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Vinylogous nitroaldol (Henry) reaction using 3,5-diethyl-4-nitroisoxazole and carbonyl compounds

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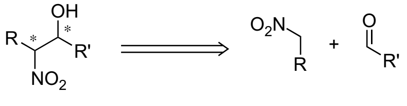
ABSTRACT

3,5-Diethyl-4-nitroisoxazole reacted with carbonyl compounds in the presence of an amine catalyst. The vinylogous nitroaldol adducts were isolated in good yields.

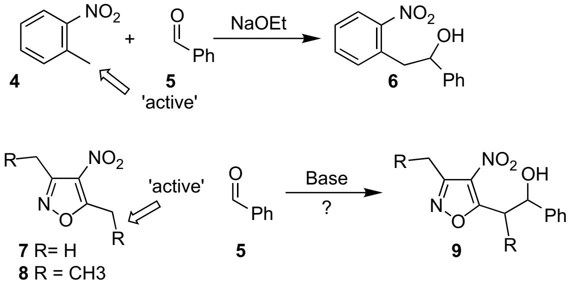
1. Introduction

The Henry or nitroaldol reaction is one of the important reactions in organic synthesis.[1] Essentially a coupling between a carbonyl compound **2** and an alkylnitro group **1** bearing α-hydrogens (Scheme 1), this reaction gives a β-nitroalcohol moiety **3**,[2] that served as starter for the generation of several compounds including nitroalkenes, β-aminoalcohols, α-hydroxy carbonyl compounds and β-nitro ketones. In this process two new asymmetric centres are generated at the new carbon–carbon juncture. The Henry reaction is an example of a classical organic reaction, which has undergone extensive development.[1d]



Scheme 1. Nitroaldol (Henry) reaction.

Several variations of the Henry reaction such as intramolecular[3] or aza-Henry[4] processes have received considerable attention. Additionally, a few examples of vinylogous Henry reaction involving *ortho*-nitrotoluenes have been reported.[5–8] In particular, 2-nitrotoluene **4** (Scheme 2) underwent addition to benzaldehyde in the presence of sodium ethoxide;[5] 3-methoxy-4-methyl-5-nitrobenzoic acid methyl ester reacted with an aliphatic aldehyde in the key step of the synthesis of mitosene-based antitumour agents.[6–8] The processes employing *ortho*-nitrotoluenes were based on the remarkable acidity of the *ortho*-methyl group that is activated by conjugation with the nitro group. In previous reports, we have shown that 3,5-dimethyl-4-nitroisoxazole **7** (R=H) (Scheme 2) is a useful building block that could be employed for the synthesis of 5-heteroarylethenylisoxazoles,[9] spiroisoxazolines,[10] 3-heteroarylpropionic acids,[11] 3-indolepropionic acids,[12] isoxazolopyridones, pyrazolopyridones,[13] isoxazoloazepinones, pyrazoloazepinones[14] and 3-arylglutaric acids.[15] In these syntheses, isoxazole **7** was efficiently deprotonated by secondary or tertiary amines and the resulting nitro enolate reacted with various electrophiles. Considering the similarity between compounds **4** and **7**, we posed the question of whether the latter could be employed in



Scheme 2. Vinylogous aldol (Henry) reaction.

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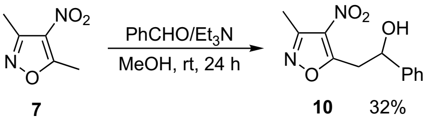
a vinylogous Henry reaction (Scheme 2). Resulting adducts **9** would contain several chemo-differentiable functionalities and could be subsequently employed to generate chemical diversity. Additionally, although a few reports appeared describing a vinylogous approach to the Henry reaction,[5–8] a comprehensive methodological study of this transformation has not been reported yet. With these goals in mind we set out to develop a vinylogous Henry reaction using 4-nitro-5-alkylisoxazoles **7** and **8**.

2. Results and discussion

We started our investigation by reacting 3,5-dimethyl-4-nitroisoxazole **7** and aldehydes. We and others have shown that reacting isoxazole **7** with aromatic aldehydes **5** (Scheme 2) in the presence of organic bases and in hot solvents generated 3-methyl-4-nitro-5-styryl isoxazoles in excellent yields.[9,16] This reaction run faster under the catalysis of a secondary amine[9] and proceeded through the formation of aldol like adduct **10** (Scheme 3) followed by elimination of water.



Scheme 3. Reaction of 3,5-dimethyl-4-nitroisoxazole and benzaldehyde.

In order to intercept adduct **10** (Scheme 3), we have reacted **7** (1 equiv) with benzaldehyde (2 equiv) in the presence of triethylamine (0.3 equiv) at room temperature. In this experiment, we have isolated product **10** in 32% yield (Scheme 3) together with 60% of unreacted isoxazole **7**. Variation of solvent, nature and amount of the amine catalyst and reaction stoichiometry did not improve the yields of **10**.

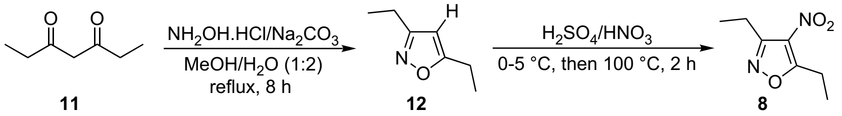
This set of experiments set a proof of principle for the desired vinylogous nitroaldol reaction. To substantiate this finding, we have prepared 3,5-diethyl-4-nitroisoxazole **8** (Scheme 4). Compound **8** was obtained in two steps from commercially available 3,5-heptanedione **11**. Condensation of **11** with hydroxylamine furnished 3,5-diethylisoxazole **12** that was subsequently nitrated to obtain desired **8**.[17]

Compound **8** was dissolved in methanol and reacted with 2 equiv of freshly distilled benzaldehyde **5** in the presence of 30 mol % of triethylamine. Under these conditions, product **13** was formed in excellent yields (Table 1, entry 1). Compound **13** was obtained as a 1:1 mixture of diastereoisomers. In order to improve the diastereoselectivity of this process a solvent study was undertaken (Table 1). This study revealed the following facts: (a) experiments run at higher concentration of reactants (10 M) gave high yields irrespectively of the nature of the solvent used; (b) experiments run at higher concentration (10 M) gave compound **13** as a 1:1 mixture of diastereoisomers; (c) experiments run at lower concentration (1 M) gave decreased yields of **13**; (d) experiments run at lower concentration (1 M) in non-polar aprotic solvents (Table 1, entries 3–7) gave **13** as a 7:3 mixture of diastereoisomers; (e) highest yield of **13** was obtained when reaction was carried out in methanol (Table 1, entry 1). It was noted that the use of at least 30 mol % of amine, and excess aldehyde (2 equiv) was required to ensure high conversion.

Several amines were used as catalysts (Table 2): tertiary amines were superior catalysts compared to secondary ones (compare entries 1 and 5, Table 2) and triethylamine was the best. When secondary amines were used, compound **13** was obtained in low yields along with a similar amount of alkene **14** (Table 2, entries 3, 5 and 13) that was formed as a single isomer. The stereochemistry of **14** was assigned by NOE studies. Significant enhancement was observed between the C*H*$_3$ and the =C*H*. Non-nitrogenous base PPh$_3$ was a poor catalyst. Compound **13** was obtained as 1:1 mixture of *syn* and *anti* diastereomers. This occurred similarly carrying out the reaction either at room temperature or at 0 °C. In order to improve the diastereoselectivity we have run the reaction at low temperature and in the presence of lithium bases. Hence **8** was treated with a stoichiometric amount of LDA and at temperatures of −78 °C or −30 °C then the nitronate formed was quenched by the addition of excess aldehyde. This procedure gave product **13** in 30% yield in a similar 1:1 ratio of *syn* and *anti* diastereoisomers. The use of chiral amines like quinine, hydroquinine or (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine, that often have been shown guiding the stereochemical outcome of related processes,[18] led to 1:1 diastereomeric mixture of **13** as obtained for Et$_3$N. We have analyzed the samples of **13** obtained using chiral amines by HPLC (on Chiralcel OD, Chiralcel OJ and Chiralpak AD) to establish whether an enantiomeric excess within each diastereoisomer was present, but no enantiomeric enrichment was observed.

