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Tetrahedron 60 (2004) 2301–2310
Tetrahedron

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☆

Amrendra K. Roy, Rajaraman B.† and Sanjay Batra*

Medicinal Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001, India

Received 11 November 2003; revised 4 December 2003; accepted 8 January 2004

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 synthesis 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 the carboxylate at 4-position in the 3-substituted-5-isoxazole-carbaldehyde would provide a more fast reacting substrate than the one reported by us earlier. Such an isoxazole-carbaldehyde had previously been synthesized through the cycloaddition of nitrile oxides to methyl 4,4-di-methoxybut-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 followed by oxidation could yield the desired aldehyde. Oxidation of the 3-aryl-5-methyl-isoxazole-4-carboxylate (**1**) 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 the 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-carboxylates (**1a–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 (**2**). 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-isoxazole-carboxylate (**1**) failed to deliver the desired aldehyde (**2**) (Scheme 1). In a different strategy, compound **1** was

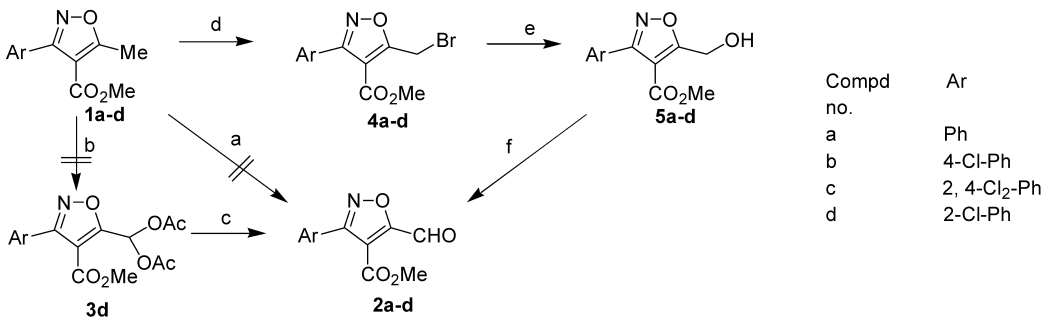
☆ CDRI Communication no. 6489.

Keywords: Isoxazole; Bromination; NBS; 3-Aryl-5-bromomethyl-isoxazole-4-carboxylate; 3-Aryl-5-formyl-isoxazole-4-carboxylate.

* Corresponding author. Tel.: +91-522-2212411-18x4368; fax: +91-522-2223405/2223938; e-mail address: batra_san@yahoo.co.uk

† Graduate Trainee for 6 months (July 2003 to December 2003) from Birla Institute of Technology, Pilani Rajasthan.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.01.009



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 °C, 24 h; (e) DMSO, H_2O, 4 h, heat; (f) PCC, CH_2Cl_2, 10 h.

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.[9–18] Our findings are reported below.

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—see Section 3), furnished the *gem*-dibromo-derivatives (**6a–d**) (CAUTION—see Section 3) in excellent yields (Scheme 2). These results were contrary to previous reports, except by Dannhardt et al.[11] and Lecrec et al.[18] where the formation of a *gem*-dibromo derivative was initially reported in 22 and 8% yields, respectively, from a NBS-promoted bromination reaction. 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 the corresponding aldehyde is a 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 to furnish the mono-bromo product **4** exclusively. This led to evaluation of various conditions in which the radical

