Highly Substituted Isoxazoles: The Baylis–Hillman Reaction of Substituted 4-Isoxazolecarbaldehydes and Attempted Cyclization to Isoxazole-Annulated Derivatives[1]

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Abstract: In an attempt to understand the effect of position of the formyl group on the efficiency of Baylis–Hillman reaction within isoxazolecarbaldehydes, the reactions of substituted 4-isoxazolecarbaldehydes to obtain highly substituted isoxazoles are described. Attempts to obtain isoxazole-annulated derivatives from these Baylis–Hillman adducts involving S_NR'-S_NAr substitution strategy are also described.

Key words: Baylis–Hillman reaction, 4-isoxazolecarbaldehyde, DABCO, DMAP

The Baylis–Hillman reaction,[2] which has witnessed an extraordinary exploitation in the recent past, is now considered to be a standard synthetic methodology in the arsenal of organic and medicinal chemists. Various reasons ascribed to such phenomenal expansion in the scope of this C–C bond forming reaction include atom-economy, easy reaction conditions (even with water as the solvent),[3] multifunctional products that can be diversified further for accessing heterocycles,[4] intermediates that serve as synthons for natural products,[5] adaption for solid-phase chemistry for combinatorial synthesis, and others.[6] In addition, this reaction gains significant importance from a medicinal point of view if it is carried out with privileged scaffolds.[7] The slow reaction rate that was considered to be one of the major drawback of this reaction, has been almost overcome using either physical or chemical means.[2] However, not much attention has been paid towards understanding a plausible mechanism behind unusually fast Baylis–Hillman reaction experienced by some electrophiles.

Isoxazole is a privileged structure that is documented to be associated with wide range of biological activities.[8] In our objective to generate isoxazole-based chemical libraries in parallel utilizing solution and solid-phase chemistry, we initiated our studies with 5-isoxazolecarbaldehydes. We discovered that 5-isoxazolecarbaldehyde is one of the fastest reacting substrates for the Baylis–Hillman reaction.[9] This has been a synthetically and medicinally attractive proposition for us since it helps to obtain various intermediates in an expeditious fashion. Isoxazole derivatives from the Baylis–Hillman-mediated chemistry have led to molecules with potent bioresponse.[10] We have observed that results with this substrate, with respect to Baylis–Hillman reaction, can be generalized and extended to other aldehydes.[11] During our efforts to find reasons behind the unusually fast reactivity of 5-isoxazolecarbaldehydes we have proposed that the proton abstraction in the intermediate step is quite likely aided by the heteroatom present in the molecule thereby facilitating the elimination of base (Figure 1).[12] This hypothesis was the outcome of the earlier observation made by Hofmann and Rabe where they have proposed the formation of an zwitterionic intermediate that allows elimination of H_α and base aided by the basic heteroatom of the aldehyde.[13] To provide a chemical basis to our hypothetical assumption, we envisioned that substituted 4-isoxazolecarbaldehydes would be a slow reacting substrate as compared to its isomer since here there will be no heteroatom to assist the elimination of base. To substantiate this we carried out the synthesis of substituted 4-isoxazolecarbaldehydes and subjected them to Baylis–Hillman reaction. As expected, in contrast to 5-isoxazolecarbaldehydes, substituted 4-isoxazolecarbaldehydes are sluggish electrophiles for the Baylis–Hillman reaction. In addition it was envisaged that Baylis–Hillman adducts of 3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbaldehyde could be cyclized to obtain isoxazole-annulated derivatives employing S_NR'-S_NAr substitution strategy.[14] Our initial attempts toward this objective along with the details of conventional Baylis–Hillman reaction with substituted 4-isoxazolecarbaldehydes are presented herein.

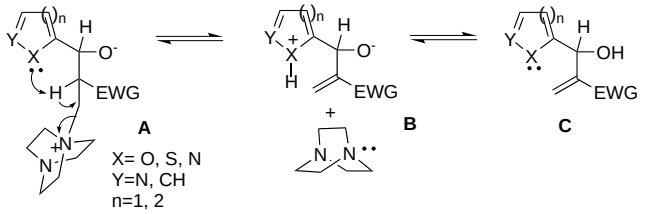

Figure 1 Proton abstraction is aided by the lone pair of the heteroatom leading to immediate release of the base

The substituted 4-isoxazolecarbaldehydes were prepared as reported in the literature.[15] In the first instance methyl acetoacetate was treated with sodium methoxide to generate the intermediate that was then reacted in situ with benzohydroximinoyl chloride to generate methyl 3-aryl

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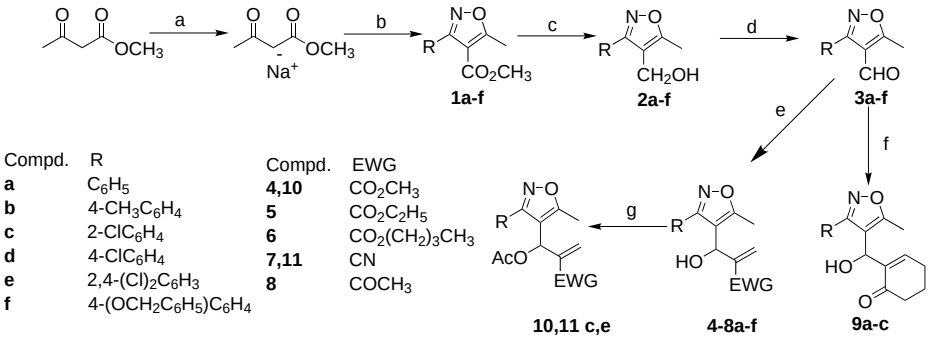
substituted 5-methyl-4-isoxazole carboxylates **1a**–**f**. These esters upon careful reduction with lithium aluminum hydride furnished the methyl alcohols **2a**–**f** quantitatively. Furthermore, these alcohols upon oxidation with pyridinium chlorochromate afforded the substituted 4-isoxazolecarbaldehydes **3a**–**f** in excellent yields (Scheme 1). These aldehydes were then subjected to Baylis–Hillman reaction under neat conditions. Interestingly even after 24 hours the reactions did not go to completion. Here it would be relevant to state that compared to aldehydes **3d** and **3f**, the reactions were fast for all other aldehydes. However, upon work-up and column chromatography we recovered 5–10% of the unreacted aldehydes along with the desired products in moderate yields only. Similar to our earlier experience with Baylis–Hillman reactions of substituted 5-isoxazolecarbaldehyde, we observed that in substituted 4-isoxazolecarbaldehydes too, as the reaction progressed the reaction mixture became unusually thick thereby preventing stirring using a magnetic bar. However, in contrast to the Baylis–Hillman reaction of 5-isoxazolecarbaldehyde, the formation of a thick slurry here was not indicative of completion of the reaction. Assuming this as the possible reason for the substrate not being consumed completely, we decided to add solvents and evaluate their effect on the progress of reaction. For our studies, we also included some recently reported observations of fast and efficient Baylis–Hillman reaction in homogenous medium.[3a] Thus, as a model we conducted the reaction of compound **3b** with methyl acrylate under various solvent conditions. The results are shown in Table 1. In contrast to an earlier report,[16] it was surprising that the neat conditions work best in our hands compared to the use of any solvent. In our earlier work[9] we have observed that DMF and DMSO too serve as good solvents for the reaction and they also address the solvent condition to be applied for solid phase reactions.[12] But in this study we found that DMSO led to formation of an unidentified highly polar product in major quantity.

