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Reaction of 5-(1-bromo-2-aryl-vinyl)-3-methyl-4-nitro-isoxazoles and 1,3-dicarbonyl compounds

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ABSTRACT

The preparation of *E*-5-(1-bromo-2-aryl-vinyl)-3-methyl-4-nitro-isoxazoles and their reaction with 1,3-dicarbonyl compounds to give cyclopropanes or dihydrofurans is described.

1. Introduction

3-Methyl-4-nitro-5-styrylisoxazoles **1** represent a class of polyfunctional scaffold, which hold excellent potential for the generation of diversity (Fig. 1).[1–10] Compounds **1** can be readily prepared from commercially available 3,5-dimethyl-4-nitro-isoxazole and aromatic aldehydes.[4] It has been shown that compounds **1** can be considered as cinnamate equivalents where the 4-nitro-isoxazole core can be hydrolyzed to give a carboxylate.[2,3,8,11] It is noteworthy that compounds **1** have enhanced reactivity compared to cinnamates due to the conjugation of the nitro group at position C-4 of the isoxazole core. Furthermore, compounds **1** have two electrophilic centers that can be selectively reacted. Enolates, which are stabilized soft nucleophiles, react at the soft electrophilic center E^2, whereas hard nucleophiles such as hydroxide react exclusively at the hard electrophilic center E^1 (Fig. 1).[1–3,8,11]

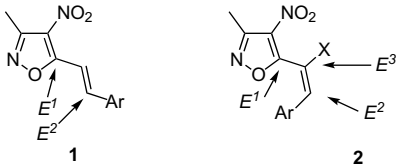

Figure 1. Polyfunctional scaffolds **1** and **2**.

As part of our programme of research devoted to the design and preparation of novel polyfunctional scaffolds[1–10] we considered the preparation of compounds **2** (Fig. 1). Isoxazoles **2**, in which a halide is introduced on the exocyclic alkene, hold an additional electrophilic center E^3 (Fig. 1) that increases the number of their possible synthetic applications.

For instance, the alkenyl halide moiety in scaffold **2** could be employed in various transition metal-mediated C–C bond forming reactions including Heck, Sonogashira and related reactions to access dienes or enynes.[12] Furthermore, the low aromaticity renders isoxazoles **2** useful intermediates, since they could be easily manipulated to obtain functionally complex derivatives, namely 1,3-dicarbonyls,[13] hydroxyketones,[14] enaminoketones,[14,15] γ-amino alcohols,[16] azirines,[17] enamines and β-hydroxynitriles,[18] and polyamino alcohols.[19] It was envisaged that the presence of two contiguous electrophilic centers E^2 and E^3 and a suitable leaving group connected to E^3 could enable compounds **2** to cyclize through a Michael addition–cyclization protocol (Fig. 1). In this respect, **2** could serve as a precursor for the preparation of cyclopropanes **4** or dihydrofurans **5** by reaction with suitable dinucleophiles, for example, 1,3-dicarbonyl compounds (Fig. 2).

2. Results and discussion

3-Methyl-4-nitro-5-styrylisoxazoles **1a–f** were brominated to give dibromo derivatives **6a–f** using the procedure described by Sarti-Fantoni.[20] Compounds **6a–f** were then treated with triethylamine to give bromo styrylisoxazoles **2a–f** in good yields (Table 1).

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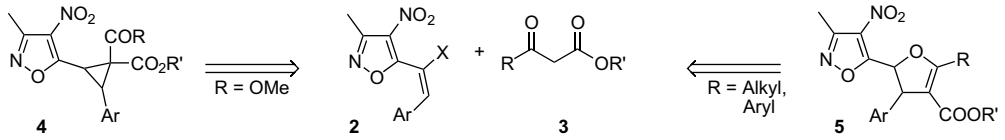
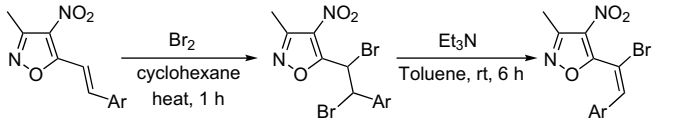


Figure 2. Retrosynthetic analysis for cyclopropanes **4** and dihydrofurans **5**.

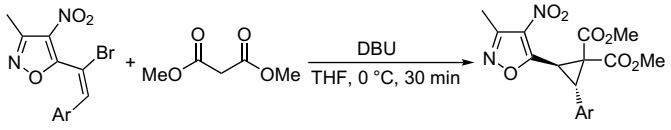
Table 1
Synthesis of bromo substituted styrylisoxazoles **2a–f**



Entry	Ar	Reactant	Product	Yield [a](%)
1	C_6H_5	**1a**	**2a**	90
2	*p*-MeC_6H_4	**1b**	**2b**	45
3	*p*-$MeOC_6H_4$	**1c**	**2c**	91
4	*p*-ClC_6H_4	**1d**	**2d**	89
5	2-Pyridyl	**1e**	**2e**	88
6	2-(5-Bromothiophenyl)	**1f**	**2f**	85

[a] The products were pure enough that obviates chromatography. Yields determined over two steps.

Table 2
Synthesis of cyclopropanes **7a–f**



Entry	Ar	Reactant	Product	% Yield (trans/cis)
1	C_6H_5	**2a**	**7a**	88 (1:0)
2	*p*-MeC_6H_4	**2b**	**7b**	98 (1:0)
3	*p*-$MeOC_6H_4$	**2c**	**7c**	92 (1:0)
4	*p*-ClC_6H_4	**2d**	**7d**	78 (1:0)
5	2-Pyridyl	**2e**	**7e**	70 (1:0)
6	2-(5-Bromothiophenyl)	**2f**	**7f**	—

Importantly, products **2a–f** were obtained as a single isomer. The *E* stereochemistry was assigned to **2d** based on X-ray crystal structure analysis (Fig. 3).[21] The nitro-isoxazole core is well-known to enhance the acidity of the proton at C-5 hence stabilizing formation of carbanions at this position. This rendered an E1cb mechanism energetically favored and furnished a rational for the exclusive *E* stereochemistry observed. It is noteworthy that α-bromo cinnamates were not obtained as a single isomer from the reaction of cinnamate esters in a bromination–dehydromination protocol.[22] Additionally, in these reactions, *Z*-bromo cinnamates were obtained as major isomers.

Initially, bromo styrylisoxazole **2a** was reacted in THF with dimethyl malonate **3a** in the presence of DBU (Table 2, entry 1). To our delight, the reaction gave cyclopropane **7a**, exclusively, in excellent yield and without the need of chromatographic purification. Importantly, only one diastereomer was observed in this reaction and a trans stereochemistry was assigned based on NOE studies. In these experiments no enhancement was observed irradiating each of the cyclopropyl C–H.

