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One-pot synthesis of 4-ethyl 2,3-dimethyl 1-(5-aryl-1,3,4-thiadiazol-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3,4-tricarboxylate derivatives via intramolecular Wittig reaction

Samin Iravani and Abbas Ali Esmaeili

Abstract

A facile one-pot synthesis of highly functionalized dialkyl 1-(5-aryl-1,3,4-thiadiazol-2-yl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate derivatives via the reaction between acetylenic esters, triphenylphosphine, and ethyl 2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino]-2-oxoacetate is developed. The structure of the products is confirmed by spectroscopic methods.

Keywords

acetylenic esters, intramolecular Wittig reaction, pyrrolidinone, ethyl 2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino]-2-oxoacetate, triphenylphosphine

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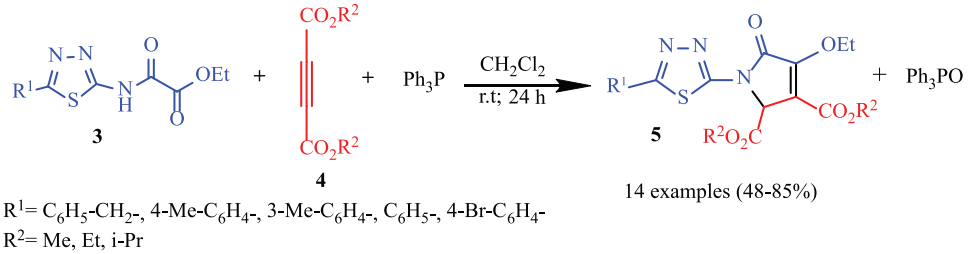
One-pot synthesis of 4-ethyl 2,3-dimethyl 1-(5-aryl-1,3,4-thiadiazol-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3,4-tricarboxylate derivatives *via* intramolecular Wittig reaction.



Introduction

Exhibiting interesting biological behavior, heterocyclic compounds have found a special place in the pharmaceutical industry.[1,2] Many substances containing five-membered heterocycles demonstrate a variety of interesting biological activities. In this category, 1,3,4-thiadiazoles and 2-pyrrolidinones have been used as structural motifs in the construction of substances having multi-target active, such as anti-inflammatory,[3,4] antimicrobial,[5] anticonvulsant,[6,7] and antihypertensive.[8,9] 1,3,4-Thiadiazoles have also been frequently used as important building blocks for the synthesis of biologically active heterocyclic molecules. Heterocycles, bearing a 1,3,4-thiadiazole moiety, are reported to demonstrate a broad spectrum of biological activity such as antimicrobial, tranquilizer, antiepilepsy, antiinflamatory, antiviral, anti-coagulant, and antitumor (Figure 1, structures **A** and **B**).[10,11] As for other examples, and compound **C** displays both antibacterial along with antifungal activity, while compound **D** is an effective antitumor agent (Figure 1).[12]

Moreover, 2-pyrrolidinones, as a class of five-membered lactams with a four-carbon heterocyclic ring structure, are of interest to biologists.[13,14] 2-Pyrrolidinone play a significant role in natural products and pharmaceuticals. Some known biologically important natural products

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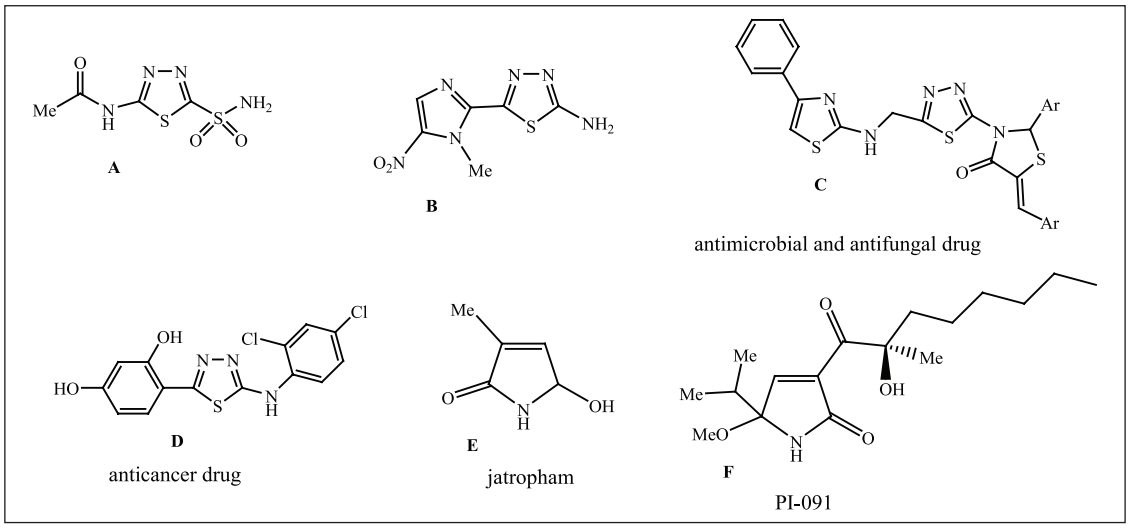
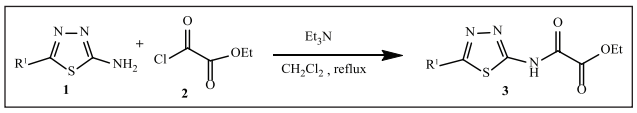


