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Insights into the bromination of 3-aryl-5-methyl-isoxazole-4-carboxylate: Synthesis of 3-aryl-5-bromomethyl-isoxazole-4-carboxylate as precursor to 3-aryl-5-formyl-isoxazole-4-carboxylate[§]

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Abstract—Results of the detailed investigations on the bromination of the methyl group of 3-aryl-5-methyl-isoxazole-4-carboxylate a precursor to obtain 3-aryl-5-formyl-isoxazole-4-carboxylate are described. The products generated during the study have been utilized as substrates for the syntheses of isoxazole-fused heterocycles.

1. Introduction

This study owes its origin to our continued interest in the Baylis-Hillman reaction of isoxazolecarbaldehydes. We have reported earlier[1-3] that compared to substituted-4-isoxazolecarbaldehyde, 3- and 5-isoxazolecarbaldehydes undergo significantly faster Baylis-Hillman reaction and the reason ascribed to this was the proximity of the heteroatom to the formyl group for the higher reactivity of aldehydes. This perception prompted us to conceive that the presence of an electron-withdrawing group, such as carboxylate at the 4-position in the 3-substituted-5-isoxazolecarbaldehyde, would provide a more fast reacting substrate than the one reported by us earlier. Such an isoxazolecarbaldehyde had previously been synthesized through the cycloaddition of nitrile oxides to methyl 4,4-dimethoxybut-2-ynoate and (*E*)-4,4-dimethoxy-3-(pyrrolidin-l-yl)but-2-enoate or p-toluene-sulfinyl derivatives in respectable yields.[4-5] In view of the fact that we had 3-aryl-5-methyl-isoxazole-4-carboxylate, we directed our efforts to obtain the desired aldehyde from this compound. In principle this aldehyde can be obtained through direct oxidation of the methyl group of 3-aryl-5-methyl-isoxazole-4-carboxylate or by generating the bromo-methyl derivative which on subsequent hydrolysis

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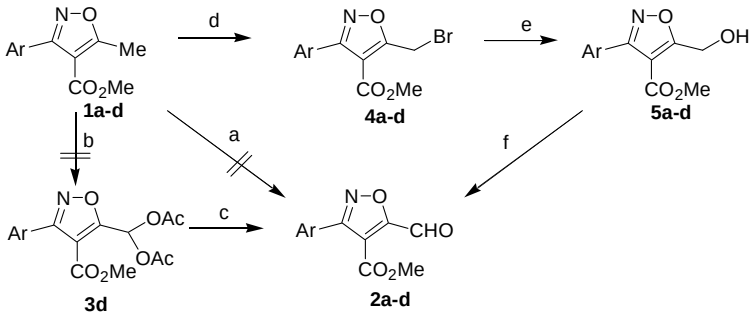
followed by oxidation could yield the desired aldehyde. Oxidation of the 3-aryl-5-methyl-isoxazole-4-carboxylate (**1a-d**) by SeO_2, $KMnO_4$ or CAN[6-8] failed in our hands to deliver the desired aldehyde. Search for literature precedence revealed that the bromination of the methyl group at 5-position of isoxazole ring was widely reported.[9-18] It is not only a key step in synthesis of a variety of AMPA agonists[9-14] but has also been utilized for generation of intermediates towards the synthesis of isoxazole-fused derivatives which are precursor to cyclic trione system present in natural products.[15-17]

Initial efforts to brominate the methyl group of the 3-aryl-5-methyl-isoxazole-4-carboxylate did not yield the desired results. It was observed that bromination was extremely sensitive to the reaction conditions which led us to carry out detailed investigations on the bromination of the methyl group in 3-aryl-5-methyl-isoxazole-4-carboxylate (1**a-d**). This study furnished a number of novel observations and helped us to develop an optimized procedure for obtaining 3-aryl-5-bromomethyl- and 5-dibromomethyl isoxazole-4-carboxylate which then easily furnished the desired aldehyde (**2a-d**). The intermediates generated facilitate access to isoxazole-annulated ring systems. The details of our study are presented here.

2. Results and Discussion

The oxidation of the 3-aryl-5-methyl-4-isoxazolecarboxylate **(1)** failed in our hands to deliver the desired aldehyde (**2**). (Scheme 1). In a different strategy, compound **1** was subjected to chromium diacetate-promoted oxidation to furnish the diacetate (**3)** which hydrolyzed in the presence of acid to furnish aldehyde (**2)**.[19] However, this reaction led to a complex mixture and the purification of the desired product was difficult. We therefore opted to brominate the methyl group which on the basis of literature precedence appeared to be easy and straightforward. However our observations were contrary to these reports[##]. Our findings are reported below.



Scheme 1. *Reagents and Conditions*: a) SeO_2, $KMnO_4$ or CAN, heat, 48 h. b) $CrO_2(OAc)_2$, AcOH, heat. c) HCl. d) NBS, UV light, CCl_4, 40-45^oC, 24h. e) DMSO, H_2O, 4h, heat. f) PCC, CH_2Cl_2, 10h.

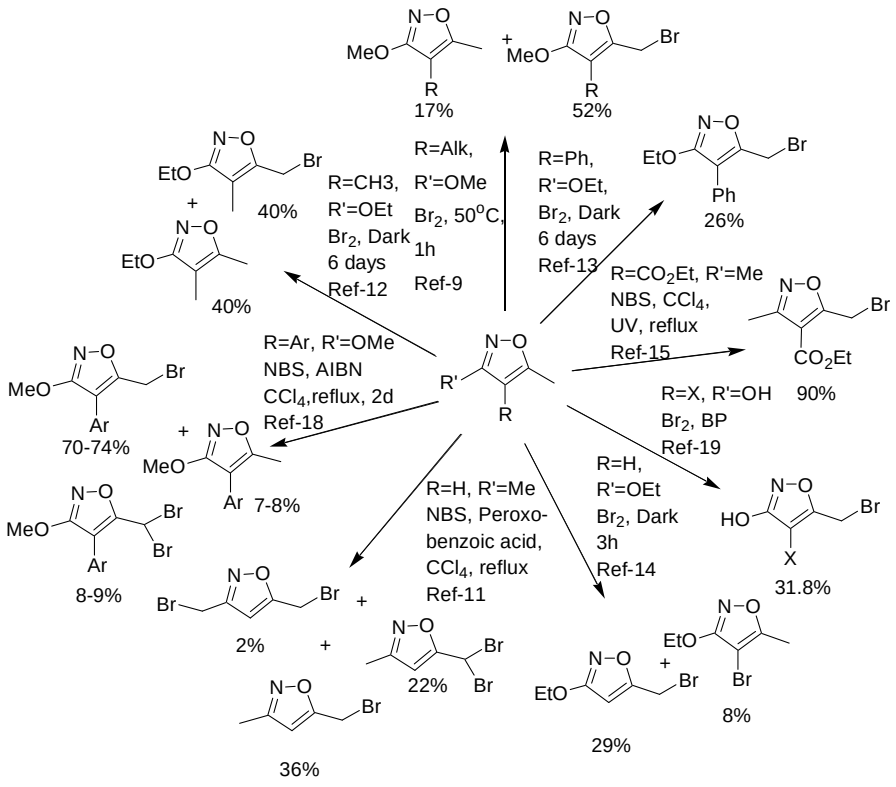
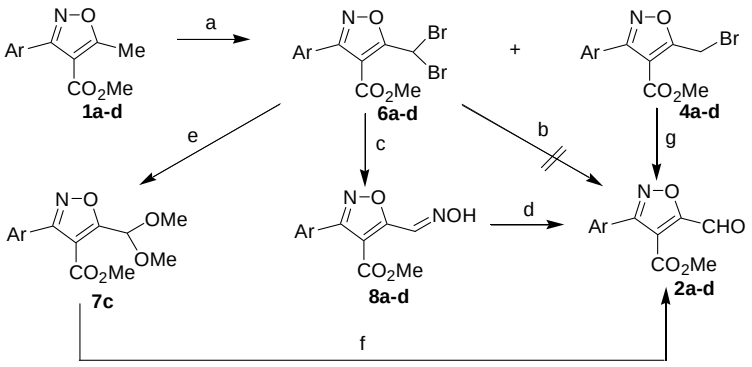


Figure 1. Few examples showing the variation in nature of products and yields of brominated derivative in reported procedures.