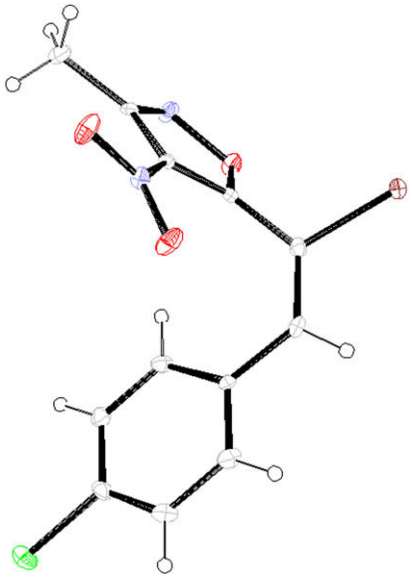


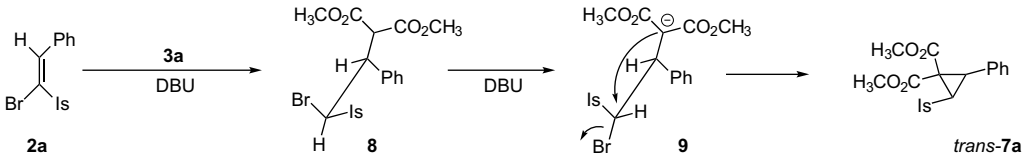
Figure 3. ORTEP representation of crystal structure of **2d** (thermal ellipsoids are drawn at 30% probability).

The exclusive formation of *trans*-**7a** was explained as follows (Scheme 1). Initial Michael addition of **3a** to **2a** generated intermediate **8**. Deprotonation of **8** gave enolate **9** (herein shown as its conjugated anion), which underwent cyclization through an intermolecular S_N2 reaction. In this step, the nucleophile and the bromide leaving group lay antiperiplanar, giving *trans*-**7a** as the only product.

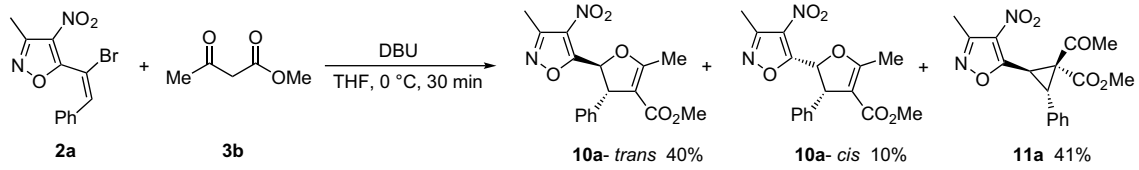
We then studied the scope of this reaction by reacting bromo styrylisoxazoles **2a–f** and dimethyl malonate **3a** (Table 2). The reaction of **3a** and bromo styrylisoxazoles **2b**,**c** gave the corresponding cyclopropanes *trans*-**7b–d** in excellent yields (Table 2, entries 2–4). Bromo styrylisoxazole **2e** bearing a 2-pyrydyl substituent also gave the corresponding cylcopropane *trans*-**7e** in good yield (Table 2, entry 5). Reaction of **2f** and **3a** did not give the corresponding cyclopropane, but a complex reaction mixture.

With the objective to synthesize dihydrofurans (Fig. 2), we have reacted bromo styrylisoxazole **2a** and methyl acetoacetate **3b** in the presence of DBU in THF at 0 °C (Scheme 2). Reaction of **2a** and **3b** was completed in 30 min and furnished the desired dihydrofuran **10a** in 50% yield. Dihydrofuran **10a** was formed as an 8:2 mixture of diastereoisomers, which were inseparable by silica gel chromatography. The trans stereochemistry was assigned to the major isomer of **10a** by X-ray crystal structure analysis run on a pure sample of *trans*-**10a** obtained by slow crystallization from methanol (Fig. 4).[23]

In addition, this reaction furnished cyclopropane **11a** in 41% yield (Scheme 2), which was obtained as a single diastereoisomer. It is interesting to note that compound **11a** contains three stereocenters including a quaternary one. The exclusive formation of **11a** could be explained as follows (Scheme 3). Michael addition of **3b** to **2a** generated intermediate **12**. Deprotonation of **12** gave enolate **13** (herein shown as its conjugated anion), which underwent cyclization through an intramolecular S_N2 reaction. In this step, the enolate nucleophile and the bromide leaving group lay antiperiplanar, giving *trans*-**11a** as the only product.



Scheme 1. Proposed mechanism for the formation of *trans*-**7a**.



Scheme 2. Reaction of **2a** and methyl acetoacetate **3b**.

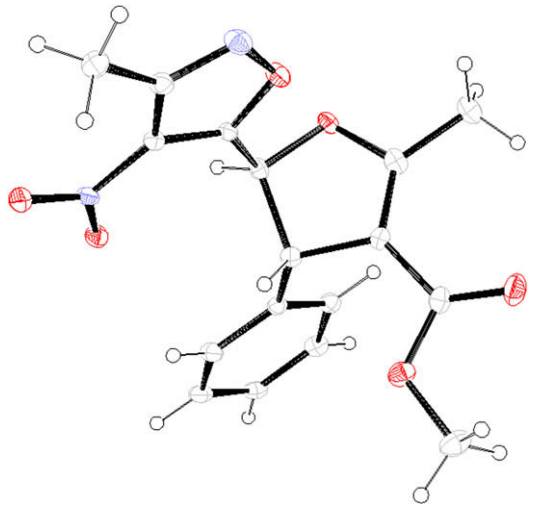


Figure 4. ORTEP representation of crystal structure of dihydrofuran **10a** (thermal ellipsoids are drawn at 30% probability).

The stereoselective formation of the quaternary stereogenic center in compound **11a** could be explained considering a steric clash occurring between the methoxyester and the phenyl group in intermediate **13** (Scheme 3).

The reaction of **2a** and **3b** was conducted under various reaction conditions in order to identify a set of conditions to obtain compound **10a** or **11a** exclusively. In particular, the ratio of reactants, solvent, amount of base, and temperature were studied (Table 3). Unfortunately, these experiments gave dihydrofurans and cyclopropanes in similar amounts. Reaction of **2a** with 1 equiv of **3b** and 1 equiv of DBU in THF gave dihydrofuran **10a** in 25% yield as a 8:2 trans/cis mixture accompanied by 19% of cyclopropane **11a** (Table 3, entry 1). When methanol was used, reactant **2a** was completely consumed; however a complex reaction mixture was formed (Table 3, entries 2 and 3). Use of Et_3N in THF gave unreacted starting material **2a** (Table 3, entry 4), while use of excess DBU (Table 3, entry 5) lead to a complex reaction mixture.