In an attempt to find optimal conditions to obtain maximum yield we increased the amount of the base and also the activated alkene. With 0.5 equivalent of the base and 2 equivalents of the activated alkene, the reaction was more efficient and the yields were better. Of the different activated alkenes employed, acrylonitrile gave the best results since no starting material was recovered and yields of 79–89% were achieved. This was in precedence with the earlier observation made by Basavaiah et al.[17] Notably in these aldehydes though the reactions were allowed to run for more than 72 hours, in no case we observed the formation of ether side-product as in the 5-isomer.[18]

During this study, we also carried out base-mediated Baylis–Hillman reaction with cyclohexenone and acrylamide. The aldehydes **3a**–**c** were treated with cyclohexenone in the presence of DMAP in dioxane–water. Here too, as compared to 5-isoxazolecarbaldehydes, the reactions did not go to completion and products **9a**–**c** were isolated in low yields only (Scheme 1). On the other hand, the initial attempts of Baylis–Hillman reaction of these aldehydes with acrylamide in the presence of DABCO were unsuccessful. For solid-phase Baylis–Hillman reactions using substituted 4-isoxazolecarbaldehyde as electrophile, the acrylic acid was immobilized onto the 2-chlorotrityl chloride resin using standard technique. The acrylate resin was then subjected to Baylis–Hillman reaction with **3b**,**c** in DMF. The reaction was continued for 48 hours followed by a repeat cycle. The resin was washed, dried and finally cleaved to obtain the Baylis–Hillman adduct **13a**–**c** in low yields (Scheme 2). Hence, as compared to the 5-isomer,[14] reactions were slow and yields were also only average.

Thus as envisioned, the substituted 4-isoxazolecarbaldehydes are less reactive electrophiles for Baylis–Hillman reaction as compared to their 5-isomer. It was suggested[13] that the basicity of the heteroatom affecting the migration of protons could be the reason for fast Baylis–Hillman reaction. However, we have observed that 5-isoxazolecarbaldehyde reacts even faster than the 3-pyridinecarbaldehyde (exemplified by Hoffman and Rabe as the fastest reacting electrophile) during the Baylis–Hillman reaction that could be possibly explained as shown in Figure 1. The proximity of the heteroatom to the methyl bond bearing the base is greater in 5-isoxazole than in 4-isoxazole derivatives thus facilitating the elimi-



Compd.	R
a	C_6H_5
b	4-$CH_3C_6H_4$
c	2-ClC_6H_4
d	4-ClC_6H_4
e	2,4-$(Cl)_2C_6H_3$
f	4-$(OCH_2C_6H_5)C_6H_4$

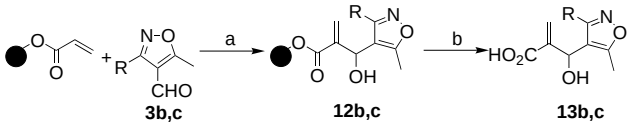
Compd.	EWG
4,10	CO_2CH_3
5	$CO_2C_2H_5$
6	$CO_2(CH_2)_3CH_3$
7,11	CN
8	$COCH_3$

Scheme 1 *Reagents and conditions*: a) NaOMe in MeOH; b) RCH(Cl)=NOH, 0 °C, MeOH, 4 h; c) $LiAlH_4$, anhyd Et_2O, 40 °C 1 h; d) PCC, CH_2Cl_2, r.t., 30 min; e) DABCO, alkene, r.t., 2 d; f) DMAP, cyclohexenone, r.t., 7 d; g) AcCl, pyridine, r.t., 30 min

Table 1 Effect of Alkene, Base and Solvent on Baylis–Hillman Reaction of the Substituted 4-Isoxazolecarbaldehyde **3b**[a,b]

Entry	Alkene (equiv)	Base (equiv)	Solvent	Time (d)	Yield (%)[c]
1	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	neat	2	42
2	CH_2=$CHCO_2Me$ (2.0)	DABCO (0.5)	neat	2	59
3	CH_2=CHCN (1.0)	DABCO (0.5)	neat	2	56
4	CH_2=CHCN (2.0)	DABCO (0.5)	neat	2	89
5	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	MeOH	7	07
6	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	MeOH–H_2O (1:1)	7	05
7	CH_2=$CHCO_2Me$ (1.5)	aq Me_3N 30% (2.5)	MeOH	5	23
8	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	dioxane–H_2O (1:1)	7	n.r
9	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	CH_2Cl_2	7	n.r
10	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	THF	7	n.r.
11	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	DMSO	1	10
12	CH_2=$CHCO_2Me$ (1.0)	DABCO (0.5)	DMF	1	20
13	 (1.0)	DABCO (0.5)	neat	7	n.r.
14[d]	 (1.0)	DMAP (1.0)	dioxane–H_2O (3:2)	7	21

[a] All reactions were carried out with 2.5 mmol of **3b**.
[b] For comparison with substituted 5-isoxazolecarbaldehyde, see Ref.[9]
[c] n.r. = no reaction.
[d] Reactions of substituted 5-isoxazolecarbaldehydes with cyclohexenone in the presence of DMAP (0.2 equiv) in dioxane–H_2O are completed within 1 h to give products in 90–95% yields (unpublished).

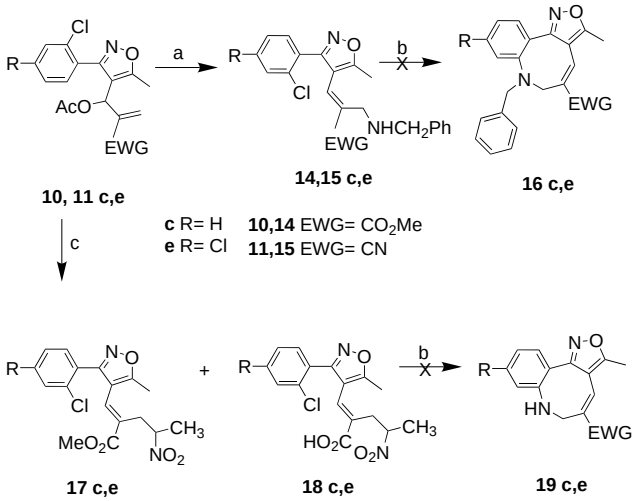


Scheme 2 *Reagents and Conditions*: a) DABCO, DMF, r.t., 2 × 48 h; b) TFA–CH_2Cl_2 (5:95), 20 min

nation of the base. This fact was also confirmed through the Drieding's model of the intermediate.

To explore the synthetic utility of the Baylis–Hillman products described herein we decided to work upon an earlier reported[14] synthetic strategy. It was envisioned that if acetates **10** and **11** of the Baylis–Hillman adducts of the 2-halophenyl substituted aldehyde are treated with amines under forced conditions, the Michael adduct could undergo cyclization in situ through S_NAr substitution to yield isoxazole annulated derivatives **16** (Scheme 3).

Toward this objective in the first instance, compounds **4c**,**e** and **7c**,**e** were converted to the corresponding acetates **10** and **11c**,**e**. The acetates **10c**,**e** were then refluxed with benzylamine in the presence of triethylamine. However, in all cases we obtained the allyl amines **14c**,**e** while no cyclized derivative **16** was formed (Scheme 3). The amines were produced within an hour of reaction time and the product remained unchanged even after refluxing for 48 hours. TLC (hexane–ethyl acetate, 70:30) on basic alumina indicated the presence of two spots very close to



Scheme 3 *Reagents and Conditions*: a) $PhCH_2NH_2$, Et_3N, THF, 70 °C, 1 h; b) continued for 48 h; c) $EtNO_2$, K_2CO_3, 60–70 °C, 30 min, **18c**,**e** were formed only if the reaction was continued for 24 h

each other, which upon separation and spectroscopic analysis were identified as *E*- (less polar) and *Z*- (more polar) isomers. The ^{1}H NMR spectrum of the mixture indicated these isomers to be present in almost equal quantity. The stereochemistry of the amines was assigned on the basis of NOE studies across the double bond of the polar isomer because the =CH proton could be easily irradiated in this spectrum. Irradiation of =CH proton at $\delta = 6.50$ showed an increase of the allylic CH_2 protons at $\delta = 3.70$ by 3.07% while irradiation of allylic CH_2 led to an increase for =CH proton by 5.74% indicating the *Z*-stereochemistry of amines. In the *E*-isomer, the =CH was merged with the aromatic proton that made it difficult to irradiate. We also carried out a similar synthetic sequence with compounds **7c** and **7e** to obtain the allylic amines **15c**,**e** via the acetates **11c**,**e**. These amines were notably less polar compared to **14** and could even be monitored on silica gel plates using the same solvent system. These amines were obtained with a high degree of stereoselectivity. During NOE studies of these amines, the stereochemistry across the double bond was assigned as *Z* since irradiation of =CH proton at $\delta = 6.72$ led to an enhancement of allylic CH_2 at $\delta = 3.48$ (5.02%) while irradiation of CH_2 proton led to an increase in the signal of =CH proton by 6.73%. Thus irrespective of the stereochemistry, the amines failed to cyclize to furnish the desired products (Figure 2).