2.1. Studies on the bromination of 3-aryl-5-methyl-4-isoxazolecarboxylate

Bromination of the 5-methyl group in isoxazole is reported[9-19] to be accomplished with either bromine or NBS in CCl_4 in the presence of a radical initiator that could be UV light, AIBN or benzoyl peroxide (BP) or bromine in dark (Fig. 1). Based on these reports, the brominations of 3-aryl-5-methyl-4-isoxazolecarboxylates **(1a-d)** were carried out. The NBS-mediated bromination (using 2.0 or 1.5 equiv of NBS and a radical initiator) of the methyl group instead of mono-bromo derivatives **(4a-d)** (*CAUTION*), furnished the gem-dibromo-derivatives **(6a-d)** (*CAUTION*) in excellent yields (Scheme 2). These results were contrary to all earlier reports except by Dannhardt et al.[11] and Lecrec et al.[18] where the formation of a gem-dibromo derivative in 22% and 8% yields, respectively was reported as one of the product during NBS-promoted bromination. In the light of our objective to obtain the 5-formyl derivatives **(2a-d)**, the formation of gem dibromo-derivatives initially was not considered to be disadvantageous since the hydrolysis of gem-dibromo compounds to corresponding aldehyde is well-documented procedure.[20-27] It was disappointing to note that our attempts to generate the formyl derivatives **(2a-d)** directly from the gem-dibromo derivative **(6a-d)** in the presence of strong acid or alkali were unsuccessful. We, therefore, decided to modulate the bromination reaction in a manner to furnish exclusively the mono-bromo product **4**. This led to evaluation of various conditions in which the radical initiator, amount of NBS, temperature and solvent dilution were varied to determine the optimum reaction condition to obtain the mono-brominated derivative **(4)** in good yields. The bromination of compound **1a** in CCl_4 as solvent was chosen for the model study and the details of various conditions evaluated during this study are presented in Table 1. It would be appropriate here to mention that since the spots for the starting substrate **(1a)**, mono-bromo **(4a)** and gem-dibromo **(6a)** compounds do not resolve well on TLC, the progress of the reaction was monitored through HPLC. A gradient of 10-98 % methanol/ water containing 0.1 % TFA in 45 min at a flow rate of 2 mL/ min. on a RP-18 column (4.6 X 250 mm) resolved the three components of the reaction mixture (R_t; **1a**= 16.6 min; **4a**= 17.5 min; **6a**=20.3 min). As evident from the table the reaction under reflux invariably led to formation of compound **6a** as the major product. However when the reaction was carried out with 0.8 equiv NBS with respect to compound **1a** at a temperature between 40-45 ^oC the mono-bromo derivative **4a** was obtained in high yields. Thus reaction condition to obtain exclusively either monobromo or gem dibromo derivative could be developed. Contrary to the NBS-promoted bromination, all attempts to brominate the compound **1a** with neat bromine in dark led to a complex mixture. In order to confirm that the gem-dibromo derivative is formed through the corresponding mono-bromo derivative, compound **4a** was subjected to further bromination with NBS under UV light to afford the product **6a** almost instantaneously. This observation suggested that the monobromo compound was extremely susceptible to bromination and could explain the sensitivity of the reaction conditions for the bromination of the 5-methyl group in 3-aryl-5-methyl-isoxazole-4-carboxylate.



Scheme 2. *Reagents and Conditions*: a) NBS (2.0 equiv), UV light, CCl_4, reflux, 12h for compound **6** as major product or NBS (0.8 equiv), UV light, CCl_4, 40-45 ^oC, 24h for compound **4** as major product. b) conc. H_2SO_4, heat, 48 h or $CaCO_3$, heat,

48h. c) $NH_2OH.HCl$, NaOAc, MeOH, reflux, 6-7h. d) aq. HCHO (30%), conc. HCl, r.t., 1h or PDC, CH_2Cl_2, 14h. e) NaOMe, MeOH, r.t., 30 min. f) HCl, r.t., 30 min. g) i. DMSO, H_2O, 4h, heat. ii. PCC, CH_2Cl_2, 10h.

Table 1. Result of bromination of 3-phenyl-5-methyl-isoxazole-4-carboxylate **1a** with NBS in varying conditions

Entry	Reaction variables					Ratio of the product as % Area observed in HPLC		
	NBS equiv[a]	Solvent CCl_4	Radical initiator	Temp.	Time (h)	Monobromo **4a**	Dibromo **6a**	Unreacted **1a**
1	2.0	1:50	BP or AIBN	reflux	12	0	100 (80)[b]	0
2	2.0	1:50	UV	reflux	12	0	100 (84)[b]	0
3	1.5	1:50	BP	reflux	12	9	37	54
4	1.5	1:50	AIBN	reflux	12	11	49	40
					24	0	87	13
5	1.5	1:50	UV	reflux	12	13	56	31
					24	0	83	17
				40-45ºC	12	28	0	72
					24	14	43	43
6	1.5 (3 x 0.5 1.5h interval)	1:50	UV	reflux	12	14	58	28
					24	3	81	16
7	1.5	1:200	UV	reflux	12	2	68	30
8	1.0	1:50	UV	reflux	12	24	2	74
					24	9	76	15
				40-45ºC	12	12	0	84
					24	55	31	14
9[c]	**0.8**	1:50	UV	reflux	12	19	0	81
					24	20	75	5
				40-45ºC	12	15	0	85
					24	**81 (76)**[b, d]	**3**	**16**
10	0.5	1:50	UV	40-45ºC	24	27	2	71
11	Neat Br_2	-	dark	r.t.	144	Mixture of products		

[a] 3.0 equiv of NBS leads to compound **6a** within 4 h of reaction time. [b] Figure in parentheses are yields. [c]This condition holds true for 50 g batch size too. [d]The yield of compound **4a** is based on the amount of the alcohol **5a** obtained after hydrolysis. It excludes the amount of recovered starting material.

