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Note

One-pot synthesis of 1-[(2-oxooxazolidin-5-yl)methyl] ureas and carbamates from 5-azidomethyl-2-oxazolidinone

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A mild and an efficient one-pot method for the synthesis of 1-[(2-oxooxazolidin-5-yl)methyl]ureas and ethyl (2-oxooxazolidin-5-yl)methylcarbamates from 5-azidomethyl-2-oxazolidinone is described.

Keywords: 2-Oxazolidinone, 5-azidomethyl-2-oxazolidione, 1-[(2-oxooxazolidin-5-yl)methyl] urea, ethyl (2-oxooxazolidin-5-yl)methylcarbamate

Oxazolidinones are the first new class of synthetic antibacterial agents introduced since the discovery of quinolones more than 30 years ago. Linezolid[1], is the first drug of this class having antibacterial activity, that contains 3-aryl-5-aminomelthyl-2-oxazolidinone moiety.

Ureas and carbamates are an important class of compounds. Especially, the substituted ureas, in the form of sulfonylureas, have found an important use as oral antidiabetic drugs[2] and herbicides[3]. The condensation of primary amines with phosgene or isocyanates is a classic method for the synthesis of organic ureas[4]. However, due to their high toxicity and reactivity, phosgene and isocyanates are difficult to handle in the laboratory. Although several substitutes for phosgene, such as triphosgene and carbonyldiimidazole have been developed during the last few decades[5], these reagents are themselves prepared from phosgene. Alternate methods involve drastic reaction conditions, such as direct reactions of amines with dialkyl carbonates at high temperature[6] and the reaction of amines with *N*,*N*-diphenylurea in the presence of Et_3N in refluxing DMF[7]. Hanss-Joachim Knolker reported[8] a novel procedure for the preparation of isocyanates under mild conditions by DMAP-catalyzed reaction of amines with $(Boc)_2O$ and *in-situ* derivatization of the isocyanates by addition of amines and alcohols affording the corresponding ureas and carbamates. The *S*,*S*-dimethyldithiocarbonate (DMDTC), was reported as a convenient reagent for the synthesis of symmetrical and unsymmetrical ureas[9]. However, they are mostly limited to symmetrical ureas and the problem while preparing the unsymmetrical ureas is that the formation of symmetrical ureas as a major by-product.

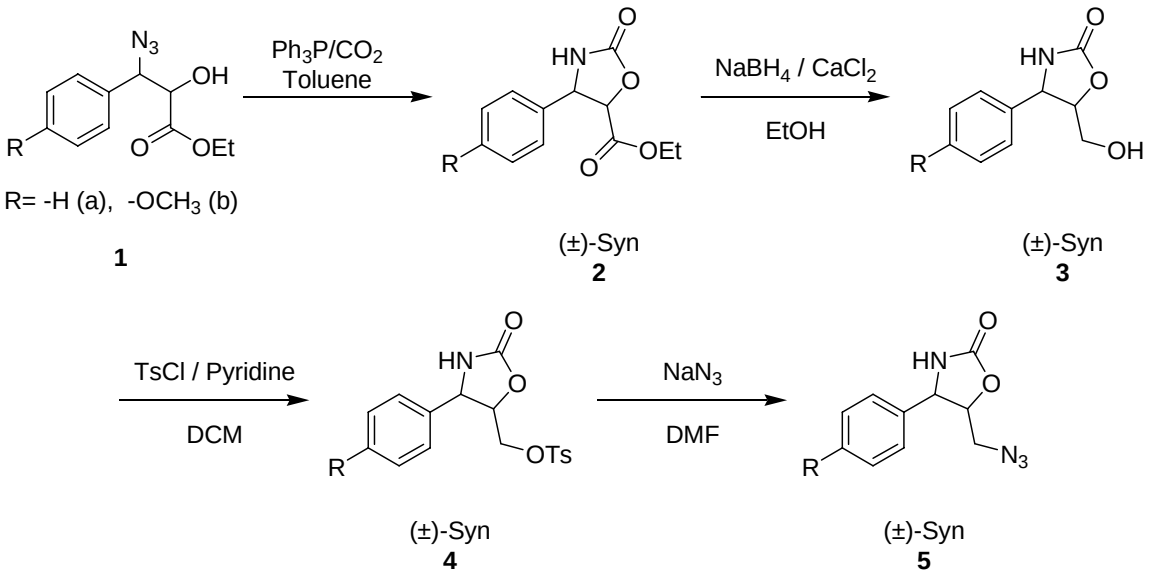
As part of an ongoing program on oxazolidinone derivatives to discover potent antibacterial drugs[10], it is interested to the synthesis of substituted 1-[(2-oxooxazolidin-5-yl)methyl]ureas from corresponding azides under mild reaction conditions to avoid the formation of symmetrical ureas as by-products. In this communication, a method has been developed with Ph_3P/CO_2 conditions to synthesize unsymmetrical ureas and carbamates from azides.