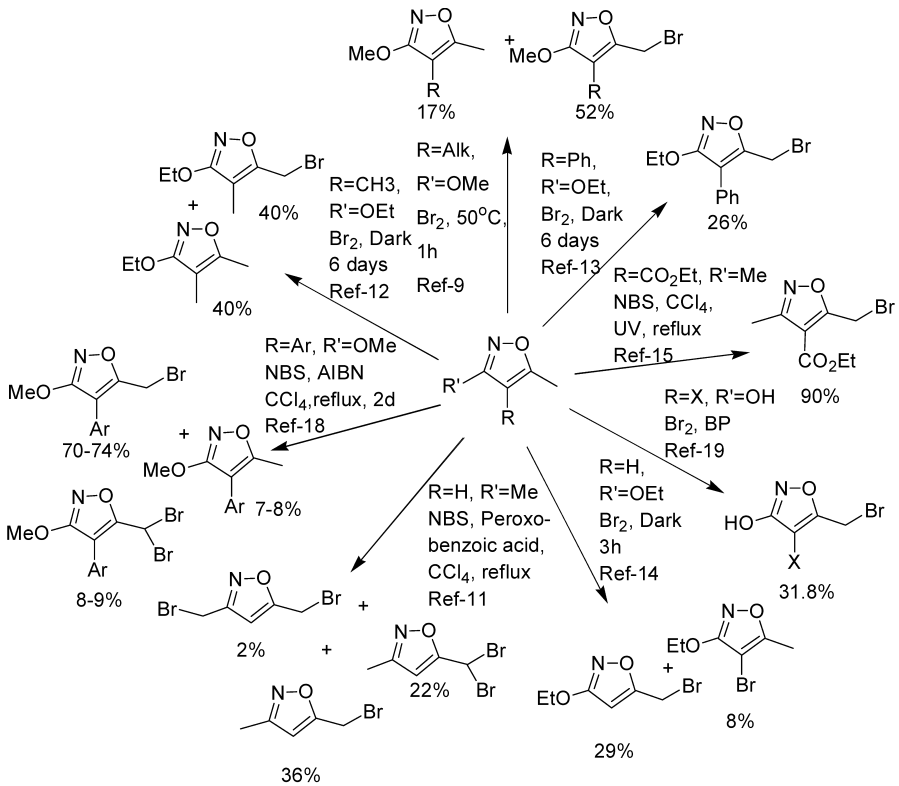
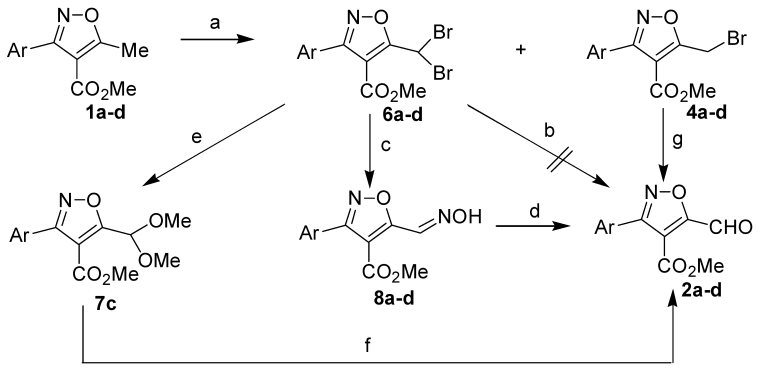


Figure 1. Few examples showing the variation in nature of products and yields of brominated derivative in reported procedures.



Scheme 2. Reagents and conditions: (a) NBS (2.0 equiv.), UV light, CCl_4, reflux, 12 h for compound **6** as major product or NBS (0.8 equiv.), UV light, CCl_4, 40–45 °C, 24 h for compound **4** as major product; (b) Conc. H_2SO_4, heat, 48 h or $CaCO_3$, heat, 48 h; (c) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, reflux, 6–7 h; (d) aq. HCHO (30%), conc. HCl, rt, 1 h or PDC, CH_2Cl_2, 14 h; (e) NaOMe, MeOH, rt, 30 min; (f) HCl, rt, 30 min; (g) (i) DMSO, H_2O, 4 h, heat; (ii) PCC, CH_2Cl_2, 10 h.

