Interesting Results of Catalytic Hydrogenation of 3-(2-Nitrophenyl)isoxazoles and 3-(Nitrophenyl)-4,5-dihydroisoxazoles[1]

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Received 20 December 2005; revised 10 February 2006

Abstract: The palladium-on-carbon assisted hydrogenolysis of substituted 3-(2-nitrophenyl)isoxazoles, irrespective of substitution on the isoxazole ring, invariably leads to reduction of the nitro to the amino group with concomitant regiospecific ring closure to yield substituted 4-aminoquinolines. In contrast similar hydrogenation of 3-(2-, 3-, and 4-nitrophenyl)-4,5-dihydroisoxazoles (2-isoxazolines) results in reduction of the nitro group only with conservation of the dihydroisoxazole ring to yield the corresponding 3-(aminophenyl)-4,5-dihydroisoxazoles.

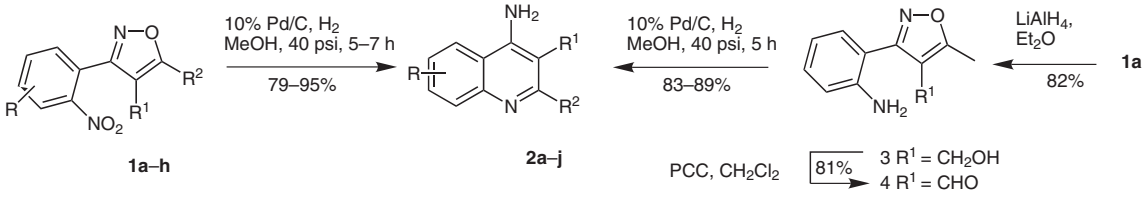
Key words: isoxazole, 4-aminoquinoline, hydrogenation, ring transformation, regiospecific

Hydrogenation of 3-(2-nitrophenyl)-substituted isoxazole derivatives can be utilized for the synthesis of substituted 4-aminoquinoline-2- and 3-carbaldehyde[2] derivatives. There are two reports[3,4] wherein 3-(2-nitrophenyl)-5-phenylisoxazole and 3-(2-nitrophenyl)-5-methylisoxazole-4-carboxylate were hydrogenated in the presence of Raney nickel in acetic acid for 20 hours or ethanol at room temperature to furnish 4-aminoquinoline derivatives. However, in our hands the reaction in acetic acid did not work well and the hydrogenation at room temperature took a long time and several side products were formed. Since the previous reports described only one example each, no comments were made on the scope and limitation of the synthetic strategy. In principle, if the regiospecificity of the ring-closure reaction between the amino group present on the phenyl and the carbonyl group generated by the cleavage of the isoxazole ring is maintained, even in the presence of different groups on the isoxazole nucleus, this would become an alternate and convenient route to substituted 4-aminoquinolines which is the substructural unit of several pharmacologically active compounds with antimalarial,[5] antiulcer,[6] immuno-stimulant,[7] anti-HIV,[8] AChE inhibitory,[9] and noniceptin antagonist[10] activity. In addition, this procedure may serve as a method to obtain fluorinated 4-aminoquinoline derivatives which otherwise require complex strategies.[11] In order to evaluate the scope of this procedure to generate substituted 4-aminoquinolines, we investigated several different substitutions on the isoxazole nucleus employing palladium-on-carbon. Compared to the Raney nickel mediated reaction, it was observed that the reaction is fast and smooth in the presence of palladium-on-carbon. Additionally, the ring-closure reaction between the amino and the carbonyl groups generated by cleavage of the isoxazole ring is highly regiospecific even in the presence of another formyl group. As an extension of this study, we also explored the hydrogenolysis of the 3-(2-nitrophenyl)-4,5-dihydroisoxazole (2-isoxazoline) system. Surprisingly the 4,5-dihydroisoxazole ring, which is otherwise known to readily undergo catalytic hydrogenolysis, is highly stable to ring cleavage when nitrophenyl substitution is present on it. Our results on the catalytic hydrogenations of substituted 3-(2-nitrophenyl)isoxazoles and 3-(nitrophenyl)-4,5-dihydroisoxazoles are presented in this communication.

Methyl 3-(2-Nitrophenyl)-5-methylisoxazole-4-carboxylate (**1a**) was prepared through an earlier reported[12] procedure and subjected to palladium-on-carbon mediated catalytic hydrogenation to afford methyl 4-amino-2-methylquinoline-3-carboxylate (**2a**) in 5–7 hours and with excellent yields (Scheme 1). To assess the general applicability of the procedure, several other substituted 2-nitrophenyl substrates **2b**–**d** were evaluated with similar outcome (Table 1). Subsequently it was decided to hydrogenate 3-(2-nitrophenyl)isoxazole-4-carbaldehyde (**1e**). In principle, if ring opening of the isoxazole and subsequent cyclization is highly regiospecific, it would lead to 4-aminoquinoline-3-carbaldehyde. On the other hand, after reduction of the nitro group to the amino group there is a possibility that it may form a Schiff base with the formyl group on the isoxazole ring resulting in 3-acetyl-4-aminoquinoline. Hence, the compound **1e** was synthesized by the literature method[13] and hydrogenated. This reaction resulted in the formation of 4-aminoquinoline-3-carbaldehyde (**2e**) in excellent yield suggesting that the intramolecular cyclization between the amino group on the phenyl ring and the carbonyl group generated from the cleavage of the isoxazole ring is regiospecific. We have been interested in the transformations of Baylis–Hillman derivatives afforded from substituted isoxazolecarbaldehydes to other heterocycles.[14] Consequently, two of the Baylis–Hillman derivatives **1g** and **1h** (entry 7 and 8), obtained from 3-(2-nitrophenyl)isoxazole-5-carbaldehyde, were also hydrogenated to afford the corresponding 4-aminoquinoline derivatives **2g** and **2h**.