Results and Discussion

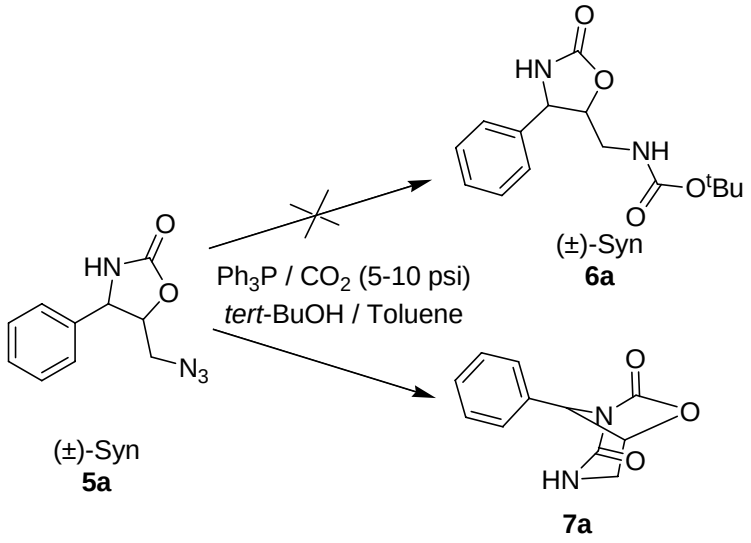
Synthesis of 5-(azidomethyl)-4-aryl-2-oxazolidinones, **5** is described. Azido alcohol, **1** was treated with PPh_3 under mild CO_2 pressure (5-10 psi) in toluene to obtain ethyl 2-oxo-4-aryl oxazolidine-5-carboxylate, **2**. Reduction of the ethyl ester of **2** was accomplished with $NaBH_4/CaCl_2$ in absolute ethanol to get corresponding alcohol, **3**. In the absence of calcium chloride, the reaction rate was slow and yield was poor. The hydroxy group of **3** was selectively tosylated in the presence of pyridine to give the mono tosyl compound, **4** and converted to azide derivative **5** by nucleophilic displacement of tosyl group with NaN_3 in DMF (**Scheme I**). The compound **5** was used for derivatization.

5-(Azidomethyl)-4-aryl-2-oxazolidinones, **5** was treated with different amines and alcohols using PPh_3 and CO_2 in toluene to give corresponding ureas and carbamates.

5-(Azidomethyl)-4-phenyl-2-oxazolidinone, **5a** was treated with *tert*-butyl alcohol using Ph_3P under mild CO_2 pressure (5-10 psi) in toluene. Instead of expected carbamate **6a**, another product was isolated. Based on ^1H NMR data, the isolated compound could be a new heterobicyclic system, 8-phenyl-6-oxa-1,3-diazabicyclo (3.2.1)octane-2,7-dione **7a** (**Scheme II**).