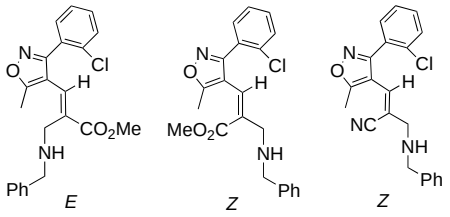


Figure 2 Stereochemistry of allyl amines

In another strategy, the compounds **10c**,**e** were treated with a nitroalkane. Here too, though the S_NR' reaction of the nitronate ion was successful to afford **17c**,**e**, the intramolecular S_NAr and subsequent elimination of nitrous acid to furnish the desired compound **19** did not take place (Scheme 3). The stereochemistry of these products was assigned as *E*, based on the literature.[19] However, heating the reaction mixture for a prolonged period decreased the yield of the products as there was appreciable formation of polar impurities that were not isolated. But a mass spectrum of the mixture did indicate the presence of molecular ion peaks corresponding to acrylic acid derivatives **18c**,**e** that may have obviously resulted due to hydrolysis of the ester in the presence of base.

In conclusion, we have described the Baylis–Hillman reactions of substituted 4-isoxazolecarbaldehyde in solution- and solid-phase and have shown the influence of position of the formyl group within a heterocycle on the rate of reaction. We speculate that Baylis–Hillman adducts of 4-isoxazolecarbaldehyde described herein will be of high synthetic importance for obtaining isoxazole-annulated carbocycles and heterocycles and isoxazole-based biodynamic agents. In addition it will be interesting to study the Baylis–Hillman reaction of substituted 3-isoxazolecarbaldehyde, which we presume will be faster as compared to the 4-isomer and will also give an insight into the basicity of the heteroatom affecting the rate of Baylis–Hillman reaction within a heterocycle. Work toward these perspectives is under way and will form part of our future communications.

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 Spectrum RX I FTIR spectrophotometer while 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 spectra 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 either on Carlo Erba 1108 or Elementar's Vario EL *III* microanalyzer. All yields of Baylis–Hillman adducts are based on exclusion of 5–10% aldehyde that was recovered unreacted in all reactions except for that with acrylonitrile.

Baylis–Hillman Reaction of Substituted 4-Isoxazolecarbaldehydes with Alkenes; General Procedure

To a mixture of DABCO (0.3 g, 2.67 mmol) and the appropriate alkene (10.6 mmol), that had been stirred at r.t. for 20 min, was added the appropriate aldehyde **3a**–**f** (5.3 mmol) under stirring and the reaction was allowed to proceed for a period of 72 h. Thereafter 5% aq HCl (50 mL) was added to the reaction mixture to neutralize the base and the resulting mixture was extracted with EtOAc (2×100 mL). The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4) and evaporated under vacuum to yield an oily residue. The residue was purified by column chromatography over silica gel (60–120 mesh) using hexane–EtOAc as eluent. A mixture of hexane–EtOAc (85:15) yielded the starting material while further elution with hexane–EtOAc (60:40) furnished the desired products.

2-[Hydroxy-(5-methyl-3-phenylisoxazol-4-yl)methyl]acrylic Acid Methyl Ester (4a)

Yield: 59%; colorless oil.

IR (neat): 1719 (ester C=O), 3407 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.49$ (s, 3 H, CH_3), 2.96, 2.97 (d, 1 H, $J = 3.8$ Hz, OH), 3.74 (s, 3 H, CO_2CH_3), 5.62 (t, 1 H, $J_1 = 1.4$ Hz, $J_2 = 2.0$ Hz, CH), 5.733, 5.736 (d, 1 H, $J = 0.6$ Hz, =C*H*H), 6.32 (s, 1 H, =CH*H*), 7.42–7.45 (m, 3 H, ArH), 7.56–7.61 (m, 2 H, ArH).

MS (FAB+): $m/z = 274$ ($M^+ + 1$).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.89; H, 5.50; N, 5.22.

2-{Hydroxy-[5-methyl-3-(4-methylphenyl)isoxazol-4-yl]methyl}acrylic Acid Methyl Ester (4b)

Yield: 59%; pale yellow oil.

IR (neat): 1710 (ester C=O), 3397 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.39$ (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 2.98, 2.99 (d, 1 H, $J = 3.6$ Hz, OH), 3.74 (s, 3 H, CO_2CH_3), 5.61 (br s, 1 H, CH), 5.73 (s, 1 H, =C*H*H), 6.32 (s, 1 H, =CH*H*), 7.21, 7.25 (d, 2 H, $J = 8.0$ Hz, ArH), 7.45, 7.49 (d, 2 H, $J = 8.0$ Hz, ArH).

MS (FAB+): $m/z = 288$ ($M^+ + 1$).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.66; H, 5.98; N, 4.70.

2-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Methyl Ester (4c)
Yield: 59%; colorless oil.

IR (neat): 1718 (ester C=O), 3402 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.52 (s, 3 H, CH_3), 2.82 (br s, 1 H, OH), 3.66 (s, 3 H, CO_2CH_3), 5.37 (s, 1 H, CH), 5.69 (s, 1 H, =CH*H*), 6.20 (s, 1 H, =C*H*H), 7.35–7.48 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 308 (M^+ + 1).

Anal. Calcd for $C_{15}H_{14}ClNO_4$: C, 58.55; H, 4.59; N, 4.55. Found: C, 58.60; H, 4.69; N, 4.50.

2-{[3-(4-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Methyl Ester (4d)
Yield: 54%; colorless oil.

IR (neat): 1718 (ester C=O), 3402 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.48 (s, 3 H, CH_3), 2.97, 2.99 (d, 1 H, *J* = 3.6 Hz, OH), 3.74 (s, 3 H, CO_2CH_3), 5.60 (br s, 1 H, CH), 5.73 (s, 1 H, =C*H*H), 6.31 (s, 1 H, =CH*H*), 7.44, 7.48 (d, 2 H, *J* = 8.0 Hz, ArH), 7.56, 7.60 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 308 (M^+ + 1).

Anal. Calcd for $C_{15}H_{14}ClNO_4$: C, 58.55; H, 4.59; N, 4.55. Found: C, 58.36; H, 4.28; N, 4.89.

2-{[3-(2,4-Dichlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Methyl Ester (4e)
Yield: 51%; colorless oil.

IR (neat): 1718 (ester C=O), 3402 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.51 (s, 3 H, CH_3), 2.76, 2.78 (d, 1 H, *J* = 4.0 Hz, OH), 3.68 (s, 3 H, CO_2CH_3), 5.35, 5.37 (d, 1 H, *J* = 4.0 Hz, CH), 5.71 (s, 1 H, =C*H*H), 6.22 (s, 1 H, =CH*H*), 7.31 (s, 2 H, ArH), 7.49 (s, 1 H, ArH).

MS (FAB+): *m*/*z* = 342 (M^+ + 1).