initiator, amount of NBS, temperature and solvent dilution were varied to determine the optimum reaction conditions to obtain the mono-brominated derivative (**4**) in good yields. The bromination of compound **1a** in CCl_4 as the 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 components 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 using 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 (4.6×250 mm) resolved the three components of the reaction mixture (R_t; **1a**=16.6 min; **4a**=17.5 min; **6a**=20.3 min). As is evident in the table, the reaction under reflux invariably led to the 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 and 45 °C the mono-bromo derivative **4a** was obtained in high yields. Thus reaction conditions to obtain exclusively either mono-bromo or *gem*-dibromo derivative could be developed. Contrary to the NBS-promoted bromination, all attempts to brominate compound **1a** with neat bromine in dark led to a complex mixture. In order to confirm that the *gem*-dibromo derivative was 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 mono-bromo 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-carboxylates (**1a–d**).

Table 1. Results of bromination of 3-phenyl-5-methyl-isoxazole-4-carboxylate **1a** with NBS under various conditions

Entry	Reaction variables		Radical initiator	Temperature	Time (h)	Ratio of the product as % area observed in HPLC		
	NBS (equiv.)[a]	Solvent CCl_4 (g/mL)				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
				40–45 °C	12	28	0	72
					24	14	43	43
6	1.5 (3×0.5 1.5 h 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
				40–45 °C	12	12	0	84
					24	55	31	14
9[c]	**0.8**	1:50	UV	Reflux	12	19	0	81
					24	20	75	5
				40–45 °C	12	15	0	85
					24	**81 (76)**[b,d]	**3**	**16**
10	0.5	1:50	UV	40–45 °C	24	27	2	71
11	Neat Br_2	—	Dark	rt	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.

2.2. Studies on the hydrolysis of mono- and *gem*-dibromo derivatives

Since compounds **1**, **4** and **6** present in the residue obtained after work up could not be separated efficiently by column chromatography, the residue was directly used 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 (**5a–d**), in the presence of PCC, furnished the corresponding aldehydes (**2a–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 modest yield.[28] In another strategy the reaction of *gem*-dibromo derivatives (**6a–d**) with hydroxylamine hydrochloride, under 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 give the aldehydes in moderate yields (Scheme 3).

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 example 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; compounds **4a–c** on nucleophilic substitution with various amines furnished the secondary amines (**9–11a–c**) in short reaction times 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**).

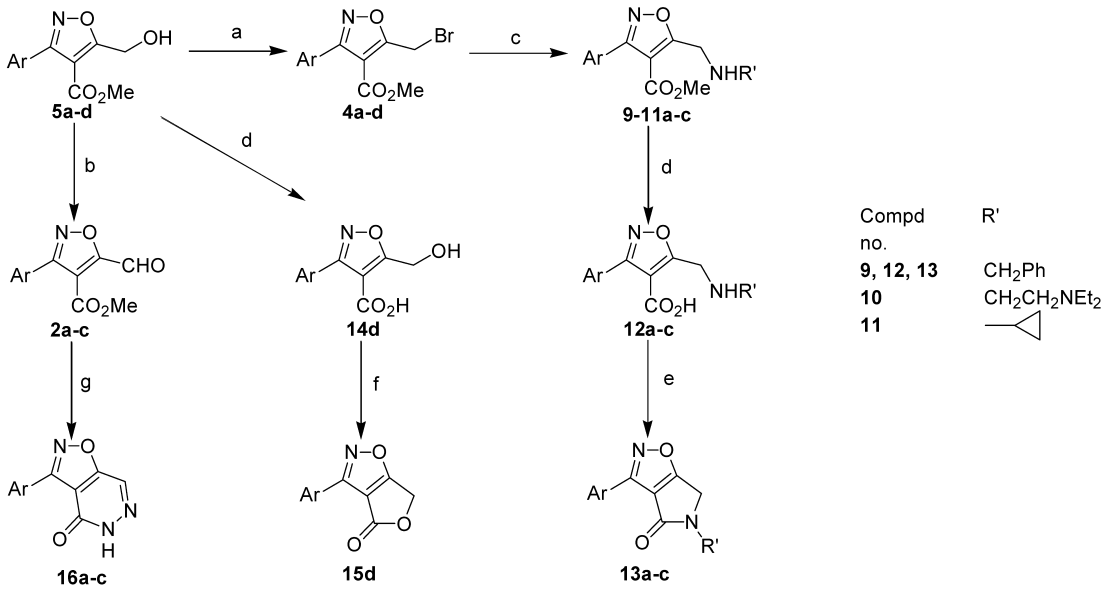
The synthesis of another isoxazole-fused ring system 3-(2-chlorophenyl)-6*H*-furo[3,4-*d*]isoxazol-4-one (**15d**) was carried out from the acid (**14d**). The latter was obtained after the saponification of the alcohol **5d**. A DIC-promoted cyclization of this hydroxy acid **14d** furnished **15d**.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