Scheme I



Scheme II

Due to the instability of **7a**, complete characterization could not be carried out. The formation of urea, **7a** due to the conversion of azide to imino phosporane which on reaction with CO_2 gave the isocyanate and this intermediate further reacted with the amine to yield corresponding urea derivative (**Figure 1**).

The formation of **7a** as a by-product in the synthesis of ethyl carbamate, **9a** has been observed. The **9a** was alternatively prepared by reduction of **5a** followed by the reaction of amine, **8a** with ethyl chloroformate (**Scheme III**).

To avoid bicyclic urea formation, 5-(azidomethyl)-4-(4-methoxyphenyl)-3-tosyloxazolidin-2-one **11** was prepared from **3** by ditosylation using Et_3N followed by treatment with NaN_3. Compound **11,** was reacted with benzylamine and *p*-substituted benzylamine to give ureas **12** and **13** respectively, in good yield. However, **11** on treatment with PPh_3 and CO_2 in *tert*-BuOH and toluene gave isocyanate **15** instead of expected product **14.** Compound **15** was converted to required ethyl carbamate **16** on treatment with EtOH. Compound **16** also prepared directly from **11** using PPh_3 and CO_2 in EtOH and toluene, however poor yields were obtained (**Scheme IV**).

In conclusion, the unsymmetrical substituted 1-[(2-oxooxazolidin-5-yl)methyl]ureas and carbamates were prepared under mild reaction conditions from readily available azides without using toxic reagents

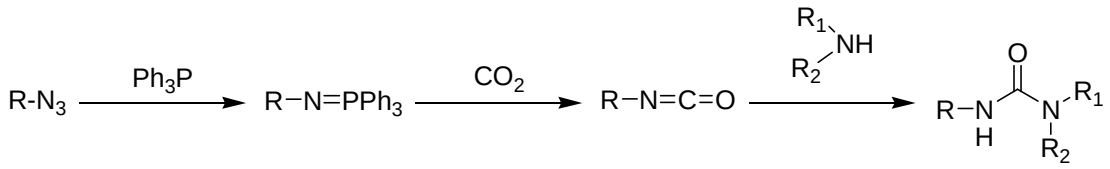
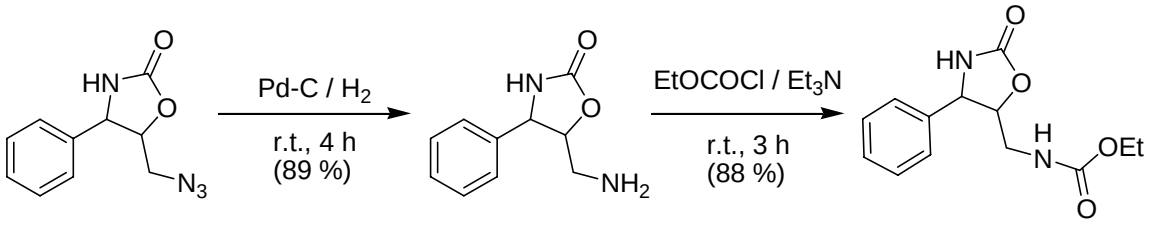
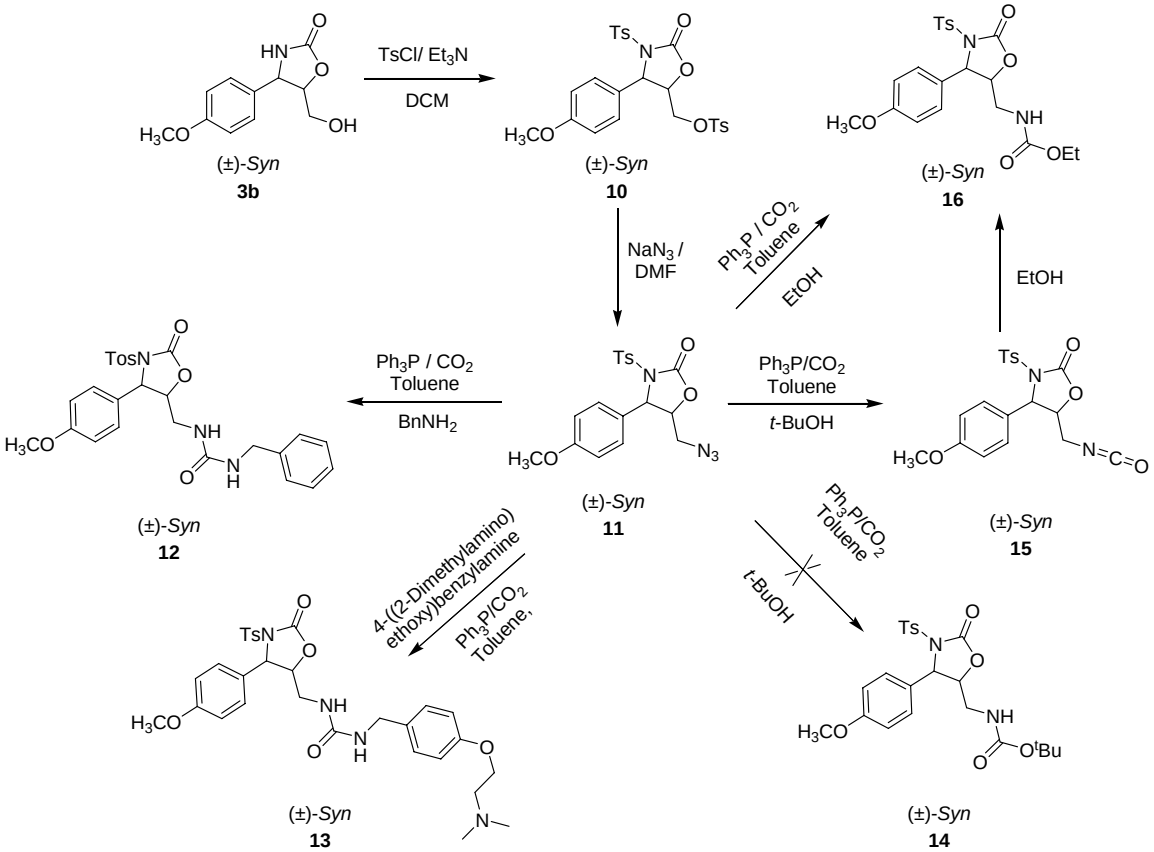