Anal. Calcd for $C_{15}H_{13}Cl_2NO_4$: C, 52.65; H, 3.83; N, 4.09. Found: C, 52.67; H, 3.95; N, 3.90.

2-{[3-(4-Benzyloxyphenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Methyl Ester (4f)
Yield: 47%; colorless oil.

IR (neat): 1718 (ester C=O), 3399 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3 H, CH_3), 2.98 (br s, 1 H, OH), 3.74 (s, 3 H, CO_2CH_3), 5.10 (s, 2 H, OCH_2), 5.62 (s, 1 H, CH), 5.73 (s, 1 H, =CH*H*), 6.32 (s, 1 H, =C*H*H), 7.00, 7.04 (d, 2 H, *J* = 8.0 Hz, ArH), 7.28–7.35 (m, 5 H, ArH), 7.52, 7.56 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 380 (M^+ + 1).

Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.64; H, 5.75; N, 3.79.

2-[Hydroxy-(5-methyl-3-phenylisoxazol-4-yl)methyl]acrylic Acid Ethyl Ester (5a)
Yield: 57%; colorless oil.

IR (neat): 1707 (ester C=O), 3431 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.25 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.49 (s, 3 H, CH_3), 3.02, 3.04 (d, 1 H, *J* = 3.6 Hz, OH), 4.20 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.62 (t, 1 H, J_1 = 1.4 Hz, J_2 = 1.8 Hz, CH), 5.71 (s, 1 H, =C*H*H), 6.32 (s, 1 H, =CH*H*), 7.41–7.45 (m, 3 H, ArH), 7.56–7.61 (m, 2 H, ArH).

MS (FAB+): *m*/*z* = 288 (M^+ + 1).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.11; H, 6.01; N 4.77.

2-{Hydroxy-[5-methyl-3-(4-methylphenyl)isoxazol-4-yl]methyl}acrylic Acid Ethyl Ester (5b)
Yield: 55%; colorless oil.

IR (neat): 1710 (ester C=O), 3397 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.25 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.39 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 2.98, 2.99 (d, 1 H, *J* = 3.6 Hz, OH), 4.20 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.61 (br s, 1 H, CH), 5.72 (s, 1 H, =C*H*H), 6.32 (s, 1 H, =CH*H*), 7.21, 7.25 (d, 2 H, *J* = 8.0 Hz, ArH), 7.45, 7.49 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 302 (M^+ + 1).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.81; H, 6.66; N, 4.70.

2-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Ethyl Ester (5c)
Yield: 50%; colorless oil.

IR (neat): 1711 (ester C=O), 3401 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.23 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.52 (s, 3 H, CH_3), 2.77 (br s, 1 H, OH), 4.14 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.37 (s, 1 H, CH), 5.64 (s, 1 H, =CH*H*), 6.17 (s, 1 H, =C*H*H), 7.35–7.44 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 322 (M^+ + 1).

Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 60.04; H, 5.02; N, 4.57.

2-{[3-(4-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Ethyl Ester (5d)
Yield: 50%; colorless oil.

IR (neat): 1711 (ester C=O), 3402 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.50 (s, 3 H, CH_3), 3.04, 3.06 (d, 1 H, *J* = 3.6 Hz, OH), 4.20 (q, 2 H, *J* = 7.2 Hz, CO_2CH_2), 5.59 (br s, 1 H, CH), 5.70 (s, 1 H, =CH*H*), 6.26 (s, 1 H, =C*H*H), 7.42, 7.44 (d, 2 H, *J* = 8.0 Hz, ArH), 7.52, 7.56 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 322 (M^+ + 1).

Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 59.36; H, 4.92; N, 4.42.

2-{[3-(2,4-Dichlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Ethyl Ester (5e)
Yield: 52%; colorless oil.

IR (neat): 1709 (ester C=O), 3402 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ 1.24 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.52 (s, 3 H, CH_3), 2.87, 2.89 (d, 1 H, *J* = 4.0 Hz, OH), 4.14 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.35, 5.37 (s, 1 H, *J* = 4.0 Hz, CH), 5.65 (s, 1 H, =C*H*H), 6.19 (s, 1 H, =CH*H*), 7.31 (s, 2 H, ArH), 7.48 (s, 1 H, ArH).

MS (FAB+): *m*/*z* = 356 (M^+ + 1).

Anal. Calcd for $C_{16}H_{15}Cl_2NO_4$: C, 53.95; H, 4.24; N, 3.93. Found: C, 54.19; H, 4.37; N, 4.01.

2-{[3-(4-Benzyloxyphenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Ethyl Ester (5f)
Yield: 45%; colorless oil.

IR (neat): 1718 (ester C=O), 3399 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.50 (s, 3 H, CH_3), 3.04, 3.06 (d, 1 H, *J* = 3.6 Hz, OH), 4.20 (q, 2 H, *J* = 7.2 Hz, CO_2CH_2), 5.59 (br s, 1 H, CH), 5.70 (s, 1 H, =C*H*H), 6.26 (s, 1 H, =CH*H*), 7.42, 7.44 (d, 2 H, *J* = 8.0 Hz, ArH), 7.52, 7.56 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 394 (M^+ + 1).

Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.28; H, 6.19; N, 3.84.

2-[Hydroxy-(5-methyl-3-phenylisoxazol-4-yl)methyl]acrylic Acid Butyl Ester (6a)
Yield: 56%; colorless oil.

IR (neat): 1709 (ester C=O), 3430 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.25–1.38 (m, 2 H, CH_2), 1.53–1.63 (m, 2 H, CH_2), 2.48 (s, 3 H, CH_3), 3.02, 3.04 (d, 1 H, *J* = 3.8 Hz, OH), 4.14 (t, 2 H, *J* = 6.6 Hz, CO_2CH_2), 5.61 (t, 1 H, J_1 = 1.4 Hz, J_2 = 2.2 Hz, CH), 5.71 (s, 1 H, =CH*H*), 6.31 (s, 1 H, =C*H*H), 7.41–7.44 (m, 3 H, ArH), 7.57–7.62 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 12.60 (CH_3), 14.04 (CH_3), 19.44 (CH_2), 30.87 (CH_2), 64.30 (CH), 65.38 (CH_2), 109.97 (CH), 113.51 (CH), 126.16 (CH_2), 128.96 (2 × CH), 129.11 (2 × CH), 129.39 (CH), 129.93 (CH), 140.78 (C), 162.93 (C), 166.59 (C), 168.90 (C).

MS (FAB+): *m*/*z* = 316 (M^+ + 1).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.58; H, 7.04; N, 4.51.

2-[Hydroxy-[5-methyl-3-(4-methylphenyl)isoxazol-4-yl)methyl]acrylic Acid Butyl Ester (6b)
Yield: 56%; colorless oil.

IR (neat): 1711 (ester C=O), 3409 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.28–1.39 (m, 2 H, CH_2), 1.53–1.64 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 3.01, 3.03 (d, 1 H, *J* = 3.6 Hz, OH), 4.14 (t, 2 H, *J* = 6.6 Hz, CO_2CH_2), 5.61 (br s, 1 H, CH), 5.72 (s, 1 H, =C*H*H), 6.32 (s, 1 H, =CH*H*), 7.21, 7.25 (d, 2 H, *J* = 8.0 Hz, ArH), 7.49, 7.53 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 330 (M^+ + 1).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.66; H, 7.39; N, 4.26.

2-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Butyl Ester (6c)
Yield: 55%; colorless oil.

IR (neat): 1710 (ester C=O), 3403 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.27–1.42 (m, 2 H, CH_2), 1.51–1.65 (m, 2 H, CH_2), 2.54 (s, 3 H, CH_3), 2.91 (br s, 1 H, OH), 4.08 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.37 (s, 1 H, CH), 5.63 (s, 1 H, =C*H*H), 6.16 (s, 1 H, =CH*H*), 7.31–7.48 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 350 (M^+ + 1).