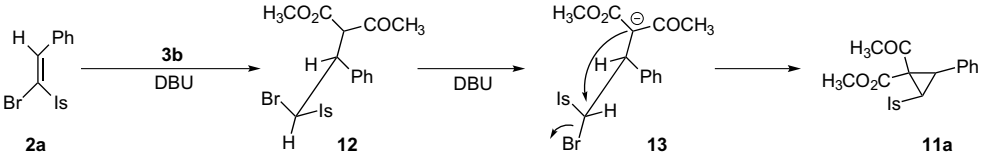
Table 3
Reaction of **2a** and **3b** using different solvents and bases

Entry	**3b** (equiv)	Base (equiv)	Solvent	% Yield of **10a** (trans/cis)	% Yield of **11a** (trans/cis)
1	1	DBU (1)	THF	25 (8:2)	19 (1:0)
2[a]	1	DBU (1)	MeOH	—	—
3[a]	1	DBU (1)	THF/MeOH	—	—
4[b]	1	Et_3N (10)	THF	—	—
5[a]	1	DBU (2)	THF	—	—
6	2	DBU (1)	THF	43 (8:2)	36 (1:0)
7	3	DBU (1)	THF	50 (8:2)	42 (1:0)
8	4	DBU (1)	THF	45 (8:2)	36 (1:0)
9	5	DBU (1)	THF	50 (8:2)	42 (1:0)
10	4	DBU (1)	EtOH	48 (2:8)	—
11	3	DBU (1)	THF anhydrous	50 (8:2)	42 (1:0)

[a] The reactant **2a** was consumed completely.
[b] The reactant **2a** was recovered.

The reaction of **2a** with an excess of **3b** in THF using 1 equiv of DBU as the base gave dihyrofuran **10a** and cyclopropane **11a** in moderate yields and with good to excellent stereoselectivity (Table 3, entries 6–9). It was interesting to observe a complete switch-over in the stereoselectivity of **10a** when the reaction of **2a** and **3b** was carried out in ethanol (Table 3, entry 10).

Since there was an interesting stereochemical outcome in the formation of **10a** using THF and ethanol as solvents (Table 3, compare entries 9 and 10), we considered to study the effect of solvent in this reaction. Compound **10a**, obtained using THF as a solvent (Table 3, entry 9), was treated with DBU in different solvents. The results are in given in Table 4. No change in the diastereomeric ratio was observed when **10a** (trans/cis=8:2) was treated with DBU in solvents like *n*-hexane, 1,4-dioxane, CH_3CN, DMSO, and 2-propanol (Table 4, entries 1–5). The reaction of **10a** (trans/cis=8:2) with DBU in methanol resulted in the enrichment of diastereoisomeric ratio (trans/cis=9.5:0.5) (Table 4, entry 6). Interestingly, compound **10a** (trans/cis=8:2) provided **10a** with inverted diastereoisomeric ratio (trans/cis=2:8) when reacted



Scheme 3. Proposed mechanism for the formation of **11a**.

Table 4
Reaction of **10a** with DBU (1 equiv) in different solvents

Entry	Starter (trans/cis)	Solvent	Product (trans/cis)
1	**10a** (8:2)	*n*-Hexane	**10a** (8:2)
2	**10a** (8:2)	1,4-Dioxane	**10a** (8:2)
3	**10a** (8:2)	CH_3CN	**10a** (8:2)
4	**10a** (8:2)	DMSO	**10a** (8:2)
5	**10a** (8:2)	2-Propanol	**10a** (8:2)
6	**10a** (8:2)	Methanol	**10a** (9.5:0.5)
7	**10a** (8:2)	EtOH	**10a** (2:8)

with DBU in ethanol (Table 4, entry 7). This could be explained considering that: (i) *trans*-**10a** and *cis*-**10a** possess different thermodynamic stability in different media; (ii) *trans*-**10a** and *cis*-**10a** are in thermodynamic equilibrium under the experimental conditions used. This was demonstrated by submitting a sample containing cis-enriched **10a** (trans/cis=2:8) to reaction with DBU in methanol. This reaction gave trans-enriched **10a** (trans/cis=9.5:0.5) providing a rationale for the interconversion of *trans*-**10a to** *cis*-**10a**.

We have next studied the reaction of different bromo styrylisoxazoles **2a–f** with methyl acetoacetate **3b** (Table 5). The reaction of **2a–d** and methyl acetoacetate furnished dihydrofurans **10a–d** in moderate yields and with good diastereoselection. Cyclopropanes **11a–f** were also obtained in moderate yields and with excellent diastereoselectivity (Table 5, entries 1–4). The relative stereochemistry for cyclopropanes was assigned based on the single crystal X-ray structure analysis of **11b**[24] and **11f**[25] (Figs. 5 and 6). The reaction of **2e**, having a 2-pyridyl group, gave cyclopropane **11e**, exclusively (Table 5, entry 5). The reaction of **2f**, containing a 2-(5-bromothiophenyl) substituent, and **3b** gave dihydrofuran *trans*-**10f** exclusively (Table 5, entry 6). In this latter example, the presence of a large substituent provided a large difference in energy between *trans*-**10f** and *cis*-**10f** and the most thermodynamically stable *trans*-**10f** was formed exclusively.

In summary, we have described the preparation of a new polyfunctional scaffolds **2a–f** that has three electrophilic centers. The reactivity of **2a–f** toward dinucleophiles was then studied. Reaction of **2a–f** with malonate was shown as an efficient means to prepare cyclopropanes *trans*-**7a–e** in high yields. The reaction of **2a–f** with methyl acetoacetate allowed the preparation of dihydrofurans **10a–f** and cyclopropanes **11a–f** in moderate yields. Cyclopropanes **11a–f** with three chiral centers were obtained as a single diastereoisomer. Considering the reactivity of cyclopropanes, dihydrofurans, and 4-nitro-isoxazoles it is easy to envisage the potential of compounds **7** and **10**,**11** in organic synthesis.

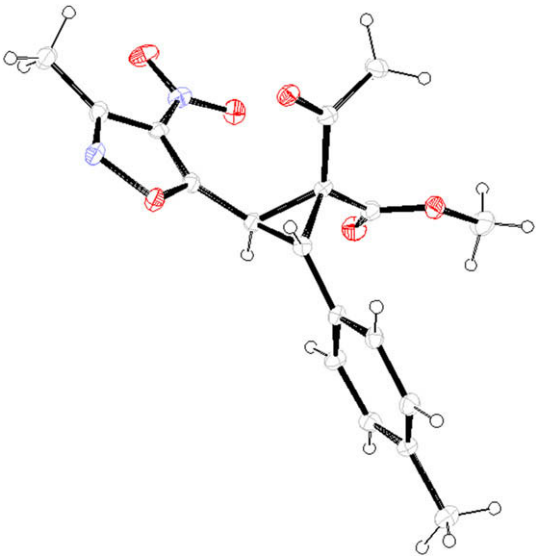


Figure 5. ORTEP representation of crystal structure of dihydrofuran **11b**; only one of the two enantiomers was shown for clarity (thermal ellipsoids are drawn at 30% probability).