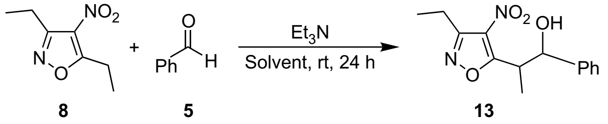
The scope of reaction was then studied by reacting various carbonyl compounds with isoxazole **8**. Data collected indicated that carbonyl compounds of wide nature gave the corresponding alkanol products in moderate to excellent isolated yields (Table 3).

Reactive aldehydes, conjugated with an electron withdrawing group, gave best yields of Henry adducts **16a**–**c** (Table 3, entries 2–4). Aromatic aldehydes bearing electron donating groups gave desired compounds **16d**, **16e** in moderate yields (Table 3, entries 5 and 6). These observations are in line with other reports on the Henry reaction.[1,2] Heteroaromatic aldehydes such as 2-furaldehyde (Table 3, entry 7), α,β-unsaturated aldehydes such as *trans* cinnamaldehyde (Table 3, entry 8), ethyl glyoxalate (Table 3, entry 9) and methyl phenylglyoxalate (Table 3, entry 10) were also good substrates. Importantly, the reaction of **8** with cinnamaldehyde furnished exclusively the expected aldol product **16g**, uncontaminated by the alternative conjugate addition adduct. The reaction of **8** with isobutyraldehyde run at 10 M concentration of reactants furnished the corresponding alkanol product **16j** in low yield (21%) and in good diastereoselectivity (81:19). In order to increase the yield, this reaction was conducted at high concentration (10 M) and prolonged reaction times. Delightfully, under these conditions, significant increase of the yield was observed with no change of the diastereoselectivity (Table 3, entry 11). Isovaleraldehyde, *n*-heptaldehyde and cyclohexane carbaldehyde reacted with **8** giving the corresponding products **16k**–**m** in excellent yields and good diastereoselectivity (Table 3, entries 12–14). The reaction of 2-ethylbutyraldehyde gave the alkanol **16n** product in moderate yield and with good selectivity (Table 3, entry 15). In the case of pivalaldehyde product **16o** was isolated in low yield but in high diastereoselectivity (Table 3, entry 16). *syn* and *anti* diastereomers of **16i**–**k**, **16m**, **16n** could be separated using flash column chromatography. This was an important point as the separation of *syn* and *anti* diastereomers of **13**, **16a**–**h**, **16l**, **16o** was not possible. We have carried out NOE experiments to assign a *syn* or an *anti* relative



Scheme 4. Synthesis of 3,5-diethyl-4-nitroisoxazole **8**.

Table 1
Reaction of 3,5-diethyl-4-nitroisoxazole **8** and benzaldehyde **5** in different solvents



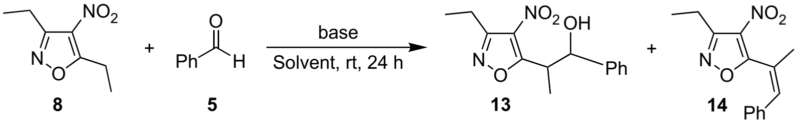
Entry	Solvent	Yield of **13** at 10 M concn (%)	dr	Yield of **13a** at 1 M concn (%)	dr
1	Methanol	94	53:47	94	53:47
2	Diethylether	63	58:42	57	58:42
3	Toluene	59	51:49	39	63:37
4	Petroleum ether	61	51:49	18	69:31
5	*n*-Hexane	68	50:50	44	67:33
6	Cyclohexane	73	50:50	15	70:30
7	*n*-Heptane	60	54:46	40	69:31
8	Ethanol	78	51:49	—	—
9	*tert*-Butanol	79	53:47	—	—
10	Dimethylsufoxide	72	50:50	—	—
11	Acetonitrile	47	53:47	—	—
12	Tetrahydrofuran	82	50:50	—	—
13	1,4-Dioxane	68	52:48	—	—

configuration to the **16i** and *epi*-**16i** diastereomers, but these experiments were inconclusive.

The low level of diastereoselectivity observed for some of compounds **16** arose from the acidity of the methine group in compounds **13** and **16a**–**i**. This was demonstrated by dissolving pure **16i** and *epi*-**16i** in methanol (1 M) and reacting them with triethylamine (30 mol %) for 4 h at room temperature (Scheme 5). The crude mixtures were analyzed by ^{1}H NMR that confirmed the presence of **16i** and *epi*-**16i** in both samples. The two experiments furnished the same 6:4 mixture of **16i** and *epi*-**16i**. This experiment demonstrated that **16i** and *epi*-**16i** established equilibrium with nitronate **17** when the base was present. Alkene **18**, arising from a base promoted dehydration of **16i** and *epi*-**16i**, was also identified in these experiments (Scheme 5). Detection of **18** gave additional support to the presence of nitronate **17**. This data pointed out the following facts: (a) the product distribution was under kinetic control only when the vinylogous nitroaldol reaction was carried out at lower concentration (1 M) and in aprotic apolar solvents (see Table 1, entries 1–7); unfortunately under these conditions the reaction was slow and limited conversion was observed; (b) the product distribution was under thermodynamic control when the vinylogous nitroaldol reaction was carried out at higher concentration (1 M) and in protic and apolar solvents (see Tables 1 and 3). In the latter case, the diastereoselectivity depended on the relative thermodynamic stability of the two diastereoisomers. This was particularly evident for compounds **16** arising from aliphatic aldehydes in which the steric demand of R_1 and R_2 groups was remarkably different (Table 3, entries 13–16).

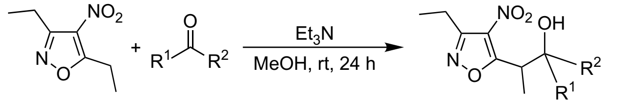
In conclusion, we have described a novel variant of the Henry reaction in which a new bond between 3,5-diethyl-4-nitroisoxazole **8** and carbonyl compounds was formed. This reaction worked under the catalysis of a simple and inexpensive triethylamine and gave a novel class of β-heteroaryl alkanol products in high yields. Application of this novel concept to the synthesis of naturally occurring compounds and efforts aimed at controlling the stereochemistry are in progress.