In conclusion, we have established an optimized procedure for the bromination of 3-aryl-5-methyl-isoxazole-4-carboxylates (**1a–d**) to obtain, exclusively, either the mono-bromo or *gem*-dibromo methyl derivative in excellent yields. The mono-bromo methyl derivatives (**4a–d**) have 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



Scheme 3. Reagents and conditions: (a) PBr_3, CH_2Cl_2, 0 °C, 30 min; (b) PCC, CH_2Cl_2, 10 h; (c) R'NH_2, Et_3N, anhyd. Benzene, reflux, 30 min; (d) KOH in MeOH/H_2O, rt, 1 h; (e) EDCI, DIEA, DMAP, CH_2Cl_2, rt, 45 min; (f) DIC, DMAP, rt, 24 h; (g) $NH_2NH_2{\cdot}H_2O$, MeOH, rt, 15 min.

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 spectrometer, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The FABMS were recorded on JEOL/SX-102 spectrometer 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 (**6a**–**d**) and monobromo (**4a**–**d**) derivatives cause severe irritation on exposure leading to small blisters occasionally. The stated yields of the alcohols (**5a**–**d**) are the ones obtained by hydrolysis of pure mono-bromo-derivatives (**4a**–**d**). Similarly, the yields of the mono-bromo derivatives (**4a**–**d**) are those observed during the PBr_3-promoted bromination of alcohols (**5a**–**d**). The yields of dibromo-derivatives (**6a**–**d**) are those obtained from the bromination reaction carried out with 2 mol of NBS under UV light.

3.2. Bromination and hydrolysis—general procedure

To the appropriate solution of compounds **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 conditions or at 40–45 °C (maintained by placing the reaction in a water bath and changing the water after every 2–3 h). The optimum reaction time for phenyl and 4-chlorophenyl substitutions was 24 h while that for 2-chloro-phenyl and 2, 4-dichlorophenyl was observed to be 40 h. On completion, the reaction was cooled to 10 °C, and the precipitated succinimide was filtered. The filtrate was evaporated under vacuum to furnish a reddish brown oil. This residue consists of an 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 °C for 4 h. The reaction mixture was quenched with excess of cold water (250 mL) and extracted with diethyl ether (2×150 mL). The combined and dried (Na_2SO_4), the organic phase was evaporated under reduced pressure and the residue subjected to column chromatography over silica gel (60–120 mesh) using hexane/ethyl acetate mixture as eluent. (9.5:0.5, v/v) to give the *gem*-dibromo derivative. Further elution with 8.5:1.5 (v/v) hexane/ethyl acetate yielded the unreacted starting material while a mixture of hexane/ethyl acetate (1:1, v/v) furnished the alcohol.