Anal. Calcd for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.00. Found: C, 62.02; H, 5.89; N, 4.01.

2-{[3-(4-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Butyl Ester (6d)
Yield: 49%; colorless oil.

IR (neat): 1711 (ester C=O), 3401 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.27–1.42 (m, 2 H, CH_2), 1.51–1.65 (m, 2 H, CH_2), 2.54 (s, 3 H, CH_3), 2.91 (br s, 1 H, OH), 4.08 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.37 (s, 1 H, CH), 5.63 (s, 1 H, =C*H*H), 6.16 (s, 1 H, =CH*H*), 7.31–7.48 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 350 (M^+ + 1).

Anal. Calcd for $C_{18}H_{20}ClNO_4.H_2O$: C, 58.78; H, 6.03; N, 3.81. Found: C, 58.81; H, 6.29; N, 4.12.

2-{[3-(2,4-Dichlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Butyl Ester (6e)
Yield: 56%; colorless oil.

IR (neat): 1711 (ester C=O), 3401 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.28–1.39 (m, 2 H, CH_2), 1.52–1.63 (m, 2 H, CH_2), 2.51 (s, 3 H, CH_3), 2.85, 2.87 (d, 1 H, *J* = 4.4 Hz, OH), 4.08 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.55, 5.37 (d, 1 H, *J* = 4.0 Hz, CH), 5.65 (s, 1 H, =CH*H*), 6.18 (s, 1 H, =C*H*H), 7.31 (s, 2 H, ArH), 7.48 (s, 1 H, ArH).

MS (FAB+): *m*/*z* = 384 (M^+ + 1).

Anal. Calcd for $C_{18}H_{19}Cl_2NO_4$: C, 56.26; H, 4.98; N, 3.65. Found: C, 55.95; H, 4.73; N, 3.30.

2-{[3-(4-Benzyloxyphenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid Butyl Ester (6f)
Yield: 46%; colorless oil.

IR (neat): 1718 (ester C=O), 3399 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.27–1.42 (m, 2 H, CH_2), 1.51–1.65 (m, 2 H, CH_2), 2.54 (s, 3 H, CH_3), 2.91 (br s, 1 H, OH), 4.08 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2), 5.37 (s, 1 H, CH), 5.63 (s, 1 H, =C*H*H), 6.16 (s, 1 H, =CH*H*), 7.31–7.48 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 422 (M^+ + 1).

Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.21; H, 6.83; N, 3.56.

2-[Hydroxy-(5-methyl-3-phenylisoxazol-4-yl)methyl]acrylonitrile (7a)
Yield: 90%; white solid; mp 86–88 °C.

IR (KBr): 2234 (C≡N), 3402 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.53 (m, 4 H, s of CH_3 merged with d of OH), 5.33 (t, 1 H, J_1 = 2.0 Hz, J_2 = 2.4 Hz, CH), 6.02, 6.03 (2 s almost merged, 2 H, =CH_2), 7.44–7.49 (m, 3 H, ArH), 7.54–7.59 (m, 2 H, ArH).

MS (FAB+): *m*/*z* = 241 (M^+ + 1).

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.14; H, 5.22; N, 11.59.

2-{Hydroxy-[5-methyl-3-(4-methylphenyl)isoxazol-4-yl]methyl}acrylonitrile (7b)
Yield: 89%; white solid; mp 116–118 °C.

IR (KBr): 2223 (C≡N), 3404 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.39 (s, 3 H, CH_3), 2.45 (s, 2 H, CH_3), 3.39, 3.41 (d, 1 H, *J* = 4.0 Hz, OH), 5.27, 5.28 (d, 1 H, *J* = 3.6 Hz, CH), 6.00 (s, 2 H, =CH_2), 7.20, 7.24 (d, 2 H, *J* = 8.0 Hz, ArH), 7.39, 7.43 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 255 (M^+ + 1).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.05; H, 5.68; N, 11.18.

2-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylonitrile (7c)
Yield: 79%; pale yellow oil.

IR (neat): 2231 (C≡N), 3397 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.55 (s, 3 H, CH_3), 2.72 (br s, 1 H, OH), 5.11 (s, 1 H, CH), 5.88 (s, 1 H, =C*H*H), 5.89 (s, 1 H, =CH*H*), 7.36–7.47 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 275 (M^+ + 1).

Anal. Calcd for $C_{15}H_{14}ClN_2O_2$: C, 62.18; H, 4.87; N, 9.67. Found: C, 62.34; H, 5.10; N, 10.05.

2-{[3-(4-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylonitrile (7d)
Yield: 79%; pale yellow solid; mp 75–77 °C.

IR (KBr): 2230 (C≡N), 3425 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.53 (s, 3 H, CH_3), 2.59, 2.61 (d, 1 H, *J* = 3.6 Hz, OH), 5.32 (s, 1 H, CH), 6.05 (2 s almost merged, 2 H, =CH_2), 7.41, 7.45 (d, 2 H, *J* = 8.0 Hz, ArH), 7.54, 7.58 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 275 (M^+ + 1).

Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.03; N, 10.19. Found: C, 60.89; H, 4.29; N, 9.85.

2-{[3-(2,4-Dichlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylonitrile (7e)
Yield: 79%; white solid; mp 127–129 °C.

IR (KBr): 2230 (C≡N), 3397 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.44, 2.46 (d, 1 H, *J* = 4.0 Hz, OH), 2.56 (s, 3 H, CH_3), 5.11 (t, 1 H, $J_1 = J_2$ = 2.0 Hz, CH), 5.94 (t, 2 H, J_1 = 1.8 Hz, J_2 = 2.2 Hz, =CH_2), 7.36 (s, 2 H, ArH), 7.51 (s, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 Hz): δ = 12.52 (CH_3), 65.56 (CH), 113.75 (C), 116.87 (C), 124.24 (C), 126.66 (C), 127.91 (CH), 130.06 (CH_2), 130.23 (CH), 133.29 (CH), 134.69 (C), 137.27 (C), 159.89 (C), 169.58 (C).

MS (FAB+): *m*/*z*=309 (M^+ + 1).

Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_2$: C, 54.39; H, 3.26; N, 9.06. Found: C, 54.77; H, 3.26; N, 8.84.

2-{[3-(4-Benzyloxyphenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylonitrile (7f)
Yield: 79%; white solid; mp 66–68 °C.

IR (KBr): 2231 (C≡N), 3396 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3 H, CH_3), 3.02, 3.04 (d, 1 H, *J* = 3.6 Hz, OH), 5.09 (s, 2 H, OCH_2), 5.28 (s, 1 H, CH), 6.02 (s, 2 H, =CH_2), 6.99–7.04 (d, 2 H, *J* = 8.6 Hz, ArH), 7.33–7.52 (m, 7 H, ArH).

MS (FAB+): *m*/*z* = 346 (M^+ + 1).

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.66; H, 5.42; N, 8.21.

3-[Hydroxy-(5-methyl-3-phenylisoxazol-4-yl)methyl]but-3-en-2-one (8a)
Yield: 48%; pale yellow oil.

IR (neat): 1685 (C=O), 3433 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.49 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 3.10 (br s, 1 H, OH), 5.67 (s, 1 H, CH), 5.87 (s, 1 H, =C*H*H), 6.15 (s, 1 H, =CH*H*), 7.40–7.49 (m, 3 H, ArH), 7.54–7.64 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 12.58 (CH_3), 26.77 (CH_3), 64.15 (CH), 127.22 (CH_2), 128.91 (2 CH), 129.21 (2 CH), 129.51(CH), 129.92 (CH), 148.16 (C), 162.66 (C), 168.90 (C), 200.53 (C).

MS (FAB+): *m*/*z* = 258 (M^+ + 1).