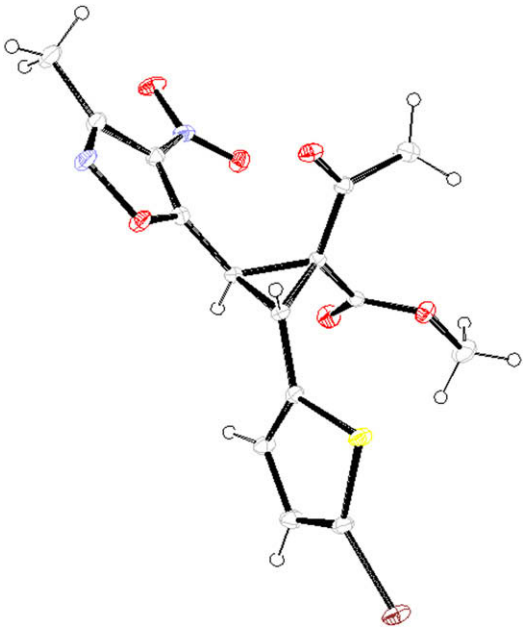
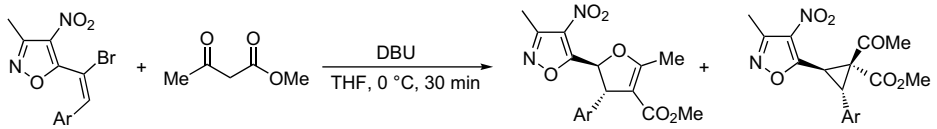


Figure 6. ORTEP representation of crystal structure of dihydrofuran **11f**; only one of the two enantiomers was shown for clarity (thermal ellipsoids are drawn at 30% probability).

Table 5
Reaction of **2a–f** and methyl acetoacetate **3b**



2a-f **3b** **10a-f** **11a-f**

Entry	Ar	% Yield of **10** (trans/cis)	% Yield of **11**
1	C_6H_5	**10a**, 50 (8:2)	**11a**, 42
2	*p*-MeC_6H_4	**10b**, 45 (8:2)	**11b**, 29
3	*p*-$MeOC_6H_4$	**10c**, 56 (8:2)	**11c**, 35
4	*p*-ClC_6H_4	**10d**, 40 (8:2)	**11d**, 36
5	2-Pyridyl	**10e**, —	**11e**, 50
6	2-(5-Bromothiophenyl)	**10f**, 10 (1:0)	**11f**, 10

3. Experimental section

3.1. General experimental

^{1}H and ^{13}C NMR Spectra were recorded on a 200 or a 400 MHz spectrometer at ambient temperatures. ^{1}H NMR spectral assignments are supported by ^{1}H–^{1}H COSY and ^{13}C–^{1}H COSY where necessary. For ^{1}H 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 wavenumbers (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. Elemental analysis was carried out using a CE440 Elemental Analyser purchased from Exeter Analytical (UK) Ltd. 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 aluminum 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. Typical experimental procedure for the preparation of 2a–f

A suspension of styrylisoxazoles **1a**–**f** (4 mmol) in cyclohexane (40 mL) was heated to reflux with a heat gun until a homogeneous solution was observed. Bromine (4 mmol, 640 mg) was added drop wise and the mixture was slowly cooled down to room temperature and stirred for 30 min. The solution was quenched with 10% aqueous $Na_2S_2O_3$ solution (40 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude dibromides **6a**–**f** thus obtained were used in the next reaction without further purification. Dibromides **6a**–**f** (4 mmol) were taken in toluene (40 mL) and added Et_3N (20 mmol, 4.2 mL) at room temperature. The reaction mixture was stirred at rt for 8 h. After this time toluene was removed under reduced pressure. The crude was diluted with dichloromethane (30 mL) and it was washed with 3 N HCl (10 mL), water (20 mL), and brine (10 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give products **2a**–**f**.

3.2.1. 5-(1-Bromo-2-phenyl-vinyl)-3-methyl-4-nitro-isoxazole ***2a***

Yellow solid, 1.39 g, 90% yield, mp 192–195 °C (methanol), R_f=0.37 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 3010 w, 2928 w, 2870 w, 1561 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (Ar–H, m, 2H), 7.66 (Ar–C*H*, s, 1H), 7.40 (Ar–H, m, 3H), 2.54 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 167.0, 156.4, 141.3, 133.3, 131.1, 130.6, 130.0, 128.6, 101.3, 11.9. Anal. Calcd for $C_{12}H_9BrN_2O_3$: C 47.23%, H 2.93%, N 9.06%. Found: C 47.05%, H 3.04%, N 8.95%.

3.2.2. 5-(1-Bromo-2-p-tolyl-vinyl)-3-methyl-4-nitro-isoxazole ***2b***

Yellow solid, 0.73 g, 45% yield, mp 178–180 °C (methanol), R_f=0.30 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 3011 w, 2928 w, 2870 w, 1557 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (Ar–H, d, 2H, J=8.0 Hz), 7.64 (Ar–C*H*, s, 1H), 7.20 (Ar–H, d, 2H, J=8.0 Hz), 2.53 (Is–CH_3, s, 3H), 2.34 (Ar–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 167.15, 156.45, 141.31, 141.24, 131.0, 130.50, 130.11, 129.36, 100.14, 21.64, 11.88. Anal. Calcd for $C_{13}H_{11}BrN_2O_3$: C 48.32%, H 3.43%, N 8.67%. Found: C 48.44%, H 3.61%, N 8.48%.

3.2.3. 5-[1-Bromo-2-(4-methoxy-phenyl)-vinyl]-3-methyl-4-nitro-isoxazole ***2c***

Yellow solid, mp 169–174 °C (methanol), 1.54 g, 95% yield, R_f=0.36 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 3015 w, 2928 w, 2872 w, 1600 s, 1563 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (Ar–H, d, 2H, J=9.0 Hz), 7.64 (Ar–CH, s, 1H), 6.92 (Ar–H, d, 2H, J=9.0 Hz), 3.81 (Ar–OCH_3, s, 3H), 2.53 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 167.8, 161.5, 156.5, 140.9, 132.2, 130.9, 125.9, 114.9, 99.1, 55.5, 11.9. Anal. Calcd for $C_{13}H_{11}BrN_2O_4$: C 46.04%, H 3.27%, N 8.26%. Found: C 46.19%, H 3.31%, N 8.09%.

3.2.4. 5-[1-Bromo-2-(4-chloro-phenyl)-vinyl]-3-methyl-4-nitro-isoxazole ***2d***

Yellow solid, mp 189–192 °C (methanol), 1.53 g, 89% yield, R_f=0.31 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 2998 w, 2928 w, 2872 w, 1540 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (Ar–H, d, 2H, J=8.8 Hz), 7.61 (Ar–C*H*, s, 1H), 7.38 (Ar–H, d, 2H, J=8.8 Hz), 2.54 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 166.7, 156.5, 140.0, 136.6, 131.7, 131.2, 130.8, 129.0, 102.1, 11.8. Anal. Calcd for $C_{12}H_8BrClN_2O_3$: C 41.95%, H 2.35%, N 8.15%. Found: C 41.76%, H 2.19%, N 8.32%.