Figure 1. Biologically active thiadiazole and lactam molecules.



Scheme 1. Synthesis of ethyl 2-oxo-2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino] acetates.

comprising a 2-pyrrolidinone unit are cotinine, a tobacco alkaloid,[15] doxapram, a respiratory stimulatant,[16] and ethosuximide, a succinimide containing anticonvulsant.[17] Moreover, substituted 2-pyrrolidinone derivatives have various therapeutic properties, for example, anti-cancer,[18] antitumor,[19] HIV-1 integrase inhibition,[20,21] antimicrobial,[22] antibacterial,[23] and anti-inflammatory.[24] In addition, the 2-pyrrolidinone moiety is used in the drug PI-091, consisting of anti-coagulant properties, as well as in Jatropham, which is an antitumor alkaloid (Figure 1, structures **E** and **F**).[25,26] Due to their importance, a variety of synthetic protocols have been reported for the preparation of substituted pyrrolidinones.[27–36]

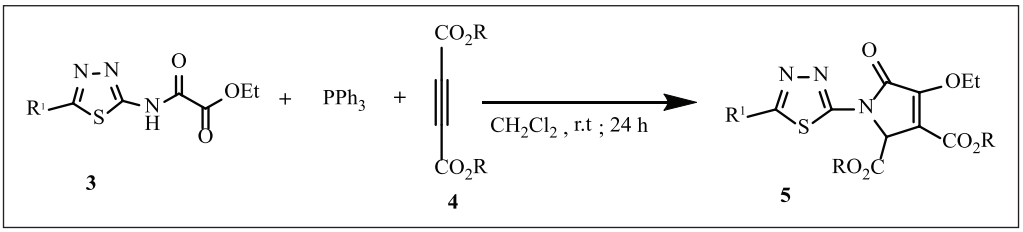
The Wittig reaction of phosphonium ylides with carbonyl compounds has been adopted widely for the construction of C=C double bonds in an inter- or intramolecular approach under mild reaction conditions.[37,38] The intramolecular Wittig reaction is one of the most common methods for the synthesis of different five-membered heterocycles through intramolecular cyclization of phosphorus ylides with various carbonyl groups, such as aldehyde, ketone, ester, amide, and imide.[39–43] To date, a number of synthetic approaches to pyrrolidinones structures have been developed.[44–49] In 2007, Anary-Abbasinejad et al.[50] reported the synthesis of novel highly functionalized pyrrolidinones via intramolecular Wittig reactions. Inspired by the biological profiles of 1,3,4-thiadiazoles and pyrrolidinones and as part of our interest in the synthesis of heterocyclic compounds via intramolecular Wittig reactions,[51,52] we sought to synthesize the title compounds. For this purpose, first ethyl chlorooxoacetate was reacted with 2-amino-1,3,4-thiadiazoles for the synthesis of ethyl 2-oxo-2-[(5-aryl-1,3,4-thiadiazol-2-yl) amino]acetate derivatives (Scheme 1). Subsequent reaction with triphenylphosphine and acetylenic esters gave the desired products (Scheme 2).

Results and discussion

Initially, a model reaction was conducted using triphenylphosphine (1 mmol), ethyl (5-benzyl-1,3,4-thiadiazol-2-ylcarbamoyl)formate (**3a**) (1 mmol), and dimethyl acetylenedicarboxylate (DMAD) (**4a**) (1 mmol) in CH_2Cl_2 at room temperature. This model reaction was examined under different conditions, as shown in Table 1. Upon changing the solvent, temperature, and amount of triphenylphosphine, it was found that using CH_2Cl_2 and 1.5 equiv. of Ph_3P the desired product can be afforded in 70% yield in 24 h (Table 1, entry 8).

