DOI: 10.1002/ejoc.201000401

Ethyl α-Nitrocinnamates in the Synthesis of Highly Functionalized Isoxazoles

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Keywords: Nitrogen heterocycles / Michael addition / Alkylation / Multicomponent reactions

An effective method for the synthesis of highly functionalized isoxazoles from readily available starting ethyl α-nitrocinnamates has been developed. Ethyl α-nitrocinnamates react smoothly with α-nitro carbonyl compounds to produce isoxazoles in good yields. Michael addition of pyridinium ylides to ethyl α-nitrocinnamates can also produce these isoxazoles effectively. These pyridinium salts can be generated in situ from the corresponding alkyl bromides. The one-pot multicomponent process was also developed. Isoxazoles can be produced directly from readily available aromatic aldehydes, ethyl nitroacetate, and pyridinium salts.

Introduction

Isoxazoles have long been targeted in synthetic investigations for their known biological activities and pharmacological properties, which include antibacterial, COX-2 inhibitory, $GABA_A$ antagonist, antinociceptive, and anticancer activity.[1] The development of new and efficient methods for their syntheses remains an area of current interest, and many synthetic methods have been employed in the synthesis of isoxazoles including oximation of 1,3-dicarbonyl compounds or α,β-unsaturated compounds,[2] condensation of oxime dianions,[3] and cycloaddition of nitrile oxides to alkynes.[4] The reaction of activated acetylenes and alkyl nitroacetates in the presence of triphenylphosphane also provided isoxazoles.[5] Nitro compounds can be considered as versatile building blocks in organic synthesis, as both the activating effect of the nitro group and its facile transformation into various functionalities have extended the importance of nitro compounds in the preparation of complex molecules.[6] Although a number of methods are available as cited above, the search for newer methods for the synthesis of isoxazoles is continuously being pursued. Nitronate anions can be generated from α-nitro carbonyl compounds by using a wide range of bases and act as carbon nucleophiles with common electrophiles, including aldehydes and electron-poor alkenes, leading to carbon–carbon bond formation.[6a–6d] Ethyl α-nitrocinnamates are readily accessible from aromatic aldehydes and ethyl nitroacetate.[7] As part of our study on the development of new routes to heterocyclic systems,[8–10] we now report a new method for the synthesis of highly functionalized isoxazoles from ethyl α-nitrocinnamates.

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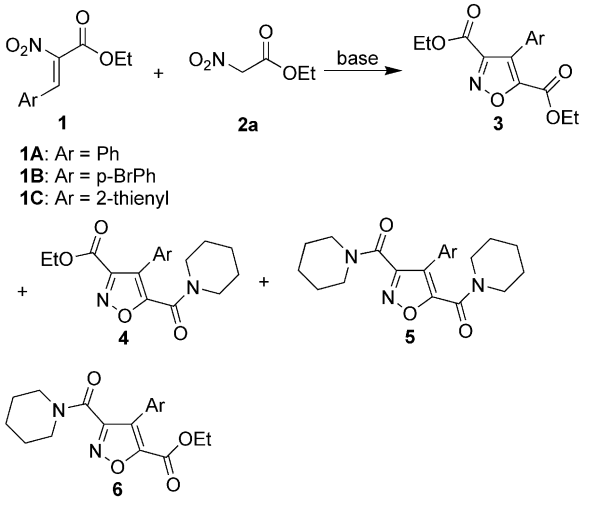
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000401.

Results and Discussion

The initial study started with the reaction between ethyl α-nitrocinnamate (**1A**, Ar = Ph) and ethyl nitroacetate (**2a**; Scheme 1). Treatment of **1A** with **2a** and triethylamine in acetonitrile at 60 °C furnished isoxazole **3Aa** exclusively in 93% yield (Table 1, Entry 1). The structure of **3Aa** was clearly assigned by ^1H NMR and ^{13}C NMR spectroscopy. A plausible reaction mechanism is shown in Scheme 2. Deprotonation of **2a** forms nitronate anion **7a** and then Michael addition of **7a** to **1A** afforded enolate anion **8Aa**. Intramolecular nucleophilic *O*-alkylation[11] of **10Aa** gave **11Aa**. Finally, isoxazoline *N*-oxide **11Aa** was converted into cycloadduct **3Aa** via *N*-hydroxy compound **12Aa** by elimination of H_2O (Scheme 2, path a). In this reaction, the formation of cyclopropane **9Aa** derived from intramolecular nucleophilic C-alkylation[12] of **8Aa** was not observed (Scheme 2, path b). In an attempt to investigate the range of solvents compatible with this reaction, ethyl α-nitrocinnamate (**1a**) and ethyl nitroacetate (**2a**) were chosen as model compounds, and this reaction was performed in various solvents. The results are summarized in Table 1 (Entries 2–4). A change in the solvent to chloroform, ethanol, and DME gave isoxazole **3Aa** in 88–65% yield. In chloroform and DME, the reaction proceeds at a much slower rate. Further studies showed that bases influenced strongly the reaction yields. As shown in Table 1, DABCO gave 60% yield of **3Aa**, and **3Aa** was not isolated when DBU was employed as the base (Table 1, Entries 5 and 6). With piperidine, instead of expected product **3Aa**, **4Aa** derived from the selective amidation of **3Aa** was obtained in 89% yield, and isomeric product **6Aa** was not isolated (Table 1, Entry 7). The reason for this interesting selective amidation is not clear. On the basis of these results, by choosing acetonitrile as solvent, triethylamine and piperidine as bases, the generalities of this reaction were examined with α-nitrocinnamates **1B** and **1C** (Table 1, Entries 8–11). The reaction worked well, and isoxazoles **3** and **4** were formed selectively

depending on the base used. The structure of **4** was revealed by ^{1}H NMR and ^{13}C NMR spectroscopy. In addition, the structure of **4Ba** was confirmed by single-crystal X-ray analysis (Figure 1).[13] Diamides **5** can be formed as the major products by prolonging the reaction time and increasing the amount of piperidine (Table 1, Entries 12–14). The best yield of **5** was obtain when the reaction was carried out by using piperidine (7 equiv.) at 60 °C for 56 h. As shown in Table 1 (Entries 13 and 14), under these conditions, diamides **5** were formed predominantly accompanying a small amount of **4**.



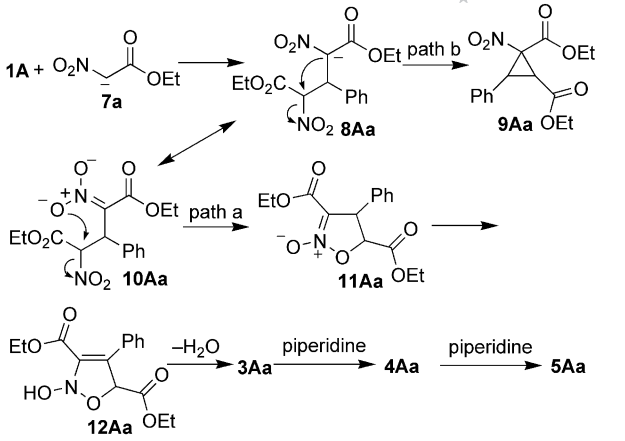
Scheme 1. Reactions with ethyl nitroacetate (**2a**).

Table 1. Reactions with ethyl nitroacetate (**2a**).

Entry	**1**	Solvent	Base	Time [h]	Product, % yield[a]
1	**1A**	CH_3CN	Et_3N[b]	4	**3Aa**, 93
2	**1A**	$CHCl_3$	Et_3N[b]	24	**3Aa**, 88
3	**1A**	EtOH	Et_3N[b]	4	**3Aa**, 74
4	**1A**	DME	Et_3N[b]	48	**3Aa**, 65
5	**1A**	CH_3CN	DABCO[b]	4	**3Aa**, 60
6	**1A**	CH_3CN	DBU[b]	4	**3Aa**, 0
7	**1A**	CH_3CN	piperidine[b]	4	**4Aa**, 89
8	**1B**	CH_3CN	Et_3N[b]	4	**3Ba**, 90
9	**1C**	CH_3CN	Et_3N[b]	4	**3Ca**, 75
10	**1B**	CH_3CN	piperidine[b]	4	**4Ba**, 87
11	**1C**	CH_3CN	piperidine[b]	4	**4Ca**, 76
12	**1A**	CH_3CN	piperidine[c]	56	**4Aa**, 28; **5Aa**, 53
13	**1A**	CH_3CN	piperidine[d]	56	**4Aa**, 12; **5Aa**, 75
14	**1B**	CH_3CN	piperidine[d]	56	**4Ba**, 8; **5Ba**, 75

[a] Isolated yield based on ethyl α-nitrocinnamates **1**. [b] 3 equiv. of base was used. [c] 5 equiv. of base was used. [d] 7 equiv. of base was used.