2.2. Studies on the hydrolysis of mono- and gem di-bromo derivatives

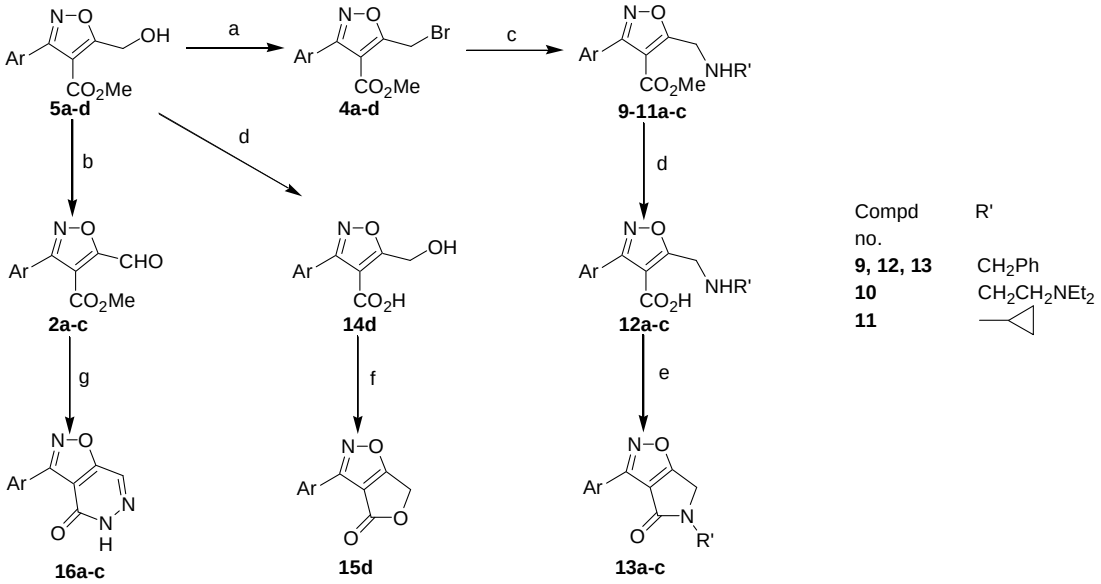
Since the compounds **1, 4** and **6** present in the residue obtained after work up of the bromination could not be separated efficiently through the column chromatography, the residue was directly utilized for studying the fate of hydrolysis. The hydrolysis of the mono-bromo compounds **4a-d** was accomplished in the presence of DMSO-water. The resulting mixture of hydroxy-derivative **(5)**, gem-dibromo derivative **(6)** and the starting substrate **(1)** was separated through column chromatography. Subsequent oxidation of alcohols **(5 a-d)** in the presence of PCC furnished the corresponding aldehydes **(2 a-d)** in good yields.

The dibromo derivative **(6c)**, on reaction with freshly prepared NaOMe furnished the dimethoxy acetal **(7c)** that upon acid hydrolysis furnished the formyl derivative **2c** in ordinary yield.[28] In another strategy the reaction of gem-dibromo derivatives **(6a-d)** with hydroxylamine hydrochloride on prolonged heating yielded the corresponding oximes **(8a-d)**,[29-30] from which the corresponding formyl derivatives **(2a-d)** could again be

generated by acid hydrolysis in presence of formaldehyde in high yields.[31] The PDC method[32] of hydrolysis of oximes was also evaluated to furnish the aldehydes in fair yields only.

2.3. Access to Isoxazole-annulated heterocycles

In our efforts to exemplify the usefulness of the compounds generated during this study, the syntheses of 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-ones **(13a-c)**, isoxazolo[4, 5-d]furanone **(15d)** and isoxazole [4, 5-d] pyridazin-4-ones **(16a-c)** were carried out. Synthesis of 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-ones **(11a-c)** were analogous to the one reported by Jones et al.[16] The required bromo-derivatives **(4a-d)** were obtained from alcohols **(5a-d)** via PBr_3-mediated bromination in quantitative yields. The compounds **4a-c** on nucleophilic substitution with various amines furnished the secondary amines **(9-11-a-c)** in short



Scheme 3. *Reagents and Conditions*: a) PBr_3, CH_2Cl_2, 0 ^oC, 30 min. b) PCC, CH_2Cl_2, 10h. c) $R'NH_2$, Et_3N, anhyd. Benzene, reflux, 30 min. d) KOH in MeOH: H_2O, r.t., 1h. e) EDCI, DIEA, DMAP, CH_2Cl_2, r.t., 45 min. f) DIC, DMAP. g) NH_2NH_2. H_2O, MeOH, r.t..

periods and in excellent yields. As reported earlier[16] no cyclization was observed at this stage. Thereafter, the ester was saponified in the presence of methanolic KOH to afford the corresponding acids **12a-c**. These acids were then subjected to EDCI mediated coupling to furnish the bicyclic lactams **(13a-c)**.

The synthesis of another isoxazole-fused ring system 3-(2-chlorophenyl)-6*H*-furo[3,4-*d*]isoxazol-4-one **(15d)** was carried out from the acid **(14d)**. The latter was obtained after the saponification of the alcohol **5d**. A DIC-promoted cyclization of this hydroxy acid **14d** furnished the product **15d**. The formation of 3-phenyl-5*H*-isoxazolo [4,5-*d*]pyridazin-4-one **(16a)** is reported as one pot two step procedure where the formyl derivative **(2a)** generated in situ is reacted with hydrazine hydrate in water: acetic acid mixture.[5] In contrast to this report, when the reactions of pure formyl derivatives **(2a-c)** were carried out with hydrazine hydrate we could isolate the 3-substituted phenyl-5*H*-isoxazolo [4,5-*d*]pyridazin-4-ones **(16a-c)** were isolated in excellent yields at room temperature without any additive.

In conclusion we have established optimized procedure for the bromination of 3-aryl-5-methyl-isoxazole-4-carboxylates to obtain exclusively either the mono-bromo or gem dibromo methyl derivative in excellent yields. The mono-bromo methyl derivative has been shown to be an excellent substrate for obtaining the 3-aryl-5-formyl-isoxazole-4-carboxylate. The substrates generated during the study are exemplified for facile synthesis of isoxazole-annulated ring systems. Evaluation of Baylis-Hillman reaction of this highly substituted-5-isoxazolecarbaldehyde will form part of our future communications.

3. Experimental

3.1. General. Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using

Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-200 FT spectrometers, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL *III* microanalyzer. *CAUTION*: The gem-dibromo and mono-bromo derivatives cause severe irritation on exposure leading to small blisters occasionally. The stated yields of the alcohols **(5a-d)** are the one obtained by the hydrolysis of pure mono-bromo-derivatives **(4a-d)**. Similarly the yields of the mono-bromo derivatives **(4a-d)** are the one observed during the PBr_3-promoted bromination of alcohols **(5a-d)**.

3.2. Bromination and Hydrolysis-General Procedure

To the appropriate solution of compounds from **1a-d** (46.0 mmol) in CCl_4 (250 mL) was added NBS in the required quantity (from Table 1) and the reaction was allowed to stir either under refluxing or at 40-45 ^{o}C (maintained by placing the reaction in a water bath and changing the water after every 2-3 hour). The optimum reaction time for phenyl and 4-chlorophenyl substitution was 24h while that for 2-chloro-phenyl and 2, 4-dichlorophenyl was observed to be 40h. On completion, the reaction was cooled to 10 ^{o}C, and the precipitated succinimide was filtered. The filtrate was evaporated under vacuum to furnish a reddish brown oil. This residue consists of inseparable mixture of gem-dibromo derivative, starting material and mono-bromo derivative. This residue was taken up in DMSO: water (100 mL, 90: 10 v/v) and stirred at 80 ^{o}C for 4h. The reaction mixture was quenched with excess of cold water (250 mL) and extracted with diethyl ether (2 X 150 mL). The combined and dried (Na_2SO_4) organic phase was evaporated and the residue was subjected to column chromatography over silica gel (60-120 mesh) using hexane: ethyl acetate mixture as eluent. Elution with 5% ethyl acetate in hexane (v/v) gave the gem-dibromo derivative. Further elution with 15 % ethyl acetate in hexane yielded the unreacted starting material while a mixture of 50% ethyl acetate in hexane furnished the alcohol.

