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# Cross-Metathesis Coupling for Access to Some New α,β-Unsaturated Esters Derived from 2-Mercaptobenzoxazole

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**Abstract:**
This study involves the synthesis of eight α,β-unsaturated ester compounds, obtained from 2-mercaptobenzoxazoles **3-10** by a two-step reaction. The first step included *S*-allylation of 2-mercaptobenzoxazole (**1**) with allyl bromide to furnish 2-(allylthio)benzo[d]oxazole (**2**) in a good yield (71%). The second step involved a cross-metathesis reaction of compound **2** with acrylate esters, which afforded the title products **3-10** in yields between 70 and 86%. The structure of the prepared compounds (**2-10**) was confirmed by FT-IR, $^{1}$H NMR, and $^{13}$C NMR spectroscopy.

**Keywords:** Allylation, Cross-Metathesis Coupling, 2-Mercaptobenzoxazole.

# ازدواج التقاطع المتبادل للوصول الى بعض استرات ألفا،بيتا–غير المشبعة الجديدة المشتقة من 2–مركابتوبنزوكسازول

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**الخلاصة**
تتضمن هذه الدراسة تحضير ثمانية استرات ألفا،بيتا–غير المشبعة مشتقة من 2–مركابتوبنزوكسازول **3–10** عن طريق تفاعل من خطوتين. تضمنت الخطوة الأولى S–allylation لـ 2–مركابتوبنزوكسازول (**1**) مع بروميد الأليل لتزويد مركب **2** بإنتاجية جيدة (71%). تضمنت الخطوة الثانية تفاعل تقاطع متبادل لمركب **2** مع استرات الأكريليت، مما أعطى النواتج المعنونة **3–10** في إنتاجية تتراوح بين 70 و 86%. تم التأكد من تركيب المركبات المحضرة (**2–10**) بواسطة مطيافية مطيافية الاشعة تحت الحمراء و الرنين النووي المغناطيسي للهيدروجين و الكاربون.

## 1. Introduction

Benzoxazole, also known as 1-oxa-3-aza-1*H*-indene, is a highly significant heterocyclic pharmacophore [1]. This molecule contains fused benzene and oxazole earrings, forming a bicyclic heteroaromatic machine. Moreover, this bicyclic scaffold has been identified in numerous natural products, which play a pivotal role in drug discovery and the development of pharmacological probes. Heterocycles like benzoxazole are considered privileged scaffolds because of their tremendous presence and importance in medicinal chemistry. For instance, Neosalvianen (anticancer), Calcimycin (antibacterial and antifungal), Nakijinol B (anticancer), Cezomycin (antibacterial), Nocarbenzoxazole G (anticancer), and Pseudopteroxazole

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(antitubercular) [2-5] (Figure 1, A). It is also present in a variety of pharmaceutically active synthetic products, such as Caboxamycin and Zinbo-5, which show significant antibiotic and antifungal activities. Tafamidis is used as a medication for deadly neurodegenerative diseases. Also, Benoxaprofen and Funoxaprofen were employed as anti-inflammatory drugs. Boxazomycin B showed important activity against bacteria [6-13] (Figure 1, B). Moreover, numerous other different benzoxazole derivatives showed significant biological activities, such as anticancer [14], antileishmanial [15], anti-HIV [16], anti-inflammatory [17], antituberculosis [18], antimicrobial [19], antifungal [20], anticonvulsant [21], cyclooxygenase inhibitory [22], 5-lipoxygenase inhibitory [23], antihyperglycemic [24], dopamine $D_4$ agonists [25], amyloidogenesis inhibitors [26], rho kinase inhibitors [27], analgesic [28], and antioxidant [29]. Due to these features, new derivatives of benzoxazole will be synthesized in this work using a two-step synthetic strategy. Allylation of 2-mercaptobenzoxazole (**1**) with allyl bromide will be conducted in the first step to give the corresponding allyl derivative. This derivative will be subjected to cross-metathesis reactions with various acrylate esters to yield the desired, α,β-unsaturated esters containing the benzoxazole moiety.