Mechanistically, the initial step is the reduction of the nitro group, followed by ring fission (Scheme 2) and subse-

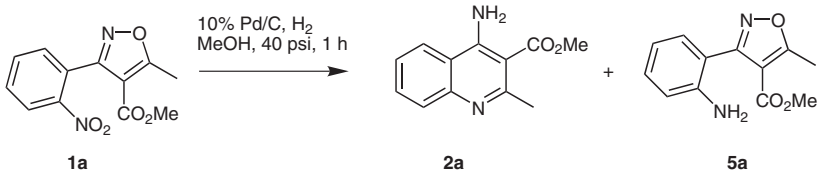
SYNTHESIS 2006, No. 12, pp 1995–2004
Advanced online publication: 08.05.2006
DOI: 10.1055/s-2006-942388; Art ID: P19605SS



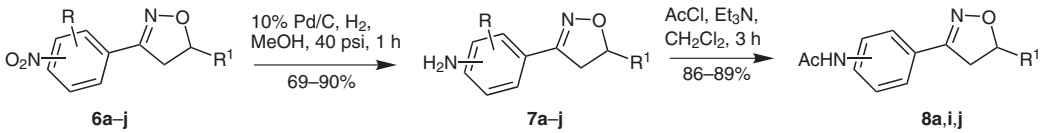
Scheme 1

quent cyclization. The evidence for this was obtained by arresting the hydrogenation reaction in one hour, which gave 3-(2-aminophenyl)isoxazole (**5a**) along with the expected 4-aminoquinoline derivative (Scheme 2). Although during the hydrogenation of 3-(2-nitrophenyl)isoxazole-4-carbaldehyde (**1e**) we could isolate only the 4-aminoquinoline-3-carbaldehyde, it was envisaged that if the nitro group is reduced by circumventing the hydrogenolysis, the internal cyclization through the Schiff base formation between the amino group on the phenyl ring and the formyl group on the isoxazole ring is possible. Indeed a literature report indicated the formation of isoxazolo[4,3-*c*]quinoline from the 3-(2-azidophenyl)isoxazoles by reaction with triphenylphosphine leading to an iminophosphorane which cyclizes through an aza-Wittig reaction.[15] Hence, compound **1a** was reduced with lithium aluminum hydride to furnish the product **4**. However, all attempts to perform the intramolecular cyclization with this substrate failed to yield the desired result. Nevertheless, similar to 3-(2-nitrophenyl)-substituted isoxazoles, the catalytic hydrogenation of compound **4** yielded the corresponding 4-aminoquinoline-3-carbaldehyde derivative **2j** in high yield. Thus, irrespective of the functional groups present on the isoxazole ring, the palladium-on-carbon promoted catalytic hydrogenation invariably leads to substituted 4-aminoquinolines.

These results prompted us to explore similar hydrogenolysis in 3-(2-nitrophenyl)-4,5-dihydroisoxazoles. It is generally accepted that 4,5-dihydroisoxazoles undergo ring cleavage to yield the β-diketo or β-keto hydroxy system under hydrogenation conditions in the presence of palladium-on-carbon or Raney nickel with few exceptions.[16] Because of this reason, the selective reduction of the nitro group on the phenyl ring attached to the dihydroisoxazole nucleus has been achieved either by tin(II) chloride or hydrogen sulfide in concentrated ammonia.[17,18] However, none of the earlier workers have reported the results with 3-(2-, 3-, and 4-nitrophenyl)-4,5-dihydroisoxazoles. Thus 3-(2-nitrophenyl)-4,5-dihydroisoxazoles **6a–g** were hydrogenated in the presence of palladium-on-carbon to yield the products **7a–g** (Scheme 3, Table 2). The structure of products **7a–g** was proven by the X-ray crystallography of a representative product **7d**.[19] Further support for the presence of amino group was obtained by carrying out the acetylation of a representative compound **7a** to furnish the acetyl derivative **8a**. Thus, our results indicate that the reduction of nitro group in these substrates is highly chemoselective. In order to evaluate whether this observation was restricted to palladium-on-carbon promoted reactions, hydrogenations of compounds **6a–c** were also carried out in the presence of Raney nickel. Surprisingly, here too similar products **7a–c** were afforded in two hours in good yields. The reduction of the nitro group was complete in 1–2 hours and continuing the reaction even for more than 24 hours in the presence of palladium-on-carbon or Raney nickel did not lead to any change as the isolated products were the anilines only. In our quest to further evaluate the behavior of 3-(nitrophenyl)-derivatives of 4,5-dihydroisoxazoles, 3-(3-nitrophenyl)-4,5-dihydroisoxazoles, and 3-(4-nitrophenyl)-4,5-dihydroisoxazoles were synthesized and subjected to palladium-on-carbon and Raney nickel promoted hydrogenations. Similar to 2-nitrophenyl

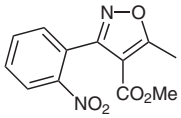
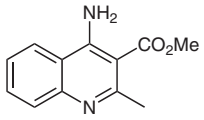
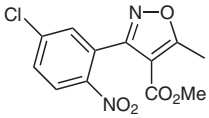
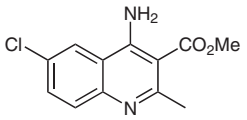
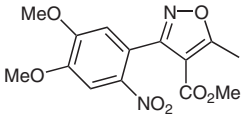
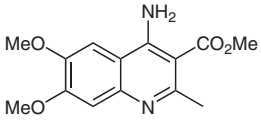
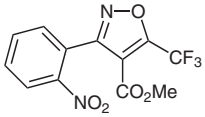
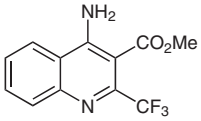
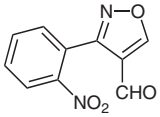
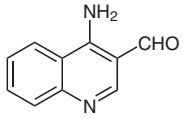
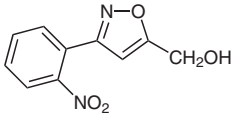
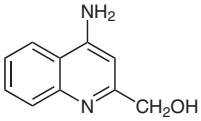
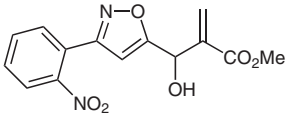
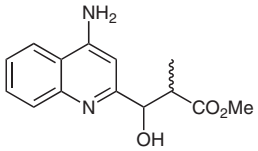
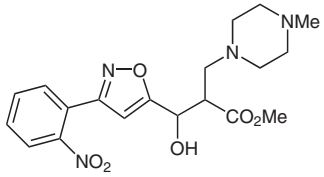
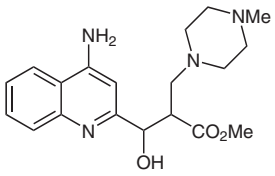
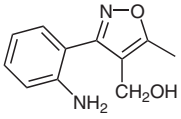
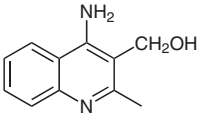
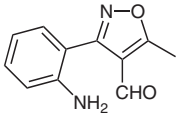
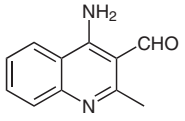