Table 2
Reaction of 3,5-diethyl-4-nitroisoxazole **8** and benzaldehyde **5** using different bases



Entry	Base	Yield of **13** (%)	Yield of **14** (%)
1	Triethylamine	92	—
2	4-(*N*,*N*-Dimethylamino)pyridine	49	—
3	*N*,*N*,*N*′-Trimethylethylenediamine	26	30
4	1,4-Diazabicyclo[2.2.2]octane	52	—
5	Piperidine	21	13
6	1,5-Diazabicyclo[4.3.0]non-5-ene	19	—
7	*N*,*N*-Diisopropylethylamine	79	—
8	1,3-Imidazole	17	—
9	Triphenylphosphine	0	—
10	Quinine	51	—
11	Hydroquinine	71	—
12	*N*-Methylmorpholine	25	—
13	(*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine	25	20

Table 3
Reaction of 3,5-diethyl-4-nitroisoxazole with various carbonyl compounds



8 **15** **13** and **16a-o**

Entry	R^1	R^2	Concn (M)	Time (h)	Yield[a] of **13** and **16** (%)	dr
1	C_6H_5	H	1	24	(**13**) 92	53:47[b]
2	*p*-ClC_6H_4	H	1	24	(**16a**) 78	53:47[b]
3	*p*-CNC_6H_4	H	1	24	(**16b**) 88	51:49[b]
4	*p*-$NO_2C_6H_4$	H	1	24	(**16c**) 60	54:46[b]
5	*p*-MeC_6H_4	H	1	24	(**16d**) 49	59:41[b]
6	*p*-$OMeC_6H_4$	H	1	24	(**16e**) 44	55:45[b]
7	2-Furyl	H	1	24	(**16f**) 69	60:40[b]
8	$CH{=}CHC_6H_5$	H	1	24	(**16g**) 45	52:48[b]
9	$COOC_2H_5$	H	1	24	(**16h**) 52	62:38[b]
10	$COOCH_3$	C_6H_5	1	24	(**16i**) 70	61:39[c]
11	$CH(CH_3)_2$	H	10	72	(**16j**) 83	79:21[c]
12	$CH_2CH(CH_3)_2$	H	10	72	(**16k**) 86	72:28[c]
13	$CH_2(CH_2)_4CH_3$	H	10	72	(**16l**) 89	88:12[d]
14	Cyclohexyl	H	10	72	(**16m**) 96	74:26[c]
15	$CH(C_2H_5)_2$	H	10	72	(**16n**) 46	86:14[c]
16	$C(CH_3)_3$	H	10	72	(**16o**) 15	90:10[c]

[a] Yields are for isolated products.
[b] Diastereomeric ratios were estimated using ^1H NMR data.
[c] The diastereomers were separated using flash chromatography.
[d] Diastereomeric ratio was estimated using ^{13}C NMR data.

3. Experimental section

3.1. General experimental

^1H and ^{13}C NMR spectra were recorded on a 200 or a 400 MHz spectrometers at ambient temperatures. ^1H NMR spectral assignments are supported by ^1H–^1H COSY and ^{13}C–^1H COSY where necessary. For ^1H NMR recorded in $CDCl_3$ chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, dt, doublet of triplets, tt, triplet of triplets, m, multiplet and br, broad. Coupling constants (J) were recorded in hertz (Hz) to the nearest 0.5 Hz. Carbon spectra are supported by DEPT analysis where necessary. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum (ν_{max}) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV. Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm, 230–400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with silica gel 60, which were visualized by quenching of UV fluorescence (λ_{max}=254 nm) or by staining with either 10% w/v ammonium molybdate in 2 M sulfuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors (R_f) are reported to ±0.05.

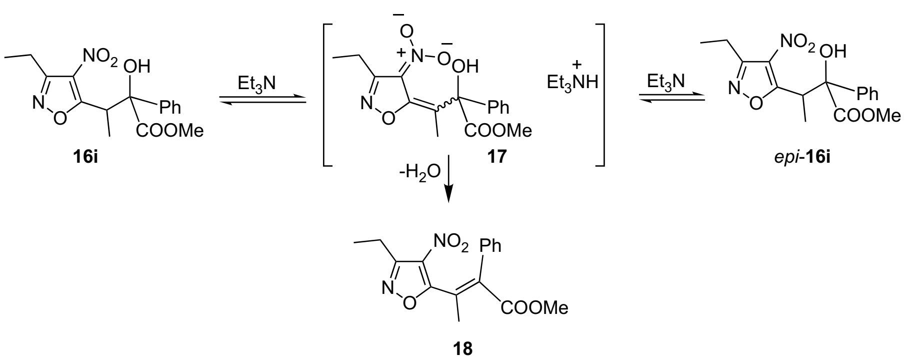
3.2. Preparation of 3,5-diethyl-4-nitroisoxazole 8

To a solution of hydroxylamine hydrochloride (7.3 g, 105 mmol) in methanol/water (50:100 mL) was added sodium carbonate (5.3 g, 50 mmol) in portions and at room temperature. To this solution was added 3,5-heptanedione **11** (13.4 g, 105 mmol) and reaction mixture was refluxed for 8 h. After this time, the reaction mixture was allowed to reach room temperature and extracted using diethylether (2×200 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain 3,5-diethylisoxazole **12** in quantitative yield. This material was pure enough to be carried through the next step without further purification.

A 250 mL reaction flask fitted with a thermometer was charged with H_2SO_4 concd (26 mL) and cooled to 0 °C and then were sequentially added 3,5-diethylisoxazole (12.5 g, 100 mmol), HNO_3 concd (10 mL) and H_2SO_4 concd (40 mL). The addition of 3,5-diethylisoxazole and further amounts of acids were carried out drop wise in order to keep the temperature in the range 0–5 °C. When the addition was completed, the reaction mixture was heated at 100 °C for 2 h, then allowed to reach room temperature and poured in ice. The organic phase was separated, diluted in ethyl acetate (300 mL), washed with water (2×100 mL), then brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was distilled under vacuum (100 °C at 10–20 mm/Hg) to give 12.71 g of pure 3,5-diethyl-4-nitroisoxazole **8** (71% yield). Colourless liquid, R_f=0.7 (petroleum ether/EtOAc, 90:10), IR (Neat): 2989 w, 1586 s; ^1H NMR (400 MHz, $CDCl_3$): 1.34 (CH_3, t, 3H, J=7.6 Hz), 1.40 (CH_3, t, 3H, J=7.6 Hz), 3.00 (CH_2, q, 2H, J=7.6 Hz), 3.24 (CH_2, q, 2H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 10.4 (CH_3), 11.3 (CH_3), 19.8 (CH_2), 21.7 (CH_2), 139.1 (C–NO_2), 160.1 (C=N), 176.5 (C–O); HRMS: m/z found [M^+] 170.0692, $C_7H_{10}N_2O_3$ requires 170.0691; m/z: 170 (100%, M^+).

3.3. Preparation of 2-(3-methyl-4-nitro-isoxazol-5-yl)-1-phenyl-ethanol 10

In a round bottomed flask were put 3,5-dimethyl-4-nitroisoxazole **7** (284 mg, 2 mmol), triethylamine (60 mg, 0.6 mmol) and methanol (2 mL) and the reaction mixture stirred for 15 min. Then benzaldehyde (424 mg, 4 mmol) was added and the solution stirred for 24 h at room temperature. After this time, the solvent was



Scheme 5. Reaction of pure diastereomer of **16i** with Et_3N.

evaporated and the oil so obtained subjected to column chromatography on silica gel [petroleum ether and ethyl acetate (95:5)] to give **10** as a colourless viscous oil, 159 mg, 32%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (KBr): 3430 br, 2989 w, 1598 s; ^{1}H NMR (400 MHz, $CDCl_3$): 2.21 (OH, br s, 1H), 2.48 (CH_3, s, 3H), 3.48 (CH_2, dd, 1H, J_1=4 Hz, J_2=4.4 Hz), 3.59 (CH_2, dd, 1H, J_1=9.2 Hz, J_2=8.8 Hz), 5.15–5.19 (CH, m, 1H), 7.25–7.28 (Ar–H, m, 2H), 7.30–7.35 (Ar–H, m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.7 (CH_3), 37.3 (CH_2), 71.7 (CH), 125.5 (Ar–CH), 128.6 (Ar–CH), 128.9 (Ar–CH), 142.2 (Ar–C), 155.7 (C=N), 172.0 (=C–O); HRMS: *m*/*z* found [M$^+$] 248.0781, $C_{12}H_{12}N_2O_4$ requires 248.0797; *m*/*z*: 248 (100%, M$^+$).