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.36; H, 5.47; N, 5.28.

3-[Hydroxy-{5-methyl-3-[(4-methxlphenyl)isoxazol-4-yl]methyl}but-3-en-2-one (8b)
Yield: 48%; pale yellow oil.

IR (neat): 1674 (C=O), 3421 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.34 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 3.11, 3.33 (d, 1 H, *J* = 3.2 Hz, OH), 5.66 (s, 1 H, CH), 5.86 (s, 1 H, =CH*H*), 6.15 (s, 1 H, =C*H*H), 6.03 (s, 2 H, =CH_2), 7.19, 7.23 (d, 2 H, *J* = 8.0 Hz, ArH), 7.43, 7.47 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 272 (M^+ + 1).

Anal. Calcd for $C_{16}H_{17}NO_3 \cdot 0.5H_2O$: C, 68.32; H, 6.40; N, 4.98. Found: C, 68.78; H, 6.60; N, 5.00.

3-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}but-3-en-2-one (8c)
Yield: 56%; pale yellow oil.

IR (neat): 1680 (C=O), 3434 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.22 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 2.56, 2.57 (d, 1 H, *J* = 3.2 Hz, OH), 5.41 (s, 1 H, CH), 5.84 (s, 1 H, =CH*H*), 6.02 (s, 1 H, =C*H*H), 7.33–7.46 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 292 (M^+ + 1).

Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.80; H, 5.01; N, 4.97%.

3-{[3-(4-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}but-3-en-2-one (8d)
Yield: 46%; pale yellow oil.

IR (neat): 1676 (C=O), 3424 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.31 (s, 3 H, CH_3), 2.49 (s, 3 H, CH_3), 2.54, 2.55 (d, 1 H, *J* = 3.2 Hz, OH), 5.41 (s, 1 H, CH), 5.83 (s, 1 H, =C*H*H), 6.03 (s, 1 H, =CH*H*), 7.36–7.63 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 292 (M^+ + 1).

Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.91; H, 5.15; N, 4.69.

3-{[3-(2,4-Dichlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}but-3-en-2-one (8e)
Yield: 48%; pale yellow oil.

IR (neat): 1629 (C=O), 3434 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.25 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 2.74, 2.76 (d, 1 H, *J* = 4.0 Hz, OH), 5.39, 5.41 (d, 1 H, *J* = 3.6 Hz, CH), 5.88 (s, 1 H, =CH*H*), 6.06 (s, 1 H, =C*H*H), 7.33 (s, 2 H, ArH), 7.47 (s, 1 H, ArH).

MS (FAB+): *m*/*z* = 326 (M^+ + 1).

Anal. Calcd for $C_{15}H_{13}Cl_2NO_3$: C, 55.23; H, 4.02; N, 4.29. Found: C, 54.88; H, 4.37; N, 4.18.

3-{[3-(4-Benzyloxyphenyl)-5-methylisoxazol-4-yl]hydroxymethyl}but-3-en-2-one (8f)
Yield: 42%; pale yellow oil.

IR (neat): 1679 (C=O), 3434 cm^{-1} (OH).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.31 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 2.50 (s, 1 H, OH), 5.08 (s, 1 H, OCH_2), 5.65 (s, 1 H, CH), 5.87 (s, 1 H, =C*H*H), 6.13 (s, 1 H, =CH*H*), 6.97, 7.01 (d, 2 H, *J* = 8.0 Hz, ArH), 7.29–7.61 (m, 7 H, ArH).

MS (FAB+): *m*/*z* = 363 (M^+ + 1).

Anal. Calcd for $C_{22}H_{21}NO_4 \cdot H_2O$: C, 69.27; H, 6.07; N, 3.67. Found: C, 69.38; H, 5.68; N, 3.72.

Baylis–Hillman Reaction of Substituted 4-Isoxazolecarbaldehydes with Cyclohexenone; General Procedure

A mixture of the appropriate aldehyde **1a–d** (4 mmol), DMAP (50 mol%) and cyclohexenone (4 mmol) in dioxane–H_2O (5 mL, 3:2) mixture was stirred at r.t. for 7 d. Thereafter, the reaction mixture was extracted with EtOAc (2 × 30 mL). The usual work-up of the organic layer furnished a residue that was column chromatographed over silica gel. Elution with a mixture of hexane–EtOAc (85:15) as eluent yielded the starting aldehyde, while further elution with the same eluent mixture with a ratio of 40:60 furnished the desired products.

2-[Hydroxy-(5-methyl-3-phenylisoxazol-4-yl)methyl]cyclohex-2-enone (9a)

Yield: 23%; yellow solid; mp 79–81 °C.

IR (KBr): 1668 (C=O), 3330 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.87–1.92 (m, 2 H, CH_2), 2.24–2.26 (m, 2 H, CH_2), 2.37–2.42 (m, 2 H, CH_2), 2.51 (s, 3 H, CH_3), 3.38, 3.39 (d, 1 H, *J* = 3.4 Hz, OH), 5.30 (s, 1 H, CH), 6.64 (t, 1 H, *J* = 4.0 Hz, =CH), 7.41–7.46 (m, 3 H, ArH), 7.52–7.55 (m, 2 H, ArH).

MS (FAB+): *m*/*z* = 284 (M^+ + 1).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.29; H, 5.85; N, 4.77.

2-{Hydroxy-[5-methyl-3-(4-methylphenyl)isoxazol-4-yl]methyl}cyclohex-2-enone (9b)

Yield: 25%; light brown solid; mp 79–81 °C.

IR (KBr): 1670 (C=O), 3336 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.91–1.98 (m, 2 H, CH_2), 2.26–2.28 (m, 2 H, CH_2), 2.38–2.46 (m, 5 H, s of CH_3 merged with m of CH_2), 2.49 (s, 3 H, CH_3), 3.46 (br s, 1 H, OH), 5.64 (s, 1 H, CH), 6.66 (t, 1 H, *J* = 4.0 Hz, =CH), 7.18, 7.22 (d, 2 H, *J* = 8.0 Hz, ArH), 7.40, 7.44 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 298 (M^+ + 1).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.98; H, 6.08; N, 5.00.

2-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}cyclohex-2-enone (9c)

Yield: 17%; pale yellow oil.

IR (neat): 1664 (C=O), 3398 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.79–1.88 (m, 2 H, CH_2), 2.15–2.21 (m, 2 H, CH_2), 2.23–2.30 (m, 2 H, CH_2), 2.56 (s, 3 H, CH_3), 3.08, 3.10 (d, 1 H, *J* = 3.8 Hz, OH), 5.36, 5.38 (d, 1 H, *J* = 3.8 Hz, CH), 6.58 (t, 1 H, *J* = 4.0 Hz, =CH), 7.32–7.46 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 317 (M^+ + 1).

Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N, 4.41. Found: C, 64.45; H, 5.08; N, 4.56.

Baylis–Hillman Reaction of Substituted 4-Isoxazolecarbaldehydes 3b,c with Acrylic Acid on Solid Support; General Procedure

The 2-chlorotrityl chloride resin (200 mg, 1.4 mmol/g, Novabiochem) after swelling in anhyd CH_2Cl_2 was treated with acrylic acid (4 equiv) and Et_3N (6 equiv) in CH_2Cl_2 as reported earlier.[6d] Two PP syringes fitted with frits were charged with the resins. To each of this reaction vessel, DABCO (3 equiv) in DMF (200 μL) was added and left aside for 15 min. Thereafter, a solution of different aldehydes **3b**,**c** (5 equiv) in DMF (300 μL) was added to the respective reaction vessel and the reaction mixture was shaken at 600 rpm. After 48 h, the reaction sequence was repeated for another 48 h. Thereafter, the resins were washed with DMF (3 ×), MeOH (3 ×), CH_2Cl_2 (2 ×), and Et_2O (2 ×). Finally, the resins were cleaved with 5% TFA in CH_2Cl_2 for 20 min. The filtrate was evaporated and lyophilized using *t*-BuOH–H_2O (4:1).