3.2.1. 5-Dibromomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (**6a).** Compound obtained as white solid; mp 69-71 ^{o}C; [Found C, 38.78; H, 2.51; N, 4.00. $C_{12}H_9Br_2NO_3$ requires C, 38.43; H, 2.42; N, 3.74]; ν_{max} (KBr) 1706 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.82 (s, 3H, CO_2CH_3), 7.30 (s, 1H, $CHBr_2$), 7.46-7.52 (m, 3H, ArH), 7.59-7.64 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32MHz) δ= 23.03, 52.91, 105.98, 127.71, 128.67, 129.84, 130.76, 161.26, 162.86, 171.88; Mass (FAB+) m/z % 376 (M^++1).

3.2.2. 3-(4-Chloro-phenyl)-5-dibromomethyl-isoxazole-4-carboxylic acid methyl ester (6b). Compound obtained as pale yellow solid, mp 87-88 ^{o}C; [Found C, 35.57; H, 2.06; N, 3.69. $C_{12}H_8Br_2ClNO_3$ requires C, 35.20; H, 1.97; N, 3.42]; ν_{max} (KBr) 1707 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.85 (s, 3H, CO_2CH_3), 7.29 (s, 1H, $CHBr_2$), 7.43, 7.47 (d, 2H, *J*= 8.4 Hz, ArH), 7.56, 7.60 (d, 2H, *J*= 8.4 Hz, ArH); Mass (FAB+) m/z % 410 (M^++1).

3.2.3. 5-Dibromomethyl-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (6c). Compound obtained as white solid, mp 128-130 ^{o}C; [Found C, 32.56; H, 1.73; N, 3.25. $C_{12}H_7Br_2Cl_2NO_3$ requires C, 32.47; H, 1.59; N, 3.16]; ν_{max} (KBr) 1704 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.76 (s, 3H, CO_2CH_3), 7.28 (s, 1H, $CHBr_2$), 7.39 (s, 2H, ArH), 7.52 (d, 1H, ArH); Mass (FAB+) m/z % 444 (M^++1).

3.2.4. 3-(2-Chloro-phenyl)-5-dibromomethyl-isoxazole-4-carboxylic acid methyl ester (6d). Compound obtained as white solid, mp 74-75 ^{o}C; [Found C, 35.41; H, 1.87; N, 3.23. $C_{12}H_8Br_2ClNO_3$ requires C, 35.20; H, 1.97; N, 3.42]; ν_{max} (KBr) 1728 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.74 (s, 3H, CO_2CH_3), 7.29 (s, 1H, $CHBr_2$), 7.33- 7.49 (m, 4H, ArH); Mass (FAB+) m/z % 410 (M^++1).

3.2.5. 5-Hydroxymethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (5a). Yield 93 %; Compound obtained as pale yellow solid; mp 62-64 ^{o}C; [Found: C, 61.81; H, 4.76; N, 6.06. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01]. ν_{max} (KBr) 1735 (CO_2Me), 3498 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.78 (s, 3H, CO_2CH_3), 4.97 (s, 2H, CH_2), 7.44-7.49 (m, 3H, ArH), 7.57-7.62 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32MHz) δ= 52.61, 57.17, 109.35, 128.27, 128.54, 129.75, 130.42, 162.77, 163.35, 178.01; Mass (FAB+) m/z % 234 (M^++1).

3.2.6. 3-(4-Chloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid methyl ester (5b). Yield 87 %; Compound obtained as light brown solid; mp 95-96 ^{o}C; [Found C, 53.69; H, 3.69; N, 5.39. $C_{12}H_{10}ClNO_4$ requires C, 53.85; H, 3.77; N, 5.23]; ν_{max} (KBr) 1728 (CO_2Me), 3427 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.79 (s, 3H, CO_2CH_3), 4.97 (s, 2H, CH_2), 7.41, 7.45 (d, 2H, *J*= 8.4 Hz, ArH), 7.53, 7.57 (d, 2H, *J*= 8.4 Hz, ArH); Mass (FAB+) m/z % 268 (M^++1).

3.2.7. 3-(2,4-Dichloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid methyl ester (5c). Yield 79 %; Compound obtained as pale yellow oil; [Found C, 47.77; H, 3.30; N, 4.49. $C_{12}H_9Cl_2NO_4$ requires C, 47.71; H, 3.00; N, 4.64]; ν_{max} (KBr) 1725 (CO_2Me), 3405 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.75 (s, 3H, CO_2CH_3), 4.99 (s, 2H, CH_2), 7.359, 7.364 (d, 2H, *J*= 1.1 Hz, ArH), 7.52 (d, 1H, ArH); Mass (FAB+) m/z % 302 (M^++1).

3.2.8. 3-(2-Chloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid methyl ester (5d). Yield 76 %; Compound obtained as white solid, mp 94-96 ^{o}C; [Found: C, 53.55; H, 4.14; N, 5.24. $C_{12}H_{10}ClNO_4$ requires C, 53.85; H, 3.77; N, 5.23]; ν_{max} (KBr) 1735 (CO_2Me), 3427 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.69 (s, 3H, CO_2CH_3), 4.99 (s, 2H, CH_2), 7.35-7.47 (m, 4H, ArH); Mass (FAB+) m/z % 268 (M^++1);

3.3. Oxidation of alcohol with PCC-General Procedure

To the solution of appropriate alcohol from **5a-d** (46 mmol) in dry CH_2Cl_2 was added PCC (11.0 g, 51 mmol) and the resulting mixture was stirred at r.t. for 10-12h. Thereafter the reaction mixture was passed through a column of silica gel (60-120 mesh) using ethyl acetate: hexane (50: 50, v/v) to afford the aldehydes.

3.3.1. 5-Formyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (2a). Yield 92 %; Compound obtained as off white solid, mp 65-67 ^oC; [Found 62.49; H, 4.18; N, 5.91. $C_{12}H_9NO_4$ requires C, 62.34; H, 3.92; N, 6.06]; ν_{max} (KBr)1730 (CO_2Me), 1701 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.91 (s, 3H, CO_2CH_3), 7.44-7.52 (m, 3H, ,ArH), 7.65-7.70 (m, 2H, ArH), 10.34 (s, 1H, CHO); Mass (FAB+) m/z % 232 (M^++1).