3.4. General experimental procedure for the synthesis of compounds 13 and 16a–i (Table 3)

3,5-Diethyl-4-nitroisoxazole **8** (340 mg, 2 mmol) and triethylamine (60 mg, 0.6 mmol) were dissolved in methanol (2 mL) and the contents stirred for 15 min. Then a carbonyl compound (4 mmol) **5** or **15a**–**i** was added to the reaction mixture and this stirred for 24 h at room temperature. After this time, the solvent was evaporated and the crude material so obtained purified by flash column chromatography on silica gel [petroleum ether and ethyl acetate (95:5)] to give **13** and **16a**–**i**.

3.4.1. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-phenyl-propan-1-ol ***13***

Colourless viscous oil, 508 mg, 92%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (KBr): 3424 br, 2986 w, 1597 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 (CH–CH_3, d, 3H, *J*=8 Hz), 1.18 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.26 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.35 (CH–CH_3, d, 3H, *J*=7.2 Hz), 2.30 (OH, s, 1H), 2.37 (OH, s, 1H), 2.83 (CH_2–CH_3, q, 2H, *J*=7.2 Hz), 2.91 (CH_2–CH_3, q, 2H, *J*=7.6 Hz), 4.07–4.14 (*CH*–CH_3, m, 2H), 4.84 (*CH*–OH, d, 1H, *J*=9.6 Hz), 4.99 (*CH*–OH, d, 1H, *J*=6.0 Hz), 7.19–7.22 (Ar–H, m, 5H), 7.29–7.32 (Ar–H, m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1 (CH_2–CH_3), 11.2 (CH_2–CH_3), 12.0 (CH–CH_3), 14.7 (CH–CH_3), 19.7 (CH_2–CH_3), 19.9 (CH_2–CH_3), 40.6 (*CH*–CH_3), 40.9 (*CH*–CH_3), 75.4 (CH–OH), 76.7 (CH–OH), 125.8 (Ar–CH), 126.7 (Ar–CH), 128.2 (Ar–CH), 128.5 (Ar–CH), 128.7 (Ar–CH), 128.8 (Ar–CH), 141.0 (Ar–C), 141.3 (Ar–C), 159.9 (C=N), 160.0 (C=N), 176.1 (=C–O), 176.3 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 275.1028, $C_{14}H_{15}N_2O_4$ requires 275.1032; *m*/*z*: 275 (100%, M−H$^+$).

3.4.2. 1-(4-Chloro-phenyl)-2-(3-ethyl-4-nitro-isoxazol-5-yl)-propan-1-ol ***16a***

Pale yellow viscous oil, 482 mg, 78%, R_f=0.2 (petroleum ether/EtOAc, 90:10), IR (KBr): 3432 br, 2989 w, 1599 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (CH–CH_3, d, 3H, *J*=7.2 Hz), 1.21 (CH_2–CH_3, t, 3H, *J*=7.6 Hz), 1.26 (CH_2–CH_3, t, 3H, *J*=7.6 Hz), 1.33 (CH–CH_3, d, 3H, *J*=6.8 Hz), 2.39 (OH, s, 1H), 2.43 (OH, s, 1H), 2.83–2.95 (CH_2–CH_3, m, 4H), 4.01–4.09 (*CH*–CH_3, m, 2H), 4.84 (*CH*–OH, d, 1H, *J*=9.2 Hz), 5.01 (*CH*–OH, d, 1H, *J*=5.6 Hz), 7.20–7.26 (Ar–H, m, 4H), 7.28–7.31 (Ar–H, m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.2 (CH_2–CH_3), 11.8 (CH_2–CH_3), 14.2 (CH–CH_3), 14.7 (CH–CH_3), 19.8 (CH_2–CH_3), 19.9 (CH_2–CH_3), 40.6 (*CH*–CH_3), 40.8 (*CH*–CH_3), 74.6 (CH–OH), 76.1 (CH–OH), 127.3 (Ar–CH), 128.1 (Ar–CH), 128.7 (Ar–CH), 129.0 (Ar–CH), 133.9 (Ar–C), 134.5 (Ar–C), 139.6 (Ar–C), 139.8 (Ar–C), 160.0 (C=N), 160.1 (C=N), 175.8 (=C–O), 176.0 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 309.0651, $C_{14}H_{14}ClN_2O_4$ requires 309.0642; *m*/*z*: 309 (100%, M−H$^+$).

3.4.3. 4-[2-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-hydroxy-propyl]-benzonitrile ***16b***

Pale yellow viscous oil, 531 mg, 88%, R_f=0.2 ($CHCl_3$/MeOH, 98:2), IR (KBr): 3433 br, 2989 w, 2222 s, 1598 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (CH–CH_3, d, 3H, *J*=7.2 Hz), 1.21 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.25 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.30 (CH–CH_3, d, 3H, *J*=7.2 Hz), 2.86–2.94 (CH_2–CH_3, OH, m, 6H), 4.04–4.11 (*CH*–CH_3, m, 2H), 4.96 (*CH*–OH, d, 1H, *J*=9.2 Hz), 5.13 (*CH*–OH, d, 1H, *J*=5.6 Hz), 7.42–7.45 (Ar–H, m, 4H), 7.54 (Ar–H, d, 2H, *J*=8 Hz), 7.59 (Ar–H, d, 2H, *J*=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 11.0 (CH_2–CH_3), 11.1 (CH_2–CH_3), 11.2 (CH–CH_3), 14.5 (CH–CH_3), 19.8 (CH_2–CH_3), 19.9 (CH_2–CH_3), 40.5 (*CH*–CH_3), 40.8 (*CH*–CH_3), 74.1 (CH–OH), 75.8 (CH–OH), 111.6 (Ar–C), 112.2 (Ar–C), 118.4 (Ar–C≡N), 118.6 (Ar–C≡N), 126.8 (Ar–CH), 127.5 (Ar–CH), 129.2 (C–NO_2), 130.3 (C–NO_2), 132.3 (Ar–CH), 132.5 (Ar–CH), 146.6 (Ar–C), 146.7 (Ar–C), 160.1 (C=N), 160.1 (C=N), 175.3 (=C–O), 175.6 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 300.0988, $C_{15}H_{14}N_3O_4$ requires 300.0984; *m*/*z*: 300 (100%, M−H$^+$).

3.4.4. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-(4-nitro-phenyl)-propan-1-ol ***16c***

Pale yellow viscous oil, 386 mg, 60%, R_f=0.1 ($CHCl_3$/MeOH, 98:2), IR (KBr): 3436 br, 2990 w, 1598 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (CH–CH_3, d, 3H, *J*=7.2 Hz), 1.24 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.27 (CH_2–CH_3, t, 3H, *J*=7.6 Hz), 1.32 (CH–CH_3, d, 3H, *J*=7.2 Hz), 2.45–2.47 (OH, m, 2H), 2.88–2.97 (CH_2–CH_3, m, 4H), 4.07–4.16 (*CH*–CH_3, m, 2H), 5.02–5.06 (*CH*–OH, m, 1H), 5.21–5.23 (*CH*–OH, m, 1H), 7.49–7.52 (Ar–H, m, 4H), 8.12–8.19 (Ar–H, m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.0 (CH_2–CH_3), 11.1 (CH_2–CH_3), 14.5 (CH–CH_3), 19.7 (CH_2–CH_3), 19.8 (CH_2–CH_3), 40.5 (*CH*–CH_3), 40.7 (*CH*–CH_3), 74.1 (CH–OH), 75.6 (CH–OH), 123.7 (Ar–CH), 123.9 (Ar–CH), 126.9 (Ar–CH), 127.6 (Ar–CH), 147.6 (Ar–C), 147.9 (Ar–C), 148.1 (Ar–C), 148.3 (Ar–C), 160.0 (C=N), 160.1 (C=N), 175.1 (=C–O), 175.4 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 320.0878, $C_{14}H_{14}N_3O_6$ requires 320.0883; *m*/*z*: 320 (100%, M−H$^+$).

