up. We isolated two isomeric analogues of benzothiazine along with benzothiazepine in diverse yields during first two cyclization attempts. The two analogues of benzothiazine differ in the position of double bond. The analogue in which double bond lies in the thiazine ring

(**12**) dominated in yield over the other exocyclic double bond containing isomer (**13**) (38.2 % and 2.3 %, respectively). The benzothiazepines (**14, 17**) were also isolated in comparative yields (37.3%, 33.4%). These isomeric products are the logical outcome of Heck coupling^{45,46} recipe.

The key feature in current research was not only to avoid usage of a bulky ligand, but also to derive the environment where only one required type of product could be the destination. Therefore, we carried out ligand-free palladium catalyzed cyclization to yield six-membered sultams, taking following reasons into consideration.

I. A good leaving group like iodo- instead of bromo- might facilitate the formation of six membered sultams.

II. Presence of a sterically crowded group at alkene terminal of the sulfonamides (**6-11**) might be supportive towards formation of one type of product only.

Many citations⁴⁷ have been found, which consider the first point as mere option to render significant outcomes. We jumped into the second option, used 3,3-dimethyl allyl and cinnamyl alkyl groups (**7, 8, 10, 11**) to target the planned six membered cyclic molecules. 3,3-Dimethyl allyl group containing derivatives (**7, 10**) yielded both six- (**18, 19**) and seven- (**20, 21**) membered sultams. Eventually, the cinnamyl sulfonamide derivatives (**8, 11**) produced purely thiazine-containing cyclic products (**22, 23**) with exo-cyclic double bond (54 %).

The overall results justify that the presence of bulky group at 'N' of the sulfonamide (**4, 5**), away from the point of arylation, does not contribute towards selection for six-/seven-membered products. Secondly, the crowding produced at point of C-C cross-coupling (**8, 11**) has exclusively decided the fate of final products in term of six-membered sultams (**22, 23**) only. This conclusion is the success of present methodology.

No.	4	5	6	7	8	9	10	11	12-14	15-17	18-19	20-21	22	23
R1	CH ₃	2, 3-DMA	CH ₃	CH ₃	CH ₃	2, 3-DMA	2, 3-DMA	2, 3-DMA	CH ₃	2, 3-DMA	CH ₃	2, 3-DMA	CH ₃	2, 3-DMA
R2	-	-	H	CH ₃	H	H	CH ₃	H	H	H	CH ₃	CH ₃	H	H
R3	-	-	H	CH ₃	Ph-	H	CH ₃	Ph-	H	H	CH ₃	CH ₃	Ph-	Ph-

Scheme 2: Synthesis of sultams

4. CONCLUSION

The current studies explain the synthesis of six membered cyclic sultams in successive manner using Pd-catalysed chemistry without any ligand. The effects of simple and satirically hindered groups were evaluated in synthesis of targeted compounds to avoid isomeric products.

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