3.3.2. 3-(4-Chloro-phenyl)-5-formyl-isoxazole-4-carboxylic acid methyl ester (2b). Yield 84 %; Compound obtained as off white solid, mp 88-90 ^oC; [Found: C, 54.46; H, 3.40; N, 4.98. $C_{12}H_8ClNO_4$ requires C, 54.26; H, 3.04; N, 5.27]; ν_{max} (KBr) 1728 (CO_2Me), 1700 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.93 (s, 3H, CO_2CH_3), 7.45, 7.49 (d, 2H, *J*= 8.4 Hz, ArH), 7.62, 7.66 (d, 2H, *J*= 8.4 Hz, ArH), 10.34 (s, 1H, CHO); Mass (FAB+) m/z % 266 (M^++1);

3.3.3. 3-(2,4-Dichloro-phenyl)-5-formyl-isoxazole-4-carboxylic acid methyl ester (2c). Yield 77 %; Compound obtained as white solid, mp 58-59 ^oC; [Found 48.03; H, 2.35; N, 4.67. $C_{12}H_7Cl_2NO_4$ requires C, 47.88; H, 1.99; N, 4.66]; ν_{max} (KBr) 1724 (CO_2Me), 1697 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.79 (s, 3H, CO_2CH_3), 7.359, 7.364 (d, 2H, *J*= 1.1 Hz, ArH), 7.52 (d, 1H, ArH), 10.37 (s, 1H, CHO); Mass (FAB+) m/z % 300 (M^++1).

3.3.4. 3-(2-Chloro-phenyl)-5-formyl-isoxazole-4-carboxylic acid methyl ester (2d). Yield 60 %; Compound obtained as brown oil; [Found C, 54.55; H, 2.81; N, 5.29. $C_{12}H_8ClNO_4$ requires C, 54.26; H, 3.04; N, 5.27]; ν_{max} (Neat) 1730 (CO_2Me), 1700 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.82 (s, 3H, CO_2CH_3), 7.39-7.51 (m, 4H, ArH), 10.37 (s, 1H, CHO); Mass (FAB+) m/z % 266 (M^++1).

3.4. Bromination of Alcohol-General Procedure

To the stirred solution of appropriate alcohol from **5a-d** (5.0 mmol) in anhyd. CH_2Cl_2 (5 mL) was added dropwise a solution of PBr_3 (0.475 mL, 5.0 mmol) in anhyd. CH_2Cl_2 (10 mL) at 0 ^oC. The reaction was continued at same temperature for 30 min. Thereafter the solvent was evaporated to obtain a residue which was partitioned between ethyl acetate (30mL) and water (25 mL) (extraction with CH_2Cl_2 led to a micelle that was difficult to separate). The organic layer was separated, dried (Na_2SO_4) and evaporated to obtain an oily residue that was used as such for further reaction. However the analytical samples were obtained through column chromatography over silica gel (100-200 mesh) using 5% ethyl acetate in hexane as eluent.

3.4.1. 5-Bromomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (4a). Yield 99 %; Compound obtained as yellow oil; [Found C, 48.92; H, 3.70; N, 4.58. $C_{12}H_{10}BrNO_3$ requires C, 48.67; H, 3.40; N, 4.73]; ν_{max} (Neat) 1727 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.82 (s, 3H, CO_2CH_3), 4.81 (s, 2H, CH_2Br), 7.43-7.48 (m, 3H, ArH), 7.59-7.66 (m, 2H, ArH); Mass (FAB+) m/z % 296 (M^++1).

3.4.2. 5-Bromomethyl-3-(4-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4b). Yield 92 %; Compound obtained as dark yellow oil; [Found C, 43.40; H, 2.87; N, 4.11. $C_{12}H_9BrClNO_3$ requires C, 43.60; H, 2.74; N, 4.24]; ν_{max} (Neat) 1729 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.85 (s, 3H, CO_2CH_3), 4.80 (s, 2H, CH_2Br), 7.42, 7.46 (s, 2H, *J*= 8.2 Hz, ArH), 7.58, 7.62 (s, 2H, *J*= 8.2 Hz, ArH); Mass (FAB+) m/z % 332 (M^++1).

3.4.3. 5-Bromomethyl-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4c). Yield 86 %; Compound obtained as light brown oil; [Found C, 39.11; H, 2.23; N, 4.01. $C_{12}H_8BrCl_2NO_3$ requires C, 39.49; H, 2.21; N, 3.84]; ν_{max} (Neat) 1730 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.82 (s, 3H, CO_2CH_3), 4.80 (s, 2H, CH_2Br), 7.42-7.50 (m, 1H, ArH), 7.60-7.66 (m, 2H, ArH); Mass (FAB+) m/z % 365 (M^++1).

3.4.4. 5-Bromomethyl-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4d). Yield 69 %; Compound obtained as yellow oil; [Found C, 43.87; H, 2.79; N, 4.00. Anal. $C_{12}H_9BrClNO_3$ requires C, 43.60; H, 2.74; N, 4.24]; ν_{max} (Neat) 1730 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 3.74 (s, 3H, CO_2CH_3), 4.83 (s, 2H, CH_2Br), 7.35-7.47 (m, 4H, ArH); Mass (FAB+) m/z % 332 (M^++1).

3.5. Oximation of gem-dibromo derivatives-General procedure

A mixture of appropriate gem-dibromo derivative from **6a-d** (11.3 mmol), NaOAc (33.9 mmol) and $NH_2OH.HCl$ (33.9 mmol) in methanol (75mL) mixture was refluxed for 6-7h. The excess solvent was removed and reaction mixture was quenched with water to furnish the oximes as white solids. To obtain the analytical samples the products were column chromatographed over silica gel using hexane: ethyl acetate (60:40, v/v) mixture as eluent.

3.5.1. 5-(Hydroxyimino-methyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (8a). Yield 85 %; Compound obtained as white solid, mp 164-165 ^oC; [Found: C, 58.26; H, 3.77; N, 11.15. $C_{12}H_{10}N_2O_4$ requires C, 58.54; H, 4.09; N, 11.38]; ν_{max} (KBr) 1732 (CO_2Me), 3260 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200MHz) δ= 3.83 (CO_2CH_3), 7.46-7.51 (m, 3H, Ar-H), 7.63-7.67 (m, 2H, Ar-H), 8.67 (s, 1H, =CH), 8.98 (s, 1H, NOH); ^{13}C NMR ($CDCl_3$, 50.32MHz) δ= 52.06, 127.76, 128.63, 129.77, 130.62, 139.09, 161.69, 163.12, 166.28; Mass (FAB+) m/z % 247 (M^+).

3.5.2. 3-(4-Chloro-phenyl)-5-(hydroxyimino-methyl)-isoxazole-4-carboxylic acid methyl ester (8b). Yield 80 %; Compound obtained as white solid, mp 130-132 ^{o}C; [Found C, 51.69; H, 3.61; N, 9.60. $C_{12}H_9ClN_2O_4$ requires C, 51.35; H, 3.23; N, 9.98]; ν_{max} (KBr) 1732 (CO_2Me), 3260 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$+ $DMSOd_6$, 200MHz) δ= 3.83 (CO_2CH_3), 7.46-7.51 (m, 3H, Ar-H), 7.63-7.67 (m, 2H, Ar-H), 8.67 (s, 1H, =CH), 8.98 (s, 1H, NOH); Mass (FAB+) m/z % 247 (M^+).

3.5.3. 3-(2,4-Dichloro-phenyl)-5-(hydroxyimino-methyl)-isoxazole-4-carboxylic acid methyl ester (8c). Yield 78 %; Compound obtained as white solid, mp 184-186 ^{o}C; [Found C, 45.68; H, 2.93; N, 9.01. $C_{12}H_8Cl_2N_2O_4$ requires C, 45.74; H, 2.56; N, 8.89] IR (KBr); 1715 (CO_2Me), 3402 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$, 200MHz) δ= 3.77 (CO_2CH_3), 7.39 (s, 2H, Ar-H), 7.53 (m, 1H, Ar-H), 8.65 (s, 1H, =CH), 9.15 (s, 1H, NOH); Mass (FAB+) m/z % 314 (M^+).