3.4.5. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-p-tolyl-propan-1-ol ***16d***

Pale yellow viscous oil, 283 mg, 49%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (KBr): 3429 br, 2991 w, 1596 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (CH–CH_3, d, 3H, *J*=7.2 Hz), 1.14 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.21 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.30 (CH–CH_3, d, 3H, *J*=7.6 Hz), 2.19 (Ar–CH_3, s, 3H), 2.26 (Ar–CH_3, s, 3H), 2.56 (OH, s, 1H), 2.70 (OH, s, 1H), 2.77 (CH_2–CH_3, q, 2H, *J*=7.2 Hz), 2.86 (CH_2–CH_3, q, 2H, *J*=7.2 Hz), 3.95–4.07 (*CH*–CH_3, m, 2H), 4.74 (*CH*–OH, d, 1H, *J*=9.2 Hz), 4.88 (*CH*–OH, d, 1H, *J*=5.6 Hz), 6.97 (Ar–H, d, 2H, *J*=8 Hz), 7.04–7.09 (Ar–H, m, 4H), 7.14 (Ar–H, d, 2H, *J*=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1 (CH_2–CH_3), 12.1 (CH_2–CH_3), 14.7 (CH–CH_3), 19.7 (CH_2–CH_3), 19.9 (CH_2–CH_3), 21.1 (Ar–CH_3), 21.2 (Ar–CH_3), 40.6 (*CH*–CH_3), 40.9 (*CH*–CH_3), 75.2 (CH–OH), 76.5 (CH–OH), 125.8 (Ar–CH), 126.6 (Ar–CH), 129.1 (Ar–CH), 129.4 (Ar–CH), 137.8 (Ar–C), 138.2 (Ar–C), 138.5 (Ar–C), 159.9 (C=N), 160.0 (C=N), 176.3 (=C–O), 176.6 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 289.1181, $C_{15}H_{17}N_2O_4$ requires 289.1188; *m*/*z*: 289 (100%, M−H$^+$).

3.4.6. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-(4-methoxy-phenyl)-propan-1-ol ***16e***

Pale brown viscous oil, 268 mg, 44%, R_f=0.1 ($CHCl_3$/MeOH, 99:1), IR (KBr): 3427 br, 2992 w, 1596 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 (CH–CH_3, d, 3H, *J*=7.2 Hz), 1.20 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.28 (CH_2–CH_3, t, 3H, *J*=7.2 Hz), 1.38 (CH–CH_3, d, 3H, *J*=7.2 Hz), 2.04 (OH, s, 1H), 2.11 (OH, s, 1H), 2.84 (CH_2–CH_3, q, 2H, *J*=7.6 Hz), 2.94 (CH_2–CH_3, q, 2H, *J*=7.6 Hz), 3.71 (Ar–OCH_3, s, 3H), 3.76 (Ar–OCH_3, s, 3H), 4.07–4.13 (*CH*–CH_3, m, 2H), 4.81 (*CH*–OH, d, 1H, *J*=9.6 Hz), 4.96 (*CH*–OH, d, 1H, *J*=6.4 Hz), 6.75 (Ar–H, d, 2H, *J*=8.8 Hz), 6.84–6.86 (Ar–H, m, 2H), 7.15 (Ar–H, d, 2H, *J*=6.8 Hz), 7.25 (Ar–H, d, 2H, *J*=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 11.2 (CH_2–CH_3), 12.6 (CH_2–CH_3), 14.8 (CH–CH_3), 19.8 (CH_2–CH_3), 19.9 (CH_2–CH_3), 40.7 (*CH*–CH_3), 40.9 (*CH*–CH_3), 55.3 (Ar–OCH_3), 55.4 (Ar–OCH_3), 75.3 (CH–OH), 76.6 (CH–OH), 113.9 (Ar–CH), 114.2 (Ar–CH), 127.2 (Ar–CH), 127.9 (Ar–CH), 133.2 (Ar–C), 133.5 (Ar–C), 159.4 (Ar–C), 159.9 (C=N), 160.0 (C=N), 176.1 (=C–O), 176.5 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 305.1133, $C_{15}H_{17}N_2O_5$ requires 305.1137; *m*/*z*: 305 (100%, M−H$^+$).

3.4.7. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-furan-2-yl-propan-1-ol **16f**

Pale yellow viscous oil, 369 mg, 69%, R_f=0.2 (petroleum ether/EtOAc, 90:10), IR (KBr): 3430 br, 2993 w, 1595 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (CH–CH_3, d, 3H, J=7.2 Hz), 1.21 (CH_2–CH_3, t, 3H, J=7.2 Hz), 1.26 (CH_2–CH_3, t, 3H, J=7.2 Hz), 1.41 (CH–CH_3, d, 3H, J=7.2 Hz), 2.43 (OH, d, 1H, J=6.4 Hz), 2.52 (OH, d, 1H, J=5.6 Hz), 2.84–2.96 (CH_2–CH_3, m, 4H), 4.25–4.29 (*CH*–CH_3, m, 1H), 4.31–4.37 (*CH*–CH_3, m, 1H), 4.91 (*CH*–OH, dd, 1H, J_1=6.4 Hz, J_2=6.4 Hz), 4.98–5.01 (*CH*–OH, m, 1H), 6.14–6.15 (Ar–H, m, 1H), 6.20–6.21 (Ar–H, m, 1H), 6.30 (Ar–H, s, 2H), 7.24–7.25 (Ar–H, m, 1H), 7.35–7.36 (Ar–H, m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.4 (CH_2–CH_3), 13.1 (CH–CH_3), 14.5 (CH–CH_3), 19.8 (CH_2–CH_3), 19.9 (CH_2–CH_3), 38.7 (*CH*–CH_3), 69.4 (CH–OH), 69.9 (CH–OH), 107.3 (Ar–CH), 108.5 (Ar–CH), 110.3 (Ar–CH), 110.4 (Ar–CH), 142.6 (Ar–CH), 142.9 (Ar–CH), 153.1 (Ar–C), 153.3 (Ar–C), 159.9 (C=N), 160.1 (C=N), 175.3 (=C–O), 175.7 (=C–O); HRMS: m/z found $[M-H]^+$ 265.0831, $C_{12}H_{13}N_2O_5$ requires 265.0824; m/z: 265 (100%, M−H$^+$).