3.2.1. 5-Dibromomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (6a). Yield 84%; compound obtained as white solid; mp 69–71 °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 ($CDCl_3$, 200 MHz) 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 ($CDCl_3$, 50.32 MHz) 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). Yield 77%; compound obtained as pale yellow solid, mp 87–88 °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 ($CDCl_3$, 200 MHz) 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). Yield 76%; compound obtained as white solid, mp 128–130 °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 ($CDCl_3$, 200 MHz) δ=3.76 (s, 3H, CO_2CH_3), 7.28 (s, 1H, $CHBr_2$), 7.39 (s, 2H, ArH), 7.52 (s, 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). Yield 82%; compound obtained as white solid, mp 74–75 °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 ($CDCl_3$, 200 MHz) 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 °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 ($CDCl_3$, 200 MHz) 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 ($CDCl_3$, 50.32 MHz) 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 °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 ($CDCl_3$, 200 MHz) 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} (Neat) 1725 (CO_2Me), 3405 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) 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 (s, 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 °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 ($CDCl_3$, 200 MHz) 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 a solution of the 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 rt for 10–12 h. Thereafter, the reaction mixture was passed through a column of silica gel (60–120 mesh) using ethyl acetate/hexane (1:1, v/v) to afford the aldehydes.

3.3.1. 5-Formyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (2a). Yield 82%; compound obtained as off white solid; mp 65–67 °C; [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 ($CDCl_3$, 200 MHz) 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 64%; compound obtained as off white solid; mp 88–90 °C; [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 ($CDCl_3$, 200 MHz) 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 67%; compound obtained as white solid; mp 58–59 °C; [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 ($CDCl_3$, 200 MHz) δ=3.79 (s, 3H, CO_2CH_3), 7.359, 7.364 (d, 2H, *J*=1.1 Hz, ArH), 7.52 (s, 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 ($CDCl_3$, 200 MHz) 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 a stirred solution of the appropriate alcohol from **5a–d** (5.0 mmol) in anhyd. CH_2Cl_2 (5 mL) was added a solution of PBr_3 (0.475 mL, 5.0 mmol) in anhyd. CH_2Cl_2 (10 mL) at 0 °C dropwise. The reaction was continued at the same temperature for 30 min. Thereafter, the solvent was evaporated to obtain a residue which was partitioned between ethyl acetate (30 mL) 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 under reduced pressure 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 hexane/ethyl acetate (9.5:0.5, v/v) mixture 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 ($CDCl_3$, 200 MHz) 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 ($CDCl_3$, 200 MHz) δ=3.85 (s, 3H, CO_2CH_3), 4.80 (s, 2H, CH_2Br), 7.42, 7.46 (d, 2H, *J*=8.2 Hz, ArH), 7.58, 7.62 (d, 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 ($CDCl_3$, 200 MHz) 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 ($CDCl_3$, 200 MHz) 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. Oxidation of *gem*-dibromo derivatives—general procedure

A mixture of the appropriate *gem*-dibromo derivative from **6a–d** (11.3 mmol), NaOAc (2.78 g, 33.9 mmol) and NH_2-OH·HCl (2.37 g, 33.9 mmol) in methanol (75 mL) mixture was refluxed for 6–7 h. The excess solvent was removed and the reaction mixture quenched with water to furnish the oximes as white solids. Analytical samples of the products were obtained by column chromatography over silica gel using hexane/ethyl acetate (3:2, 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 °C; [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 ($CDCl_3$+$DMSOd_6$, 200 MHz) 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 ($CDCl_3$, 50.32 MHz) 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^++7).

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 °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}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) 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 °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}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) 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 °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}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) 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 a stirred solution of sodium methoxide (10.0 mmol) in methanol (30 mL) was added compound **6c** (5.0 mmol) at 0 °C and the reaction was allowed to proceed for 30 min at the same temperature. The excess methanol was evaporated and the reaction mixture was extracted with water (40 mL) and ethyl acetate (2×50 mL). The organic layers were combined, dried (Na_2SO_4) and reduced under vacuum to give a residue which was purified by column chromatography with silica gel (230–400 mesh) using a mixture of hexane/ethyl acetate (4:1, 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 °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_2-Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.53 (s, 6H, 2×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 rt for 1 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2×50 mL). The organic layers were pooled, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue. This residue was purified by column chromatography over silica gel using a mixture of hexane/ethyl acetate (7:3, 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 rt. The reaction was continued for 14 h. Thereafter the reaction mass was filtered through silica gel column (60–120 mesh) using a mixture of hexane/ethyl acetate (7:3, v/v) to obtain the pure aldehydes in 45–50% yields.