Figure 1



(±)-Syn **5a** (±)-Syn **8a** (±)-Syn **9a**

Scheme III



(±)-*Syn* **3b**; (±)-*Syn* **10**; (±)-*Syn* **16**; (±)-*Syn* **12**; (±)-*Syn* **11**; (±)-*Syn* **15**; (±)-*Syn* **13**; (±)-*Syn* **14**

Scheme IV

like phosgene. In this method, the formation of symmetrical ureas has been completely avoided which are commonly encountered as by-products in the synthesis of unsymmetrical ureas.

Experimental Section

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. IR spectra were recorded in KBr/$CHCl_3$ on a Perkin-Elmer 1650 spectrometer, ^1H and ^{13}C NMR were recorded in $CDCl_3$ using 200 MHz Varian Gemini spectrometer (chemical shifts in δ ppm) with TMS as internal standard and mass spectra on a HP-5989A spectrometer. The Analytical Research Department of Inogent laboratories private limited carried out all analytical work. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on pre-coated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95 v/v) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

General procedure for the preparation of alcohol, **3a,b**: Oxazolidinone **2** (0.021 moles) was dissolved in absolute EtOH (50 mL), $CaCl_2$ (4.72 g, 0.042 moles) and $NaBH_4$ (1.61 g, 0.042 moles) were added to it. Reaction-mixture was stirred at RT for 2 hr. The excess $NaBH_4$ was quenched by adding saturated NH_4Cl (50 mL). Ethanol was removed under vacuum. The aqueous layer was extracted with ethyl acetate (300 mL) and washed with 5% aq. NaCl (2 × 100 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The obtained residue was stirred in pet. ether/diethyl ether to give **3** as a white solid.