Scheme 2



Scheme 3

Table 1 Physical Parameters of Substituted 4-Aminoquinolines

Entry	Substrate	Product	Yield (%)	Physical appearance	Mp (°C)	ESI-MS or FABMS (M^+) (*m*/*z*)
1	 **1a**	 **2a**	79	brown solid	162–165 (158–160)[2]	217.33
2	 **1b**	 **2b**	82	yellow solid	188–190	251
3	 **1c**	 **2c**	85	dark brown solid	145–147	277.27
4	 **1d**	 **2d**	88	yellow solid	135–137	271
5	 **1e**	 **2e**	90	yellow solid	250–252 (258)[2]	173.16
6	 **1f**	 **2f**	89	brown solid	152–154	175
7	 **1g**	 **2g**	93	brown solid	100–102	261
8	 **1h**	 **2h**	86	brown solid	78–80	359.1
9	 **3**	 **2i**	83	off-white solid	156–158	189.13
10	 **4**	 **2j**	89	yellow solid	227–229 (262)[2]	187

derivatives, these compounds too did not undergo ring cleavage as evident from their spectroscopic and analytical data. The presence of the amino group on the phenyl ring was further established by the preparation of the corresponding acetates **8i** and **8j**. To prove that this unusual observation is restricted to the nitrophenyl derivatives of 4,5-dihydroisoxazoles, the methyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate (**9**) was hydrogenated in the presence of palladium-on-carbon and Raney nickel separately. As reported, under these conditions hydrogenolysis did occur to yield the corresponding 3-hydroxy-5-phenylpyrrolidin-2-one (**10**) (Scheme 4).

Table 2 Physical Parameters of 3-(2-, 3-, and 4-Aminophenyl)-4,5-dihydroisoxazoles **7a–j** via Scheme 3

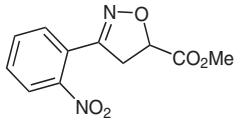
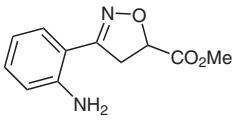
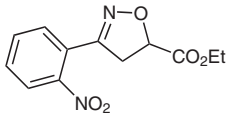
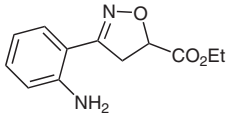
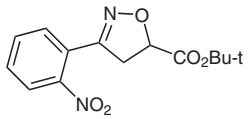
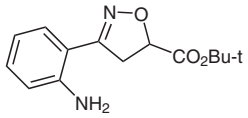
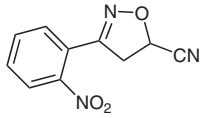
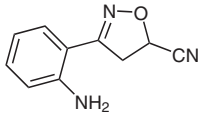
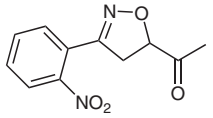
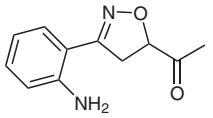
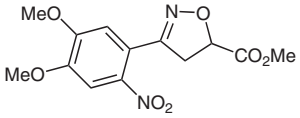
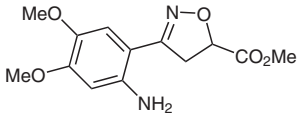
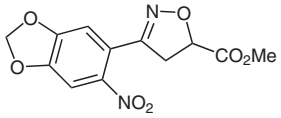
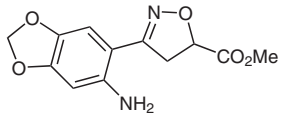
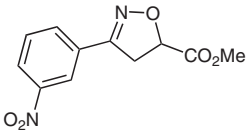
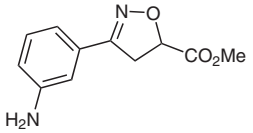
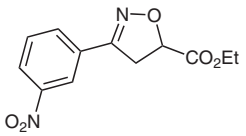
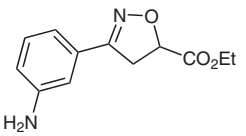
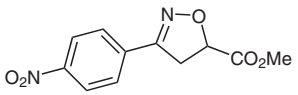
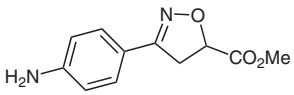
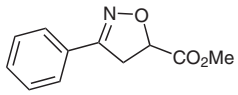
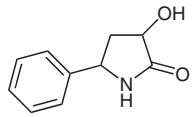
Entry	Substrate	Product	Yield (%)	Physical appearance	Mp (°C)	FAB-MS[a] (*m*/*z*)
1			88	brown solid	58–60	220 (M^+), 221 ($M^+ + 1$)
	6a	**7a**				
2			86	brown solid	88–90	234 (M^+), 235 ($M^+ + 1$)
	6b	**7b**				
3			89	brown solid	102–104	262 (M^+), 263 ($M^+ + 1$)
	6c	**7c**				
4			79	off-white solid	82–84	187 (M^+), 188 ($M^+ + 1$)
	6d	**7d**				
5			83	brown oil	–	204 (M^+), 205 ($M^+ + 1$)
	6e	**7e**				
6			81	yellow solid	128–130	280 (M^+), 281 ($M^+ + 1$)
	6f	**7f**				
7			84	off-white solid	132–134	264 (M^+), 265 ($M^+ + 1$)
	6g	**7g**				
8			85	brown solid	78–80	220 (M^+), 221 ($M^+ + 1$)
	6h	**7h**				
9			79	brown solid	80–82	234 (M^+), 235 ($M^+ + 1$)
	6i	**7i**				

Table 2 Physical Parameters of 3-(2-, 3-, and 4-Aminophenyl)-4,5-dihydroisoxazoles **7a–j** via Scheme 3 (continued)

Entry	Substrate	Product	Yield (%)	Physical appearance	Mp (°C)	FAB-MS[a] (*m/z*)
10	 **6j**	 **7j**	81	pale yellow solid	110–112	220 (M^+), 221 ($M^+ + 1$)
11	 **9**	 **10**	69	white solid	146–148 (150)	178

[a] It was observed that all anilines show peaks for (M^+) and ($M^+ + 1$) in FAB mass spectra.