3.2.5. 2-[2-Bromo-2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-pyridine ***2e***

Dark green solid, mp 201–202 °C (methanol), 1.36 g, 88% yield, R_f=0.24 (petroleum ether/EtOAc, 75:25); IR (KBr)/cm^{-1}: 2999 w, 2938 w, 2870 w, 1554 s; ^{1}H NMR (400 MHz, $CDCl_3$): 8.66 (Py–H, m, 1H), 8.04 (Py–H, d, 1H, J=8.0 Hz), 7.78 (Py–H, m, 1H), 7.75 (Py–C*H*, s, 1H), 7.30 (Py–H, m, 1H), 2.55 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 166.5, 156.4, 152.1, 149.8, 140.5, 136.6, 130.5, 125.0, 124.4, 104.4, 11.8; HRMS: m/z found $[M+H]^+$ 309.9837, $C_{11}H_9BrN_3O_3$ requires 309.9827, m/z: 309 (100%, $[M+H]^+$). Anal. Calcd for $C_{11}H_8BrN_3O_3$: C 42.60%, H 2.60%, N 13.55%. Found: C 42.79%, H 2.65%, N 13.35%.

3.2.6. 5-[1-Bromo-2-(5-bromothiophen-2-yl)-vinyl]-3-methyl-4-nitro-isoxazole ***2f***

Brown solid, mp 158–160 °C (methanol), 1.67 g, 85% yield, R_f=0.30 (petroleum ether/EtOAc, 90:10); IR (KBr)/cm^{-1}: 3010 w, 2930 w, 2852 w, 1533 s; ^{1}H NMR (400 MHz, $CDCl_3$): 8.07 (Thiop–CH, s, 1H), 7.22 (Thiop–H, d, 1H, J_1=3.6 Hz), 7.10 (Thiop–H, d, 1H, J=3.6 Hz), 2.52 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 165.8, 156.9, 138.6, 135.8, 134.8, 131.1, 130.1, 120.2, 99.0, 12.0. Anal. Calcd for $C_{10}H_6Br_2N_2O_3S$: C 30.48%, H 1.53%, N 7.11%. Found: C 30.28%, H 1.61%, N 7.23%.

3.3. Experimental procedure for the reaction of 2a–f and dimethyl malonate

Isoxazoles **2a**–**f** (0.5 mmol) and dimethyl malonate (1.5 mmol) were taken in THF (5 mL) and added DBU (1.5 mmol) drop wise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then the reaction mixture was diluted with EtOAc (10 mL) and washed with 3 N HCl (5 mL), water (10 mL), and brine (5 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give a crude oil. The excess dimethyl malonate was removed under high vacuum to obtain the product cyclopropanes **7a**–**f** in pure form without need of column chromatography.

3.3.1. 2-(3-Methyl-4-nitro-isoxazol-5-yl)-3-phenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester ***7a***

Yellow oil, 158 mg, 88% yield, R_f=0.1 (petroleum ether/EtOAc, 95:5); IR (neat)/cm^{-1}: 2999 w, 2955 w, 2875 w, 1749 s, 1550 s; ^{1}H

NMR (400 MHz, $CDCl_3$): 7.25 (Ar–H, m, 5H), 4.19 (Is–CH, d, 1H, J=8.4 Hz), 3.89 (Ar–CH, d, 1H, J=8.4 Hz), 3.67 (CO_2CH_3, s, 3H), 3.43 (CO_2CH_3, s, 3H), 2.51 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 167.57, 165.25, 163.94, 154.99, 131.03, 130.5, 127.56, 127.44, 127.25, 52.48, 52.05, 43.81, 35.28, 25.25, 10.59; HRMS: m/z found $[M+Na]^+$ 383.0858, $C_{17}H_{16}N_2O_7Na$ requires 383.0855, m/z: 383 (100%, $[M+Na]^+$).

3.3.2. 2-(3-Methyl-4-nitro-isoxazol-5-yl)-3-p-tolyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester ***7b***

Yellow oil, 183 mg, 98% yield, R_f=0.1 (petroleum ether/EtOAc, 95:5); IR (neat)/cm^{-1}: 3003 w, 2985 w, 2873 w, 1735 s, 1546 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.12 (Ar–H, d, 2H, J=8.4 Hz), 7.06 (Ar–H, d, 2H, J=8.0 Hz), 4.16 (Is–CH, d, 1H, J=8.4 Hz), 3.85 (Ar–CH, d, 1H, J=8.0 Hz), 3.66 (CO_2CH_3, s, 3H), 3.45 (CO_2CH_3, s, 3H), 2.50 (Is–CH_3, s, 3H), 2.25 (Ar–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 167.7, 165.3, 164.0, 155.0, 137.0, 130.7, 128.2, 127.9, 127.3, 52.4, 52.1, 43.8, 35.1, 25.3, 20.1, 10.6; HRMS: m/z found $[M+Na]^+$ 397.0996, $C_{18}H_{18}N_2O_7Na$ requires 397.1012, m/z: 397 (100%, $[M+Na]^+$).

3.3.3. 2-(4-Methoxy-phenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester ***7c***

Yellow oil, 180 mg, 92% yield, R_f=0.1 (petroleum ether/EtOAc, 75:25); IR (neat)/cm^{-1}: 2999 w, 2954 w, 1750 s, 1558 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (Ar–H, d, 2H, J=8.0 Hz), 6.78 (Ar–H, d, 2H, J=8.0 Hz), 4.14 (Is–CH, d, 1H, J=8.4 Hz), 3.83 (Ar–CH, d, 1H, J=8.4 Hz), 3.72 (CO_2CH_3, s, 3H), 3.66 (CO_2CH_3, s, 3H), 3.46 (Ar–OCH_3, s, 3H), 2.50 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 168.8, 166.4, 165.1, 159.5, 156.0, 131.0, 129.6, 123.9, 114.0, 55.3, 53.5, 53.1, 44.9, 35.9, 26.4, 11.6; HRMS: m/z found $[M+Na]^+$ 413.0959, $C_{18}H_{18}N_2O_8Na$ requires 413.0961, m/z: 413 (100%, $[M+Na]^+$).

3.3.4. 2-(4-Chloro-phenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester ***7d***

Yellow oil, 154 mg, 78% yield, R_f=0.1 (petroleum ether/EtOAc, 75:25); IR (neat)/cm^{-1}: 3001 w, 2954 w, 2865 w, 1749 s, 1560 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.21 (Ar–H, m, 5H), 4.14 (Is–CH, d, 1H, J=8.0 Hz), 3.82 (Ar–CH, d, 1H, J=8.0 Hz), 3.66 (CO_2CH_3, s, 3H), 3.47 (CO_2CH_3, s, 3H), 2.49 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 168.21, 166.04, 164.82, 156.04, 134.24, 131.91, 130.67, 129.91, 128.80, 53.56, 53.24, 44.70, 35.56, 26.33, 11.56; HRMS: m/z found $[M+Na]^+$ 417.0454, $C_{17}H_{15}ClN_2O_7Na$ requires 417.0465, m/z: 417 (100%, $[M+Na]^+$).