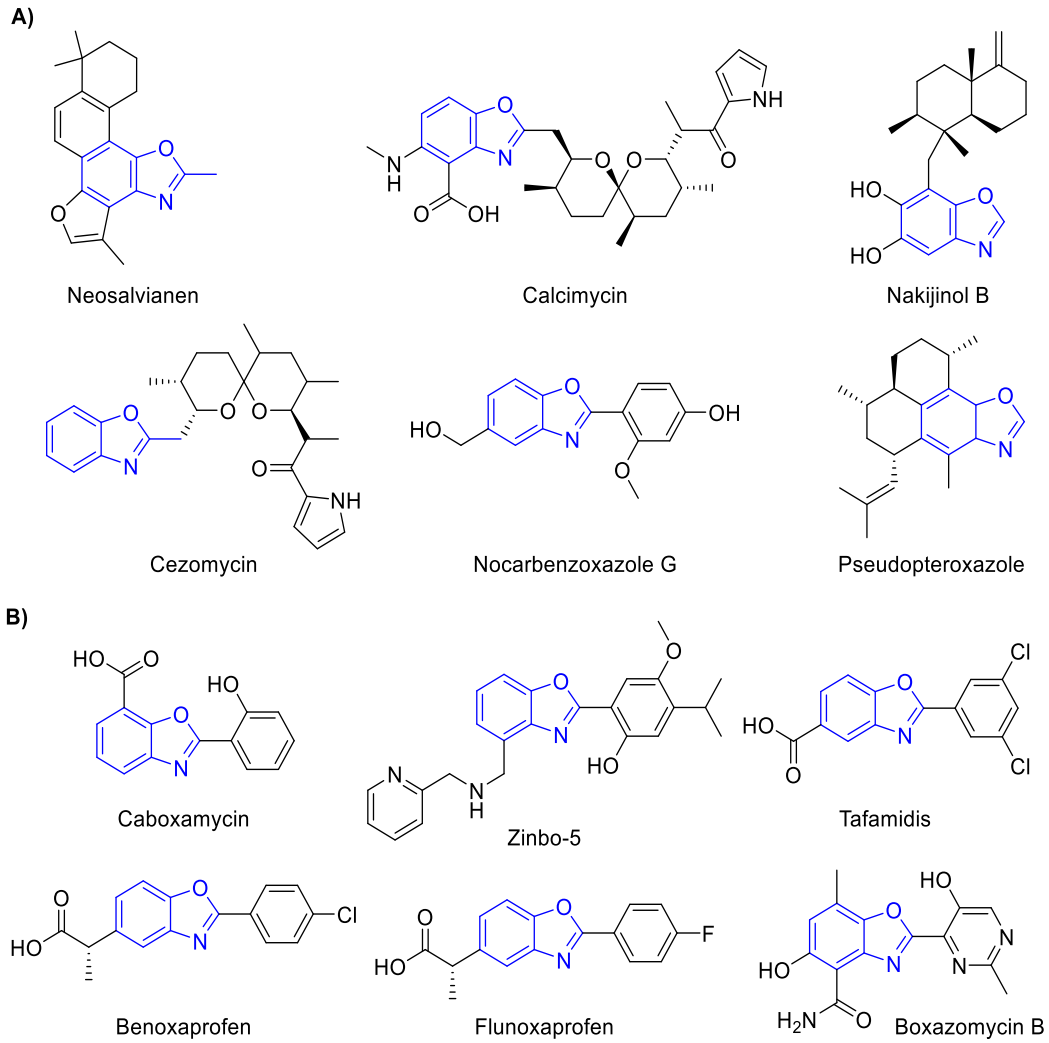



**Figure 1** : Some molecules bearing a benzoxazole moiety in their structures (A) Natural products (B). Synthetic pharmaceutical drugs