For the formation of isoxazoles **3** bearing a 5-keto group, the reaction between ethyl α-nitrocinnamates **1** and α-nitroacetophenone (**2b**) was also studied (Scheme 3). Treatment of **1A** with **2b** and triethylamine in acetonitrile at 60 °C furnished isoxazole **3Ab** in 76% yield (Table 2, Entry 1). Isoxazole **3Ab** was produced by intramolecular nucleophilic *O*-alkylation of **10Ab**. In addition to **3Ab**, a small amount (5%) of **13Ab** was formed by similar *O*-alkylation of **14Ab**. The structure of **3Ab** was confirmed by NMR spectroscopy,



Scheme 2. Plausible reaction mechanism for the reaction between ethyl α-nitrocinnamates **1** and ethyl nitroacetate (**2a**).

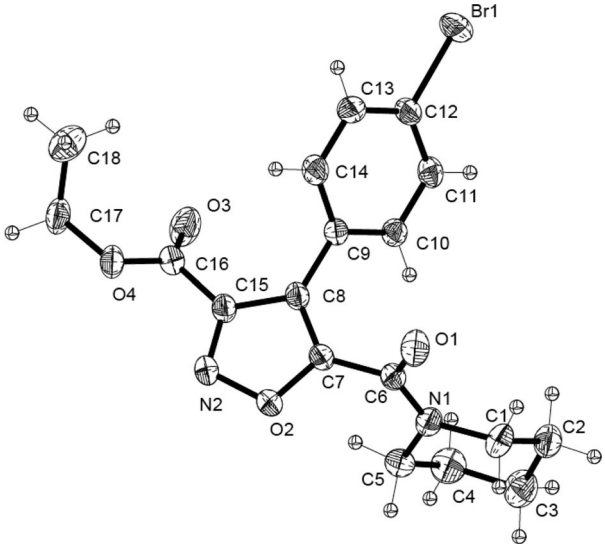
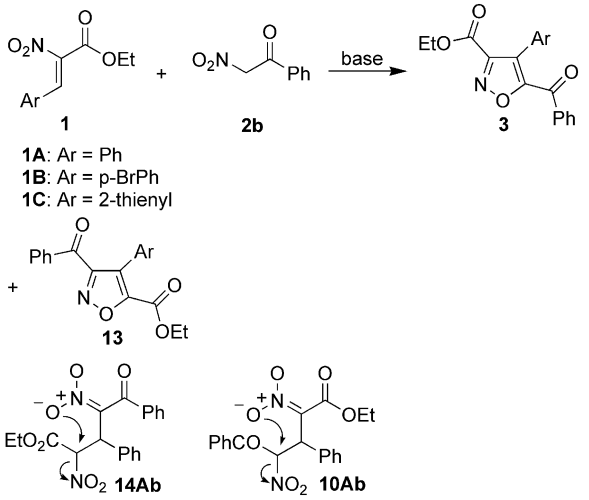


Figure 1. The molecular structure of **4Ba**.

as its ^{1}H NMR and ^{13}C NMR spectroscopic data are identical to those for the product obtained by the reaction of **1A** with **15b** (Scheme 4; Table 3, Entry 1). The high regioselectivity for the formation of **3Ab** can be rationalized by considering that the stronger electron-withdrawing effect of the benzoyl group over that of the carbethoxy group makes the nitronate intermediate undergo intramolecular nucleophilic *O*-alkylation mainly via **10Ab**. We next applied the Et_3N/CH_3CN reaction conditions to α-nitrocinnamates **1B** and **1C** (Table 2, Entries 2 and 3). The reaction worked well, and isoxazoles **3Bb** and **3Cb** were formed predominantly in 78 and 69% yield, respectively. This method proved to be of general applicability on ethyl α-nitrocinnamates **1** and α-nitro carbonyl compounds **2**. In all cases, isoxazoles **3**, **4**, and **5** were obtained effectively.

Pyridinium ylides have found wide application in the synthesis of tetrahydroindolizine and pyridine derivatives.[14,15] Because pyridinium salts are more accessible than the corresponding α-nitro carbonyl compounds, we continued to

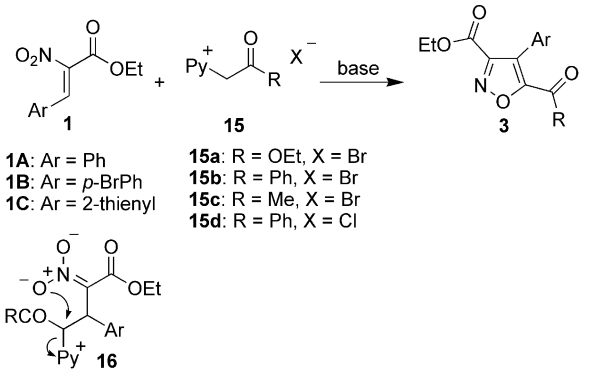


Scheme 3. Reactions with α-nitroacetophenone (**2b**).

Table 2. Reactions with α-nitroacetophenone (**2b**).

Entry	1	Base	Time [h]	Product, % yield[a]
1	**1A**	Et_3N[b]	5	**3Ab**, 76; **13Ab**, 5
2	**1B**	Et_3N[b]	4	**3Bb**, 78; **13Bb**, 6
3	**1C**	Et_3N[b]	4	**3Cb**, 69

[a] Isolated yield based on ethyl α-nitrocinnamates **1**. [b] 3 equiv. of base was used.



Scheme 4. Reactions with pyridinium salts **15**.

report the synthesis of isoxazoles via pyridinium ylides. The reaction between ethyl α-nitrocinnamate (**1A**, Ar = Ph) with preformed phenacylpyridinium bromide (**15b**, R = Ph, X = Br) was first examined (Scheme 4). Treatment of pyridinium salt **15b** with triethylamine and **1A** in acetonitrile at 60 °C for 2 h gave isoxazole **3Ab** as the only product in 92% yield (Table 3, Entry 1). Isoxazole **3Ab** was formed presumably through a reaction route similar to that outlined in Scheme 1, by intramolecular nucleophilic *O*-alkylation of **16Ab**. Again, the formation of cyclopropane **9Ab** was not detected. Various solvents such as chloroform and ethanol could also be useful for this reaction (Table 3, Entries 2 and 3). In acetonitrile, different bases were next screened for this reaction. Replacement of triethylamine with other bases except DBU also led to **3Ab** in a similar reaction yield (Table 3, Entries 4–6). We next applied the Et_3N/CH_3CN reaction condition to α-nitrocinnamates **1B** and **1C** (Table 3, Entries 7 and 8). The reaction worked well, and isoxazoles **3Bb** and **3Cb** were formed in 94 and 91% yield, respectively. Pyridinium salts **15a** and **15c** bearing other carbonyl groups were also investigated, and isoxazoles **3** were produced in moderate yields (Table 3, Entries 9–12). This reaction provides an efficient method for the formation of isoxazoles **3** from ethyl α-nitrocinnamates **1** and pyridinium salts **15**.

Table 3. Reactions with preformed pyridinium salts **15**.