5-(Hydroxymethyl)-4-phenyloxazolidin-2-one, **3a**: This compound was obtained according to the general method mentioned above. 78.5% yield; m.p. 99-101°C; IR: 3383, 3278, 1739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.15-3.5 (m, 2H), 4.95 (m, 1H), 5.05 (d, 1H), 5.8 (s, 1H), 7.25-7.4 (m, 5H); mass: *m*/*z* 194 [M^++1].

5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one, 3b: This compound was obtained according to the general method mentioned above. 72.8% yield; m.p. 146-48°C; IR: 3378, 3251, 1732, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.2-3.5 (m, 2H), 3.8 (s, 3H), 4.95 (m, 1H), 5.5 (d, 1H), 5.3 (s, 1H), 6.9 (d, 2H), 7.25 (d, 2H); mass: *m*/*z* 224 [M^++1].

General procedure for monotosylation, **4a,b**: To a solution of alcohol **3** (0.0155 moles) in pyridine (6 mL), *p*-toluenesulfonyl chloride (3.36 g, 0.017 moles) was added in portion wise. Reaction was stirred at RT for 8 hr and progress of the reaction was monitored by TLC. After completion of the reaction, reaction-mixture was poured into dil. HCl and extracted with ethyl acetate (3 × 40 mL). The combined organic layers was washed with water (2 × 40 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain crude solid. The crude compound **4** was stirred in diethyl ether to obtain **4** in pure form.

(2-Oxo-4-phenyloxazolidin-5-yl)methyl 4-methyl-benzenesulfonate, **4a**: This compound was obtained according to the general procedure mentioned above. 92.6% yield; m.p. 158-60°C; IR: 3357, 1760, 1716, 1354, 1172, 989, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.4 (s, 3H), 3.65-3.85 (m, 2H), 5.0 (s, 2H), 5.4 (s, 1H), 7.2-7.4 (m, 7H), 7.6 (d, 2H); mass: *m*/*z* 348 [M^++1].

4-(4-Methoxyphenyl)-2-oxooxazolidin-5-yl-methyl-4-methylbenzenesulfonate, **4b**: This compound was obtained according to the general procedure mentioned above. Yield 90.8%; m.p. 158-60°C; IR: 3314, 1754, 1723, 1516, 1357 cm^{-1}; ^1H NMR: (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.65-3.85 (m, 2H), 3.85 (s, 3H), 5.0 (s, 2H), 5.45 (s, 1H), 6.9, 7.15, 7.3 and 7.65 (4d, 8H), 7.6 (d, 2H); mass: *m*/*z* 378 [M^++1].

4-(4-Methoxyphenyl)-2-oxo-3-tosyloxazolidin-5-yl-methyl-4-methylbenzenesulfonate, **10**: To a solution of alcohol **3b** (4.0 g, 0.0179 moles), Et_3N (4.54 g, 0.0448 moles) in DCM (40 mL), *p*-toluenesulfonyl chloride (7.41 g, 0.0376 moles) was added portion-wise. Reaction was stirred at RT for 8 hr and progress of the reaction was monitored by TLC. After completion of the reaction, reaction-mixture was poured into dil. HCl and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was washed with water (2 × 40 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain crude solid which was stirred in diethyl ether to obtain pure **10**; 85.0% yield; m.p.: 144-46°C; IR: 1793, 1516, 1360, 1177, 1001, 665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.4 (s, 3H), 2.45 (s, 3H), 3.65-3.9 (m, 2H), 3.8 (s, 3H), 4.95 (q, 1H), 5.4 (d, 1H, *J* = 7.81), 6.7, 6.9, 7.1, 7.3, 7.4, 7.5 (6d, 12H); mass: *m*/*z* 532 [M^++1].