2-{Hydroxy-[5-methyl-3-(4-methylphenyl)isoxazol-4-yl]methyl}acrylic Acid (13b)

Purity: 34% based on analytical HPLC of crude product (R_t 13.78 min at λ_{max} = 220 nm in a gradient run of 0–100% MeCN in H_2O (containing 0.1% TFA) in 20 min on a RP-18e column (150 × 5 mm) having particle size of 5 μm); yield: 21%; white solid; mp 165–166 °C.

IR (KBr): 1697 (C=O), 3446 cm^{-1} (OH).

^1H NMR ($CDCl_3$ + a drop of DMSO-d_6, 200 MHz): δ = 2.38 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 2.76 (s, 1 H, OH), 5.54 (s, 1 H, CH), 5.88 (s, 1 H, =C*H*H), 6.28 (s, 1 H, =CH*H*), 7.20, 7.24 (d, 2 H, *J* = 8.0 Hz, ArH), 7.58, 7.62 (d, 2 H, *J* = 8.0 Hz, ArH).

MS (FAB+): *m*/*z* = 274 (M^+ + 1).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.18; H, 5.59; N, 4.81.

2-{[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]hydroxymethyl}acrylic Acid (13c)

Purity: 29% based on analytical HPLC of crude product (R_t 12.93 min at λ_{max} = 220 nm in a gradient run of 0–100% MeCN in H_2O (containing 0.1% TFA) in 20 min on a RP-18e column (150 × 5mm) having particle size of 5 μm); yield: 19%; pale yellow solid; mp 148–149 °C.

IR (KBr): 1702 (acid C=O), 3395 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.50 (s, 3 H, CH_3), 3.73 (s, 1 H, OH), 5.35 (s, 1 H, CH), 5.82 (s, 1 H, =C*H*H), 6.32 (s, 1 H, =CH*H*), 7.31–7.48 (m, 4 H, ArH).

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

Anal. Calcd for $C_{16}H_{14}ClNO_5$: C, 57.25; H, 4.12; N, 4.77. Found: 57.11; H, 4.39; N, 4.51.

Acetylation of Alcohols 4, 7c,e; General Procedure

To a stirred solution of the appropriate alcohol **4**, **7c**,**e** (3.25 mmol) in anhyd CH_2Cl_2 (5 mL) was added pyridine (0.48 mL, 6.0 mmol) followed by dropwise addition of a solution of acetyl chloride (0.46 mL, 6.5 mmol) in anhyd CH_2Cl_2 (3 mL) at 0 °C. After the addition was complete, the stirring was continued at r.t. for 1 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 30 mL) and H_2O (50 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4) and evaporated to give an oily residue. The residue was purified on a small band of silica gel (60–120 mesh) using hexane–EtOAc (85:15) as eluent to obtain pure acetates.

2-{Acetoxy-[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]methyl}acrylic Acid Methyl Ester (10c)

Yield: 85%; white solid; mp 93–95 °C.

IR (KBr): 1708 (ester C=O), 1745 cm^{-1} (acetyl C=O).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.06 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 5.36 (s, 1 H, =CH*H*), 6.12 (s, 1 H, =C*H*H), 6.45 (s, 1 H, CH), 7.22–7.47 (m, 4 H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 12.08 (CH_3), 21.11 (CH_3), 52.43 (CH_3), 64.89 (CH), 111.89 (C), 125.98 (CH_2), 126.63 (CH), 128.87 (CH), 129.89 (CH), 131.21 (CH), 132.17 (CH), 134.56 (C), 136.69 (C), 160.88 (C), 165.27 (C), 169.46 (C).

MS (FAB+): *m*/*z* = 350 (M^+ + 1).

Anal. Calcd for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; N, 4.00. Found: C, 58.49; H, 4.43; N, 4.05.

2-{Acetoxy-[3-(2,4-dichlorophenyl)-5-methylisoxazol-4-yl]methyl}acrylic Acid Methyl Ester (10e)
Yield: 82%; white solid; mp 76–78 °C.

IR (KBr): 1704 (ester C=O), 1738 cm^{-1} (acetyl C=O).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.06 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 5.44 (s, 1 H, =C*H*H), 6.16 (s, 1 H, =CH*H*), 6.43 (s, 1 H, CH), 7.24–7.35 (m, 2 H, ArH), 7.48–7.49 (m, 1 H, ArH).

MS (FAB+): *m*/*z* = 384 (M^+ + 1).

Anal. Calcd for $C_{17}H_{15}Cl_2NO_5$: C, 53.14; H, 3.94; N, 3.65. Found: C, 52.88; H, 3.91; N, 3.70.

Acetic Acid 1-[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]-2-cyanoallyl Ester (11c)
Yield: 88%; white solid; mp 49–51 °C.

IR (neat): 1750 (acetyl C=O), 2231 cm^{-1} (C≡N).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.09 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 5.68, 5.69 (d, 1 H, *J* = 1.4 Hz, =C*H*H), 5.91, 5.92 (d, 1 H, *J* = 1.4 Hz, =CH*H*), 6.13 (s, 1 H, CH), 7.35–7.47 (m, 4 H, ArH).

MS (FAB+): *m*/*z* = 317 (M^+ + 1).

Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.93; H, 4.14; N, 8.92.

Acetic Acid 2-Cyano-1-[3-(2,4-dichlorophenyl)-5-methylisoxazol-4-yl]allyl Ester (11e)
Yield: 86%; white solid; mp 80–82 °C.

IR (neat): 1744 (acetyl C=O), 2232 cm^{-1} (C≡N).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.11 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 5.76 (s, 1 H, =CH*H*), 5.97 (s, 1 H, =C*H*H), 6.12 (s, 1 H, CH), 7.31–7.39 (s, 2 H, ArH), 7.50–7.53 (m, 7 H, ArH).

MS (FAB+): *m*/*z* = 351 (M^+ + 1).

Anal. Calcd for $C_{16}H_{12}Cl_2N_2O_3$: C, 54.72; H, 3.44; N, 7.98. Found: C, 54.54; H, 3.38; N, 7.60.

Attempted Conversion of Baylis–Hillman Products to Annulated Isoxazoles

1. Reaction with Benzylamine; General Procedure
To the appropriate acetate **10**, **11c**,**e** (0.7 mmol) in THF was added Et_3N (0.2 mL, 1.4 mmol) followed by benzylamine (0.234 mL, 2.1 mmol) and the mixture was refluxed under stirring in an oil bath. After completion of the reaction, the mixture was extracted with EtOAc (2 × 30 mL) and H_2O (40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to obtain an oily residue. The amines **14c**,**e** were purified by chromatography on basic alumina using hexane–EtOAc (75:25) as eluent. Amines **15c**,**e** were purified on silica gel (230-400 mesh) using hexane–EtOAc (70:30) as eluent.

2-(Benzylaminomethyl)-3-[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]acrylic Acid Methyl Ester (14c)
Yield: 81%; mixture of *E*- and *Z*-isomers (colorless oil).

IR (neat): 1718 (ester C=O), 3350 cm^{-1} (NH).