Entry	1	15	Solvent	Base[a]	Time [h]	Product, % yield[b]
1	**1A**	**15b**	CH_3CN	Et_3N	2	**3Ab**, 92
2	**1A**	**15b**	$CHCl_3$	Et_3N	2	**3Ab**, 92
3	**1A**	**15b**	EtOH	Et_3N	2	**3Ab**, 84
4	**1A**	**15b**	CH_3CN	DABCO	2	**3Ab**, 92
5	**1A**	**15b**	CH_3CN	DBU	2	**3Ab**, 37
6	**1A**	**15b**	CH_3CN	piperidine	2	**3Ab**, 92
7	**1B**	**15b**	CH_3CN	Et_3N	2	**3Bb**, 94
8	**1C**	**15b**	CH_3CN	Et_3N	2	**3Cb**, 91
9	**1A**	**15a**	CH_3CN	Et_3N	3	**3Aa**, 75
10	**1B**	**15a**	CH_3CN	Et_3N	4	**3Ba**, 68
11	**1C**	**15a**	CH_3CN	Et_3N	3	**3Ca**, 53
12	**1A**	**15c**	CH_3CN	Et_3N	2	**3Ac**, 64

[a] 3 equiv. of base was used. [b] Isolated yield based on ethyl α-nitrocinnamates **1**.

The pyridinium salts are readily accessible from pyridines and alkyl halides.[16] To enhance the efficiency of this reaction, we next investigated the process in which pyridinium salts **15** and hence the ylides were generated in situ from the corresponding alkyl halides. Phenacylpyridinium chloride (**15d**, R = Ph, X = Cl) was formed by the reaction of pyridine and phenacyl chloride in acetonitrile at room temperature for 16 h. Subsequent addition of triethylamine and ethyl α-nitrocinnamate (**1A**) and stirring the reaction mixture at 60 °C for another 2 h produced isoxazole **3Ab** in 59% yield (Table 4, Entry 1). This poor reaction yield is presumably due to the slow reaction rate between phenacyl chloride and pyridine. Phenacyl bromide was next used as the in situ precursor of pyridinium salt **15b** and the reaction yield (93%) of desired isoxazole **3Ab** was dramatically increased (Table 4, Entry 2). Analogous results were obtained with α-nitrocinnamates **1** and α-bromo carbonyl compounds and are summarized in Table 4 (Entries 3–10). When pyridinium salts **15** were generated in situ from the corresponding bromides, isoxazoles were obtained in a better reaction yield than those with preformed pyridinium salts. This modified process offers significant advantages, as it precludes the necessity to generate and isolate pyridinium salts **15** in a separate step.

One-pot multicomponent reactions have attracted considerable attention in organic synthesis, as they can produce target products from readily available starting materials in a single operation without isolating the intermediates, thus reducing reaction times, labor, cost, and waste production. In an attempt to enhance the efficiency of the synthesis of isoxazoles, we then turned our attention to the development of a one-pot process, in which ethyl α-nitrocinnamates **1** could be generated in situ from aromatic aldehydes **17** and

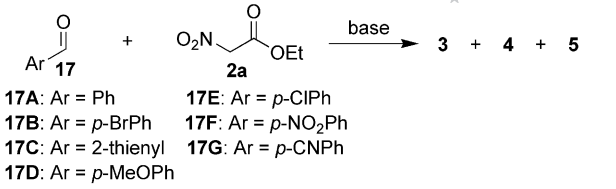
Table 4. Reactions with pyridinium salts **15** generated in situ from the corresponding alkyl halides.

Entry	1	15	Base[a]	Time [h]	Product, % yield[b]
1	**1A**	**15d**[c]	Et_3N	2	**3Ab**, 59
2	**1A**	**15b**[d]	Et_3N	2	**3Ab**, 93
3	**1B**	**15b**[d]	Et_3N	2	**3Bb**, 94
4	**1C**	**15b**[d]	Et_3N	2	**3Cb**, 93
5	**1A**	**15a**[d]	Et_3N	3	**3Aa**, 85
6	**1B**	**15a**[d]	Et_3N	3	**3Ba**, 80
7	**1C**	**15a**[d]	Et_3N	3	**3Ca**, 60
8	**1A**	**15c**[d]	Et_3N	2	**3Ac**, 68
9	**1B**	**15c**[d]	Et_3N	2	**3Bc**, 63
10	**1C**	**15c**[d]	Et_3N	4	**3Cc**, 48

[a] 3 equiv. of base was used. [b] Isolated yield based on ethyl α-nitrocinnamates **1**. [c] The pyridinium salt was generated in situ from pyridine and phenacyl chloride. [d] The pyridinium salt was generated in situ from pyridine and the corresponding alkyl bromides.

ethyl nitroacetate (**2a**). The transformation of *p*-bromobenzaldehyde (**17B**, Ar = *p*-BrPh) and ethyl nitroacetate (**2a**) into isoxazole **3Ba** was first studied (Scheme 5). Under the optimal conditions shown in Table 1, that is, triethylamine (3 equiv.) as base and acetonitrile as solvent, 60% yield of isoxazole **3Ba** was obtained from **2a** and **17B** (1 equiv.) after heating at 60 °C for 24 h. (Table 5, Entry 1). The reaction yield of **3Ba** could be improved to 75% when the reaction was performed with 2 equiv. of **17B** and 5 equiv. of triethylamine at 60 °C for 36 h (Table 5, Entry 4). Investigation of the scope of this triethylamine-initiated one-pot reaction revealed that aromatic aldehydes **17** (bearing electron-withdrawing and electron-donating groups) could be utilized in this protocol (Table 5, Entries 1–9). The reaction of ethyl nitroacetate (**2a**) with electron-deficient aromatic aldehydes was faster than with electron-rich aromatic aldehydes. In contrast, when piperidine (3 equiv.) was employed as base, reaction of benzaldehyde (**17A**, Ar = Ph) and ethyl nitroacetate (**2a**) produced **4Aa** (73%) derived from the selective amidation of **3Aa** (Table 5, Entry 10). A variety of aromatic aldehydes **17** was also employed under piperidine-initiated one-pot reaction conditions. As shown in Table 5 (Entries 10–16), not only electron-rich aromatic aldehydes but also electron-deficient aromatic aldehydes afforded desired isoxazole derivatives **4** in moderate yields with high regioselectivity. With electron-deficient aromatic aldehydes, small amounts of diamides **5** were also formed (Table 5, Entries 11, 14–16). By prolonging the reaction time and increasing the amount of piperidine (5 equiv.), diamides **5** became the major products (Table 5, Entries 17–21). In this one-pot process between aromatic aldehydes **17** and ethyl nitroacetate (**2a**), isoxazoles **3**, **4**, and **5** could be formed selectively depending on the base used and the reaction time. These results demonstrate that a one-pot process for the efficient synthesis of highly functionalized isoxazole derivatives has been successfully established.

In view of the good results on the one-pot process between aromatic aldehydes **17** and ethyl nitroacetate (**2a**), we reasoned that it might be possible to form isoxazole derivatives bearing a 5-keto group through a three-component reaction of aromatic aldehydes **17**, ethyl nitroacetate (**2a**), and pyridinium salts **15** (Scheme 6). Indeed, using triethylamine as base, benzaldehyde (**17A**, Ar = Ph), ethyl nitroacetate (**2a**) and preformed phenacylpyridinium bromide (**15b**) were transformed into isoxazole **3Ab** in 50% yield after heating at 60 °C for 24 h (Table 6, Entry 1). When piperidine was employed, desired product **3Ab** was obtained in a much better reaction yield (92%) and the reaction time was shortened to 2 h (Table 6, Entry 2). A similar result was obtained when phenacylpyridinium bromide (**15b**) was generated in situ from pyridine and phenacyl bromide (Table 6, Entry 3). Using these piperidine/acetonitrile conditions, we examined the generality of this three-component process with various aromatic aldehydes **17** and pyridinium salts **15**. As shown in Table 6 (Entries 3–12), isoxazoles **3** bearing a 5-keto group were obtained in moderate to good yields. This one-pot three-component process offers significant advantages, as it precludes the necessity to prepare ethyl α-nitrocinnamates **1** in a separate step and 5-ketoisoxazoles were produced effectively from readily available aromatic aldehydes **17**, ethyl nitroacetate (**2a**), and pyridinium salts **15**.