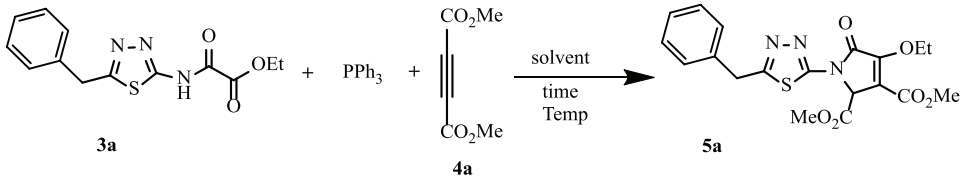
Ultimately, CH_2Cl_2, room temperature, and 1.5 mmol triphenylphosphine were selected as the optimized conditions. With optimized conditions established, we next tested the scope of various reactants. Ethyl 2-oxo-2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino]acetates **3** were examined in reactions with dialkyl acetylenedicarboxylates **4** in the presence of Ph_3P via a one-pot procedure leading to the corresponding products **5a–n** in 48%–85% yields (Table 2). Ethyl 2-oxo-2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino] acetates containing electron-donating groups at positions 5, such as benzyl-, phenyl-, 4-methylphenyl-, and 3-methyphenyl-thiadiazole, exhibited good reactivities (**5**, 51%–71% yield). Ethyl 2-oxo-2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino] containing electron-withdrawing groups such as 4-bromophenyl group were also well tolerated (**5i**, 85% and **5n**, 48%).

The structure elucidation of compounds **5a–n** was carried out on the basis of ^{1}H NMR, ^{13}C NMR, Fourier-transform infrared spectroscopy (FTIR), mass spectrometry, and elemental analysis (Supplemental material). For example, the ^{1}H NMR spectrum of **5a** contained a triplet for CH_3 (1.42 ppm, $^3J_{HH} = 6.0$ Hz), two singlets for CH_3O (3.84 and 3.85 ppm), a singlet for $PhCH_2$ (4.36 ppm), a quartet for OCH_2 (4.75 ppm, $^3J_{HH} = 6.0$ Hz), a singlet for CH (5.58 ppm), and a multiplet for ArH (7.28–7.34 ppm). The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** is



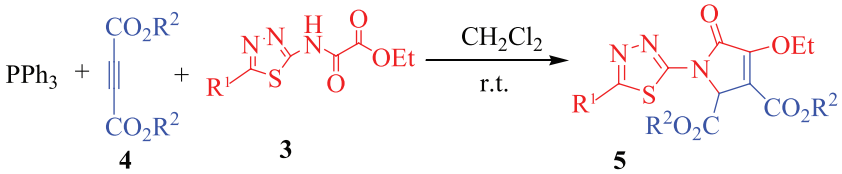
Scheme 2. Synthesis of the final products.

Table 1. Optimization of the reaction conditions.



Entry	Solvent	Time (h)	Temperature	Yield (%)
1	EtOAc	24	r.t.	50
2	MeCN	24	r.t.	65
3	MeCN	24	Reflux	65
4	EtOH	24	r.t.	43
5	THF	24	r.t.	27
6	DMF	24	r.t.	10
7	Et_2O	24	r.t.	60
8	CH_2Cl_2	24	r.t.	70
9	CH_2Cl_2	12	r.t.	50

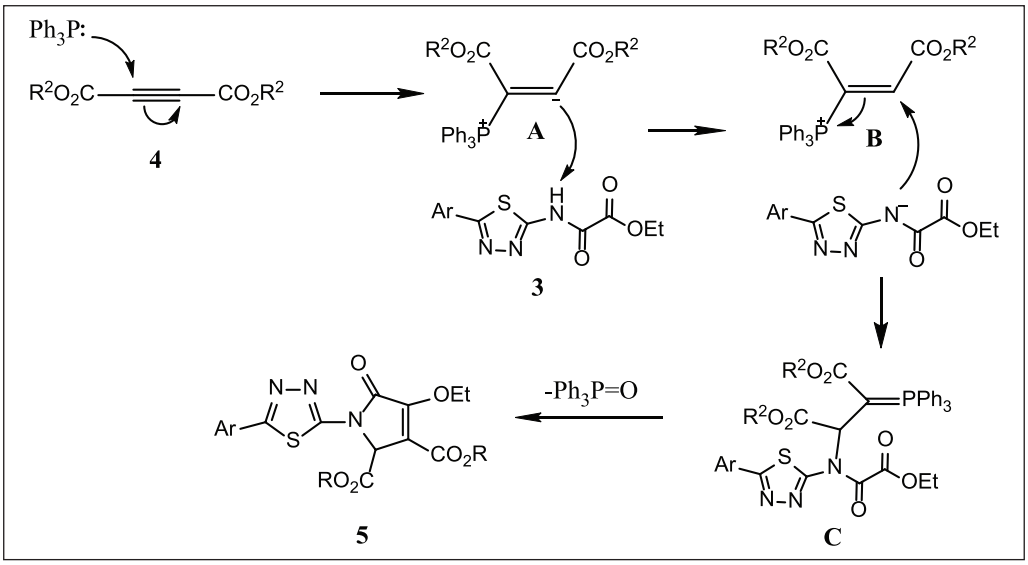
Table 2. Synthesis of compounds **5a–n**.