3.3.5. 2-(3-Methyl-4-nitro-isoxazol-5-yl)-3-pyridin-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester ***7e***

Yellow oil, 126 mg, 70% yield, R_f=0.2 (petroleum ether/EtOAc, 75:25); IR (neat)/cm^{-1}: 2990 w, 2985 w, 2880 w, 1740 s, 1544 s; ^{1}H NMR (400 MHz, $CDCl_3$): 8.41 (Py–H, m, 1H), 7.62 (Py–H, m, 1H), 7.38 (Py–H, d, 1H, J=7.6 Hz), 7.14 (Py–H, m, 1H), 4.22 (Is–CH, d, 1H, J=7.6 Hz), 3.75 (Py–CH, d, 1H, J=7.6 Hz), 3.65 (CO_2CH_3, s, 3H), 3.57 (CO_2CH_3, s, 3H), 2.50 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 168.4, 166.7, 165.2, 156.0, 152.5, 149.2, 136.7, 130.1, 124.4, 122.8, 53.6, 53.0, 44.4, 36.3, 27.4, 11.7; HRMS: m/z found $[M+H^+]$ 362.0982, $C_{16}H_{16}N_3O_7$ requires 362.0988, m/z: 362 (100%, $[M+H^+]$).

3.4. Experimental procedure for the reaction of 2a–f and methyl acetoacetate 3b

Isoxazoles **2a–f** (1 mmol) and methyl acetoacetate **3b** (3 mmol) were taken in THF (10 mL) and added DBU (1 mmol) drop wise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then the reaction mixture was diluted with EtOAc (20 mL) and washed with 3 N HCl (10 mL), water (20 mL), and brine (10 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the crude. The crude was subjected to column chromatography on silica gel using a mixture of petroleum ether and EtOAc (9:1) as an eluent to obtain dihyrofurans **10a–f** and cyclopropanes **11a–f**.

3.4.1. 2-Methyl-5-(3-methyl-4-nitro-isoxazol-5-yl)-4-phenyl-4,5-dihydrofuran-3-carboxylic acid methyl ester ***10a***

Pale yellow solid, 86 mg, 50% yield, R_f=0.2 (petroleum ether /EtOAc, 95:5); IR (KBr)/cm^{-1}: 2971 w, 2878 w, 1725 s, 1534 s; for trans isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (Ar–H, m, 5H), 5.99 (Is–CH, d, 1H, J=4.0 Hz), 4.39 (Ar–CH, m, 1H), 3.51 (CO_2CH_3, s, 3H), 2.54 (Is–CH_3, s, 3H), 2.38 (CH_3–C–O, s, 3H); ^{13}C NMR (100.6 MHz): 170.6, 168.3, 164.9, 156.0, 141.0, 130.2, 128.9, 127.8, 127.1, 107.1, 82.0, 54.1, 51.2, 14.0, 11.5; for cis isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.03 (Ar–H, m, 3H), 6.87 (Ar–H, m, 2H), 6.39 (Is–CH, d, 1H, J=8.8 Hz), 4.90 (Ar–CH, d, 1H, J=8.8 Hz), 3.49 (CO_2CH_3, s, 3H), 2.42 (Is–CH_3, s, 3H), 2.22 (CH_3–C–O, s, 3H); ^{13}C NMR (100.6 MHz): 170.0, 155.1, 130.9, 128.4, 81.4, 52.6, 22.7, 11.0; HRMS: m/z found $[M+Na]^+$ 367.0911, $C_{17}H_{16}N_2O_6Na$ requires 367.0906, m/z: 367 (100%, $[M+Na]^+$).

3.4.2. 1-Acetyl-2-(3-methyl-4-nitro-isoxazol-5-yl)-3-phenyl-cyclopropanecarboxylic acid methyl ester ***11a***

Pale yellow solid, mp 125 °C (methanol), 72 mg, 42% yield, R_f=0.1 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 2962 w, 2882 w, 1737 w, 1712 s, 1551 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.19–7.27 (Ar–H, m, 5H), 4.04 (Is–CH, d, 1H, J=8.0 Hz), 3.95 (Ar–CH, d, 1H, J=8.0 Hz), 3.43 (CO_2CH_3, s, 3H), 2.50 (Is–CH_3, s, 3H), 2.33 ($COCH_3$, s, 3H); ^{13}C NMR (100.6 MHz): 198.6, 168.9, 166.4, 155.9, 132.5, 131.0, 128.6, 128.5, 128.3, 52.8, 50.3, 36.9, 29.8, 28.5, 11.6; HRMS: m/z found $[M+Na]^+$ 367.0900, $C_{17}H_{16}N_2O_6Na$ requires 367.0906, m/z: 367 (100%, $[M+Na]^+$).

3.4.3. 2-Methyl-5-(3-methyl-4-nitro-isoxazol-5-yl)-4-p-tolyl-4,5-dihydrofuran-3-carboxylic acid methyl ester ***10b***

Yellow solid, 81 mg, 45% yield, R_f=0.2 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 2987 w, 2859 w, 1731 s, 1544 s; for trans isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.08 (Ar–H, m, 4H), 5.97 (Is–CH, d, 1H, J=4.0 Hz), 4.36 (Ar–CH, m, 1H), 3.51 (CO_2CH_3, s, 3H), 2.53 (Is–CH_3, s, 3H), 2.37 (CH_3–C–O, s, 3H), 2.27 (Ar–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 170.8, 168.2, 165.0, 156.0, 138.1, 137.5, 130.6, 129.6, 127.0, 107.1, 82.1, 53.8, 51.2, 21.2, 14.0, 11.5; for cis isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 6.84 (Ar–H, d, 2H, J=8.0 Hz), 6.76 (Ar–H, d, 2H, J=8.0 Hz), 6.37 (Is–CH, d, 1H, J=10.0 Hz), 4.87 (Ar–CH, dd, 1H, J_1=10.0 Hz, J_2=1.2 Hz), 3.50 (CO_2CH_3, s, 3H), 2.41 (Is–CH_3, s, 3H), 2.25 (CH_3–C–O, s, 3H), 2.13 (Ar–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 170.1, 129.1, 81.5, 52.2, 11.1; HRMS: m/z found $[M+Na]^+$ 381.1053, $C_{18}H_{18}N_2O_6Na$ requires 381.1063, m/z: 381 (100%, $[M+Na]^+$).

3.4.4. 1-Acetyl-2-(3-methyl-4-nitro-isoxazol-5-yl)-3-p-tolyl-cyclopropanecarboxylic acid methyl ester ***11b***

Pale yellow solid, mp 115 °C (methanol), 52 mg, 29% yield, R_f=0.1 (petroleum ether/EtOAc, 95:5); IR (neat)/cm^{-1}: 2962 w, 2927 w, 2842 w, 1750 s, 1705 s, 1554 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (Ar–H, m, 4H), 4.10 (Is–CH, d, 1H, J=8.4 Hz), 4.00 (Ar–CH, d, 1H, J=8.4 Hz), 3.55 (CO_2CH_3, s, 3H), 2.59 (Is–CH_3, s, 3H), 2.42 ($COCH_3$, s, 3H), 2.36 (Ar–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 198.7, 169.0, 166.5, 155.9, 138.1, 130.4, 129.3, 128.4, 52.9, 50.3, 36.9, 29.8, 28.5, 21.2, 11.6; HRMS: m/z found $[M+Na]^+$ 381.1045, $C_{18}H_{18}N_2O_6Na$ requires 381.1063, m/z: 381 (100%, $[M+Na]^+$).