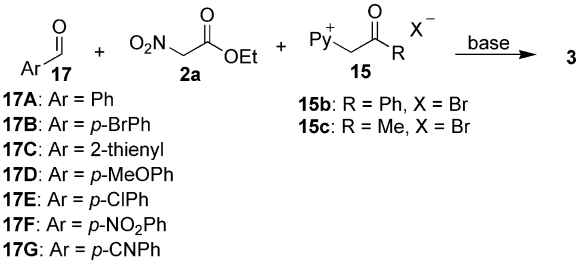


Scheme 5. One-pot synthesis of isoxazoles with ethyl nitroacetate (**2a**).

Table 5. One-pot synthesis of isoxazoles with ethyl nitroacetate (**2a**).

Entry	17	Base	Time [h]	Product, % yield[a]
1	**17B**[b]	Et_3N[d]	24	**3Ba**, 60
2	**17B**[b]	Et_3N[d]	36	**3Ba**, 63
3	**17B**[b]	Et_3N[e]	36	**3Ba**, 68
4	**17B**[c]	Et_3N[e]	36	**3Ba**, 75
5	**17A**[c]	Et_3N[e]	36	**3Aa**, 74
6	**17C**[c]	Et_3N[e]	72	**3Ca**, 46
7	**17D**[c]	Et_3N[e]	54	**3Da**, 65
8	**17E**[c]	Et_3N[e]	36	**3Ea**, 77
9	**17F**[c]	Et_3N[e]	14	**3Fa**, 60
10	**17A**[c]	piperidine[d]	14	**4Aa**, 73
11	**17B**[c]	piperidine[d]	14	**4Ba**, 71; **5Ba**, 6
12	**17C**[c]	piperidine[d]	14	**4Ca**, 64
13	**17D**[c]	piperidine[d]	14	**4Da**, 71
14	**17E**[c]	piperidine[d]	10	**4Ea**, 66; **5Ea**, 5
15	**17F**[c]	piperidine[d]	10	**4Fa**, 54; **5Fa**, 12
16	**17G**[c]	piperidine[d]	10	**4Ga**, 64; **5Ga**, 9
17	**17A**[c]	piperidine[e]	48	**4Aa**, 22; **5Aa**, 54
18	**17B**[c]	piperidine[e]	56	**4Ba**, 4; **5Ba**, 72
19	**17E**[c]	piperidine[e]	56	**4Ea**, 4; **5Ea**, 69
20	**17F**[c]	piperidine[e]	56	**4Fa**, 0; **5Fa**, 57
21	**17G**[c]	piperidine[e]	56	**4Ga**, 7; **5Ga**, 64

[a] Isolated yield based on ethyl nitroacetate (**2a**). [b] Reactions were carried out with 1 equiv. of **17**. [c] Reactions were carried out with 2 equiv. of **17**. [d] 3 equiv. of base was used. [e] 5 equiv. of base was used.



Scheme 6. One-pot synthesis of isoxazoles **3** with pyridinium salts **15**.

Table 6. One-pot synthesis of isoxazoles **3** with pyridinium salts **15**.

Entry	17	15	Base[a]	Time [h]	Product, % yield[b]
1	**17A**	**15b**	Et_3N	16	**3Ab**, 50
2	**17A**	**15b**	piperidine	2	**3Ab**, 92
3[c]	**17A**	**15b**	piperidine	2	**3Ab**, 90
4[c]	**17B**	**15b**	piperidine	2	**3Bb**, 85
5[c]	**17C**	**15b**	piperidine	2	**3Cb**, 58
6[c]	**17D**	**15b**	piperidine	2	**3Db**, 90
7[c]	**17E**	**15b**	piperidine	2	**3Eb**, 85
8[c]	**17F**	**15b**	Piperidine	2	**3Fb**, 81
9[c]	**17G**	**15b**	piperidine	2	**3Gb**, 83
10[c]	**17A**	**15c**	piperidine	2	**3Ac**, 67
11[c]	**17B**	**15c**	piperidine	2	**3Bc**, 71
12[c]	**17C**	**15c**	piperidine	2	**3Cc**, 53

[a] 5 equiv. of base was used. [b] Isolated yield based on ethyl nitroacetate (**2a**). [c] Pyridinium salts **15** were generated in situ by the reaction of pyridine and the corresponding alkyl bromides.

Conclusions

We have developed a new reaction for the synthesis of highly functionalized isoxazoles from readily available starting ethyl α-nitrocinnamates. Ethyl α-nitrocinnamates react smoothly with α-nitro carbonyl compounds to produce isoxazoles in good yields. This protocol provides novel and effective methodology for the preparation of isoxazoles. The reaction is applicable to a range of ethyl α-nitrocinnamates and α-nitro carbonyl compounds with a variety of versatile functional groups. Conjugate addition of pyridinium ylides to ethyl α-nitrocinnamates can also generate these isoxazoles. These pyridinium salts can be generated in situ from the corresponding alkyl bromides. To increase the efficiency of this reaction, the one-pot multicomponent process was also developed. Isoxazoles can be produced directly from readily available aromatic aldehydes and ethyl nitroacetate. In this one-pot process, isoxazoles **3**, **4**, and **5** were formed selectively depending on the base used and the reaction time. 5-Ketoisoxazoles can also be produced directly from readily available aromatic aldehydes, ethyl nitroacetate, and pyridinium salts.

Experimental Section

General Considerations: The NMR spectra were recorded with a Bruker Avance 300 or AMX-400 spectrometer. Chemical shifts are reported in ppm relative to TMS as internal reference. Elemental analyses were performed with a Heraeus CHN-Rapid Analyzer. HRMS were recorded with a JEOL JMS-SX 102A mass spectrometer. X-ray diffraction structure analyses were performed with a Nonius Kappa CCD diffractometer. Structure analysis was made by using the SHELXTL program on a personal computer. Analytical thin-layer chromatography was performed with precoated silica gel 60 F-254 plates (0.25 mm thick) and visualized by UV light. The reaction mixture was purified by column chromatography over silica gel (70–230 mesh).

Typical Procedure for the Reactions with α-Nitro Carbonyl Compounds 2: A solution of ethyl α-nitrocinnamate (**1A**, 142 mg, 0.64 mmol), ethyl nitroacetate (**2a**, 128 mg, 0.96 mmol), and triethylamine (195 mg, 1.93 mmol) in CH_3CN (6 mL) was heated at 60 °C for 4 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g; hexane/EtOAc, 8:1) followed by crystallization (hexane/EtOAc) to give **3Aa** (173 mg, 93%).

Typical Procedure for the Reactions with Pyridinium Salts 15: A solution of ethyl α-nitrocinnamate (**1A**, 152 mg, 0.69 mmol), phenacylpyridinium bromide (**15b**, 288 mg, 1.04 mmol), and triethylamine (209 mg, 2.07 mmol) in CH_3CN (6 mL) was heated at 60 °C for 2 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g; hexane/EtOAc, 8:1) followed by crystallization (hexane/EtOAc) to give **3Ab** (204 mg, 92%).

Typical Procedure for the One-pot Reactions between Aromatic Aldehydes 17 and Ethyl Nitroacetate (2a): A solution of benzaldehyde (**17A**, 137 mg, 1.29 mmol), ethyl nitroacetate (**2a**, 172 mg, 1.29 mmol), and triethylamine (653 mg, 6.47 mmol) in CH_3CN (5 mL) was stirred at 60 °C for 36 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g; hexane/EtOAc, 8:1) followed by crystallization (hexane/EtOAc) to give **3Aa** (138 mg, 74%).

Typical Procedure for the One-Pot Reactions between Aromatic Aldehydes 17, Ethyl Nitroacetate (2a), and Pyridinium Salts 15: A solution of benzaldehyde (**17A**, 114 mg, 0.93 mmol), ethyl nitroacetate (**2a**, 102 mg, 0.77 mmol), phenacylpyridinium bromide (**15b**, 315 mg, 1.13 mmol), and piperidine (319 mg, 3.75 mmol) in CH_3CN (5 mL) was stirred at 60 °C for 2 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (20 g; hexane/EtOAc, 8:1) followed by crystallization (hexane/EtOAc) to give **3Ab** (228 mg, 92%).