Product	R^1	R^2	Yield (%)
5a	C_6H_5–CH_2–	Me	70
5b	4-Me–C_6H_4–	Me	55
5c	3-Me–C_6H_4–	Me	79
5d	C_6H_5–	Me	57
5e	C_6H_5–CH_2–	Et	51
5f	4-Me–C_6H_4–	Et	54
5g	3-Me–C_6H_4–	Et	71
5h	C_6H_5–	Et	69
5i	4-Br–C_6H_4–	Et	85
5j	C_6H_5–CH_2–	i-Pr	71
5k	4-Me–C_6H_4–	i-Pr	67
5l	3-Me–C_6H_4–	i-Pr	61
5m	C_6H_5–	i-Pr	72
5n	4-Br–C_6H_4–	i-Pr	48

in agreement with the suggested structure. The mass spectrum of **5a**, for example, demonstrated the molecular ion peak at m/z=418. Also, the IR spectrum of compound **5a** showed absorption bands at 1750, 1641, and 1702 cm^{-1} due to the nonconjugated, conjugated, and Y-lactam carbonyl groups.

The reaction mechanism is presented in Scheme 3. The initial step is formation of zwitterion intermediate **A** from



Scheme 3. The mechanism of reaction.

the reaction of Ph_3P and dicarboxylate **4**. Next, the intermediate **A** is protonated by the NH amide of **3** to produce triphenylphosphonium salt **B**. The resulting phosphonium salt **B** is attacked by the conjugate base of the NH acid to give ylide **C**, which undergoes intramolecular cyclization to produce triphenylphosphine oxide and product **5** (Scheme 3).

Conclusion

In summary, we have established that the one-pot reaction between Ph_3P, acetylenic esters **4** and 2-[(5-aryl-1,3,4-thiadiazol-2-yl)amino]-2-oxoacetates **3** represents a simple method for the preparation of dialkyl 1-(5-aryl-1,3,4-thiadiazol-2-yl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **5** of potential synthetic and pharmacological interest. The ready availability of the starting materials, the simplicity of the reaction, and mild conditions are among the distinguishing features of this method. The present method is applied under neutral conditions with no prior activation required.

Experimental

Melting points were determined on an Electrothermal 9100 apparatus. Infrared (IR) spectra were recorded using a Nicolet Avatar 370 FTIR Therma spectrometer as KBr pellets and are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 Avance instrument at 300 and 75.47 MHz, respectively. $CDCl_3$ were used as the solvent and shifts are given in ppm. Elemental analyses were performed using a Thermo Finnegan Flash EA 1112 series instrument. Mass spectra were recorded with a Varian Meth ch-7 at 70 eV. Column chromatography was performed on silica gel (160–200 mesh, E. Merck). Thiadiazole derivatives 3, were prepared according to the literature source.[53]

Dimethyl 1-(5-benzyl-1,3,4-thiadiazol-2-yl)-4-ethoxy-2,5-dihydro-5-oxo-1*H*-pyrrole-2,3-dicarboxylate (**5a**); typical procedure

To a stirred solution of ethyl (5-benzyl-1,3,4-thiadiazol-2-ylcarbamoyl)formate (**5a**; 0.291 g, 1 mmol) and Ph_3P (0.393 g, 1.5 mmol) in CH_2Cl_2 (10 mL) at room temperature was added dropwise a solution of DMAD (0.142 g, 1.0 mmol) in CH_2Cl_2 (2 mL) over 10 min. The reaction mixture was stirred for 24 h. The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel (hexane/EtOAc) to obtain the dimethyl 1-(5-benzyl-1,3,4-thiadiazol-2-yl)-4-ethoxy-2,5-dihydro-5-oxo-1*H*-pyrrole-2,3-dicarboxylate (**5a**) (0.292 g, 70%) as a pale yellow powder.