## 2. Experimental part

### *2.1. Chemicals and instruments*

The chemicals that were used in this research were obtained from commercial sources and employed without undergoing any further purification steps. The progress of all reactions was observed *via* TLC plates, and the presence of spots was identified by means of aqueous alkaline potassium permanganate. Flash column chromatography was performed over Fluka 60 silica gel. The Perkin-Elmer 1600 FT-IR spectrometer was used to collect the infrared spectrum data. The melting points were determined without any corrections and measured using the Stuart Scientific SMP20 apparatus in open capillary tubes. Using a Bruker AV(III)400HD spectrometer at the School of Chemistry, University of Nottingham, $^{1}H$ and $^{13}C$ NMR analysis data were obtained. Chemical shifts are often expressed in ppm relative to tetramethylsilane (TMS) as an internal standard or $CDCl_3$ as a reference point in both $^{1}H$ NMR ($\delta_H$ 7.26 ppm) and $^{13}C$ NMR ($\delta_H$ 77.16 ppm).

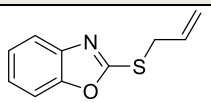
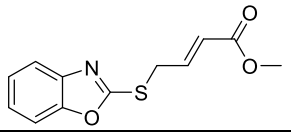
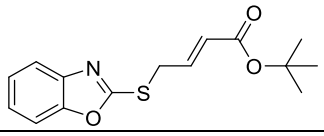
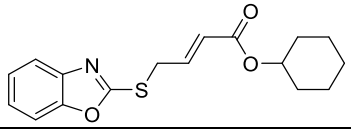
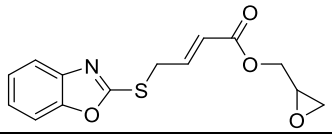
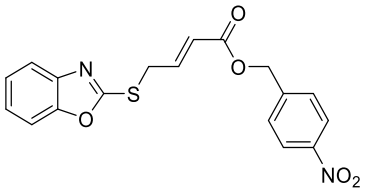
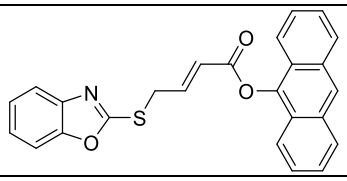
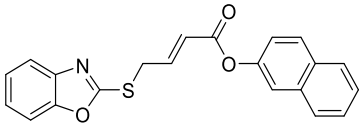
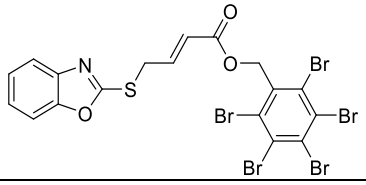
### *2.2. Preparation of 2-(allylthio)benzo[d]oxazole (**2**)*

The synthesis of compound **2** was carried out following a modified literature procedure [30]. Benzo[d]oxazole-2-thiol (1) (5 g, 33 mmol, 1.0 eq.) was dissolved in dioxane (60 mL), and the solution was cooled to 0 °C. Subsequently, sodium hydride (1.32 g, 55 mmol, 1.0 eq., 60% dispersion in mineral oil) in dioxane (15 mL) was added dropwise. After stirring for 15 minutes, allyl bromide (3.14 mL, 36.3 mmol, 1.2 eq.) was slowly added. The reaction mixture was then heated at 60 °C for 7 hours. The progress of the reaction was monitored using TLC (eluent with petroleum ether/ethyl acetate, 5:1) until no benzo[d]oxazole-2-thiol remained. Subsequently, the reaction was quenched using a saturated aqueous solution of $NH_4Cl$ (30 mL). The organic layer was separated with ethyl acetate (2 × 20 mL), rinsed with brine (30 mL), dried with $Na_2SO_4$ (anhydrous), and concentrated under reduced pressure. Purification using flash column chromatography (petroleum ether/ethyl acetate, 5:1) provided the title product **2**. The physical properties of product **2** are listed in Table 1.