Diethyl 4-Phenylisoxazole-3,5-dicarboxylate (3Aa): White crystals; m.p. 51–52 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1735, 1235, 1200, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.27 (t, J = 7.1 Hz, 3 H, CH_3), 4.32 (q, J = 7.1 Hz, 2 H, OCH_2), 4.33 (q, J = 7.1 Hz, 2 H, OCH_2), 7.34–7.39 (m, 2 H, ArH), 7.40–7.45 (m, 3 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.78 (q), 13.81 (q), 62.3 (t), 62.4 (t), 125.5 (s), 126.8 (s), 127.8 (2 d), 129.0 (d), 129.9 (2 d), 155.5 (s), 156.4 (s), 157.1 (s), 159.1 (s) ppm. $C_{15}H_{15}NO_5$ (289.10): calcd. C 62.28, H 5.23, N 4.84; found C 62.11, H 5.28, N 4.83.

Diethyl 4-(4-Bromophenyl)isoxazole-3,5-dicarboxylate (3Ba): White crystals; m.p. 90–91 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1740, 1260, 1205, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.0 Hz, 3 H, CH_3), 1.30 (t, J = 7.0 Hz, 3 H, CH_3), 4.34 (q, J = 7.0 Hz, 2 H, OCH_2), 4.35 (q, J = 7.0 Hz, 2 H, OCH_2), 7.25 (d, J = 8.4 Hz, 2 H, ArH), 7.57 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR

(75.4 MHz, $CDCl_3$): δ = 13.82 (q), 13.85 (q), 62.5 (2 t), 123.4 (s), 124.4 (s), 125.8 (s), 131.0 (2 d), 131.7 (2 d), 155.1 (s), 156.2 (s), 157.1 (s), 158.9 (s) ppm. $C_{15}H_{14}BrNO_5$ (367.01): calcd. C 48.93, H 3.83, N 3.80; found C 48.92, H 3.89, N 3.76.

Diethyl 4-(Thiophen-2-yl)isoxazole-3,5-dicarboxylate (3Ca): White crystals; m.p. 42–43 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1735, 1235, 1020, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.326 (t, J = 7.2 Hz, 3 H, CH_3), 1.329 (t, J = 7.2 Hz, 3 H, CH_3), 4.38 (q, J = 7.2 Hz, 2 H, OCH_2), 4.39 (q, J = 7.2 Hz, 2 H, OCH_2), 7.11 (dd, J = 5.0, 3.6 Hz, 1 H, ArH), 7.28 (dd, J = 3.6, 0.8 Hz, 1 H, ArH), 7.49 (dd, J = 5.0, 0.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 (2 q), 62.5 (t), 62.6 (t), 118.5 (s), 125.7 (s), 126.8 (d), 128.1 (d), 130.6 (d), 155.7 (s), 156.2 (s), 157.1 (s), 159.0 (s) ppm. $C_{13}H_{13}NO_5S$ (295.31): calcd. C 52.87, H 4.44, N 4.74, S 10.86; found C 52.78, H 4.46, N 4.73, S 10.98.

Diethyl 4-(4-Methoxyphenyl)isoxazole-3,5-dicarboxylate (3Da): White crystals; m.p. 60–61 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1740, 1615, 1515, 1230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.34 (q, J = 7.1 Hz, 2 H, OCH_2), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 6.95 (d, J = 8.8 Hz, 2 H, ArH), 7.32 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (2 q), 55.1 (q), 62.1 (t), 62.2 (t), 113.1 (2 d), 118.5 (s), 125.2 (s), 131.3 (2 d), 155.4 (s), 156.4 (s), 156.6 (s), 159.2 (s), 160.0 (s) ppm. $C_{16}H_{17}NO_6$ (319.11): calcd. C 60.18, H 5.37, N 4.39; found C 60.08, H 5.36, N 4.30.

Diethyl 4-(4-Chlorophenyl)isoxazole-3,5-dicarboxylate (3Ea): White crystals; m.p. 75–76 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1740, 1495, 1450, 1235 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, CH_3), 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 4.34 (q, J = 7.1 Hz, 2 H, OCH_2), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 7.31 (d, J = 8.6 Hz, 2 H, ArH), 7.41 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (2 q), 62.3 (2 t), 124.2 (s), 125.2 (s), 127.9 (2 d), 131.3 (2 d), 135.0 (s), 155.1 (s), 156.0 (s), 157.1 (s), 158.8 (s) ppm. $C_{15}H_{14}ClNO_5$ (323.06): calcd. C 55.65, H 4.36, N 4.33; found C 55.69, H 4.40, N 4.27.

Diethyl 4-(4-Nitrophenyl)isoxazole-3,5-dicarboxylate (3Fa): White crystals; m.p. 112–113 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1740, 1735, 1520, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 4.36 (q, J = 7.1 Hz, 2 H, OCH_2), 7.57 (d, J = 8.8 Hz, 2 H, ArH), 8.30 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.81 (q), 13.84 (q), 62.73 (t), 62.77 (t), 123.0 (2 d), 123.6 (s), 131.3 (2 d), 133.8 (s), 148.1 (s), 154.8 (s), 155.9 (s), 157.7 (s), 158.7 (s) ppm. $C_{15}H_{14}N_2O_7$ (334.08): calcd. C 53.89, H 4.22, N 8.38; found C 53.89, H 4.23, N 8.35.

Ethyl 5-Benzoyl-4-phenylisoxazole-3-carboxylate (3Ab): White crystals; m.p. 71–72 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1735, 1230, 1180, 1015 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2), 7.33–7.42 (m, 5 H, ArH), 7.45 (t, J = 7.6 Hz, 2 H, ArH), 7.60 (t, J = 7.6 Hz, 1 H, ArH), 7.93 (d, J = 7.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 (q), 62.4 (t), 124.8 (s), 126.7 (s), 128.0 (2 d), 128.6 (2 d), 128.9 (d), 130.00 (2 d), 130.01 (2 d), 134.3 (d), 135.3 (s), 155.1 (s), 159.4 (s), 163.2 (s), 182.3 (s) ppm. $C_{19}H_{15}NO_4$ (321.10): calcd. C 71.02, H 4.71, N 4.36; found C 71.06, H 4.71, N 4.33.

Ethyl 5-Benzoyl-4-(4-bromophenyl)isoxazole-3-carboxylate (3Bb): Yellow oil. IR (KBr): $\tilde{\nu}$ = 2925, 1740, 1230, 1180, 1010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 4.39 (q, J = 7.2 Hz, 2 H, OCH_2), 7.29 (d, J = 8.5 Hz, 2 H, ArH), 7.49 (t, J = 7.9 Hz, 2 H, ArH), 7.52 (d, J = 8.5 Hz, 2 H, ArH), 7.64 (t, J = 7.9 Hz, 1 H, ArH), 7.95 (d, J = 7.9 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9 (q), 62.6 (t), 123.5 (s), 123.9 (s), 125.7 (s), 128.8 (2 d), 130.1 (2 d), 131.3 (2 d), 131.7 (2 d), 134.5 (d), 135.2 (s), 154.9 (s), 159.2 (s), 163.4 (s), 182.0 (s) ppm. HRMS (EI): calcd. for $C_{19}H_{14}BrNO_4$ 399.0109; found 399.0106.

Ethyl 5-Benzoyl-(4-thiophen-2-yl)isoxazole-3-carboxylate (3Cb): Pale-yellow crystals; m.p. 55–56 °C. IR (KBr): $\tilde{\nu}$ = 2980, 1740, 1235, 1180, 1010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3 H, CH_3), 4.45 (q, J = 7.1 Hz, 2 H, OCH_2), 7.03 (dd, J = 5.1, 3.7 Hz, 1 H, ArH), 7.33 (dd, J = 3.7, 1.0 Hz, 1 H, ArH), 7.42 (dd, J = 5.1, 1.0 Hz, 1 H, ArH), 7.48 (t, J = 7.6 Hz, 2 H, ArH), 7.63 (t, J = 7.6 Hz, 1 H, ArH), 7.93 (d, J = 7.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9 (q), 62.7 (t), 117.7 (s), 125.9 (s), 127.0 (d), 128.3 (d), 128.7 (2 d), 130.0 (2 d), 130.8 (d), 134.5 (d), 135.2 (s), 155.1 (s), 159.4 (s), 163.1 (s), 182.3 (s) ppm. $C_{17}H_{13}NO_4S$ (327.06): calcd. C 62.37, H 4.00, N 4.28, S 9.80; found C 62.46, H 3.97, N 4.26, S 9.89.