General procedure for azidolysis, **5a,b and 11**: To a solution of *p*-toluenesulfonate compound **4a,b** or **10** (0.0115 moles) in DMF (12 mL), NaN_3 (1.12 g, 0.017 moles) and benzyltributylammonium chloride (0.35 g, 0.0011 moles) were added. Reaction-mixture was stirred at 80°C for 8 hr and completion of the reaction was monitored by TLC. After completion of the reaction, reaction-mixture was poured into ice-cold water. The product was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with water (2 × 30 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain crude product **5a,b** or **11,** which was stirred in diethyl ether. The free flowing solid obtained was filtered to get corresponding azido compound.

5-(Azidomethyl)-4-phenyloxazolidin-2-one, **5a**: This compound was obtained according to the general procedure mentioned above. 71.0% yield; m.p. 129-30°C; IR: 3245, 2138, 2104, 1754, 1718 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.8-2.95 (dd, 1H, *J* = 13.16, 4.83), 3.15-3.3 (dd, 1H, *J* = 13.16, 7.52), 4.9 (m, 1H), 5.05 (d, 1H), 5.5 (s, 1H), 7.2-7.5 (m, 5H); mass: *m*/*z* 219 [M^++1].

5-(Azidomethyl)-4-(4-methoxyphenyl)oxazolidin-2-one, 5b: This compound was obtained according to the general procedure mentioned above. 91.6% yield; m.p. 113-16°C; IR: 3251, 2105, 2101, 1751, 1725, 1513, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.85-2.95 (dd, 1H, *J* = 13.18, 4.39), 3.15-3.3 (dd, 1H, *J* = 13.18, 7.81), 3.85 (s, 3H), 4.9 (m, 1H), 5.0 (d, 1H), 6.05 (s, 1H), 6.95 (d, 2H), 7.2 (d, 2H); mass: *m*/*z* 249 [M^++1].

5-(Azidomethyl)-4-(4-methoxyphenyl)-3-tosyloxazolidin-2-one, **11**: This compound was obtained according to the general procedure mentioned above. 93.0% yield; m.p. 111-13°C; IR: 3391, 2928, 2112, 1768, 1515, 1372 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.4 (s, 3H), 2.9-3.0 (dd, 1H, *J* = 13.18, 5.37), 3.2-3.35 (dd, 1H, *J* = 13.18, 7.32), 4.85 (q, 1H), 5.4 (d, 1H, *J* = 7.32), 6.8, 6.95, 7.15, 7.5 (4d, 8H); mass: *m*/*z* 403 [M^++1].

5-(Aminomethyl)-4-phenyloxazolidin-2-one, **8a**: A solution of azide **5a** (0.5 g, 0.0023 moles) in ethyl acetate (10 mL) was hydrogenated in presence of 5% Pd-C (10% w/w) at 5-10 psi at RT for 4 hr and completion of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered on a pad of celite and the filtrate was concentrated to give **8a**; 89.0% yield; m.p. > 260°C; IR: 3368, 3294, 1741, 1227 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.3-2.6 (m, 2H), 4.85 (m, 1H), 5.0 (d, 1H), 5.6 (s, 1H), 7.25-7.45 (m, 5H); mass: *m*/*z* 193 [M^++1].

Ethyl (2-oxo-4-phenyloxazolidin-5-yl)methylcarbamate, 9a: To a solution of amine, **8a** (0.25 g, 0.0013 moles) and Et_3N (0.158 g, 0.0016 moles) in DCM (5 mL), ethylchloroformate (0.155 g, 0.001 moles) was added at 5°C over 5 min. Reaction mass was stirred at RT for 3 hr and completion of the reaction was monitored by TLC. After completion of the reaction, reaction-mixture was poured into water, the organic layer was separated and washed with dil. HCl followed by water. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give **9a** as amorphous solid; 88% yield; m.p. 80-82°C; IR: 3349, 2981, 2938, 1772, 1704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.6-3.2 (m, 2H), 4.05 (q, 2H), 4.8 (m, 1H), 4.9-5.1 (m, 2H), 5.5 (s, 1H); mass: *m*/*z* 265 [M^++1].