### *2.3. Cross-metathesis procedure for the preparation of α,β-unsaturated esters **3-10*** [31]

A flame-dried two-neck round bottom flask equipped with a condenser and a rubber septum containing a stirring bar was charged with 2-(allylthio)benzo[d]oxazole (**2**) (191 mg, 1.0 mmol, 1.0 eq.), acrylate ester derivatives (methyl acrylate, *tert*-butyl acrylate, cyclohexyl acrylate, oxiran-2-ylmethyl acrylate, 4-nitrobenzyl acrylate, anthracen-9-yl acrylate, naphthalen-2-yl-but-2-enoate, and (perbromophenyl)methyl acrylate (3.0 mmol, 3.0 eq.), and CuI (6 mg, 30 μmol, 3.0 mol%) in anhydrous $Et_2O$ (20 mL) under an argon atmosphere and stirred for 10 minutes. The reaction was then refluxed at 40 °C, and Grubbs II catalyst (17 mg, 20 μmol, 2.0 mol%) in anhydrous $Et_2O$ (15 mL) was slowly added over 45 minutes. The progress of the reaction was monitored using thin-layer chromatography (TLC) with a petroleum ether/ethyl acetate solvent system as the eluent. Upon consumption of the starting materials, as indicated by TLC analysis, the reaction mixture was allowed to cool to room temperature. After adding silica gel (2-4 g) to the reaction mixture, the resulting suspension was concentrated *in vacuo*. The cross-metathesis adducts **3-10** were obtained after the crude material was purified by flash column chromatography (petroleum ether/ethyl acetate). The physical properties of products **3-10** are shown in Table 1.

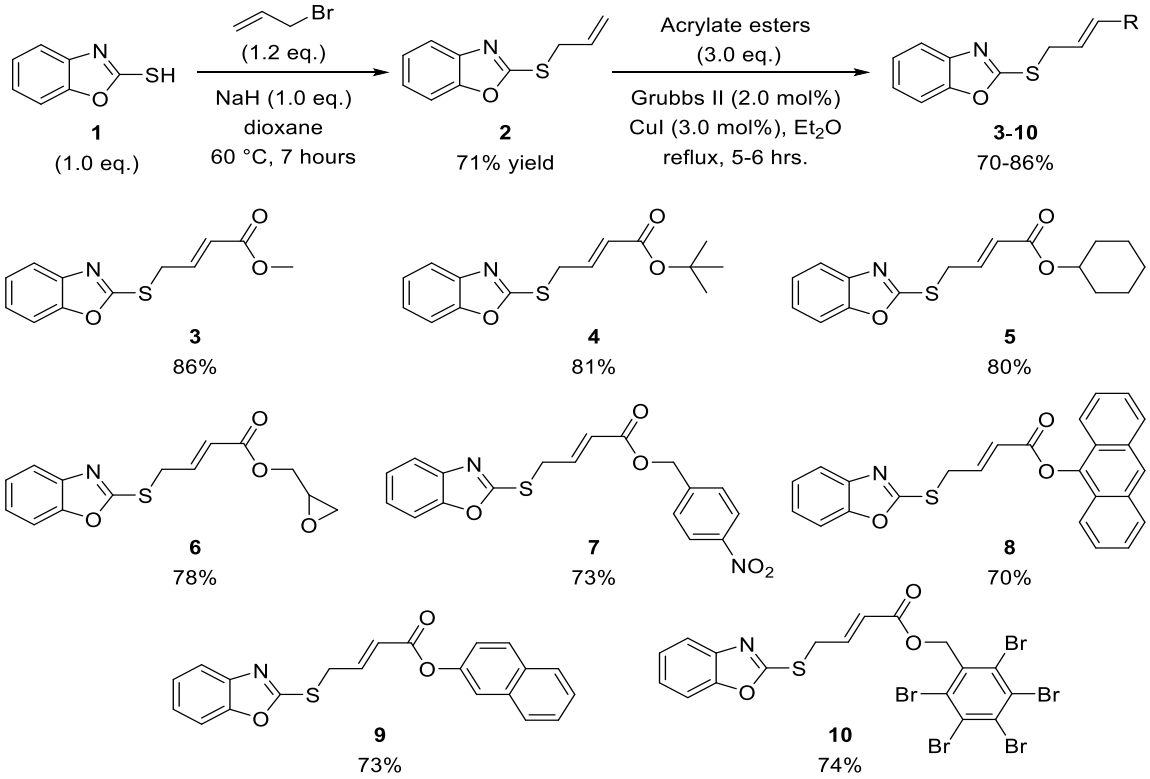
**Table 1** : Some physical properties of the synthesized products **2-10**