Pale yellow powder (0.292 g, 70%), m.p. 118 °C–119 °C; IR (KBr) (υ_{max}/cm^{-1}): 1750, 1702, 1641 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.42 (3H, t, $^3J_{HH}$ = 6.0 Hz, $CH_2\underline{CH_3}$), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.36 (2H, s, CH_2), 4.75 (2H, q, $^3J_{HH}$ = 9.0 Hz, OCH_2), 5.58 (1H, s, CH), 7.28–7.34 (5H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.63, 36.42, 52.36, 53.63, 59.88, 69.09, 114.46, 127.55, 128.88, 129.06, 136.66, 152.44, 156.38, 161.58, 162.48, 166.04, 167.53; MS *m/z* (%) = 418 (M^++1, 37), 416 (100), 401 (38), 355 (10), 312 (85), 294 (43), 266 (50), 200 (17), 148 (45), 90 (47), 59 (10), 29 (22). Anal. calcd for $C_{19}H_{19}N_3O_6S$ (417.44): C, 54.67; H, 4.59; N, 10.07%. Found: C, 54.94; H, 4.59; N, 10.35%.

*Dimethyl 4-ethoxy-5-oxo-1-[5-(p-tolyl)-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5b**): White powder: (0.300 g, 55%), m.p. 178 °C; IR (KBr) (υ_{max}/cm^{-1}): 1747, 1725, 1698 (3 C=O), ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.49 (3H, t, $^3J_{HH}$ = 9.0 Hz, $CH_2\underline{CH_3}$), 2.44 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s, CH_3), 4.83 (2H, q, $^3J_{HH}$ = 6.0 Hz, OCH_2), 5.68

(1H, s, CH), 7.31 (2H, d, $^3J_{HH} = 9.0\,Hz$, 2 CH_{Ar}), 7.85 (2H, d, $^3J_{HH} = 9.0\,Hz$, 2 CH_{Ar}); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 10.91, 16.76, 47.65, 48.95, 55.25, 64.28, 109.71, 122.50, 122.62, 125.14, 136.73, 147.77, 150.45, 156.87, 157.78, 159.94, 162.78; MS *m/z* (%) = 417 (M^+, 55), 416 (100), 355 (17), 312 (100), 294 (65), 266 (85), 200 (30), 173 (27), 134 (30), 116 (22), 59 (25), 28 (17). Anal. calcd for $C_{19}H_{19}N_3O_6S$ (417.44): C, 54.67; H, 4.59; N, 10.07%. Found: C, 54.91; H, 4.39; N, 9.77%.

*Dimethyl 4-ethoxy-5-oxo-1-[5-(m-tolyl)-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5c**): White powder: (0.330 g, 79%), m.p. 160 °C–162 °C; IR (KBr) (υ_{max}/cm^{-1}): 1748, 1719, 1702 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.45 (3H, t, $^3J_{HH} = 6.0\,Hz$, $CH_2\underline{CH_3}$), 2.40 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.85 (3H, s, CH_3), 4.78 (2H, q, $^3J_{HH} = 9.0\,Hz$, OCH_2), 5.64 (1H, s, CH), 7.26–7.76 (4H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.60, 36.42, 52.33, 53.61, 59.84, 69.06, 77.20, 84.84, 114.39, 127.53, 128.85, 129.03, 136.60, 152.42, 156.35, 161.56, 162.29, 166.04, 167.50; MS *m/z* (%) = 418 ($M^+ + 1$, 40), 415 (100), 400 (22), 356 (35), 312 (95), 267 (95), 200 (78), 173 (83), 134 (70), 117 (95), 91 (48), 59 (95), 29 (67). Anal. calcd for $C_{19}H_{19}N_3O_6S$ (417.44): C, 54.67; H, 4.59; N, 10.07%. Found: C, 54.35; H, 4.34; N, 9.81%.

*Dimethyl 4-ethoxy-5-oxo-1-[5-phenyl-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5d**): pale yellow powder: (0.228 g, 57%), m.p. 153 °C–154 °C; IR (KBr) (υ_{max}/cm^{-1}): 1750, 1720, 1699 (3 C=O), ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.45 (3H, t, $^3J_{HH} = 6.0\,Hz$, $CH_2\underline{CH_3}$), 3.85 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.79 (2H, q, $^3J_{HH} = 6.0\,Hz$, OCH_2), 5.65 (1H, s, CH), 7.70 (5H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.60, 52.37, 53.66, 59.95, 69.20, 114.44, 127.39, 129.16, 129.92, 130.97, 152.41, 155.44, 161.55, 162.52, 164.49, 167.46; MS *m/z* (%) = 403 (M^+, 10), 400 (100), 298 (47), 280 (25), 253 (33), 202 (10), 160 (20), 103 (13), 59 (8), 29 (30). Anal. calcd for $C_{18}H_{17}N_3O_6S$ (403.41): C, 53.59; H, 4.25; N, 10.42%. Found: C, 53.37; H, 3.96; N, 10.22%.