3.5.4. 3-(2-Chloro-phenyl)-5-(hydroxyimino-methyl)-isoxazole-4-carboxylic acid methyl ester (8d). Yield 75 %; Compound obtained as white solid, mp 164-165 ^{o}C; [Found: C, 51.18; H, 3.61; N, 10.02. $C_{12}H_9ClN_2O_4$ requires C, 51.35; H, 3.23; N, 9.98]; ν_{max} (KBr) 1730 (CO_2Me), 3280 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$, 200MHz) δ= 3.75 (CO_2CH_3), 7.35-7.51 (m, 4H, Ar-H), 8.67 (s, 1H, =CH), 9.18 (brs, 1H, NOH); Mass (FAB+) m/z % 281 (M^+).

3.6. Formation of dimethoxy acetal-Typical procedure

To the stirred solution of sodium methoxide (10.0 mmol) in methanol (30 mL) was added the compound **6c** (5.0 mmol) at 0 ºC and the reaction was allowed to proceed for 30 min at same temperature. The excess methanol was evaporated and the reaction mixture was extracted with water (40 mL) and ethyl acteate (2 X 50 mL). The organic layers were combined, dried (Na_2SO_4) and reduced under vacuum to obtain a residue that on chromatography over silica gel (230-400 mesh) using a mixture of hexane: ethylacetate (80: 20, v/v) furnished the acetal.

3.6.1. 3-(2,4-Dichloro-phenyl)-5-dimethoxymethyl-isoxazole-4-carboxylic acid methyl ester (7c). Yield 28%; Compound was obtained as white solid; mp 175-78 ^{o}C; [Found: C, 48.74; H, 3.71; N, 4.32. $C_{14}H_{13}Cl_2NO_5$ requires C, 48.58; H, 3.79; N, 4.05;]; ν_{max} (KBr) 1719 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ = 3.53 (s, 6H, 2 X OCH_3), 3.73 (s, 3H, CO_2CH_3), 6.08 (s, 1H, CH), 7.36 (s, 2H, ArH), 7.51 (s, 1H, ArH); Mass (FAB+) m/z % 346 (M^++1).

3.7. Hydrolysis of oxime-General procedure

3.7.1. HCHO/ HCl method

To a stirred solution of formaldehyde (33% aq.): conc. HCl (16 mL, 50: 50, v/v) was added appropriate oxime from **8a-d** (3.5 mmol) and the reaction was continued at r.t. for 1h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2 X 50 mL). The organic layers were pooled, dried (Na_2SO_4) and concentrated under reduced pressure to obtain a residue. This residue upon column chromatography over silica gel using a mixture of hexane: ethyl acetate (70: 30, v/v) as eluent yielded the pure aldehyde in 85-91 % yields.

3.7.2. PDC method

To a stirred solution of oxime (5 mmol) in 50 mL of anhyd. CH_2Cl_2 was added PDC (3.76 g, 10 mmol) at r.t. The reaction was continued for 14h. Thereafter the reaction mass was filtered through silica gel column (60-120 mesh) using using a mixture of hexane: ethyl acetate (70: 30, v/v) to obtain the pure aldehydes in 45-50% yields.

3.8. Reaction with amines-General procedure

A mixture of bromide from compound **4a-c** (5.0 mmol), Et_3N (0.9 mL, 6.5 mmol) and the appropriate amine (5.5 mmol) in anhyd. benzene (5mL) was refluxed under stirring at 80 ^{o}C. After 1h the reaction was cooled to r.t. and extracted with water (30 mL) and ethyl acetate (2 X 35 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to obtain an oily residue. The products from benzyl amine and cyclopropyl amine were purified through column chromatography over silica gel (100-200 mesh) while that obtained from amino diethyl ethyl amine were purified on basic alumina. A mixture of hexane and ethyl acetate (60:40, v/v) was used as eluent on either of the adsorbent.

3.8.1. 5-(Benzylamino-methyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (9a). Yield 74%; Compound was obtained as yellow oil; Oxalate salt as white solid, mp 199-200 ^{o}C; [Found: C, 65.73; H, 5.76; N, 7.59. $C_{19}H_{18}N_2O_3.(CO_2H)_2$ requires C, 65.96; H, 5.80; N, 7.33]; ν_{max} (Neat) 1728 (CO_2Me), 3341 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.66 (s, 3H, CO_2CH_3), 3.85 (s, 2H, N-CH_2), 4.22 (s, 2H, N-CH_2), 7.27-7.59 (m, 10H, ArH); Mass (ES+) m/z % 323.87 (M^++1).

3.8.2. 5-(Benzylamino-methyl)-3-(4-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (9b). Yield 69 %; Compound obtained as yellow oil; Oxalate salt as white solid, mp 191-193 ^{o}C; [Found C, 56.83; H, 4.18; N, 6.00. $C_{19}H_{17}ClN_2O_3$. $(CO_2H)_2$ requires C, 56.45; H, 4.29; N, 6.27]; ν_{max} (Neat) 1726 (CO_2Me), 3429 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.74 (s, 3H, CO_2CH_3), 3.85 (s, 2H, N-CH_2), 4.23 (s, 2H, N-CH_2), 7.27-7.35 (m, 5H, ArH), 7.41, 7.44 (d, 2H, *J*= 8.2 Hz, Ar-H), 7.54, 7.58 (d, 2H, *J*= 8.2 Hz, Ar-H); Mass (ES+) m/z % 357.53 (M^++1).

3.8.3. 5-(Benzylamino-methyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (9c). Yield 67 %; Compound obtained as yellow oil; [Found C 58.47; H, 4.51; N, 7.35. $C_{19}H_{16}Cl_2N_2O_3$ requires C, 58.33; H, 4.12; N, 7.16]; ν_{max} (Neat) 1726 (CO_2Me), 3427 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 3.68 (s, 3H, CO_2CH_3), 3.86 (s, 2H, NH-CH_2), 4.26 (s, 2H, NH-CH_2), 7.28-7.42 (m, 7H, ArH), 7.50 (s, 1H, Ar-H); Mass (FAB+) m/z % 391 (M^++1).

3.8.4. 5-(2-Diethylamino-ethylamino)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (10a). Yield 71 %; Compound obtained as yellow oil; Oxalate salt as white solid, mp 181-183 ^{o}C; [Found C, 50.47; H, 6 .14; N, 7.98. $C_{17}H_{23}N_3O_3$. $2(CO_2H)_2$.1/2 H_2O requires C, 50.79; H, 5.81; N, 8.07]; ν_{max} (Neat) 1728 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 1.00 (t, 6H, *J*= 7.0 Hz, 2 X CH_3), 2.42-2.75 (m, 8H, N-CH_2), 3.78 (s, 3H, CO_2CH_3), 4.25 (s, 2H, N-CH_2), 7.44-7.49 (m, 3H, ArH), 7.56-7.64 (m, 2H, ArH); Mass (ES+) m/z % 332.87 (M^++1).