3.4.5. 4-(4-Methoxy-phenyl)-2-methyl-5-(3-methyl-4-nitro-isoxazol-5-yl)-4,5-dihydrofuran-3-carboxylic acid methyl ester ***10c***

Pale yellow solid, 96 mg, 56% yield, R_f=0.3 (petroleum ether /EtOAc, 95:5); IR (KBr)/cm^{-1}: 2977 w, 2858 w, 1717 s, 1549 s; for trans isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (Ar–H, d, 2H, J=8.8 Hz), 6.90 (Ar–H, d, 2H, J=8.8 Hz), 6.05 (Is–CH, d, 1H, J=4.0 Hz),

4.44 (Ar–CH, d, 1H, J=4.0 Hz), 3.82 (Ar–OCH_3, s, 3H), 3.60 (CO_2CH_3, s, 3H), 2.62 (Is–CH_3, s, 3H), 2.46 (CH_3–C–O, s, 3H); ^{13}C NMR (100.6 MHz): 170.8, 168.1, 165.0, 159.1, 156.0, 133.2, 130.4, 128.2, 114.2, 107.2, 82.2, 55.3, 53.5, 51.2, 14.0, 11.5; for cis isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (Ar–H, d, 2H, J=8.8 Hz), 6.66 (Ar–H, d, 2H, J=8.8 Hz), 6.45 (Is–CH, d, 1H, J=10.4 Hz), 4.96 (Ar–CH, d, 1H, J=10.4 Hz), 3.72 (Ar–OCH_3, s, 3H), 3.59 (CO_2CH_3, s, 3H), 2.50 (Is–CH_3, s, 3H), 2.35 (CH_3–C–O, s, 3H); HRMS: m/z found $[M+Na]^+$ 397.1017, $C_{18}H_{18}N_2O_7Na$ requires 397.1012, m/z: 397 (100%, $[M+Na]^+$).

3.4.6. 1-Acetyl-2-(4-methoxy-phenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)-cyclopropanecarboxylic acid methyl ester **11c**

Yellow oil, 60 mg, 35% yield, R_f=0.2 (petroleum ether/EtOAc, 95:5); IR (neat)/cm^{-1}: 2986 w, 2883 w, 1747 s, 1710 s, 1560 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.12 (Ar–H, d, 2H, J=8.4 Hz), 6.79 (Ar–H, d, 2H, J=8.4 Hz), 3.99 (Is–CH, d, 1H, J=8.4 Hz), 3.91 (Ar–CH, d, 1H, J=8.4 Hz), 3.73 (Ar–OCH_3, s, 3H), 3.47 (CO_2CH_3, s, 3H), 2.50 (Is–CH_3, s, 3H), 2.33 ($COCH_3$, s, 3H); ^{13}C NMR (100.6 MHz): 198.8, 169.0, 166.5, 159.5, 155.9, 130.2, 129.7, 124.3, 114.0, 55.3, 52.9, 50.4, 36.7, 29.8, 28.7, 11.6; HRMS: m/z found $[M+Na]^+$ 397.1016, $C_{18}H_{18}N_2O_7Na$ requires 397.1012, m/z: 397 (100%, $[M+Na]^+$).

3.4.7. 4-(4-Chloro-phenyl)-2-methyl-5-(3-methyl-4-nitro-isoxazol-5-yl)-4,5-dihydrofuran-3-carboxylic acid methyl ester **10d**

Pale yellow solid, 69 mg, 40%, R_f=0.3 (petroleum ether/EtOAc, 95:5); IR (KBr)/cm^{-1}: 2998 w, 2838 w, 1730 s, 1550 s; for trans isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.25 (Ar–H, d, 2H, J=8.4), 7.13 (Ar–H, d, 2H, J=8.4 Hz), 5.95 (Is–CH, d, 1H, J=4.0 Hz), 4.36 (Ar–CH, m, 1H), 3.51 (CO_2CH_3, s, 3H), 2.53 (Is–CH_3, s, 3H), 2.38 (CH_3–C–O, s, 3H); ^{13}C NMR (100.6 MHz): 170.5, 168.6, 164.7, 156.0, 139.6, 133.6, 130.6, 129.1, 128.6, 106.9, 81.9, 53.7, 51.3, 14.0, 11.5; for cis isomer: ^{1}H NMR (400 MHz, $CDCl_3$):7.03 (Ar–H, d, 2H, J=8.4 Hz), 6.84 (Ar–H, d, 2H, J=8.4 Hz), 6.38 (Is–CH, d, 1H, J=10.4 Hz), 4.89 (Ar–CH, d, 1H, J=10.4 Hz), 3.50 (CO_2CH_3, s, 3H), 2.41 (Is–CH_3, s, 3H), 2.28 (CH_3–C–O, s, 3H); HRMS: m/z found $[M+Na]^+$ 401.0526, $C_{17}H_{15}ClN_2O_6Na$ requires 401.0516, m/z: 401 (100%, $[M+Na]^+$).

3.4.8. 1-Acetyl-2-(4-chloro-phenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)-cyclopropanecarboxylic acid methyl ester **11d**

Yellow oil, 61 mg, 36% yield, R_f=0.1 (petroleum ether/EtOAc, 95:5); IR (neat)/cm^{-1}: 2995 w, 2882 w, 1739 s, 1705 s, 1559 s; ^{1}H NMR (400 MHz, $CDCl_3$): 7.25 (Ar–H, d, 2H, J=8.4 Hz), 7.15 (Ar–H, d, 2H, J=8.4 Hz), 4.00 (Is–CH, d, 1H, J=8.4 Hz), 3.90 (Ar–CH, d, 1H, J=8.4 Hz), 3.84 (CO_2CH_3, s, 3H), 2.32 (Is–CH_3, s, 3H); ^{13}C NMR (100.6 MHz): 198.3, 168.4, 166.2, 155.9, 134.3, 131.0, 130.2, 128.8, 81.9, 53.0, 50.2, 36.0, 28.5, 11.6; HRMS: m/z found $[M+Na]^+$ 401.0522, $C_{17}H_{15}ClN_2O_6Na$ requires 401.0516, m/z: 401 (100%, $[M+Na]^+$).