3.4.8. 4-(3-Ethyl-4-nitro-isoxazol-5-yl)-1-phenyl-pent-1-en-3-ol **16g**

Yellow viscous oil, 273 mg, 45%, R_f=0.3 (petroleum ether/EtOAc, 80:20), IR (KBr): 3431 br, 3011 w, 2993 w, 1597 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.12–1.31 (CH_3, m, 9H), 1.35–1.40 (CH_3, m, 3H), 1.99 (OH, d, 1H, J=7.2 Hz), 2.06 (OH, d, 1H, J=4 Hz), 2.86–2.90 (CH_2–CH_3, m, 4H), 3.97–4.00 (*CH*–CH_3, m, 1H), 4.04–4.08 (*CH*–CH_3, m, 1H), 4.49–4.52 (*CH*–OH, m, 2H), 6.09–6.14 (CHOH–*CH*=CH, m, 2H), 6.50–6.62 (Ar–*CH*=CH, m, 2H), 7.18–7.33 (Ar–H, m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.2 (CH_2–CH_3), 12.6 (CH_2–CH_3), 14.5 (CH–CH_3), 19.8 (CH_2–CH_3), 19.9 (CH_2–CH_3), 39.3 (*CH*–CH_3), 39.5 (*CH*–CH_3), 74.9 (CH–OH), 75.4 (CH–OH), 126.6 (Ar–CH), 126.7 (Ar–CH), 127.5 (Ar–CH), 128.0 (Ar–CH), 128.2 (Ar–CH=*CH*), 128.3 (Ar–CH=*CH*), 128.6 (Ar–CH), 128.7 (Ar–CH), 128.8 (Ar–CH), 133.0 (Ar–*CH*=CH), 133.7 (Ar–*CH*=CH), 135.8 (Ar–C), 135.9 (Ar–C), 160.1 (C=N), 175.8 (=C–O), 176.1 (=C–O); HRMS: m/z found $[M-H]^+$ 301.1180, $C_{16}H_{17}N_2O_4$ requires 301.1188; m/z: 301 (100%, M−H$^+$).

3.4.9. 3-(3-Ethyl-4-nitro-isoxazol-5-yl)-2-hydroxy-butyric acid ethyl ester **16h**

Pale yellow oil, 283 mg, 52%, R_f=0.4 (petroleum ether/EtOAc, 80:20), IR (KBr): 3478 br, 2954 w, 1740 s, 1587 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (CH_2–CH_3, t, 3H, J=7.2 Hz), 1.26–1.34 (CH_2–CH_3, m, 9H), 1.40 (CH–CH_3, d, 3H, J=6.8 Hz), 1.46 (CH–CH_3, d, 3H, J=7.2 Hz), 2.92–3.04 (Is-CH_2–CH_3, m, 4H), 3.27 (OH, d, 1H, J=7.2 Hz), 3.33 (OH, d, 1H, J=5.6 Hz), 4.15–4.28 (*CH*–CH_3, COOCH_2–CH_3, m, 6H), 4.30–4.34 (*CH*–CH_3, m, 2H), 4.45–4.50 (*CH*–OH, m, 1H), 4.58–4.60 (*CH*–OH, m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.0 (CH–CH_3), 11.1 (CH_2–CH_3), 12.6 (CH–CH_3), 13.8 (CH_2–CH_3), 14.1 (CH_2–CH_3), 19.8 (Is-CH_2–CH_3), 37.2 (*CH*–CH_3), 37.6 (*CH*–CH_3), 62.4 (O–CH_2–CH_3), 62.7 (O–CH_2–CH_3), 71.2 (CH–OH), 72.2 (CH–OH), 129.1 (C–NO_2), 129.8 (C–NO_2), 160.0 (C=N), 172.4 (=C–O), 174.0 (CO_2Et), 174.8 (CO_2Et); HRMS: m/z found $[M-H]^+$ 271.0927, $C_{11}H_{15}N_2O_6$ requires 271.0930; m/z: 271 (100%, M–H$^+$).

3.4.10. 3-(3-Ethyl-4-nitro-isoxazol-5-yl)-2-hydroxy-2-phenyl-butyric acid methyl ester **16i**

White solid, mp 93–95 °C, 180 mg, 27%, R_f=0.4 (petroleum ether/EtOAc, 90:10), IR (KBr): 3477 br, 2954 w, 1741 s, 1586 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.24–1.27 (CH_2–CH_3, m, 3H), 1.35–1.37 (CH–CH_3, m, 3H), 3.03 (CH_2–CH_3, q, 2H, J=7.2 Hz), 3.66 (CO_2CH_3, s, 3H), 3.82 (s, OH), 4.78 (*CH*–CH_3, q, 1H, J=7.2 Hz), 7.38–7.46 (Ar–H, m, 3H), 7.72–7.74 (Ar–H, m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 10.2 (CH_2–CH_3), 12.5 (CH–CH_3), 18.5 (CH_2–CH_3), 39.7 (*CH*–CH_3), 53.0 (CO_2CH_3), 79.1 (C–OH), 124.0 (Ar–CH), 125.5 (Ar–CH), 127.3 (Ar–CH), 127.5 (Ar–CH), 128.8 (Ar–CH), 137.9 (Ar–C), 158.4 (C=N), 172.5 (=C–O, CO_2CH_3); HRMS: m/z found $[M^+]$ 334.1158, $C_{16}H_{18}N_2O_6$ requires 334.1165; m/z: 334 (100%, M$^+$).

3.4.11. 3-(3-Ethyl-4-nitro-isoxazol-5-yl)-2-hydroxy-2-phenyl-butyric acid methyl ester epi-**16i**

White solid, mp 98–100 °C, 286 mg, 43%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (KBr): 3477 br, 2955 w, 1741 s, 1586 s; ^{1}H NMR (400 MHz, $CDCl_3$): 1.17 (CH_2–CH_3, t, 3H, J=7.2 Hz), 1.50 (CH–CH_3, d, 3H, J=6.8 Hz), 2.79 (CH_2–CH_3, q, 2H, J=7.6 Hz), 3.96 (CO_2CH_3, s, 3H), 5.04 (*CH*–CH_3, q, 1H, J=7.2 Hz), 7.23–7.28 (m, 3H), 7.51–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.2 (CH_2–CH_3), 12.3 (CH–CH_3), 19.8 (CH_2–CH_3), 41.2 (*CH*–CH_3), 53.7 (CO_2CH_3), 79.6 (C–OH), 125.9 (Ar–CH), 128.5 (Ar–CH), 128.6 (Ar–CH), 128.9 (Ar–CH), 130.1 (Ar–CH), 138.3 (Ar–C), 159.7 (C=N), 173.6 (=C–O), 174.9 (CO_2CH_3); HRMS: m/z found $[M^+]$ 334.1170, $C_{16}H_{18}N_2O_6$ requires 334.1165; m/z: 334 (100%, M$^+$).

3.5. General experimental procedure for the synthesis of compounds 16j–o (Table 3)

3,5-Diethyl-4-nitroisoxazole **8** (340 mg, 2 mmol) and triethylamine (60 mg, 0.6 mmol) were dissolved in methanol (0.2 mL) and the contents stirred for 15 min. Then an aliphatic aldehyde (12 mmol) **15j–o** was added to the reaction mixture and this stirred for 72 h at room temperature. After this time, the solvent was evaporated and the crude material so obtained purified by flash column chromatography on silica gel [petroleum ether and ethyl acetate (95:5)] to give **16j–o**.

3.5.1. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-4-methyl-pentan-3-ol **16j**

Colourless liquid, 86 mg, 18%, R_f=0.4 (petroleum ether/EtOAc, 90:10), IR (Neat): 3427 br, 2991 w, 1598 s; ^{1}H NMR (400 MHz, $CDCl_3$): 0.89 (CH_3–CH–CH_3, d, 3H, J=6.8 Hz), 0.94 (CH_3–CH–CH_3, d, 3H, J=6.8 Hz), 1.25–1.29 (CH_2–CH_3, CH–CH_3, m, 6H), 1.56 (OH, d, 1H, J=7.6 Hz), 1.80–1.84 (CH_3–*CH*–CH_3, m, 1H), 2.93 (CH_2–CH_3, q, 2H, J=7.6 Hz), 3.65–3.70 (*CH*–OH, m, 1H), 3.91–3.99 (Is-*CH*–CH_3, m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.2 (CH_2–CH_3), 14.4 (Is-CH–CH_3), 14.9 (CH_3–CH–CH_3), 20.0 (CH_2–CH_3), 29.8 (CH_3–*CH*–CH_3), 37.2 (Is-*CH*–CH_3), 78.2 (CH–OH), 159.9 (C=N), 177.3 (=C–O); HRMS: m/z found $[M-H]^+$ 241.1185, $C_{11}H_{17}N_2O_4$ requires 241.1188; m/z: 241 (100%, M−H$^+$).