3.8.5. 3-(4-Chloro-phenyl)-5-[(2-diethylamino-ethylamino)-methyl]-isoxazole-4-carboxylic acid methyl ester (10b). Yield 66 %; Compound obtained as dark yellow oil; Oxalate salt as white solid, mp 183-185 ^{o}C; [Found C, 48.02; H, 5.16; N, 7.55. $C_{18}H_{24}ClN_3O_3$. $2(CO_2H)_2$ requires C, 48.40; H, 5.17; N, 7.70]; ν_{max} (Neat) 1727 (CO_2Me), 3331 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 1.00 (t, 6H, *J*= 7.0 Hz, 2 X CH_3), 2.46-2.75 (m, 8H, N-CH_2), 3.79 (s, 3H, CO_2CH_3), 4.25 (s, 2H, N-CH_2), 7.41, 7.45 (d, 2H, J= 8.4 Hz, ArH), 7.56, 7.60 (d, 2H, J= 8.4 Hz, ArH); Mass (ES+) m/z % 366.80 (M^++1).

3.8.6. 3-(2,4-Dichloro-phenyl)-5-[(2-diethylamino-ethylamino)-methyl]-isoxazole-4-carboxylic acid methyl ester (10c). Yield 67 %; Compound obtained as dark yellow oil; [Found: C, 54.16; H, 6.14; N, 10.18. $C_{18}H_{23}Cl_2N_3O_2$ requires C, 54.01; H, 5.79; N, 10.50]; ν_{max} (Neat) 1728 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 1.01 (t, 6H, *J*= 7.0 Hz, 2 X CH_3), 2.44-2.74 (m, 8H, N-CH_2), 3.71 (s, 3H, CO_2CH_3), 4.27 (s, 2H, N-CH_2), 7.348, 7.353 (d, 2H, *J*= 1.0 Hz, ArH), 7.50 (s, 1H, ArH); Mass (FAB+) m/z % 400 (M^++1).

3.8.7. 5-Cyclopropylaminomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (11a). Yield 73 %; Compound obtained as yellow oil; [Found C, 64.42; H, 5.89; N, 9.64. $C_{15}H_{16}N_2O_3$. 1/2H_2O requires C, 64.09; H, 6.09; N, 9.96]; ν_{max} (Neat) 1726 (CO_2Me), 3317 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 0.46-0.51 (m, 4H, CH_2), 2.16-2.22 (m, 1H, CH), 3.78 (s, 3H, CO_2CH_3), 4.27 (s, 2H, N-CH_2), 7.44-7.48 (m, 3H, ArH), 7.60-7.65 (m, 2H, ArH); Mass (ES+) m/z % 273.80 (M^++1).

3.8.8. 3-(4-Chloro-phenyl)-5-cyclopropylaminomethyl-isoxazole-4-carboxylic acid methyl ester (11b). Yield 68 %; Compound obtained as brown oil; Oxalate salt as white solid, mp 156-158 ^{o}C; [Found C, 51.71; H, 4.22; N, 6.90. $C_{15}H_{15}ClN_2O_3$. $(CO_2H)_2$ requires C, 51.46; H, 4.32; N, 7.06]; ν_{max} (Neat) 1725 (CO_2Me), 3309 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 0.43-0.54 (m, 4H, CH_2), 2.14-2.20 (m, 1H, CH), 3.80 (s, 3H, CO_2CH_3), 4.26 (s, 2H, N-CH_2), 7.42, 7.46 (d, 2H, *J*= 8.4 Hz, ArH), 7.56-7.60 (m, 2H, *J*= 8.4 Hz, ArH); Mass (ES+) m/z % 307.67 (M^++1).

3.8.90. 5-Cyclopropylaminomethyl-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (11c). Yield 59 %; Compound obtained as brown oil; [Found: C, 52.71; H, 4.22; N, 8.11. $C_{15}H_{14}Cl_2N_2O_3$ requires C, 52.80; H, 4.14; N, 8.21]; ν_{max} (Neat) 1725 (CO_2Me), 3424 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ= 0.44-0.53 (m, 4H, CH_2), 2.11-2.19 (m, 1H, CH), 3.72 (s, 3H, CO_2CH_3), 4.24 (s, 2H, N-CH_2), 7.36 (s, 2H, ArH), 7.52 (m, 1H, ArH); Mass (ES+) m/z % 307.67 (M^++1).

3.9. Saponification of the ester-General Procedure

An appropriate ester from **9a-c** or **5d** (5.0 mmol) was stirred in 15% solution of aq. methanol for 2h at r.t. On completion, 5% aq. HCl solution was added dropwise with constant monitoring of pH. At around pH 6.5 white solid separates out from the reaction mixture that was filtered and washed thoroughly with water to furnish the pure acid derivatives.

3.9.1. 5-(Benzylamino-methyl)-3-phenyl-isoxazole-4-carboxylic acid (12a). Yield 99 %; Compound obtained as white solid, mp 202-205 ^{o}C; [Found C, 68.04; H, 5.49; N, 8.55. $C_{18}H_{16}N_2O_3$. 1/2 H_2O requires C, 68.12; H, 5.39; N, 8.80]; ν_{max} (KBr) 1619 (CO_2H), 3001 (NH), 3461 (OH) cm^{-1}; ^{1}H NMR ($DMSOd_6$, 200MHz) δ= 4.01 (s, 2H, NH-CH_2), 4.34 (s, 2H, NH-CH_2), 7.35-7.46 (m, 8H, ArH), 7.62-7.66 (m, 2H, ArH); Mass (FAB+) m/z % 309 (M^++1).

3.9.2. 5-(Benzylamino-methyl)-3(4-chloro-phenyl)-isoxazole-4-carboxylic acid (12b). Yield 96 %; Compound obtained as white solid, mp 213-215 ^{o}C; [Found C, 59.61; H, 4.42; N, 7.88. $C_{18}H_{15}ClN_2O_3$. H_2O requires C, 59.92; H, 4.75; N, 7.76]; ν_{max} (KBr) 1616 (CO_2H), 3002 (NH), 3448 (OH) cm^{-1}; ^{1}H NMR ($DMSOd_6$, 200MHz) δ= 4.05 (s, 2H, NH-CH_2), 4.38 (s, 2H, NH-CH_2), 7.30-7.42 (m, 5H, ArH), 7.51, 7,55 (d, 2H, *J*= 8.4 Hz, ArH), 7.71, 7.75 (d, 2H, *J*= 8.4 Hz, ArH); Mass (ES+) m/z % 343.53 (M^++1).

3.9.3. 5-(Benzylamino-methyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid (12c). Yield 98 %; Compound obtained as white solid, mp 145-146 ^{o}C; [Found C, 54.38; H, 4.20; N, 6.89. $C_{18}H_{14}Cl_2N_2O_3$ H_2O requires C, 54.70; H, 4.08; N, 7.09]; ν_{max} (KBr) 1623 (C=O), 2999 (NH), 3443 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$+ $DMSOd_6$, 200MHz) δ= 3.98 (s, 2H,HN-CH_2) , 4.29 (s, 2H, HN-CH_2) , 7.28-7.47 (m, 8H, ArH) ; Mass (ES+) m/z % 377.53 (M^++1).

3.9.4. 3-(2-Chloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid (14d). Yield 92%; Compound obtained as off white solid, mp 174-176 ^{o}C; [Found C, 51.83; H, 3.40; N, 5.44. $C_{11}H_8ClNO_4$ requires C, 52.09; H, 3.18; N, 5.52]; ν_{max} (KBr) 1693 (CO_2H) cm^{-1}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$, 200MHz) δ= 5.01 (s, 2H, CH_2OH), 7.66 (s, 2H, ArH), 7.36-7.45 (m, 2H, ArH); Mass (FAB+) m/z % 254 (M^++1).