| No | Structure | m.p. (°C) | M.wt (g/mol) | Chemical formula | Color | Rf | Time (hour) | Yield (%) | Eluent ratio (Pet/EtOAc) |
|---|---|---|---|---|---|---|---|---|---|
| 2 |  | 161-163 | 191.25 | $C_{10}H_9NOS$ | Yellow | 0.25 | 7 | 71 | 3:1 |
| 3 |  | 102-104 | 249.28 | $C_{12}H_{11}NO_3S$ | Yellow | 0.28 | 5 | 86 | 3:1 |
| 4 |  | 111-113 | 291.37 | $C_{15}H_{17}NO_3S$ | Pale yellow | 0.25 | 5 | 81 | 3:1 |
| 5 |  | 124-126 | 317.40 | $C_{17}H_{19}NO_3S$ | Yellow | 0.3 | 6 | 80 | 4:1 |
| 6 |  | 99-101 | 291.32 | $C_{14}H_{13}NO_4S$ | Yellow | 0.25 | 5 | 78 | 3:1 |
| 7 |  | 103-105 | 325.38 | $C_{18}H_{15}NO_3S$ | Pale yellow | 0.30 | 5 | 73 | 4:1 |
| 8 |  | 209-211 | 411.48 | $C_{25}H_{17}NO_3S$ | Deep yellow | 0.27 | 6 | 70 | 5:1 |
| 9 |  | 198-200 | 361.08 | $C_{21}H_{15}NO_3S$ | Pale yellow | 0.28 | 6 | 73 | 5:1 |
| 10 |  | 155-157 | 719.86 | $C_{18}H_{10}Br_5NO_3S$ | Pale yellow | 0.25 | 6 | 74 | 3:1 |

## 3. Results and discussion

Nucleophilic substitution of 2-mercaptobenzoxazole (**1**) with allyl bromide in the first step of this study provided 2-allylthiobenzo[d]oxazole (**2**) in 71% yield (Scheme 1). The FT-IR spectral data of product **2** showed the absence of the thiol hydrogen signal of 2-mercaptobenzoxazole (**1**) [32], showing that it was converted successfully. Furthermore, the existence of C=C double bonds for the allyl group at product **2** was revealed by the formation of new absorption at 1652 $cm^{-1}$ [33]. The $^1H$ NMR spectral data of product **1** revealed multiple signals at 7.40-7.36 ppm and 7.24-7.17 ppm due to the four aromatic protons of the benzoxazole moiety. Three olefinic protons of the allyl group were observed in 5.90-5.84 (C-H) and 5.10-5.05 ($CH_2$). The chemical shift range of 2.76-2.67 is for the $CH_2$ of the allyl group. The $^{13}C$

NMR spectral data of product **2** showed the desired number of pecks (10 peaks). The second part of this work is the cross-metathesis coupling between compound **2** and different acrylate ester derivatives, which afforded the desired metathesis adducts **3-10** in 70-86% yields (Scheme 1). Because it acts as a phosphine scavenger, copper iodide was utilized in this stage as a co-catalyst with the Grubbs II catalyst to increase the reaction rate [34]. The FT-IR spectral data of products **3-10** revealed new absorption bands at 1713-1730 $cm^{-1}$ belong to the carbonyl of the ester groups that formed in this coupling. The double bond absorptions of the α,β-unsaturated ester were observed between 1602-1639 $cm^{-1}$, which were lower than the double bond absorptions in product **2**. This is attributed to the conjugation of the double bond with the carbonyl group in compounds **3-10**. In product **7**, the asymmetric and symmetric absorptions of the $NO_2$ group appeared at 1524 and 1365 $cm^{-1}$, respectively [35,36]. In the $^1H$ NMR spectral analysis of compounds **3**, **4**, **7**, and **10**, the characteristic signals are the two olefinic protons of the α,β-unsaturated ester moiety, which appeared in the normal range (6.15-5.00 ppm) [37]. New signals confirmed the conversion to products **3**, **4**, **7**, and **10**. For example, a singlet signal at 3.87 ppm belongs to the $CH_3$ group at product **3**, and nine protons appear at 1.42 ppm, attributed to the tertiary butyl group at product **4**. Also, the singlet signals at 5.47 and 5.42 ppm for the two protons of the benzyl and substituted benzyl groups, respectively, at products **7** and **10**. The desired number of signals at compounds **3**, **4**, **7**, and **10** were observed in $^{13}C$ NMR spectra. Table 2 lists all FT-IR analysis data for products **2-10**. All the $^1H$ NMR and $^{13}C$ NMR analysis data for products **2**, **3**, **4**, **7**, and **10** are shown in Table 3