Ethyl 5-Benzoyl-4-(4-methoxyphenyl)isoxazole-3-carboxylate (3Db): Yellow crystals; m.p. 58–59 °C. IR (KBr): $\tilde{\nu}$ = 2975, 1735, 1665, 1510, 1235 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.40 (q, J = 7.1 Hz, 2 H, OCH_2), 6.90 (d, J = 8.8 Hz, 2 H, ArH), 7.35 (d, J = 8.8 Hz, 2 H, ArH), 7.46 (t, J = 7.7 Hz, 2 H, ArH), 7.61 (t, J = 7.7 Hz, 1 H, ArH), 7.93 (d, J = 7.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6 (q), 54.8 (q), 62.1 (t), 113.2 (2 d), 118.3 (s), 124.2 (s), 128.3 (2 d), 129.6 (2 d), 131.2 (2 d), 133.9 (d), 135.1 (s), 154.9 (s), 159.2 (s), 159.8 (s), 162.5 (s), 182.1 (s) ppm. $C_{20}H_{17}NO_5$ (351.11): calcd. C 68.37, H 4.88, N 3.99; found C 68.12, H 4.92, N 3.89.

Ethyl 5-Benzoyl-4-(4-chlorophenyl)isoxazole-3-carboxylate (3Eb): White crystals; m.p. 59–60 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1740, 1670, 1450, 1230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 3 H, CH_3), 4.39 (q, J = 7.1 Hz, 2 H, OCH_2), 7.33–7.38 (m, 4 H, ArH), 7.49 (t, J = 7.7 Hz, 2 H, ArH), 7.64 (t, J = 7.7 Hz, 1 H, ArH), 7.95 (d, J = 7.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (q), 62.5 (t), 123.8 (s), 125.2 (s), 128.3 (2 d), 128.7 (2 d), 130.0 (2 d), 131.4 (2 d), 134.5 (d), 135.1 (2 s), 154.9 (s), 159.2 (s), 163.3 (s), 182.0 (s) ppm. $C_{19}H_{14}ClNO_4$ (355.06): calcd. C 64.14, H 3.97, N 3.94; found C 64.14, H 3.98, N 3.89.

Ethyl 5-Benzoyl-4-(4-nitrophenyl)isoxazole-3-carboxylate (3Fb): White crystals; m.p. 89–90 °C. IR (KBr): $\tilde{\nu}$ = 2995, 1740, 1660, 1520, 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 4.40 (q, J = 7.2 Hz, 2 H, OCH_2), 7.52 (t, J = 7.7 Hz, 2 H, ArH), 7.61 (d, J = 8.8 Hz, 2 H, ArH), 7.68 (t, J = 7.7 Hz, 1 H, ArH), 8.00 (d, J = 7.7 Hz, 2 H, ArH), 8.27 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.8 (q), 62.7 (t), 123.1 (2 d), 128.8 (2 d), 130.0 (2 d), 131.2 (2 d), 133.8 (s), 134.8 (d), 134.9 (s), 147.9 (s), 154.6 (s), 158.8 (s), 163.9 (s), 181.5 (s) ppm. $C_{19}H_{14}N_2O_6$ (366.09): calcd. C 62.30, H 3.85, N 7.65; found C 62.28, H 3.84, N 7.64.

Ethyl 5-Benzoyl-4-(4-cyanophenyl)isoxazole-3-carboxylate (3Gb): White crystals; m.p. 98–99 °C. IR (KBr): $\tilde{\nu}$ = 2990, 2230, 1740, 1660, 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.2 Hz, 3 H, CH_3), 4.40 (q, J = 7.2 Hz, 2 H, OCH_2), 7.51 (t, J = 7.3 Hz, 2 H, ArH), 7.54 (d, J = 8.4 Hz, 2 H, ArH), 7.67 (t, J = 7.3 Hz, 1 H, ArH), 7.70 (d, J = 7.3 Hz, 2 H, ArH), 7.98 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.8 (q), 62.7 (t), 112.7 (s), 118.2 (s), 123.4 (s), 128.8 (2 d), 130.0 (2 d), 130.9 (2 d), 131.6 (2 d), 131.8 (s), 134.7 (d), 134.9 (s), 154.6 (s), 158.8 (s), 163.7 (s), 181.6 (s) ppm. $C_{20}H_{14}N_2O_4$ (346.10): calcd. C 69.36, H 4.07, N 8.09; found C 69.36, H 4.10, N 8.11.

Ethyl 5-Acetyl-4-phenylisoxazole-3-carboxylate (3Ac): White crystals; m.p. 78–79 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1735, 1200, 1020, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 4.33 (q, J = 7.1 Hz, 2 H, OCH_2), 7.34–7.39 (m, 2 H, ArH), 7.40–7.47 (m, 3 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 (q), 28.5 (q), 62.4 (t), 123.8 (s), 126.8 (s), 128.1 (2 d), 129.2 (d), 129.8 (2 d), 155.8 (s), 159.2 (s), 162.2 (s), 186.5 (s) ppm. $C_{14}H_{13}NO_4$ (259.08): calcd. C 64.86, H 5.05, N 5.40; found C 64.80, H 5.06, N 5.34.

Ethyl 5-Acetyl-4-(4-bromophenyl)isoxazole-3-carboxylate (3Bc): White needles; m.p. 88–89 °C. IR (KBr): $\tilde{\nu}$ = 1750, 1700, 1215, 1020, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 7.25 (d, J = 8.5 Hz, 2 H, ArH), 7.57 (d, J = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 (q), 28.4 (q), 62.5 (t), 122.7 (s), 123.6 (s), 125.6 (s), 131.2 (2 d), 131.6 (2 d), 155.4 (s), 159.0 (s), 162.2 (s), 186.5 (s) ppm. $C_{14}H_{12}BrNO_4$ (336.99): calcd. C 49.73, H 3.58, N 4.14; found C 49.76, H 3.66, N 4.14.

Ethyl 5-Acetyl-4-(thiophen-2-yl)isoxazole-3-carboxylate (3Cc): Yellow oil. IR (KBr): $\tilde{\nu}$ = 2980, 1740, 1205, 1015, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 4.40 (q, J = 7.1 Hz, 2 H, OCH_2), 7.12 (dd, J = 5.2, 3.7 Hz, 1 H, ArH), 7.36 (dd, J = 3.7, 1.2 Hz, 1 H, ArH), 7.50 (dd, J = 5.2, 1.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 (q), 28.4 (q), 62.6 (t), 116.8 (s), 125.8 (s), 127.0 (d), 128.3 (d), 130.9 (d), 155.8 (s), 159.2 (s), 161.9 (s), 186.4 (s) ppm. HRMS (EI): calcd. for $C_{12}H_{11}NO_4S$ 265.0425; found 265.0417.

Ethyl 4-Phenyl-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (4Aa): White crystals; m.p. 89–90 °C. IR (KBr): $\tilde{\nu}$ = 1735, 1645, 1255, 1180, 1015 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.22 (m, 2 H, CH_2), 1.33 (t, J = 7.1 Hz, 3 H, CH_3), 1.48–1.59 (m, 4 H, 2 CH_2), 3.10 (t, J = 5.6 Hz, 2 H, NCH_2), 3.57–3.67 (m, 2 H, NCH_2), 4.39 (q, J = 7.1 Hz, 2 H, OCH_2), 7.38–7.46 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (q), 24.1 (t), 25.1 (t), 25.9 (t), 43.1 (t), 47.7 (t), 62.4 (t), 119.5 (s), 126.6 (s), 128.4 (2 d), 128.9 (d), 129.6 (2 d), 153.7 (s), 157.1 (s), 159.6 (s), 161.8 (s) ppm. $C_{18}H_{20}N_2O_4$ (328.14): calcd. C 65.84, H 6.14, N 8.53; found C 65.84, H 6.15, N 8.56.