3.10. EDCI-promoted cyclization-General Procedure

To the stirred solution of an appropriate compound from **11a-c** (2.5 mmol) in anhyd. CH_2Cl_2 were added DIEA (0.87 mL, 5.0 mmol), EDCI.HCl (0.720 g, 3.75 mmol) and a catalytic amount of DMAP at r.t. The reaction was allowed to proceed for 1h. The change of color of the reaction to red was indicative of completion of reaction. After confirming the completion of reaction through TLC, the reaction was quenched with water (40 mL) and

extracted with CH_2Cl_2 (2 X 50 mL). The organic layers were pooled, dried (Na_2SO_4) and evaporated to yield a brown residue that on column chromatography over silica gel (100-200 mesh) using hexane: ethyl acetate mixture (80: 20, v/v) furnished the pure bi-lactams as solids.

3.10.1. 5-Benzyl-3-phenyl-5,6-dihydro-pyrrolo[3,4-d]isoxazol-4-one (13a). Yield 75 %; Compound obtained as pale yellow solid, mp 110-115 ^oC; [Found C, 70.41; H, 5.51; N; 9.18. $C_{18}H_{14}N_2O_2$ H_2O requires C, 70.12; H, 5.23; N, 9.09]; ν_{max} (KBr) 1697 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 4.30 (s, 2H, N-CH_2), 4.74 (s, 2H, N-CH_2), 7.29-7.38 (m, 5H, ArH), 7.49-7.51 (m, 3H, ArH), 8.30-8.33 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32MHz) δ= 45.55, 47.33, 117.73, 127.34, 128.47, 128.94, 131.53, 136.98, 158.16, 162.19, 183.64; Mass (ES+) m/z % 313.73 (M^++Na).

3.10.2. 5-Benzyl-3-(4-chloro-phenyl)-5,6-dihydro-pyrrolo[3,4-d]isoxazol-4-one (13b). Yield 69 %; Compound obtained as white solid, mp 161-164 ^oC; [Found C, 61.53;, H, 4.78; N; 8.10. $C_{18}H_{13}ClN_2O_2$. 1.5 H_2O requires C, 61.46; H, 4.58; N, 7.96]; ν_{max} (KBr) 1681 (C=O) cm^{-1}; Anal. ^1H NMR ($CDCl_3$, 200MHz) δ= 4.32 (s, 2H, NH-CH_2), 4.75 (s, 2H, NH-CH_2), 7.30-7.37 (m, 5H, ArH), 7.46-7.49 (d, 2H, ArH), 8.26-8.29 (d, 2H, ArH); Mass (FAB+) m/z % 325 (M^++1).

3.10.3. 5-Benzyl-3-(2,4-dichloro-phenyl)-5,6-dihydro-pyrrolo[3,4-d]isoxazole-4-one (13c). Yield 70 %; Compound obtained as white solid, mp 105-106 ^oC; [Found C, 59.05; H, 357; N, 7.97. $C_{18}H_{12}Cl_2N_2O_2$ .1/2 H_2O requires C, 58.90; H, 3.57; N, 7.63]; ν_{max} (KBr) 1688 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 4.32 (s, 2H, N-CH_2) , 4.73 (s, 2H, N-CH_2), 7.27-7.58 (m, 6H, ArH), 8.03-8.07 (d, 2H, ArH); Mass (ES+) m/z % 359.67 (M^++1).

3.11. DIC-promoted cyclization-Typical procedure

To a stirred solution of compound **14d** (2.5 mmol) in anhyd. CH_2Cl_2 were added DIC (0.720 g, 3.75 mmol) and catalytic amount of DMAP at r.t and the reaction was continued for 24h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer were pooled, dried and evaporated to yield a brown oily residue. This residue on column chromatography over silica gel (100-200 mesh) using hexane: ethyl acetate mixture (80: 20, v/v) furnished the pure product.

3.11.1. 3-(2-Chloro-phenyl)-6*H*-furo[3,4-d]isoxazol-4-one (15d). Yield 41%; Compound obtained as off white solid, mp 202-204 ^oC; [Found C, 56.27; H, 2.46; N, 5.77. $C_{11}H_6ClNO_3$ requires C, 56.07; H, 2.57; N, 5.94]; ν_{max} (KBr) 1739 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ= 5.54 (s, 2H, CH_2O), 7.35-7.55 (m, 4H, ArH); Mass (FAB+) m/z % 236 (M^++1).

3.12. Reaction with hydrazine hydrate-General procedure

To the stirred solution of appropriate formyl derivative from **2 a-c** (2.0 mmol) in 1.0 mL of methanol was added hydrazine hydrate (0.2 mL, 4.0 mmol) at r.t. After few minutes white solid separates out that was filtered and washed with cold water. The analytical samples were obtained through crystalliztion from methanol.

3.12.1. 3-Phenyl-5*H*-isoxazolo[4,5-*d*]pyridazin-4-one (16a). Yield 95 %; Compound obtained as white solid, mp 220-221 ^oC [lit. 221-223 ^oC][5]; [Found C, 62.24; H, 3.05; N; 20.06. $C_{11}H_7N_3O_2$ C, 61.96; H, 3.31; N, 19.70]; ν_{max} (KBr) 1679 (C=ONH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$ (a drop), 200MHz) δ= 7.43-7.56 (m, 3H, ArH), 8.38-8.42 (m, 3H, ArH and HC=N), 13.20 (brs, 1H, NH); Mass (FAB+) m/z % 214 (M^++1).

3.12.2 3-(4-Chloro-phenyl)-5H-isoxazolo[4,5-d] pyridazin-4-one (16b). Yield 93 %; Compound obtained as white solid, mp 180-181^oC; [Found C, 52.98; H, 2.48 ; N, 16.63. $C_{11}H_6ClN_3O_2$ requires C, 53.35; H, 2.44; N, 16.97]; ν_{max} (KBr) 1671 (C=ONH) cm^{-1}; ^1H NMR ($CDCl_3$+ $DMSOd_6$ (a drop)), 200MHz) δ= 7.47, 7.51 (d, 2H, *J*= 8.4 Hz, ArH), 8.39 (s merged with d of Ar-H, 1H, CH=N), 8.40, 8.44 (d, 2H, *J*= 8.4 Hz, ArH), 13.00 (brs, 1H, NH); Mass (FAB+) m/z % 248 (M^++1).

3.12.3. 3-(2,4-Dichloro-phenyl)-5H-isoxazolo[4,5-d] pyridazin-4-one (16c). Yield 90 %; Compound obtained as white solid, mp 193-194^oC; [Found C, 46.45; H, 2.07; N, 14.61. $C_{11}H_5Cl_2N_3O_2$ requires C, 46.84; H, 1.79; N, 14.90]; ν_{max} (KBr) 1691 (C=ONH) cm^{-1}; ^1H NMR ($CDCl_3$+ $DMSOd_6$, 200MHz) δ= 7.40 (s, 2H, ArH), 7.59 (s, 1H, ArH), 8.45 (s, 1H, CH=N), 12.71 (brs, 1H, NH); Mass (FAB+) m/z % 282 (M^++1).

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