3.8. Reaction with amines—general procedure

A mixture of the bromide (**4a–c**) (5.0 mmol), Et_3N (0.9 mL, 6.5 mmol) and the appropriate amine (5.5 mmol) in anhyd. benzene (5 mL) was refluxed under stirring at 80 °C. After 1 h the reaction was cooled to rt and extracted with water (30 mL) and ethyl acetate (2×35 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure 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 (3:2, v/v) was used as eluent on either stationary phase.

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 °C; [found: C, 65.73; H, 5.76; N, 7.59. $C_{19}H_{18}N_2O_3\cdot(CO_2H)_2$ requires C, 65.96; H, 5.80; N, 7.33]; ν_{max} (Neat) 1728 (CO_2Me), 3341 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.66 (s, 3H, CO_2CH_3), 3.85 (s, 2H, NH–CH_2), 4.22 (s, 2H, NH–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 °C; [found C, 56.83; H, 4.18; N, 6.00. $C_{19}H_{17}ClN_2O_3\cdot(CO_2H)_2$ requires C, 56.45; H, 4.29; N, 6.27]; ν_{max} (Neat) 1726 (CO_2Me), 3429 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.74 (s, 3H, CO_2CH_3), 3.85 (s, 2H, NH–CH_2), 4.23 (s, 2H, NH–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}; ^1H NMR ($CDCl_3$, 200 MHz) 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 °C; [found C, 50.47; H, 6.14; N, 7.98. $C_{17}H_{23}N_3O_3\cdot2(CO_2H)_2\cdot1/2H_2O$ requires C, 50.79; H, 5.81; N, 8.07]; ν_{max} (Neat) 1728 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.00 (t, 6H, *J*=7.0 Hz, 2×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-ethyl-amino)-methyl]-isoxazole-4-carboxylic acid methyl ester (10b). Yield 66%; compound obtained as dark yellow oil; oxalate salt as white solid; mp 183–185 °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}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.00 (t, 6H, *J*=7.0 Hz, 2×CH_3), 2.46–2.75 (m, 8H, N–CH_2), 3.79 (s, 3H, CO_2CH_3), 4.25 (s, 2H, NH–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-ethyl-amino)-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}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.01 (t, 6H, *J*=7.0 Hz, 2×CH_3), 2.44–2.74 (m, 8H, N–CH_2), 3.71 (s, 3H, CO_2CH_3), 4.27 (s, 2H, NH–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. $C_{15}H_{16}N_2O_3 \cdot 1/2H_2O$ requires C, 64.09; H, 6.09; N, 9.96]; ν_{max} (Neat) 1726 (CO_2Me), 3317 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) 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, NH–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 °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}; ^1H NMR ($CDCl_3$, 200 MHz) 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, NH–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).

3.8.9. 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}; ^1H NMR ($CDCl_3$, 200 MHz) 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, NH–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