*Diethyl 1-[5-benzyl-1,3,4-thiadiazol-2-yl]-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5e**): pale yellow liquid; (0.226 g, 51%); IR (KBr) (υ_{max}/cm^{-1}): 1740, 1722, 1638 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.29 (3H, t, $^3J_{HH} = 6.0\,Hz$, CH_2CH_3), 1.33 (3H, t, $^3J_{HH} = 6.0\,Hz$, OCH_2CH_3), 1.39 (3H, t, $^3J_{HH} = 6.0\,Hz$, OCH_2CH_3), 4.24–4.32 (4H, m, OCH_2), 4.34 (2H, s, CH_2), 4.71 (2H, q, $^3J_{HH} = 9.0\,Hz$, OCH_2) 5.58 (1H, s, CH), 7.24–7.35 (5H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 14.04, 15.52, 36.38, 60.09, 61.43, 62.73, 69.07, 84.84, 114.67, 127.49, 128.81, 129.00, 136.64, 152.28, 156.41, 160.99, 162.56, 165.97, 166.87; MS m/z (%) = 445 (M+, 65), 398 (32), 369 (95), 340 (95), 294 (94), 266 (100), 241 (37), 200 (87), 173 (92), 148 (47), 116 (26), 91 (95), 53 (10), 30 (92). Anal. calcd for $C_{21}H_{23}N_3O_6S$ (445.49): C, 56.62; H, 5.20; N, 9.43%. Found: C, 56.35; H, 4.96; N, 9.32%.

*Diethyl 4-ethoxy-5-oxo-1-[5-(p-tolyl)-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5f**): White powder (0.240 g, 54%), m.p. 124 °C–125 °C; IR (KBr) (υ_{max}/cm^{-1}): 1742, 1724, 1710 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm)= 1.31 (3H, t, $^3J_{HH} = 9.0\,Hz$, $CH_2\underline{CH_3}$), 1.34 (3H, t, $^3J_{HH} = 9.0\,Hz$, $OCH_2\underline{CH_3}$), 1.44 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 2.39 (3H, s, CH_3), 4.24–4.33 (4H, m, OCH_2), 4.76 (2H, q, $^3J_{HH} = 9.0\,Hz$, OCH_2), 5.63 (1H, s, CH), 7.26 (2H, d, $^3J_{HH} = 9.0\,Hz$, 2 CH_{Ar}), 7.81 (2H, d, $^3J_{HH} = 9.0\,Hz$, 2 CH_{Ar}); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 13.97, 14.05, 15.53, 21.44, 60.20, 61.45, 62.77, 69.17, 114.72, 127.23, 127.31, 129.81, 141.34, 152.29, 155.20, 161.02, 162.60, 164.54, 166.83; MS *m/z* (%) = 445 (M^+, 100), 369 (42), 340 (92), 312 (98), 294 (93), 266 (100), 200 (50), 174 (47), 134 (38), 116 (65), 29 (100). Anal. calcd for $C_{21}H_{23}N_3O_6S$ (445.49): C, 56.62; H, 5.20; N, 9.43%. Found: C, 56.76; H, 5.10; N, 9.62%.

*Diethyl 4-ethoxy-5-oxo-1-[5-(m-tolyl)-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5g**): White powder (0.318 g, 71%), m.p. 97 °C–98 °C; IR (KBr) (υ_{max}/cm^{-1}): 1754, 1726, 1699 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.31 (3H, t, $^3J_{HH} = 6.0\,Hz$, $CH_2\underline{CH_3}$), 1.35 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 1.44 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 2.41 (3H, s, CH_3), 4.25–4.34 (4H, m, OCH_2), 4.76 (2H, q, $^3J_{HH} = 6.0\,Hz$, OCH_2), 5.65 (1H, s, CH), 7.29–7.37 (4H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 14.06, 15.54, 21.29, 60.26, 61.48, 62.79, 69.20, 84.84, 114.70, 124.63, 127.94, 129.02, 129.84, 131.72, 138.99, 152.29, 155.40, 161.02, 162.63, 164.63, 166.84; MS *m/z* (%) = 445 (M^+, 100), 397 (5), 369 (58), 340 (90), 313 (100), 294 (90), 266 (100), 200 (50), 174 (55), 134 (33), 116 (60), 90 (18), 30 (85). Anal. calcd for $C_{21}H_{23}N_3O_6S$ (445.49): C, 56.62; H, 5.20; N, 9.43%. Found: C, 56.90; H, 4.96; N, 9.14%.