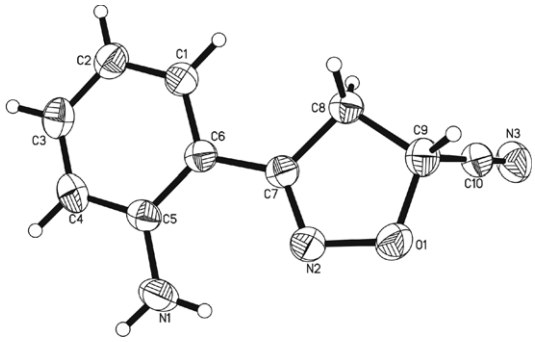
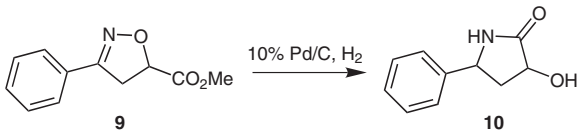


Figure 1 *ORTEP* diagram showing the crystal structure of **7d** with atomic numbering scheme for non-H atoms only at 30% probability level.



Scheme 4

In summary we have demonstrated the general applicability of the palladium-on-carbon mediated hydrogenolysis of substituted 3-(2-nitrophenyl)isoxazoles which invariably results in the formation of substituted 4-aminoquinolines through reduction of the nitro group to amino group, followed by isoxazole ring cleavage and concomitant regiospecific ring closure. This can be treated as an easy and alternative method to achieve the synthesis of this important class of heterocycle with desired substitutions. On the other hand, it has been shown that the 4,5-dihydroisoxazole ring is retained during the catalytic hydrogenation if the 3-position is substituted with a nitrophenyl group. Work is underway to explore the usefulness of this methodology to obtain compounds of medicinal interest.

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on JEOL/SX-102 spectrometers and ESI-MS (positive mode) 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. Compounds **1g** and **1h** were prepared as published earlier.[20]

Methyl 4-Amino-2-methylquinoline-3-carboxylate (2a); Typical Procedure

To a soln of **1a** (0.4 g, 1.85 mmol) in MeOH (10 mL), was added 10% Pd/C (100 mg) under N_2. The atmosphere of the vessel was replaced by hydrogen gas. The reaction was carried out on the Parr assembly at 40 psi at r.t. for 5–7 h. Thereafter, the catalyst was filtered over Celite and the filtrate was evaporated to yield a residue. This residue upon column chromatography over silica gel ($CHCl_3$–MeOH, 1–3%) yielded compound **2a** as brown solid; yield: 0.26 g (79%).

IR (KBr): 1734 (CO_2CH_3), 3363 (br, NH_2) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.81 (s, 3 H, CH_3), 3.95 (s, 3 H, CO_2CH_3), 7.01 (br s, 2 H, NH_2, exchangeable with D_2O), 7.42 (t, *J* = 7.5 Hz, 1 H, ArH), 7.68 (t, *J* = 7.5 Hz, 1 H, ArH), 7.75 (d, *J* = 8.1 Hz, 1 H, ArH), 7.87 (d, *J* = 8.1 Hz, 1 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 28.3, 51.9, 102.6, 117.4, 121.1, 125.3, 129.4, 131.6, 147.9, 154.2, 159.9, 170.3.

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.69; H, 5.52; N, 12.90.

Methyl 4-Amino-6-chloro-2-methylquinoline-3-carboxylate (2b)

IR (KBr): 1738 (CO_2CH_3), 3382 (br, NH_2) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 2.85 (s, 3 H, CH_3), 3.99 (s, 3 H, CO_2CH_3), 7.62–7.69 (m, 1 H, ArH), 7.87–7.99 (m, 1 H, ArH), 8.54–8.58 (m, 1 H, ArH).

Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.46; N, 11.20.

Methyl 4-Amino-6,7-dimethoxy-2-methylquinoline-3-carboxylate (2c)

IR (KBr): 1733 (CO_2CH_3), 3385 (br, NH_2) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 2.57 (s, 3 H, CH_3), 3.88 (s, 9 H, 2 × OCH_3 and CO_2CH_3), 7.62, 7.69 (2 × br s merged, 2 H, ArH).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.80; H, 5.78; N, 10.30.

Methyl 4-Amino-2-(trifluoromethyl)quinoline-3-carboxylate (2d)

IR (KBr): 1733 (CO_2CH_3), 3434 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, CO_2CH_3), 6.63 (br s, 2 H, NH_2), 7.60–7.64 (m, 1 H, ArH), 7.75–7.85 (m, 2 H, ArH), 8.08 (d, *J* = 8.4 Hz, 1 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 52.8, 101.7, 118.4, 119.1, 120.9, 124.6, 127.9, 131.1, 132.2, 146.7, 153.1, 168.3.

Anal. Calcd for $C_{12}H_9F_3N_2O_2$: C, 53.34; H, 3.36; N, 10.37. Found, C, 53.44; H, 3.22; N, 10.62.

4-Aminoquinoline-3-carbaldehyde (2e)

IR (KBr): 1710 (CHO), 3428 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 7.45–7.52 (m, 1 H, ArH), 7.70–7.78 (m, 1 H, ArH), 7.90 (d, *J* = 8.6 Hz, 1 H, ArH), 8.27 (d, *J* = 8.4 Hz, 1 H, ArH), 8.67 (s, 1 H, ArH), 9.97 (s, 1 H, CHO).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 109.3, 118.2, 124.1, 125.6, 129.5, 132.6, 149.1, 153.9, 155.9, 193.4.

Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.68; H, 4.62; N, 16.30.

(4-Aminoquinolin-2-yl)methanol (2f)

IR (KBr): 3331 (br, NH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 4.51 (s, 2 H, CH_2), 6.74, 6.79 (2 × s merged, 3 H, ArH and NH_2), 7.33–7.35 (m, 1 H, ArH), 7.56–7.58 (m, 1 H, ArH), 7.68 (d, 1 H, *J* = 7.8 Hz, ArH), 8.10 (d, 1 H, *J* = 7.8 Hz, ArH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 64.9, 99.5, 118.1, 122.7, 123.4, 128.3, 129.4, 147.9, 152.6, 162.4.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.84; H, 5.72; N, 16.20.

Methyl 3-(4-Aminoquinolin-2-yl)-3-hydroxy-2-methylpropionate (2g)

IR (KBr): 1724 (CO_2CH_3), 3366 (br, NH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.78–2.88 (m, 1 H, CH), 3.67 (s, 3 H, CO_2CH_3), 4.90 (d, *J* = 5.4 Hz, 1 H), 6.58 (s, 1 H, ArH), 7.41–7.46 (m, 1 H, ArH), 7.62–7.67 (m, 1 H, ArH), 7.75 (d, *J* = 8.1 Hz, 1 H, ArH), 7.93 (d, *J* = 8.1 Hz, 1 H, ArH).

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.56; H, 6.12; N, 10.60.

Methyl 3-(4-Aminoquinolin-2-yl)-3-hydroxy-2-(4-methylpiperazin-1-ylmethyl)propionate (2h)

IR (KBr): 1731 (CO_2CH_3), 3396 (br, NH_2) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.26 (s, 3 H, NCH_3), 2.30–2.45 (m, 8 H, 4 × CH_2N), 2.60–2.70 (m, 2 H, NCH_2), 3.05–3.15 (m, 1 H, C*H*CH_2), 3.63 (s, 3 H, CO_2CH_3), 4.96 (d, *J* = 1.8 Hz, 1 H, CHOH), 6.75 (s, 2 H, NH_2), 7.47–7.51 (m, 1 H, ArH), 7.68–7.75 (m, 2 H, ArH), 7.83–7.89 (m, 1 H, ArH), 8.22–8.26 (m, 1 H, ArH).

Anal. Calcd for $C_{19}H_{26}N_4O_3$: C, 63.67; H, 7.31; N, 15.63. Found: C, 63.56; H, 7.12; N, 150.60.

(4-Amino-2-methylquinolin-3-yl)methanol (2i)

IR (KBr): 3433 (br, NH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 2.55 (s, 3 H, CH_3), 4.63 (s, 2 H, CH_2), 6.59 (br s, 2 H, NH_2), 7.33 (t, *J* = 7.8 Hz, 1 H, ArH), 7.55 (t, *J* = 7.8 Hz, 1 H, ArH), 7.66 (d, *J* = 8.1 Hz, 1 H, ArH), 8.16 (d, *J* = 8.1 Hz, 1 H, ArH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 22.9, 56.4, 111.7, 117.9, 122.3, 123.3, 127.5, 128.9, 146.4, 149.8, 157.2.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.04; H, 6.35; N, 14.60.

4-Amino-2-methylquinoline-3-carbaldehyde (2j)

IR (KBr): 1707 (CHO), 3312 (br, NH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 2.71 (s, 3 H, CH_3), 6.04 (br s, 2 H, NH_2), 7.50 (t, *J* = 7.5 Hz, 1 H, ArH), 7.75 (t, *J* = 7.5 Hz, 1 H, ArH), 7.88 (d, *J* = 8.1 Hz, 1 H, ArH), 7.98 (d, *J* = 8.1 Hz, 1 H, ArH), 9.05 (s, 1 H, CHO), 9.89 (br s, 1 H, NH_2).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.04; H, 5.35; N, 15.12.

[3-(2-Aminophenyl)-5-methylisoxazol-4-yl]methanol (3)

To a stirred soln of **1a** (1.5 g, 5.72 mmol) in anhyd Et_2O (40 mL) was added $LiAlH_4$ (0.33 g, 8.6 mmol) in portions at 0 °C. The ice bath was removed and the reaction was allowed to proceed at r.t. for 1 h. Upon completion the mixture was carefully decomposed with ice-cold 10% NaOH soln. The precipitate was filtered and the filtrate was washed thoroughly with H_2O. The organic layer was dried and evaporated to yield a residue. This residue upon column chromatography over silica gel (60–120) (hexane–EtOAc, 40:60) to gave pure **3** as a brown oil; yield: 0.95 g (82%).

IR (neat): 3443 (br, NH_2 and OH) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.58 (s, 2 H, C*H*$_2$OH), 7.54–7.60 (m, 3 H, ArH), 8.12–8.17 (m, 1 H, ArH).

ESI-MS: *m*/*z* = 205.40 (M^+ + 1).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.58; H, 6.05; N, 13.60.

3-(2-Aminophenyl)-5-methylisoxazole-4-carbaldehyde (4)

To the stirred soln of **3** (0.5 g, 2.45 mmol) in anhyd CH_2Cl_2 (20 mL) was added PCC (1.05 g, 4.9 mmol) and the reaction was allowed to proceed at r.t. for 16 h. Thereafter the mixture was filtered through a silica gel column (hexane–EtOAc, 50:50) to afford compound **4** as an orange solid; yield: 0.4 g (81%); mp 134–136 °C.

IR (KBr): 1684 (CHO), 3432 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.80 (s, 3 H, CH_3), 7.54–7.58 (m, 1 H, ArH), 7.70–7.76 (m, 2 H, ArH), 8.25–8.29 (m, 1 H, ArH), 9.79 (s, 1 H, CHO).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 12.4, 116.5, 123.8, 125.4, 131.7, 132.7, 134.0, 148.8, 159.9, 177.0, 183.1.