General procedure for the preparation of carbamates, 16 and 7a: A solution of the azide (0.00124 moles), Ph_3P (0.391 g, 0.00149 moles) and alcohol (0.00248 moles) in toluene (10 mL) was taken under a CO_2 pressure (2-5 psi) at 0°C. Reaction mass was refluxed for 8 hr and completion of the reaction was monitored by TLC. After completion of the reaction, the reaction-mixture was concentrated to get corresponding carbamate in the crude form**.**

Ethyl-[4-(4-methoxyphenyl)-2-oxo-3-tosyloxazolidin-5-yl]methylcarbamate, **16**: This compound was obtained according to the general procedure mentioned above. Crude compound **16** was purified through flash column chromatography (ethylacetate:pet. ether 50:50 v/v) to get **16** as amorphous solid; 52.0% yield; m.p. 100-50°C; IR: 3340, 2982, 2932, 1770, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.4 (s, 3H), 2.6-3.2 (m, 2H), 3.9 (s, 3H), 4.05 (q, 2H), 4.85 (m, 1H), 4.95 (m, 1H), 5.5 (d, 1H, *J* = 7.3), 6.8, 7.05, 7.2, 7.5 (4d, 8H); mass: *m*/*z* 449 [M^++1].

8-Phenyl-6-oxa-1,3-diazabicyclo[3.2.1]octane-2,7-dione, **7a**: This compound was obtained according to the general procedure mentioned above. Yield 25%; unstable solid; IR: 3351, 1762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.8-3.2 (m, 2H), 4.9-5.0 (m, 1H), 5.35-5.45 (m, 1H), 7.05-7.4 (m, 5H), 7.9 (s, 1H); mass: *m*/*z* 219 [M^++1].

General procedure for the preparation of ureas, **12 and 13**: A solution of the azide (0.00124 moles), Ph_3P (0.358 g, 0.00136 moles) and aryl amine

(0.00149 mole) in toluene (10 mL) was taken under a CO_2 pressure (2-5 psi) at 0°C. Reaction mass was refluxed for 8 hr and completion of the reaction was monitored by TLC. After completion of the reaction, the reaction-mixture was concentrated to get corresponding crude urea derivative **12** or **13**.

1-Benzyl-3-[{4-(4-methoxyphenyl)-2-oxo-3-tosyl-oxazolidin-5-yl}methyl]urea, **12**: This compound was obtained according to the general procedure mentioned above. Crude urea **12** was purified using flash column chromatography (methanol:chloroform 15:85 v/v) to get **12** as amorphous solid. 93.5% yield; m.p. 94-105°C; IR: 3442, 1783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.2 (s, 3H), 2.85, 3.3 (2m, 2H), 3.8 (s, 3H), 4.3 (m, 2H), 4.7 (m, 1H), 4.9 (m, 2H), 5.4 (d, 1H, *J* = 7.5), 6.75, 6.9, 7.1, 7.35 (4d, 8H), 7.2-7.35 (m, 5H); mass: *m*/*z* 510 [M^++1].

1-[4-{2-(Dimethylamino)ethoxy}benzyl]-3-[{4-(4-methoxyphenyl)-2-oxo-3-tosyloxazolidin-5-yl}methyl]urea, **13**: This compound was obtained according to the general procedure mentioned above. Yield 89%; IR: 3375, 2926, 1783, 1514, 1168 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (m, 2H), 2.35 (s, 6H), 2.4 (s, 3H), 2.6-3.35 (m, 4H), 3.8 (s, 3H), 4.05 (t, 2H, *J* = 5.37), 4.2 (s, 2H), 4.8 (m, 1H), 5.05 (s, 1H), 5.25 (s, 1H), 5.4 (d, 1H, *J* = 7.32), 6.7-7.45 (m, 12H); mass: *m*/*z* 597 [M^++1].

Acknowledgements

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