Ethyl 4-(4-Bromophenyl)-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (4Ba): White needles; m.p. 105–106 °C. IR (KBr): $\tilde{\nu}$ = 2940, 1725, 1255, 1200, 990 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.37 (m, 2 H, CH_2), 1.33 (t, J = 7.1 Hz, 3 H, CH_3), 1.49–1.64 (m, 4 H, 2 CH_2), 3.13 (t, J = 5.6 Hz, 2 H, NCH_2), 3.56–3.66 (m, 2 H, NCH_2), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2), 7.31 (d, J = 8.5 Hz, 2 H, ArH), 7.54 (d, J = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (q), 24.1 (t), 25.2 (t), 26.2 (t), 43.3 (t), 47.8 (t), 62.5 (t), 118.8 (s), 123.3 (s), 125.6 (s), 131.3 (2 d), 131.6 (2 d), 153.6 (s), 156.8 (s), 159.5 (s), 162.0 (s) ppm. $C_{18}H_{19}BrN_2O_4$ (406.05): calcd. C 53.08, H 4.70, N 6.88; found C 53.09, H 4.70, N 6.86.

Ethyl 5-(Piperidine-1-carbonyl)-4-(thiophen-2-yl)isoxazole-3-carboxylate (4Ca): White needles; m.p. 64–65 °C. IR (KBr): $\tilde{\nu}$ = 2945, 1740, 1255, 1180, 1010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.43 (m, 2 H, CH_2), 1.39 (t, J = 7.1 Hz, 3 H, CH_3), 1.55–1.68 (m, 4 H, 2 CH_2), 3.17 (t, J = 5.5 Hz, 2 H, NCH_2), 3.57–3.75 (m, 2 H, NCH_2), 4.45 (q, J = 7.1 Hz, 2 H, OCH_2), 7.09 (t, J = 4.3 Hz, 1 H, ArH), 7.35 (d, J = 4.3 Hz, 1 H, ArH), 7.43 (d, J = 4.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0 (q), 24.2 (t), 25.2 (t), 26.1 (t), 43.2 (t), 47.8 (t), 62.6 (t), 113.2 (s), 126.1 (s), 127.3 (d), 127.7 (d), 129.7 (d), 153.5 (s), 156.9 (s), 159.5 (s), 161.8 (s) ppm. $C_{16}H_{18}N_2O_4S$ (334.10): calcd. C 57.47, H 5.43, N 8.38; found C 57.36, H 5.40, N 8.35.

Ethyl 4-(4-Methoxyphenyl)-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (4Da): Light-yellow powder; m.p. 61–62 °C. IR (KBr): $\tilde{\nu}$ = 2940, 1730, 1645, 1515, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.28 (m, 2 H, CH_2), 1.35 (t, J = 7.1 Hz, 3 H, CH_3), 1.49–1.61 (m, 4 H, 2 CH_2), 3.11 (t, J = 5.6 Hz, 2 H, NCH_2), 3.57–3.65 (m, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 4.39 (q, J = 7.1 Hz, 2 H, OCH_2), 6.94 (d, J = 8.8 Hz, 2 H, ArH), 7.37 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (q), 24.1 (t), 25.1 (t), 25.9 (t), 43.1 (t), 47.7 (t), 55.2 (t), 62.3 (t), 113.8 (2 d), 118.6 (s), 119.3 (s), 130.8 (2 d), 153.7 (s), 157.2 (s), 159.7 (s), 160.0 (s), 161.4 (s) ppm. $C_{19}H_{22}N_2O_5$ (358.15): calcd. C 63.67, H 6.19, N 7.82; found C 63.47, H 6.24, N 7.70.

4-(4-Chlorophenyl)-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (4Ea): White powder; m.p. 74–75 °C. IR (KBr): $\tilde{\nu}$ = 2940, 1740, 1650, 1445, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.32 (m, 2 H, CH_2), 1.35 (t, J = 7.2 Hz, 3 H, CH_3), 1.51–1.65 (m, 4 H, 2 CH_2), 3.14 (t, J = 5.6 Hz, 2 H, NCH_2), 3.62 (t, J = 5.6 Hz, 2 H, NCH_2), 4.39 (q, J = 7.2 Hz, 2 H, OCH_2), 7.39 (s, 4 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (q), 24.1 (t), 25.2 (t), 26.1 (t), 43.2 (t), 47.7 (t), 62.4 (t), 118.7 (s), 125.1 (s), 128.6 (2 d), 131.0 (2 d), 135.0 (s), 153.6 (s), 156.7 (s), 159.4 (s), 162.0 (s) ppm. $C_{18}H_{19}ClN_2O_4$ (362.10): calcd. C 59.59, H 5.28, N 7.72; found C 59.53, H 5.29, N 7.66.

4-(4-Nitrophenyl)-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (4Fa): Light-yellow crystals; m.p. 79–80 °C. IR (KBr): $\tilde{\nu}$ = 2940, 1740, 1650, 1520, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 3 H, CH_3), 1.38–1.45 (m, 2 H, CH_2), 1.59–1.70 (m, 4 H, 2 CH_2), 3.22 (t, J = 5.6 Hz, 2 H, NCH_2), 3.64 (t, J = 5.6 Hz, 2 H, NCH_2), 4.41 (q, J = 7.1 Hz, 2 H, OCH_2), 7.66 (d, J = 8.8 Hz, 2 H, ArH), 8.28 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.8 (q), 24.0 (t), 25.2 (t), 26.3 (t), 43.3 (t), 47.7 (t), 62.6 (t), 118.3 (s), 123.3 (2 d), 130.8 (2 d), 133.5 (s), 147.8 (s), 153.4 (s), 156.2 (s), 159.1 (s), 162.7 (s) ppm. $C_{18}H_{19}N_3O_6$ (373.13): calcd. C 57.90, H 5.13, N 11.25; found C 57.85, H 5.12, N 11.25.

Ethyl 4-(4-Cyanophenyl)-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (4Ga): White needles; m.p. 87–88 °C. IR (KBr): $\tilde{\nu}$ = 1740, 1650, 1225, 1180, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3 H, CH_3), 1.31–1.42 (m, 2 H, CH_2), 1.54–1.69 (m, 4 H, 2 CH_2), 3.20 (t, J = 5.5 Hz, 2 H, NCH_2), 3.63 (t, J = 5.5 Hz, 2 H, NCH_2), 4.40 (q, J = 7.1 Hz, 2 H, OCH_2), 7.59 (d, J = 8.6 Hz, 2 H, ArH), 7.71 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.7 (q), 23.8 (t), 25.0 (t), 26.0 (t), 43.1 (t), 47.6 (t), 62.4 (t), 112.4 (s), 118.1 (s), 118.3 (s), 130.3 (2 d), 131.4 (s), 131.8 (2 d), 153.2 (s), 156.1 (s), 158.9 (s), 162.4 (s) ppm. $C_{19}H_{19}N_3O_4$ (353.14): calcd. C 64.58, H 5.42, N 11.89; found C 64.60, H 5.46, N 11.93.

4-Phenyl(isoxazole-3,5-dicarbonyl)bispiperidine (5Aa): White crystals; m.p. 164–165 °C. IR (KBr): $\tilde{\nu}$ = 2940, 1645, 1505, 1450, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09–1.18 (m, 2 H, CH_2), 1.18–1.26 (m, 2 H, CH_2), 1.46–1.58 (m, 8 H, 4 CH_2), 3.12 (t, J = 5.5 Hz, 2 H, NCH_2), 3.13 (t, J = 5.5 Hz, 2 H, NCH_2), 3.59–3.72 (m, 4 H, 2 NCH_2), 7.32–7.44 (m, 3 H, ArH), 7.53 (dd, J = 7.6, 1.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.1 (2 t), 25.2 (2 t), 25.8 (t), 25.9 (t), 42.8 (t), 43.1 (t), 47.78 (t), 47.83 (t), 117.0 (s), 126.8 (s), 128.4 (2 d), 128.9 (3 d), 157.2 (s), 157.8 (s), 159.3 (s), 159.4 (s) ppm. $C_{21}H_{25}N_3O_3$ (367.19): calcd. C 68.64, H 6.86, N 11.44; found C 68.67, H 6.90, N 11.46.