3.4.9. 1-Acetyl-2-(3-methyl-4-nitro-isoxazol-5-yl)-3-pyridin-2-yl-cyclopropanecarboxylic acid methyl ester **11e**

Yellow oil, 87 mg, 50% yield, R_f=0.2 (petroleum ether/EtOAc, 95:5); IR (neat)/cm^{-1}: 2992 w, 2877 w, 1750 s, 1720 s, 1558 s; ^{1}H NMR (400 MHz, $CDCl_3$): 8.41 (Py–H, m, 1H), 7.31 (Py–H, m, 1H), 7.35 (Py–H, d, 1H, J=7.6 Hz), 7.14 (Py–H, m, 1H), 4.12 (Is–CH, d, 1H, J=7.6 Hz), 3.77 (Py–CH, d, 1H, J=7.6 Hz), 3.61 (CO_2CH_3, s, 3H), 2.49 (Is–CH_3, s, 3H), 2.30 ($COCH_3$, s, 3H); ^{13}C NMR (100.6 MHz): 198.6, 167.1, 155.8, 152.9, 149.2, 136.7, 130.9, 124.5, 122.8, 53.0, 37.3, 29.4, 29.3, 14.1, 11.6; HRMS: m/z found $[M+H]^+$ 346.1037, $C_{16}H_{16}N_3O_6$ requires 346.1039, m/z: 346 (100%, $[M+H]^+$).

3.4.10. 4-(5-Bromothiophen-2-yl)-2-methyl-5-(3-methyl-4-nitro-isoxazol-5-yl)-4,5-dihydrofuran-3-carboxylic acid methyl ester **10f**

Yellow solid, mp 129–130 °C (ethanol), 21 mg, 10% yield, R_f=0.2 (petroleum ether/EtOAc, 90:10); IR (KBr)/cm^{-1}: 3001 w, 2854 w, 1719 s, 1546 s; ^{1}H NMR (400 MHz, $CDCl_3$): 6.87 (Thiop–H, d, 1H, J=3.6 Hz), 6.71 (Thiop–H, dd, 1H, J_1=3.6 Hz, J_2=0.4 Hz), 6.01 (Is–CH, d, 1H, J=3.2 Hz), 4.59 (Thiop–CH, m, 1H), 3.59 (CO_2CH_3, s, 3H), 2.54 (Is–CH_3, s, 3H), 2.37 (CH_3–C–O, s, 3H); ^{13}C NMR (100.6 MHz): 170.1, 169.4, 164.5, 156.1, 145.9, 130.6, 130.1, 125.5, 111.6, 106.1, 81.9, 51.4, 49.9, 14.1, 11.4. Anal. Calcd for $C_{15}H_{13}BrN_2O_6S$: C 41.97%, H 3.05%, N 6.53%. Found: C 42.19%, H 3.19%, N 6.39%.

3.4.11. 1-Acetyl-2-(5-bromothiophen-2-yl)-3-(3-methyl-4-nitro-isoxazol-5-yl)-cyclopropanecarboxylic acid methyl ester **11f**

Yellow solid mp 114–116 °C (methanol), 21 mg, 10% yield, R_f=0.2, (petroleum ether/EtOAc, 90:10); IR (neat)/cm^{-1}: 3020 w, 2869 w, 1741 s, 1715 s, 1553 s; ^{1}H NMR (400 MHz, $CDCl_3$): 6.85 (Thiop–H, d, 1H, J=3.6 Hz), 6.68 (Thiop–H, d, 1H, J=3.6 Hz), 3.92 (Is–CH, d, 1H, J=8.0 Hz), 3.87 (Thiop–CH, d, 1H, J=8.0 Hz), 3.64 (CO_2CH_3, s, 3H), 2.50 (Is–CH_3, s, 3H), 2.33 ($COCH_3$, s, 3H); ^{13}C NMR (100.6 MHz): 197.9, 167.8, 166.0, 156.0, 136.7, 130.6, 129.9, 127.9, 112.5, 53.4, 50.4, 31.7, 29.8, 29.7, 11.6. Anal. Calcd for $C_{15}H_{13}BrN_2O_6S$: C 41.97%, H 3.05%, N 6.53%. Found: C 42.12%, H 3.21%, N 6.29%.

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References and notes

1. (a) Adamo, M. F. A.; Chimichi, S.; De Sio, F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron Lett.* **2002**, *43*, 4157; (b) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *J. Org. Chem.* **2005**, *70*, 8395.
2. Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157.
3. Adamo, M. F. A.; Konda, V. R. *Org. Lett.* **2007**, *9*, 303.
4. Adamo, M. F. A.; Duffy, E. F.; Konda, V. R.; Murphy, F. *Heterocycles* **2007**, *71*, 1173 and references cited therein.
5. Adamo, M. F. A.; Duffy, E. F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2047.
6. Adamo, M. F. A.; Duffy, E. F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2684.
7. Adamo, M. F. A.; Nagabelli, M. *Tetrahedron Lett.* **2007**, *48*, 4703.
8. Adamo, M. F. A.; Konda, V. R.; Donati, D.; Sarti-Fantoni, P.; Torroba, T. *Tetrahedron* **2007**, *63*, 9741.
9. Adamo, M. F. A.; Konda, V. R. *Tetrahedron Lett.* **2008**, *49*, 6224.
10. Adamo, M. F. A.; Bruschi, S.; Suresh, S.; Piras, L. *Tetrahedron Lett.* **2008**, *49*, 7406.
11. Sarti-Fantoni, P.; Donati, D.; De Sio, F.; Moneti, G. *J. Heterocycl. Chem.* **1980**, *17*, 1643; Baracchi, A.; Chimichi, S.; De Sio, F.; Donati, D.; Nesi, R.; Sarti-Fantoni, P.; Torroba, T. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 487.
12. (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (b) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.
13. Barbero, A.; Pulido, F. J. *Synthesis* **2004**, 401.
14. (a) Churykau, D. H.; Zinovich, V. G.; Kulinkovich, O. G. *Synlett* **2004**, 1949; (b) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587.
15. Li, C. S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565.
16. (a) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877; (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Guarneri, M.; Manfredini, S.; Pillini, G. P.; Simoni, D. *Tetrahedron Lett.* **1985**, *26*, 5319.
17. Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. *Tetrahedron* **1997**, *53*.
18. (a) Nesi, R.; Turchi, S.; Giomi, D. *J. Org. Chem.* **1996**, *61*, 7933; (b) Nesi, R.; Giomi, D.; Turchi, S. *J. Org. Chem.* **1998**, *63*, 6050.
19. Adamo, M. F. A.; Nagabelli, M. *Org. Lett.* **2008**, *10*, 1807.
20. Baracchi, A.; Chimichi, S.; De Sio, F.; Donati, D.; Nesi, R.; Sarti-Fantoni, P.; Torroba, T. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 487.
21. Data deposited at the Cambridge Crystallographic Data Centre, CCDC 715687.
22. (a) Hamelin, J.; Saoudi, A.; Benhaoua, H. *Synthesis* **2003**, 2185; (b) Concelln, J. M.; Huerta, M. *J. Org. Chem.* **2005**, *70*, 4714; (c) Shishido, Y.; Ito, F.; Morita, H.; Ikunaka, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6887.
23. Data deposited at the Cambridge Crystallographic Data Centre, CCDC 715688.
24. Data deposited at the Cambridge Crystallographic Data Centre, CCDC 715689.
25. Data deposited at the Cambridge Crystallographic Data Centre, CCDC 715690.