3.5.2. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-4-methyl-pentan-3-ol epi-**16j**

Pale yellow liquid, 316 mg, 65%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3428 br, 2990 w, 1598 s; ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (CH_3–CH–CH_3, d, 3H, J=6.8 Hz), 0.94 (CH_3–CH–CH_3, d, 3H, J=6.8 Hz), 1.27 (CH_2–CH_3, t, 3H, J=7.2 Hz), 1.34 (Is-CH–CH_3, d, 3H, J=7.2 Hz), 1.56–1.61 (OH, CH_3–*CH*–CH_3, m, 2H), 2.94 (CH_2–CH_3, q, 2H, J=7.2 Hz), 3.62–3.67 (*CH*–OH, m, 1H), 3.93–4.00 (Is-*CH*–CH_3, m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1 (CH_2–CH_3), 11.3 (Is-CH–CH_3), 17.6 (CH_3–CH–CH_3), 19.4 (CH_3–CH–CH_3), 19.9 (CH_2–CH_3), 31.5 (CH_3–*CH*–CH_3), 36.7 (Is-*CH*–CH_3), 77.7 (CH–OH), 128.6 (C–NO_2), 160.1 (C=N), 177.6 (=C–O); HRMS: m/z found $[M-H]^+$ 241.1181, $C_{11}H_{17}N_2O_4$ requires 241.1188; m/z: 241 (100%, M−H$^+$).

3.5.3. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-5-methyl-hexan-3-ol **16k**

Pale yellow oil, 123 mg, 24%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3428 br, 2991 w, 1598 s; ^{1}H NMR (400 MHz, $CDCl_3$): 0.85 (CH_3–CH–CH_3, d, 3H, J=6.4 Hz), 0.88 (CH_3–CH–CH_3, d, 3H, J=6.8 Hz), 1.25–1.33 (CH_2–CH_3, Is-CH–CH_3, CH_2–CH, m, 8H), 1.55 (OH, d, 3H, J=6.8 Hz), 1.73–1.81 (CH_3–*CH*–CH_3, m, 1H), 2.94 (CH_2–CH_3, q, 2H, J=7.6 Hz), 3.79–3.86 (Is-*CH*–CH_3, m, 1H), 3.87–3.93 (*CH*–OH, m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1 (CH_2–CH_3), 14.5 (Is-CH–CH_3), 19.9 (CH_2–CH_3), 21.4 (CH_3–CH–CH_3), 23.8 (CH_3–CH–CH_3), 24.4 (CH_3–*CH*–CH_3), 40.1 (Is-*CH*–CH_3), 44.1 (CH–CH_2), 72.2 (CH–OH), 130.0 (C–NO_2), 160.0 (C=N), 176.7 (=C–O); HRMS: m/z found $[M-H]^+$ 255.1341, $C_{12}H_{19}N_2O_4$ requires; 255.1345; m/z: 255 (100%, M−H$^+$).

*3.5.4. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-5-methyl-hexan-3-ol epi-**16k***

Pale yellow oil, 317 mg, 62%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3428 br, 2991 w, 1598 s; ^{1}H NMR (400 MHz, CDCl$_3$): 0.85 (*CH*$_3$–CH–CH$_3$, d, 3H, *J*=6.4 Hz), 0.87 (*CH*$_3$–CH–CH$_3$, d, 3H, *J*=6.8 Hz), 1.28 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.6 Hz), 1.34 (CH–*CH*$_3$, d, 3H, *J*=7.2 Hz), 1.37–1.43 (*CH*$_2$–CH, m, 2H), 1.60 (OH, br s, 1H), 1.71–1.76 (CH$_3$–*CH*–CH$_3$, m, 1H), 2.94 (*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 3.80–3.87 (Is-*CH*–CH$_3$, m, 1H), 4.02–4.04 (*CH*–OH, m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 11.1 (CH$_2$–*CH*$_3$), 11.7 (Is-CH–*CH*$_3$), 19.9 (*CH*$_2$–CH$_3$), 21.6 (*CH*$_3$–CH–CH$_3$), 23.5 (*CH*$_3$–CH–CH$_3$), 24.7 (CH$_3$–*CH*–CH$_3$), 39.3 (Is-*CH*–CH$_3$), 43.5 (CH–*CH*$_2$–CH), 71.3 (CH–OH), 160.1 (C=N), 176.9 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 255.1340, C$_{12}$H$_{19}$N$_2$O$_4$ requires; 255.1345; *m*/*z*: 255 (100%, M−H$^+$).

*3.5.5. 2-(3-Ethyl-4-nitro-isoxazol-5-yl)-nonan-3-ol **16l***

Pale yellow oil, 506 mg, 89%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3425 br, 2992 w, 1598 s; ^{1}H NMR (400 MHz, CDCl$_3$): 0.79–0.83 (m, 3H), 1.18–1.25 (m, 5H), 1.26–1.28 (m, 5H), 1.30–1.32 (m, 3H), 1.39–1.47 (m, 2H), 1.53–1.66 (m, 1H), 1.80–1.82 (OH, m, 1H), 2.93 (*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 3.81–3.89 (*CH*–CH$_3$, *CH*–OH, m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): 11.1 (CH$_3$), 14.1 (CH$_3$), 14.4 (CH$_3$), 19.9 (Is-*CH*$_2$–CH$_3$), 22.6 (CH$_2$), 25.2 (CH$_2$), 29.1 (CH$_2$), 31.7 (CH$_2$), 34.8 (CH$_2$), 39.6 (*CH*–CH$_3$), 73.9 (CH–OH), 130.0 (C–NO$_2$), 160.0 (C=N), 176.8 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 283.1661, C$_{14}$H$_{23}$N$_2$O$_4$ requires; 283.1658; *m*/*z*: 283 (100%, M−H$^+$).

*3.5.6. 1-Cyclohexyl-2-(3-ethyl-4-nitro-isoxazol-5-yl)-propan-1-ol **16m***

Pale yellow oil, 140 mg, 25%, R_f=0.4 (petroleum ether/EtOAc, 90:10), IR (Neat): 3426 br, 2991 w, 1596 s; ^{1}H NMR (400 MHz, CDCl$_3$): 1.06–1.09 (m, 1H), 1.12–1.13 (m, 1H), 1.15–1.17 (m, 1H), 1.18–1.19 (m, 2H), 1.20–1.23 (m, 2H), 1.25 (s, 1H), 1.26–1.27 (m, 3H), 1.28–1.29 (m, 2H), 1.57–1.58 (m, 1H), 1.61–1.64 (m, 1H), 1.71–1.75 (m, 3H), 2.93 (*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 3.62–3.67 (CH–OH, m, 1H), 3.99–4.02 (*CH*–CH$_3$, m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 11.2 (CH$_2$–*CH*$_3$), 15.0 (Is-CH–*CH*$_3$), 19.9 (Is-*CH*$_2$–CH$_3$), 24.9 (CH$_2$), 25.9 (CH$_2$), 26.3 (CH$_2$), 26.4 (CH$_2$), 30.3 (CH$_2$), 36.4 (Is-*CH*–CH$_3$), 40.2 (CH$_2$–*CH*–CH$_2$), 78.1 (CH–OH), 159.9 (C=N), 177.4 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 281.1505, C$_{14}$H$_{21}$N$_2$O$_4$ requires; 281.1501; *m*/*z*: 281 (100%, M−H$^+$).