FAB-MS: *m*/*z* = 203 (M^+ + 1).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.04; H, 5.15; N, 14.06.

Methyl 3-(2-Aminophenyl)-5-methylisoxazole-4-carboxylate (5a)

Yellow solid; mp 192–194 °C.

IR (KBr): 1733 (CO_2CH_3), 3391 (br, NH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.91 (s, 3 H, CH_3), 3.98 (s, 3 H, CO_2CH_3), 7.00 (br s, 2 H, NH_2), 7.59 (t, *J* = 7.5 Hz, 1 H, ArH), 7.83 (t, *J* = 7.5 Hz, 1 H, ArH), 7.99 (d, *J* = 8.1 Hz, 1 H, ArH), 8.82 (d, *J* = 8.4 Hz, 1 H, ArH).

ESI-MS: *m*/*z* = 233.4 (M^+ + 1), 255.0 (M^+ + Na).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.20; H, 5.34, N, 12.15.

3-(2-, 3-, and 4-Nitrophenyl)-4,5-dihydroisoxazoles (6)

These 4,5-dihydroisoxazoles were prepared as described in the literature.[21]

Methyl 3-(2-Nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6a)
Yellow oil; yield: 87%.

IR (neat): 1743 (CO_2CH_3) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.54–3.62 (m, 2 H, CH_2), 3.87 (s, 3 H, CO_2CH_3), 5.23–5.32 (m, 1 H, CH), 7.58–7.72 (m, 3 H, ArH), 8.10–8.14 (m, 1 H, ArH).

FAB-MS: *m*/*z* = 251 (M^+ + 1).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.87; H, 4.08; N, 11.25.

Ethyl 3-(2-Nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6b)
Brown oil; yield: 83%.

IR (neat): 1743 (CO_2Et) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$), 3.45–3.70 (m, 2 H, C*H*$_2$CH), 4.31 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 5.21–5.30 (m, 1 H, C*H*CH$_2$), 7.27–7.76 (m, 3 H, ArH), 8.10–8.13 (m, 1 H, ArH).

FAB-MS: *m*/*z* = 265 (M^+ + 1).

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.61; H, 4.50; N, 10.65.

***tert*-Butyl 3-(2-Nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6c)**
Yellow solid; yield: 80%; mp 76–78 °C.

IR (KBr): 1738 (CO_2-*t*-Bu) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.54 (s, 9 H, 3 × CH_3), 3.47–3.58 (m, 2 H, CH_2CH), 5.09–5.18 (m, 1 H, $CHCH_2$), 7.58–7.74 (m, 3 H, ArH), 8.08–8.12 (m, 1 H, ArH).

FAB-MS: *m*/*z* = 293 (M^+ + 1).

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.62; H, 5.58; N, 9.62.

3-(2-Nitrophenyl)-4,5-dihydroisoxazole-5-carbonitrile (6d)
Off-white solid; yield: 77%; mp 122–124 °C.

IR (KBr): 2248 (CN) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.52–3.88 (m, 2 H, C*H*$_2$CH), 5.43–5.51 (m, 1 H, C*H*CH$_2$), 7.60–7.78 (m, 3 H, ArH), 8.17–8.22 (m, 1 H, ArH).

FAB-MS: *m*/*z* = 218 (M^+ + 1).

Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.43; H, 3.21; N, 19.38.

1-[3-(2-Nitrophenyl)-4,5-dihydroisoxazol-5-yl]ethanone (6e)
Brown oil; yield: 79%.

IR (neat): 1722 ($COCH_3$) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 3.48–3.53 (m, 2 H, C*H*$_2$CH), 5.06–5.15 (m, 1 H, C*H*CH$_2$), 7.52–7.72 (m, 3 H, ArH), 8.08–8.13 (m, 1 H, ArH).

FAB-MS: *m*/*z* = 235 (M^+ + 1).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.49; H, 4.33; N, 11.92.

Methyl 3-(4,5-Dimethoxy-2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6f)
Pale yellow solid; yield: 75%; mp 130–132 °C.

IR (KBr): 1732 (CO_2CH_3) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.50–3.61 (m, 2 H, C*H*$_2$CH), 3.82 (s, 3 H, CO_2CH_3), 3.99 (s, 6 H, 2 × OCH_3), 5.24–5.29 (m, 1 H, C*H*CH$_2$), 6.96 (s, 1 H, ArH), 7.72 (s, 1 H, ArH).

FAB-MS: *m*/*z* = 311 (M^+ + 1).

Anal. Calcd for $C_{13}H_{14}N_2O_7$: C, 50.33; H, 4.55; N, 9.03. Found: C, 50.18; H, 4.76; N, 9.33.

Methyl 3-(6-Nitro-1,3-benzodioxol-5-yl)-4,5-dihydroisoxazole-5-carboxylate (6g)
Pale yellow solid; yield: 76%; mp 121–123 °C.

IR (KBr): 1754 (CO_2CH_3) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.47–3.57 (m, 2 H, C*H*$_2$CH), 3.86 (s, 3 H, CO_2CH_3), 5.22–5.30 (m, 1 H, C*H*CH$_2$), 6.19 (s, 2 H, CH_2), 6.93 (s, 1 H, ArH), 7.63 (s, 1 H, ArH).

FAB-MS: *m*/*z* = 295 (M^+ + 1).

Anal. Calcd for $C_{12}H_{10}N_2O_7$: C, 48.99; H, 3.43; N, 9.52. Found: C, 48.92; H, 3.35; 9.46.

Methyl 3-(3-Nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6h)
White solid; yield: 81%; mp 92–94 °C.

IR (KBr): 1755 (CO_2CH_3) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.68–3.76 (m, 2 H, C*H*$_2$CH), 3.85 (s, 3 H, CO_2CH_3), 5.24–5.33 (m, 1 H, C*H*CH$_2$), 7.62 (t, *J* = 8.0 Hz, 1 H, ArH), 8.10 (d, *J* = 7.8 Hz, 1 H, ArH), 8.27–8.32 (m, 1 H, ArH), 8.45 (s, 1 H, ArH).