*Diethyl 4-ethoxy-5-oxo-1-[5-phenyl-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5h**): White powder (0.308 g, 69%), m.p. 99 °C–101 °C; IR (KBr) (υ_{max}/cm^{-1}): 1736, 1719, 1701 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.31 (3H, t, $^3J_{HH} = 6.0\,Hz$, $CH_2\underline{CH_3}$), 1.35 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 1.44 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 4.25–4.34 (4H, m, OCH_2), 4.76 (2H, q, $^3J_{HH} = 6.0\,Hz$, OCH_2), 5.64 (1H, s, CH), 7.45–7.94 (5H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 13.98, 14.06, 15.54, 60.21, 61.49, 62.81, 69.21, 114.75, 127.41, 129.14, 129.97, 130.91, 152.25, 155.51, 161.01, 162.65, 164.42, 166.82; MS *m/z* (%) = 431 (M^+, 100), 416 (13), 364 (45), 355 (85), 327 (87), 299 (87), 253 (93), 166 (79), 160 (79), 102 (79), 76 (68), 52 (32), 29 (95). Anal. calcd for $C_{20}H_{21}N_3O_6S$ (431.46): C, 55.68; H, 4.91; N, 9.74%. Found: C, 55.58; H, 4.83; N, 9.60%.

*Diethyl 1-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5i**): White powder (0.432 g, 85%), m.p. 128 °C–129 °C; IR (KBr) (υ_{max}/cm^{-1}): 1736, 1726, 1703 (3 C=O); ^1H NMR (300.13 MHz, $CDCl_3$): δ (ppm)= 1.31 (3H, t, $^3J_{HH} = 6.0\,Hz$, $CH_2\underline{CH_3}$), 1.35 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 1.44 (3H, t, $^3J_{HH} = 6.0\,Hz$, $OCH_2\underline{CH_3}$), 4.25–4.34 (4H, m, OCH_2), 4.75 (2H, q, $^3J_{HH} = 9.0\,Hz$, OCH_2), 5.64 (1H, s, CH), 7.60 (2H, d, $^3J_{HH} = 9.0\,Hz$, 2 CH_{Ar}), 7.80 (2H, d, $^3J_{HH} = 9.0\,Hz$, 2 CH_{Ar}); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 13.98, 14.06, 15.52, 60.23, 61.53, 62.85, 69.26, 84.84, 114.84, 125.31, 128.73, 132.38, 152.15, 155.63, 160.97, 162.69, 163.26, 166.75; MS *m/z* (%) = 510 (M^+, 78), 464 (5), 437 (78), 407 (79), 358 (78), 330 (80), 264 (48), 236 (45), 197 (43), 181 (75), 125 (55), 98 (50), 53 (45), 30 (100). Anal. calcd for

$C_{20}H_{20}BrN_3O_6S$ (510.36): C, 47.07; H, 3.95; N, 8.23%. Found: C, 47.38; H, 3.94; N, 8.05%.

*Diisopropyl 1-[5-benzyl-1,3,4-thiadiazol-2-yl]-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5j**): Colorless liquid (0.336 g, 71%); IR (KBr) (υ_{max}/cm^{-1}): 1739, 1719, 1638 (3 C=O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.24 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.32 (9H, d, $^3J_{HH}$ = 6.0 Hz, 3 CHC$\underline{H}_3$), 1.40 (3H, t, $^3J_{HH}$ = 6.0 Hz, $CH_2\underline{CH}_3$), 4.35 (2H, s, CH_2), 4.69 (2H, q, $^3J_{HH}$ = 6.0 Hz, OCH_2), 5.07 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.14 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.54 (1H, s, CH), 7.24–7.35 (5H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.47, 21.51, 21.55, 21.73, 21.77, 36.38, 60.40, 68.95, 69.45, 70.84, 84.84, 115.30, 127.47, 128.79, 128.99, 136.70, 151.92, 156.47, 160.59, 165.92, 166.18; MS *m/z* (%) = 473 (M^+, 25), 428 (65), 384 (87), 368 (65), 341 (73), 284 (85), 266 (100), 241 (80), 200 (78), 173 (68), 148 (65), 116 (58), 83 (92), 66 (90), 43 (83), 29 (70). Anal. calcd for $C_{23}H_{27}N_3O_6S$ (473.54): C, 58.34; H, 5.75; N, 8.87%. Found: C, 58.52; H, 5.79; N, 8.61%.