4-(4-Bromophenyl)(isoxazole-3,5-dicarbonyl)bispiperidine (5Ba): White crystals; m.p. 221–222 °C. IR (KBr): $\tilde{\nu}$ = 2950, 1640, 1635, 1450, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.28 (m, 2 H, CH_2), 1.28–1.37 (m, 2 H, CH_2), 1.50–1.62 (m, 8 H, 4 CH_2),

3.07–3.22 (m, 4 H, 2 NCH_2), 3.58–3.74 (m, 4 H, 2 NCH_2), 7.45 (d, J = 8.5 Hz, 2 H, ArH), 7.53 (d, J = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.0 (2 t), 25.15 (t), 25.18 (t), 25.96 (t), 26.06 (t), 42.8 (t), 43.1 (t), 47.7 (t), 47.8 (t), 116.1 (s), 123.1 (s), 125.7 (s), 130.0 (2 d), 132.0 (2 d), 156.8 (s), 157.4 (s), 158.9 (s), 159.7 (s) ppm. $C_{21}H_{24}BrN_3O_3$ (445.10): calcd. C 56.51, H 5.42, N 9.41; found C 56.47, H 5.37, N 9.23.

4-(4-Chlorophenyl)(isoxazole-3,5-dicarbonyl)bispiperidine (5Ea): White crystals; m.p. 193–194 °C. IR (KBr): $\tilde{\nu}$ = 2945, 1630, 1620, 1445, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.28 (m, 2 H, CH_2), 1.28–1.37 (m, 2 H, CH_2), 1.43–1.72 (m, 8 H, 4 CH_2), 3.03–3.24 (m, 4 H, 2 NCH_2), 3.55–3.80 (m, 4 H, 2 NCH_2), 7.38 (d, J = 8.4 Hz, 2 H, ArH), 7.51 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.0 (2 t), 25.2 (2 t), 26.0 (t), 26.1 (t), 42.8 (t), 43.1 (t), 47.7 (t), 47.8 (t), 116.1 (s), 125.2 (s), 129.0 (2 d), 129.8 (2 d), 134.9 (s), 156.9 (s), 157.4 (s), 159.0 (s), 159.7 (s) ppm. $C_{21}H_{24}ClN_3O_3$ (401.15): calcd. C 62.76, H 6.02, N 10.46; found C 62.66, H 6.06, N 10.42.

4-(4-Nitrophenyl)(isoxazole-3,5-dicarbonyl)bispiperidine (5Fa): White needles; m.p. 180–181 °C. IR (KBr): $\tilde{\nu}$ = 2950, 1650, 1520, 1345, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.35 (m, 2 H, CH_2), 1.35–1.42 (m, 2 H, CH_2), 1.58–1.69 (m, 8 H, 4 CH_2), 3.20 (t, J = 5.5 Hz, 2 H, NCH_2), 3.24 (t, J = 5.5 Hz, 2 H, NCH_2), 3.63–3.73 (m, 4 H, 2 NCH_2), 7.79 (d, J = 8.8 Hz, 2 H, ArH), 8.26 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.0 (2 t), 25.20 (t), 25.25 (t), 26.17 (t), 26.25 (t), 43.0 (t), 43.3 (t), 47.8 (t), 48.0 (t), 115.7 (s), 123.9 (2 d), 129.4 (2 d), 133.5 (s), 147.6 (s), 156.6 (s), 156.9 (s), 158.5 (s), 160.8 (s) ppm. $C_{21}H_{24}N_4O_5$ (412.17): calcd. C 61.15, H 5.87, N 13.58; found C 61.11, H 5.86, N 13.61.

4-(4-Cyanophenyl)(isoxazole-2,5-dicarbonyl)bispiperidine (5Ga): White needles; m.p. 187–188 °C. IR (KBr): $\tilde{\nu}$ = 2945, 1645, 1255, 1215, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.42 (m, 4 H, 2 CH_2), 1.51–1.70 (m, 8 H, 4 CH_2), 3.18 (t, J = 5.6 Hz, 2 H, NCH_2), 3.22 (t, J = 5.6 Hz, 2 H, NCH_2), 3.64–3.72 (m, 4 H, 2 NCH_2), 7.69 (d, J = 8.7 Hz, 2 H, ArH), 7.72 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.1 (2 t), 25.29 (t), 25.33 (t), 26.2 (t), 26.3 (t), 43.1 (t), 43.4 (t), 47.9 (t), 48.0 (t), 112.6 (s), 116.0 (s), 118.2 (s), 129.2 (2 d), 131.7 (s), 132.6 (2 d), 156.7 (s), 157.1 (s), 158.7 (s), 160.7 (s) ppm. $C_{22}H_{24}N_4O_3$ (392.18): calcd. C 67.33, H 6.16, N 14.28; found C 67.08, H 6.12, N 14.29.

Ethyl 3-Benzoyl-4-phenylisoxazole-5-carboxylate (13Ab): White powders; m.p. 74–75 °C. IR (KBr): $\tilde{\nu}$ = 2980, 1740, 1230, 1210, 1015 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 4.37 (q, J = 7.1 Hz, 2 H, OCH_2), 7.29–7.44 (m, 5 H, ArH), 7.49 (t, J = 7.5 Hz, 2 H, ArH), 7.64 (t, J = 7.5 Hz, 1 H, ArH), 8.05 (d, J = 7.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9 (q), 62.4 (t), 125.8 (s), 126.7 (s), 128.1 (2 d), 128.7 (2 d), 129.0 (d), 129.9 (2 d), 130.5 (2 d), 134.6 (d), 135.7 (s), 156.0 (s), 156.7 (s), 160.4 (s), 185.9 (s) ppm. $C_{19}H_{15}NO_4$ (321.10): calcd. C 71.02, H 4.71, N 4.36; found C 70.97, H 4.68, N 4.30.

Ethyl 3-Benzoyl-4-(4-bromophenyl)isoxazole-5-carboxylate (13Bb): Yellow oil. IR (KBr): $\tilde{\nu}$ = 2925, 1735, 1230, 1180, 1005 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H, CH_3), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2), 7.27 (d, J = 8.3 Hz, 2 H, ArH), 7.50 (t, J = 7.8 Hz, 2 H, ArH), 7.51 (d, J = 8.3 Hz, 2 H, ArH), 7.66 (t, J = 7.8 Hz, 1 H, ArH), 8.06 (d, J = 7.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9 (q), 62.5 (t), 123.5 (s), 124.7 (s), 125.7 (s), 128.8 (2 d), 130.5 (2 d), 131.3 (2 d), 131.6 (2 d), 134.7 (d), 135.5 (s), 156.1 (s), 156.4 (s), 160.0 (s), 185.6 (s) ppm. HMRS (EI): calcd. for $C_{19}H_{14}BrNO_4$ 399.0109; found 399.0108.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of the isoxazoles.

Acknowledgments

We are grateful to the National Science Council of ROC for financial support. (Grant No. NSC-98–2113-M-006–003-MY2)

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[13] Crystal data for **4Ba**: $C_{18}H_{19}BrN_2O_4$, M = 407.26, T = 200(2)°K, λ = 0.71073 Å, triclinic, space group $P1$, a = 9.4050(2) Å, b = 9.5540(3) Å, c = 10.8065(3) Å, α = 91.0610(10)°, β = 113.5600(10)°, γ = 91.2630(10)°, V = 889.47(4) Å^3, Z = 2, $D_{calcd.}$ = 1.521 mg m^{-3}, μ = 2.336 mm^{-1}, F (000) = 416, crystal size 0.41 × 0.37 × 0.35 mm^3, reflections collected 9345, independent reflections 3110 (R_{int}= 0.0394), refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.203, final R indices [$I>2\sigma$ (I)] R_1 = 0.0306, wR_2 = 0.0791, R indices (all data) R_1 = 0.0372, wR_2 = 0.0962, largest diff. peak and hole 0.284 and –0.451 e Å^{-3}. CCDC-764659 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Received: March 24, 2010
Published Online: August 3, 2010