FAB-MS: *m*/*z* = 251 (M^+ + 1).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.92; H, 4.13; N, 11.27.

Ethyl 3-(3-Nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6i)
White solid; yield: 83%; mp 65–67 °C.

IR (KBr): 1748 (CO_2Et) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$CH$_2$), 3.66–3.72 (m, 2 H, C*H*$_2$CH), 4.30 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 5.20–5.30 (m, 1 H, C*H*CH$_2$), 7.58–7.66 (m, 1 H, ArH), 8.08–8.13 (m, 1 H, ArH), 8.26–8.32 (m, 1 H, ArH), 8.44–8.46 (m, 1 H, ArH).

FAB-MS: *m*/*z* = 265 (M^+ + 1).

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.64; H, 4.63; N, 10.66.

Methyl 3-(4-Nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (6j)
Off-white solid; yield: 86%; mp 159–161 °C.

IR (KBr): 1755 (CO_2CH_3) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.66–3.72 (m, 2 H, C*H*$_2$CH), 3.84 (s, 3 H, CO_2CH_3), 5.24–5.33 (m, 1 H, C*H*CH$_2$), 7.86 (d, *J* = 8.5 Hz, 2 H, ArH), 8.28 (d, *J* = 8.5 Hz, 2 H, ArH).

FAB-MS: *m*/*z* = 251 (M^+ + 1).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.96; H, 4.12; N, 11.26.

Methyl 3-(2-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7a); Typical Procedure Using Palladium-on-Carbon
To a soln of **6a** (0.75 g, 3.0 mmol) in MeOH (20 mL) was added 10% Pd/C (125 mg) under N_2. The atmosphere of the vessel was replaced by hydrogen gas. The reaction was carried out on the Parr assembly at 40 psi at r.t. for 1 h. Thereafter, the catalyst was filtered over Celite and the filtrate was evaporated to yield a residue. This

residue upon column chromatography over silica gel (hexane–EtOAc, 90:10) yielded a brown solid; yield: 0.58 g (88%).

Methyl 3-(2-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7a); Typical Procedure Using Raney Nickel

A mixture of **6a** (0.67 g, 2.68 mmol) and Raney Ni (0.1 g wet) in MeOH (10 mL) was subjected to hydrogenation at 40 psi in the Parr assembly for 3 h. The catalyst was removed by filtration over Celite and the filtrate was concentrated. The residue thus obtained was subjected to column chromatography over silica gel (hexane–EtOAc, 90:10) to afford pure **7a** as a brown solid; yield: 0.50 g (85%).

IR (KBr): 1741 (CO_2CH_3), 3467 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.72–3.83 (m, 5 H, CH_2CH and CO_2CH_3), 5.06–5.15 (m, 1 H, CHCH$_2$), 6.71–6.75 (m, 2 H, ArH), 7.14–7.27 (m, 2 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 40.8, 53.2, 76.6, 110.9, 116.3, 116.8, 130.0, 131.5, 147.3, 157.8, 171.3.

HRMS: *m*/*z* calcd for $C_{11}H_{12}N_2O_3$: 220.0848; found: 220.0837.

Ethyl 3-(2-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7b)

IR (KBr): 1738 (CO_2Et), 3447 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$), 3.71–3.76 (m, 2 H, CH_2CH), 4.27 (q, *J* = 7.2 Hz, 2 H, CH_2CH$_3$), 5.05, 5.10 (dd, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 1 H, CHCH$_2$), 5.63 (br s, 2 H, NH_2), 6.66–6.75 (m, 2 H, ArH), 7.14–7.23 (m, 2 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 14.5, 40.8, 62.4, 76.8, 111.0, 116.3, 116.8, 130.0, 131.5, 147.3, 157.7, 170.8.

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.65; H, 6.16; N, 12.03.

***tert*-Butyl 3-(2-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7c)**

IR (KBr): 1732 (CO_2-*t*-Bu), 3449 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, 3 × CH_3), 3.67 (d, *J* = 9.2 Hz, 2 H, CH_2CH), 4.96 (t, *J* = 9.2 Hz, 1 H, CHCH$_2$), 5.62 (br s, 2 H, NH_2), 6.66–6.75 (m, 2 H, ArH), 7.14–7.23 (m, 2 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 28.4, 40.7, 77.4, 111.2, 116.3, 116.8, 130.0, 131.4, 147.3, 157.6, 169.7.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.89; H, 6.73; N, 10.60.

3-(2-Aminophenyl)-4,5-dihydroisoxazole-5-carbonitrile (7d)

IR (KBr): 2249, 2213 (CN), 3466 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.81–3.86 (m, 2 H, CH_2CH), 5.28 (t, *J* = 8.6 Hz, 1 H, CHCH$_2$), 5.60 (br s, 2 H, NH_2), 6.69–6.78 (m, 2 H, ArH), 7.09–7.24 (m, 2 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 42.9, 65.5, 109.8, 116.6, 117.2, 117.7, 129.5, 130.1, 132.3, 147.5, 160.0.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.26; H, 4.89; N, 22.49.

1-[3-(2-Aminophenyl)-4,5-dihydroisoxazol-5-yl]ethanone (7e)

IR (neat): 1721 ($COCH_3$), 3470 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, $COCH_3$), 3.58–3.70 (m, 2 H, CH_2CH), 4.90, 4.95 (dd, J_1 = 6.6 Hz, J_2 = 4.80 Hz, 1 H, CHCH$_2$), 6.68–6.75 (m, 2 H, ArH), 7.15–7.24 (m, 2 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 26.7, 39.3, 83.1, 111.1, 116.3, 117.0, 130.2, 131.6, 147.2, 158.4, 208.2.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.76; H, 6.12; N, 13.86.

Methyl 3-(2-Amino-4,5-dimethoxyphenyl)-4,5-dihydroisoxazole-5-carboxylate (7f)

IR (KBr): 1744 (CO_2CH_3), 3457 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.70–3.74 (m, 2 H, CH_2CH), 3.81 (s, 6 H, 2 × OCH_3), 3.87 (s, 3 H, CO_2CH_3), 5.09 (t, *J* = 9.2 Hz, 1 H, CHCH$_2$), 6.26 (s, 1 H, ArH), 6.61 (s, 1 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 41.2, 53.2, 56.1, 57.5, 76.4, 99.9, 102.5, 113.6, 141.1, 143.4, 152.7, 157.3, 171.5.