The appropriate ester (**9a–c** or **5d**) (5.0 mmol) was stirred in 15% solution of aq. methanol for 2 h at ambient temp. On completion of the reaction, 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 °C; [found C, 68.04; H, 5.49; N, 8.55. $C_{18}H_{16}N_2O_3 \cdot 1/2\ H_2O$ requires C, 68.12; H, 5.39; N, 8.80]; ν_{max} (KBr) 1619 (CO_2H), 3001 (NH), 3461 (OH) cm^{-1}; ^1H NMR ($DMSOd_6$, 200 MHz) 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 °C; [found C, 59.61; H, 4.42; N, 7.88. $C_{18}H_{15}ClN_2O_3 \cdot H_2O$ requires C, 59.92; H, 4.75; N, 7.76]; ν_{max} (KBr) 1616 (CO_2H), 3002 (NH), 3448 (OH) cm^{-1}; ^1H NMR ($DMSOd_6$, 200 MHz) 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 °C; [found C, 54.38; H, 4.20; N, 6.89. $C_{18}H_{14}Cl_2N_2O_3 \cdot H_2O$ requires C, 54.70; H, 4.08; N, 7.09]; ν_{max} (KBr) 1623 (C=O), 2999 (NH), 3443 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=3.98 (s, 2H, NH–CH_2), 4.29 (s, 2H, NH–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 °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}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) 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 a stirred solution of **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 ambient temp. The reaction was allowed to proceed for 1 h. The change of color of the reaction to red was indicative of complete reaction. After confirming the completion of reaction through TLC, the reaction was quenched with water (40 mL) and extracted with CH_2Cl_2 (2×50 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 (4:1, 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 °C; [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 ($CDCl_3$, 200 MHz) 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 ($CDCl_3$, 50.32 MHz) 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 °C; [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. ^{1}H NMR ($CDCl_3$, 200 MHz) δ=4.32 (s, 2H, N–CH_2), 4.75 (s, 2H, N–CH_2), 7.30–7.37 (m, 5H, ArH), 7.46, 7.49 (d, 2H, *J*=8.4 Hz, ArH), 8.26, 8.29 (d, 2H, *J*=8.4 Hz, ArH); mass (FAB+) *m/z* % 325 (M^++1).

3.10.3. 5-Benzyl-3-(2,4-dichloro-phenyl)-5,6-dihydro-pyrolo[3,4-*d*]isoxazole-4-one (13c). Yield 70%; compound obtained as white solid; mp 105–106 °C; [found C, 59.05; H, 357; N, 7.97. $C_{18}H_{12}Cl_2N_2O_2{\cdot}1/2H_2O$ requires C, 58.90; H, 3.57; N, 7.63]; ν_{max} (KBr) 1688 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) 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, *J*=8.4 Hz, ArH); mass (ES+) *m/z* % 359.67 (M^++1).

3.11. DIC-promoted cyclization—typical procedure

To a stirred solution of **14d** (2.5 mmol) in anhyd. CH_2Cl_2 were added DIC (0.720 g, 3.75 mmol) and a catalytic amount of DMAP at ambient temperature and the reaction was continued for 24 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (2×25 mL). The organic layers were pooled, dried (Na_2SO_4) and evaporated in vacuo yield a brown oily residue. This residue was purified by column chromatography over silica gel (100–200 mesh) using hexane/ethyl acetate mixture (4:1, 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 °C; [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}; ^{1}H NMR ($CDCl_3$, 200 MHz) 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 a stirred solution of the appropriate formyl derivative **2a–c** (2.0 mmol) in 1.0 mL of methanol was added hydrazine hydrate (0.2 mL, 4.0 mmol) at ambient temperature. After a few minutes, white solid separates out, that was filtered and washed with cold water and dried in vacuo. The analytical samples were obtained through crystallization 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 °C [lit. 221–223 °C];[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}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$ (a drop), 200 MHz) 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)-5*H*-isoxazolo[4,5-*d*] pyridazin-4-one (16b). Yield 93%; compound obtained as white solid; mp 180–181 °C; [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}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$ (a drop), 200 MHz) 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)-5*H*-isoxazolo[4,5-*d*] pyridazin-4-one (16c). Yield 90%; compound obtained as white solid; mp 193–194 °C; [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}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) 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).

Acknowledgements

A. K. R. acknowledges the financial support from ICMR in the form of fellowship. This work was supported by financial grant under DST Project no. SR/SI/OC-04/2003.

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