**Scheme 1** : Synthesis of α,β-unsaturated esters **3-10** bearing a thiobenzoxazole moiety

**Table 2** : Characteristic FT-IR analysis data (υ, $cm^{-1}$) of products **2-10**

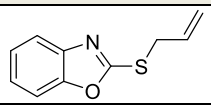
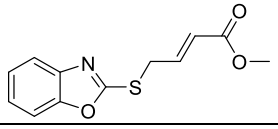
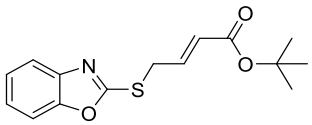
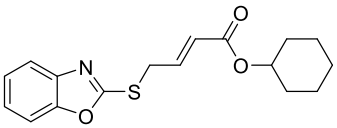
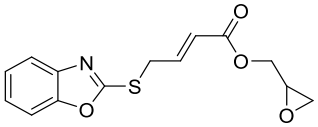
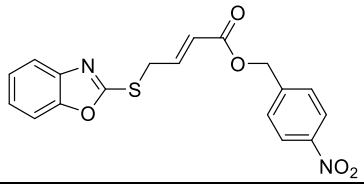
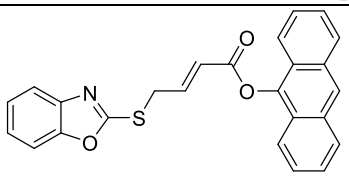
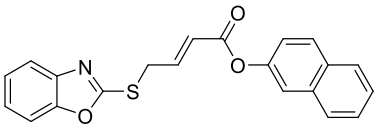
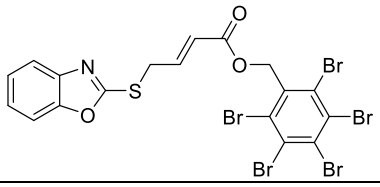
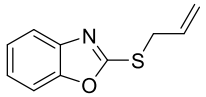
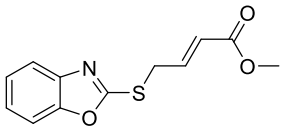
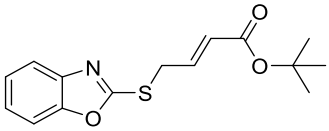
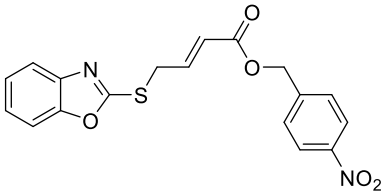
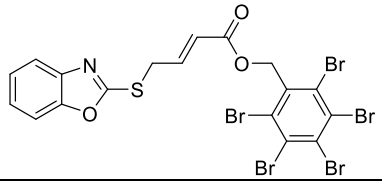
| No | Structure | C-H Aromatic | C-H Aliphatic | C=O Ester | C=N Imine | C=C Aliphatic | C=C Aromatic | C-O-C Ether |
|---|---|---|---|---|---|---|---|---|
| 2 |  | 3090<br>2841 | 2975<br>2839 | | 1684 | 1652 | 1537 | - |
| 3 |  | 3014 | 2935<br>2872 | 1730 | 1649 | 1639 | 1510 | 1212<br>1124 |
| 4 |  | 3016 | 2975<br>2974 | 1713 | 1650 | 1620 | 1576 | 1256<br>1150 |
| 5 |  | 3077<br>3034 | 2960<br>2863 | 1720 | 1653 | 1610 | 1583 | 1263<br>1155 |
| 6 |  | 3064<br>3034 | 2986<br>2877 | 1717 | 1654 | 1613 | 1589 | 1252<br>1154 |
| 7 |  | 3062<br>3007 | 2989<br>2850 | 1730 | 1649 | 1602 | 1579 | 1265<br>1116 |
| 8 |  | 3061<br>3033 | 2976<br>2865 | 1717 | 1679 | 1634 | 1597 | 1266<br>1149 |
| 9 |  | 3063<br>3033 | 2926<br>2854 | 1721 | 1652 | 1613 | 1593 | 1265<br>1120 |
| 10 |  | 3012 | 2977<br>2867 | 1726 | 1684 | 1627 | 1574 | 1267<br>1161 |