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.91. Found: C, 55.97; H, 5.62; N, 10.19.

Methyl 3-(6-Amino-1,3-benzodioxol-5-yl)-4,5-dihydroisoxazole-5-carboxylate (7g)

IR (KBr): 1740 (CO_2CH_3), 3450 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.67 (d, *J* = 8.8 Hz, 2 H, CH_2CH), 3.82 (s, 3 H, CO_2CH_3), 5.07 (t, *J* = 8.8 Hz, 1 H, CHCH$_2$), 5.89 (s, 2 H, OCH_2O), 6.27 (s, 1 H, ArH), 6.58 (s, 1 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 41.3, 53.2, 76.4, 97.3, 101.6, 102.8, 108.0, 139.7, 144.6, 150.6, 157.4, 171.4.

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.89; H, 4.66; N, 10.66.

Methyl 3-(3-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7h)

IR (KBr): 1742 (CO_2CH_3), 3449 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.58–3.72 (m, 2 H, CH_2CH), 3.82 (s, 3 H, CO_2CH_3), 5.13, 5.18 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1 H, CHCH$_2$), 6.72–6.77 (m, 1 H, ArH), 6.96–7.23 (m, 3 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 39.5, 53.2, 78.2, 113.2, 117.6, 117.7, 129.7, 130.1, 147.3, 156.8, 171.2.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.80; H, 5.46; N, 12.85.

Ethyl 3-(3-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7i)

IR (KBr): 1716 (CO_2Et), 3451 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.57–3.62 (m, 2 H, CH_2CH), 4.27 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 5.11, 5.16 (dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz, 1 H, CHCH$_2$), 6.72–6.77 (m, 1 H, ArH), 6.96–7.23 (m, 3 H, ArH).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.42; H, 5.88; N, 12.06.

Methyl 3-(4-Aminophenyl)-4,5-dihydroisoxazole-5-carboxylate (7j)

IR (KBr): 1742 (CO_2CH_3), 3458 (br, NH_2) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.55–3.59 (m, 2 H, CH_2CH), 3.78 (s, 3 H, CO_2CH_3), 5.10 (t, *J* = 9.2 Hz, 1 H, CHCH$_2$), 6.63 (d, *J* = 8.6 Hz, 2 H, ArH), 7.43 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 39.7, 53.1, 77.9, 115.0, 118.5, 128.9, 149.3, 156.4, 171.5.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.12; H, 5.72; N, 12.58.

Methyl 3-[2-(Acetylamino)phenyl]-4,5-dihydroisoxazole-5-carboxylate (8a); Typical Procedure

To a stirred soln of **7a** (0.30 g, 1.36 mmol) in dry CH_2Cl_2 (3 mL) was added Et_3N (0.28 mL, 2.04 mmol) followed by dropwise addition of a soln of AcCl (0.19 mL, 2.72 mmol) in dry CH_2Cl_2 (3 mL)

at 0 °C. When the addition was complete, the reaction was continued at r.t. for 2 h. The mixture was extracted with CH_2Cl_2 (2 × 15 mL) and H_2O (20 mL). The combined organic layer was washed with brine, dried (anhyd Na_2SO_4), and evaporated to obtain an oily residue. The residue was purified through column chromatography over silica gel (hexane–EtOAc, 80:20) to give **8a** as a pale yellow solid; yield: 0.3 g (86%); mp 150–152 °C.

IR (KBr): 1755 (CO_2CH_3), 3458 (NH) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, $COCH_3$), 3.75–3.81 (m, 2 H, CH_2CH), 3.85 (s, 3 H, CO_2CH_3), 5.14, 5.19 (dd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 1 H, C*H*CH_2), 7.08–7.16 (m, 1 H, ArH), 7.28–7.32 (m, 1 H, ArH), 7.41–7.49 (m, 1 H, ArH), 8.69–8.73 (m, 1 H, ArH), 10.49 (br s, 1 H, NH).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 25.9, 40.6, 53.4, 77.0, 115.3, 120.9, 123.3, 129.7, 132.0, 138.7, 157.8, 169.7, 170.6.

FAB-MS: *m*/*z* = 263 (M^+ + 1).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.29; H, 5.41; N, 10.72.

Ethyl 3-[3-(Acetylamino)phenyl]-4,5-dihydroisoxazole-5-carboxylate (8i)

Colorless oil; yield: 86%.

IR (neat): 1740 (CO_2Et), 3306 (NH) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H, CH_3CH$_2$), 2.19 (s, 3 H, $COCH_3$), 3.59–3.66 (m, 2 H, CH_2CH), 4.25 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 5.16 (t, *J* = 9.2 Hz, 1 H, C*H*CH_2), 7.31–7.44 (m, 2 H, ArH), 7.64–7.68 (m, 1 H, ArH), 7.79 (s, 1 H, ArH).

FAB-MS: *m*/*z* = 277 (M^+ + 1).

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.55; H, 6.58; N, 10.68.

Methyl 3-[4-(Acetylamino)phenyl]-4,5-dihydroisoxazole-5-carboxylate (8j)

White solid; yield: 89%; mp 127–129 °C.

IR (KBr): 1759 (CO_2CH_3), 3528 (NH) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, $COCH_3$), 3.63 (d, *J* = 9.0 Hz, 2 H, CH_2CH), 3.82 (s, 3 H, CO_2CH_3), 5.18 (t, *J* = 9.1 Hz, 1 H, C*H*CH_2), 7.54–7.59 (m, 4 H, ArH).

FAB-MS: *m*/*z* = 263 (M^+ + 1).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.23; H, 5.25; N, 10.44.

Acknowledgment

The financial assistance to three of the authors (VS, SM and GPY) from DST and CSIR New Delhi in the form of fellowship is gratefully acknowledged. This work was partially supported through a financial grant under DST Project no. SR/SI/OC-04/2003.

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USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. of compound **7d**: 297540.

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