^1H NMR ($CDCl_3$, 200 MHz): δ (*E*-isomer) = 2.45 (s, 3 H, CH_3), 3.18 (s, 1 H, NH), 3.56 (s, 5 H, CH_2 merged with CO_2CH_3), 3.76 (s, 2 H, CH_2), 7.15–7.48 (s, 10 H, =CH merged with ArH); δ (*Z*-isomer) = 2.38 (s, 3 H, CH_3), 3.18 (s, 1 H, NH), 3.43 (s, 2 H, CH_2), 3.56 (s, 3 H, CO_2CH_3), 3.70 (s, 2 H, CH_2), 6.49 (s, 1 H, =CH), 7.15–7.48 (s, 9 H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ (*E*/*Z*-isomeric mixture) = 12.38 (CH_3), 12.49 (CH_3), 46.32 (CH_2), 52.22 (2 CH_2), 52.47 (2 CH_3), 53.74 (CH_2), 112.14 (C), 112.87 (C), 125.99 (CH), 127.21 (2 CH), 127.47 (2 CH), 128.45 (2 CH), 128.54 (2 CH), 128.76 (2 CH), 128.99 (CH), 129.30 (CH), 130.41 (CH), 130.56, (CH), 131.27 (CH), 131.48 (CH), 131.90 (CH), 132.21 (CH), 133.73 (2 C), 135.52 (2 C), 140.09 (2 C), 161.07 (2 C), 167.11 (2 C), 167.68 (2 C).

MS (FAB+): *m*/*z* = 397 (M^+ + 1).

Anal. Calcd for $C_{22}H_{21}ClN_2O_3$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.77; H, 5.39; N, 6.95.

(*E*/*Z*)-2-(Benzylaminomethyl)-3-[3-(2,4-dichlorophenyl) -5-methylisoxazol-4-yl]acrylic Acid Methyl Ester (14e)
Yield: 75%; mixture of *E*- and *Z*-isomers (colorless oil).

IR (neat): 1714 (ester C=O), 3350 cm^{-1} (NH).

^1H NMR ($CDCl_3$, 200 MHz): δ (*E*-isomer) = 2.45 (s, 3 H, CH_3), 3.16 (s, 2 H, CH_2), 3.45 (s, 3 H, CO_2CH_3), 3.77 (s, 2 H, CH_2), 7.15–7.39 (m, 8 H, 7 × ArH and =CH_2), 7.48 (s, 1 H, ArH); δ (*Z*-isomer) = 2.37 (s, 3 H, CH_3), 3.49 (s, 2 H, CH_2), 3.56 (s, 3 H, CO_2CH_3), 3.71 (s, 2 H, CH_2), 6.48 (s, 1 H, =CH_2), 7.15–7.39 (m, 7 H, 7 × ArH), 7.48 (s, 1 H, ArH).

Mass (FAB+): *m*/*z* = 430 (M^+ + 1).

Anal. Calcd for $C_{22}H_{20}Cl_2N_2O_3$: C, 61.26; H, 4.67; N, 6.49. Found: C, 61.22; H, 4.51; N, 6.60.

(*Z*)-2-(Benzylaminomethyl)-3-[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]acrylonitrile (15c)
Yield: 69%; colorless oil.

IR (neat): 2218 (C≡N), 3399 cm^{-1} (NH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.60 (s, 3 H, CH_3), 3.47 (s, 2 H, CH_2), 3.74 (s, 2 H, CH_2), 6.72 (s, 1 H, =CH), 7.19–7.52 (m, 5 H, ArH and NH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.11 (CH_3), 51.65 (CH_2), 52.23 (CH_2), 112.08 (C), 117.18 (C), 117.61 (C), 127.60 (CH), 127.80 (CH), 128.23 (C), 128.63 (2 CH), 128.98 (2 CH), 130.44 (CH), 131.84 (CH), 132.25 (CH), 133.81 (CH), 139.18 (2 C), 161.01 (C), 168.54 (C).

MS (FAB+): *m*/*z* = 364 (M^+ + 1).

Anal. Calcd for $C_{21}H_{18}ClN_3O$: C, 69.32; H, 4.99; N, 11.55. Found: C, 69.52; H, 5.12; N, 11.66%.

(*Z*)-2-(Benzylaminomethyl)-3-[3-(2,4-dichlorophenyl) -5-methylisoxazol-4-yl]acrylonitrile (15e)
Yield: 79%; off white solid; mp 85–86 °C.

IR (neat): 2218 (C≡N), 3399 cm^{-1} (NH).

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.59 (s, 3 H, CH_3), 3.48 (s, 2 H, CH_2), 3.75 (s, 2 H, CH_2), 6.72 (s, 1 H, =CH), 7.20–7.31 (m, 5 H, ArH), 7.38 (s, 2 H, ArH), 7.50 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.05 (CH_3), 51.89 (CH_2), 52.56 (CH_2), 112.03 (C), 117.60 (C), 117.98 (C), 126.89 (C), 127.78 (CH), 128.06 (CH), 128.48 (2 CH), 128.97 (2 CH), 130.40 (CH), 132.91 (CH), 133.05 (CH), 134.57 (C), 137.39 (C), 139.52 (C), 160.19 (C), 168.77 (C).

MS (FAB+): *m*/*z* = 398 (M^+ + 1).

Anal. Calcd for $C_{21}H_{17}Cl_2N_3O$: C, 63.33; H, 4.30; N, 10.55. Found: C, 62.93; H, 4.65; N, 10.25.

2. Reaction with Nitroethane; General Procedure
To a prestirred mixture of K_2CO_3 (414 mg, 3.0 mmol) and nitroethane (0.14 mL, 2.0 mmol) in DMF (3 mL) was added a solution of the appropriate **10c**,**e** (1.0 mmol) in DMF and the reaction mixture was stirred at 60 °C for 1 h. Thereafter the mixture was neutralized with aq HCl (20%). Usual work-up of the mixture led to an oily residue that was purified through column chromatography using hexane–EtOAc (85:15) as eluent.

(*E*)-3-[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]-2-(2-nitropropyl)acrylic Acid Methyl Ester (17c)
Yield: 79%; pale yellow oil.

IR (neat): 1718 (ester C=O), 1656, 1550 cm^{-1} (NO_2).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.31, 1.34 (d, 3 H, *J* = 6.6 Hz, CH_3), 2.24–2.35 (m, 1 H,CH*H*), 2.43 (s, 3 H, CH_3), 2.60–2.71 (m, 1 H,C*H*H), 3.78 (s, 3 H, CO_2CH_3), 4.65–4.78 (m, 1 H, CH), 7.35–7.50 (m, 5 H, 4 × ArH merged with =CH).

Mass (ES+): *m*/*z* = 365.60 (M^+ + 1), 387.27 (M^+ + Na).

Anal. Calcd for $C_{17}H_{17}ClN_2O_5$: C, 55.97; H, 4.70; N, 7.68. Found: C, 56.08; H, 4.99; N, 7.63.

(*E*)-3-[3-(2,4-Dichlorophenyl)-5-methylisoxazol-4-yl]-2-(2-nitropropyl)acrylic Acid Methyl Ester (17e)
Yield: 77%; white solid; mp 115–116 °C.

IR (KBr): 1713 (ester C=O), 1643, 1546 cm^{-1} (NO_2).

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.35, 1.38 (d, 3 H, *J* = 6.6 Hz, CH_3), 2.31–2.40 (m, 1 H, CH*H*), 2.43 (s, 3 H, CH_3), 2.60–2.70 (m, 1 H, C*H*H), 3.79 (s, 3 H, CO_2CH_3), 4.76–4.80 (m, 1 H, CH), 7.32–7.42 (m, 3 H, 2 × ArH merged with =CH), 7.49 (s, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 12.54 (CH_3), 19.52 (CH_3), 34.16 (CH_2), 52.82 (CH_3), 81.91 (CH), 111.47 (C), 127.24 (C), 128.00 (CH), 130.50 (CH), 131.35 (C), 131.45 (CH), 132.78 (CH), 130.44 (CH), 134.41 (C), 137.11 (C), 159.80 (C), 166.64 (C), 168.02 (C).

Mass (FAB+): *m*/*z* = 399 (M^+ + 1).

Anal. Calcd for $C_{17}H_{16}Cl_2N_2O_5$: C, 51.14; H, 4.04; N, 7.02. Found: C, 50.83; H, 4.10; N, 6.83.

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