**Table 3** : $^{1}$H NMR and $^{13}$C NMR analysis data (δ, ppm) of products **2**, **3**, **4**, **7**, and **10**

| No. | Compound structure | $^{1}$H NMR and $^{13}$C NMR spectral data (δ, ppm) |
|---|---|---|
| 2 |  | **$^{1}$H NMR**: 7.40-7.36 (2H, m, Ar-H), 7.24-7.17 (2H, m, Ar-H), 5.90-5.84 (1H, m, CH), 5.10-5.05 (2H, m, $CH_2$), 2.76-2.67 (2H, m, $CH_2$). **$^{13}$C NMR**: 180.1, 148.1, 136.1, 131.9, 124.9, 124.4, 115.7, 110.9, 110.1, 36.2. |
| 3 |  | **$^{1}$H NMR**: 7.43-7.33 (2H, m, Ar-H), 7.32-7.17 (2H, m, Ar-H), 5.98-5.94 (1H, m, CH), 5.21-5.14 (1H, m, CH), 3.87 (3H, s, $CH_3$), 2.80-2.71 (2H, m, $CH_2$). **$^{13}$C NMR**: 180.1, 166.4, 148.1, 146.4, 132.0, 131.2, 124.8, 124.2, 110.5, 110.0, 51.4, 36.4. |
| 4 |  | **$^{1}$H NMR**: 7.46-7.34 (2H, m, Ar-H), 7.21-7.08 (2H, m, Ar-H), 6.15-6.11 (1H, m, CH), 5.28-5.22 (1H, m, CH), 2.73-2.67 (2H, m, $CH_2$), 1.42 (9H, s, $CH_3$). **$^{13}$C NMR**: 180.2, 166.0, 148.3, 146.2, 132.3, 131.1, 124.9, 124.1, 110.4, 110.1, 80.5, 36.6, 28.9. |
| 7 |  | **$^{1}$H NMR**: 7.47-6.87 (8H, m, Ar-H), 6.06-5.95 (1H, m, CH), 5.47 (2H, s, $CH_2$), 5.19-5.0 (1H, m, CH), 2.84-2.67 (2H, m, $CH_2$). **$^{13}$C NMR**: 180.1, 166.2, 148.5, 146.1, 138.2, 136.9, 136.1, 134.4, 132.4, 131.2, 124.8, 124.2, 110.5, 110.2, 66.3, 36.5. |
| 10 |  | **$^{1}$H NMR**: 7.40-7.03 (4H, m, Ar-H), 6.04-6.00 (1H, m, CH), 5.42 (2H, s, $CH_2$), 5.20-5.12 (1H, m, CH), 2.75-2.72 (2H, m, $CH_2$). **$^{13}$C NMR**: 180.2, 166.3, 148.1, 146.8, 140.5, 139.1, 138.2, 134.9, 132.4, 131.1, 125.6, 124.9, 110.9, 110.3, 66.9, 36.4. |

## 4. Conclusion

The synthesis of the new eight α,β-unsaturated ester derivatives **3-10** bearing a thiobenzoxazole moiety has been achieved successfully by a two-step method. The allylation of 2-mercaptobenzoxazole (**1**) was employed to give the corresponding allyl derivative **2**. The subsequent step involved a cross-metathesis reaction, which afforded the α,β-unsaturated ester compounds **3-10** in yields ranging from 70 to 86%. The identification of the isolated compounds was accomplished by the use of FT-IR, $^{1}$H NMR, and $^{13}$C NMR spectroscopic methods.

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