*3.5.7. 1-Cyclohexyl-2-(3-ethyl-4-nitro-isoxazol-5-yl)-propan-1-ol epi-**16m***

Pale yellow oil, 402 mg, 71%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3426 br, 2991 w, 1596 s; ^{1}H NMR (400 MHz, CDCl$_3$): 0.88–0.98 (m, 1H), 1.02–1.09 (m, 1H), 1.11 (s, 1H), 1.14 (s, 2H), 1.17–1.20 (m, 1H), 1.24 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.6 Hz), 1.32 (CH–*CH*$_3$, d, 3H, *J*=7.2 Hz), 1.61–1.66 (m, 2H), 1.70–1.76 (m, 3H), 1.83–1.86 (m, 1H), 2.93 (*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 3.62–3.66 (*CH*–OH, m, 1H), 3.95–4.01 (*CH*–CH$_3$, m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 10.4 (CH–*CH*$_3$), 11.2 (CH$_2$–*CH*$_3$), 19.9 (*CH*$_2$–CH$_3$), 25.8 (CH$_2$), 26.0 (CH$_2$), 26.1 (CH$_2$), 28.4 (CH$_2$), 29.2 (CH$_2$), 36.0 (Is-*CH*–CH$_3$), 41.0 (CH$_2$–*CH*–CH$_2$), 77.4 (CH–OH), 128.4 (C–NO$_2$), 160.1 (C=N), 177.9 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 281.1504, C$_{14}$H$_{21}$N$_2$O$_4$ requires; 281.1501; *m*/*z*: 281 (100%, M−H$^+$).

*3.5.8. 4-Ethyl-2-(3-ethyl-4-nitro-isoxazol-5-yl)-hexan-3-ol **16n***

Pale yellow liquid, 36 mg, 7%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3428 br, 2990 w, 1598 s; ^{1}H NMR (400 MHz, CDCl$_3$): 0.87 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.2 Hz), 0.92 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.2 Hz), 1.18–1.23 (m, 3H), 1.25–1.29 (m, 7H), 1.45–1.50 (m, 2H), 2.93 (Is-*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 3.86–3.91 (*CH*–OH, m, 1H), 4.00–4.08 (Is-*CH*–CH$_3$, m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 11.2 (CH$_2$–*CH*$_3$), 11.7 (CH$_2$–*CH*$_3$), 12.1 (CH$_2$–*CH*$_3$), 14.9 (CH–*CH*$_3$), 19.7 (CH–*CH*$_2$–CH$_3$), 19.9 (Is-*CH*$_2$–CH$_3$), 22.6 (CH–*CH*$_2$–CH$_3$), 36.9 (Is-*CH*–CH$_3$), 43.2 (*CH*–CH$_2$–CH$_3$), 75.2 (CH–OH), 160.0 (C=N), 177.5 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 269.1498, C$_{13}$H$_{21}$N$_2$O$_4$ requires; 269.1501; *m*/*z*: 269 (100%, M−H$^+$).

*3.5.9. 4-Ethyl-2-(3-ethyl-4-nitro-isoxazol-5-yl)-hexan-3-ol epi-**16n***

Pale yellow liquid, 214 mg, 39%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3429 br, 2991 w, 1598 s; ^{1}H NMR (400 MHz, CDCl$_3$): 0.78 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.2 Hz), 0.85 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.2 Hz), 1.09–1.14 (m, 1H), 1.21–1.23 (m, 1H), 1.27 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.6 Hz), 1.35–1.39 (m, 4H), 1.45–1.51 (m, 1H), 1.52–1.53 (m, 2H), 2.94 (Is-*CH*$_2$–CH$_3$, q, 2H, *J*=7.2 Hz), 3.87–3.92 (*CH*–OH, m, 1H), 3.97–4.02 (Is-*CH*–CH$_3$, m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 10.8 (CH$_2$–*CH*$_3$), 11.0 (CH$_2$–*CH*$_3$), 11.2 (CH$_2$–*CH*$_3$), 12.1 (CH–*CH*$_3$), 19.9 (Is-*CH*$_2$–CH$_3$), 20.5 (CH–*CH*$_2$–CH$_3$), 21.8 (CH–*CH*$_2$–CH$_3$), 36.6 (Is-*CH*–CH$_3$), 43.8 (*CH*–CH$_2$–CH$_3$), 74.0 (CH–OH), 160.0 (C=N), 177.5 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 269.1496, C$_{13}$H$_{21}$N$_2$O$_4$ requires; 269.1501; *m*/*z*: 269 (100%, M−H$^+$).

*3.5.10. 4-(3-Ethyl-4-nitro-isoxazol-5-yl)-2,2-dimethyl-pentan-3-ol **16o***

Pale brown oil, 78 mg, 15%, R_f=0.3 (petroleum ether/EtOAc, 90:10), IR (Neat): 3424 br, 2992 w, 1599 s; ^{1}H NMR (400 MHz, CDCl$_3$): 0.88 ((CH$_3$)$_3$, s, 9H), 1.27 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.2 Hz), 1.42 (CH–*CH*$_3$, d, 3H, *J*=7.2 Hz), 1.80 (OH, d, 1H, *J*=6 Hz), 2.93 (*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 3.63–3.66 (*CH*–OH, m, 1H), 4.01–4.07 (*CH*–CH$_3$, m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): 11.2 (CH$_2$–*CH*$_3$), 13.8 (CH–*CH*$_3$), 19.9 (*CH*$_2$–CH$_3$), 26.3 (C–*CH*$_3$), 35.0 (*CH*–CH$_3$), 36.2 (*C*–CH$_3$), 79.1 (CH–OH), 160.1 (C=N), 178.6 (=C–O); HRMS: *m*/*z* found [M−H]$^+$ 255.1341, C$_{12}$H$_{19}$N$_2$O$_4$ requires; 255.1345; *m*/*z*: 255 (100%, M−H$^+$).

*3.5.11. 3-Ethyl-5-(1-methyl-2-phenyl-vinyl)-4-nitroisoxazole **14***

Yellow wax, R_f=0.6 (petroleum ether/EtOAc, 90:10), IR (KBr): 3010 w, 2990 w, 1596; ^{1}H NMR (400 MHz, CDCl$_3$): 1.37 (CH$_2$–*CH*$_3$, t, 3H, *J*=7.6 Hz), 2.31 (=C–CH$_3$, s, 3H), 3.01 (*CH*$_2$–CH$_3$, q, 2H, *J*=7.6 Hz), 7.34 (CH, s, 1H), 7.36–7.37 (Ar–H, m, 1H), 7.41–7.47 (Ar–H, m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): 11.4 (CH$_2$–*CH*$_3$), 16.3 (=C–*CH*$_3$), 20.2 (*CH*$_2$–CH$_3$), 122.9 (=*C*–CH), 128.6 (Ar–CH), 128.8 (Ar–CH), 129.7 (Ar–CH), 135.2 (Ar–C), 139.4 (=C–*CH*), 160.7 (C=N), 171.9 (=C–O); HRMS: *m*/*z* found [M$^+$] 258.1010, C$_{61}$H$_{18}$N$_2$O$_6$ requires 258.1004; *m*/*z*: 258 (100%, M$^+$).

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