*Diisopropyl 4-ethoxy-5-oxo-1-[5-(p-tolyl)-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5k**): pale yellow powder (0.316 g, 67%), m.p. 146 °C–148 °C; IR (KBr) (υ_{max}/cm^{-1}): 1751, 1725, 1701 (3 C=O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.28 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.36 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.37 (6H, d, $^3J_{HH}$ = 6.0 Hz, 2 CHC$\underline{H}_3$), 1.47 (3H, t, $^3J_{HH}$ = 6.0 Hz, $CH_2\underline{CH}_3$), 2.43 (3H, s, C$\underline{H}_3$), 4.78 (2H, q, $^3J_{HH}$ = 6.0 Hz, OCH_2), 5.12 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.19 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.66 (1H, s, CH), 7.30 (2H, d, $^3J_{HH}$ = 9.0 Hz, 2 CH_{Ar}), 7.85 (2H, d, $^3J_{HH}$ = 9.0 Hz, 2 CH_{Ar}); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.54, 21.51, 21.58, 21.64, 21.79, 21.84, 60.56, 69.12, 69.57, 70.96, 115.37, 127.36, 127.41, 129.85, 141.34, 151.93, 155.32, 160.70, 162.83, 164.54, 166.16; MS *m/z* (%) = 473 (M^+, 95), 411 (40), 383 (90), 341 (77), 326 (85), 294 (82), 266 (100), 241 (78), 200 (75), 173 (73), 134 (50), 116 (73), 43 (90). Anal. calcd for $C_{23}H_{27}N_3O_6S$ (473.54): C, 58.34; H, 5.75; N, 8.87%. Found: C, 58.62; H, 5.70; N, 8.63%.

*Diisopropyl 4-ethoxy-5-oxo-1-[5-(m-tolyl)-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5l**): pale yellow powder (0.292 g, 61%), m.p. 107 °C–108 °C; IR (KBr) (υ_{max}/cm^{-1}): 1732, 1700, 1637 (3 C=O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.24 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.33 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.34 (6H, d, $^3J_{HH}$ = 6.0 Hz, 2 CHC$\underline{H}_3$), 1.44 (3H, t, $^3J_{HH}$ = 6.0 Hz, $CH_2\underline{CH}_3$), 2.41 (3H, s, C$\underline{H}_3$), 4.74 (2H, q, $^3J_{HH}$ = 6.0 Hz, OCH_2), 5.08 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.16 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.62 (1H, s, CH), 7.26–7.77 (4H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.48, 21.28, 21.52, 21.58, 21.73, 21.78, 60.50, 69.07, 69.52, 70.90, 115.33, 124.66, 127.95, 129.00, 129.91, 131.66, 138.96, 151.86, 155.45, 160.63, 162.79, 164.55, 166.09; MS *m/z* (%) = 473 (M^+, 100), 412 (5), 385 (100), 341 (60), 326 (85), 294 (67), 267 (100), 241 (45), 173 (15), 116 (18), 43 (100), 29 (82). Anal. calcd for $C_{23}H_{27}N_3O_6S$ (473.54): C, 58.34; H, 5.75; N, 8.87%. Found: C, 58.26; H, 5.71; N, 8.71%.

*Diisopropyl 4-ethoxy-5-oxo-1-[5-phenyl-1,3,4-thiadiazol-2-yl]-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5m**): White powder (0.340 g, 72%), m.p. 148 °C–149 °C; IR (KBr) (υ_{max}/cm^{-1}): 1747, 1720, 1702 (3 C=O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.24 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.33 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.34 (6H, d, $^3J_{HH}$ = 6.0 Hz, 2 CHC$\underline{H}_3$), 1.44 (3H, t, $^3J_{HH}$ = 6.0 Hz, $CH_2\underline{CH}_3$), 4.74 (2H, q, $^3J_{HH}$ = 6.0 Hz, OCH_2), 5.08 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.16 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.63 (1H, s, CH), 7.44–7.95 (5H, m, ArH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm)= 15.48, 21.52, 21.57, 21.73, 21.78, 60.52, 69.08, 69.53, 70.92, 84.84, 115.37, 127.43, 129.11, 130.05, 130.85, 151.82, 155.55, 160.61, 162.82, 166.07; MS *m/z* (%) = 459 (M^+, 78), 398 (12), 370 (80), 327 (75), 280 (75), 253 (85), 228 (75), 186 (70), 160 (75), 120 (73), 77 (53), 43 (100), 29 (78); Anal. calcd for $C_{22}H_{25}N_3O_6S$ (459.52): C, 57.50; H, 5.48; N, 9.14%. Found: C, 57.74; H, 5.42; N, 8.87%.

*Diisopropyl 1-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate* (**5n**): pale yellow powder (0.262 g, 48%), m.p. 163 °C–164 °C; IR (KBr) (υ_{max}/cm^{-1}): 1752, 1723, 1704 (3 C=O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) = 1.24 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.33 (3H, d, $^3J_{HH}$ = 6.0 Hz, CHC$\underline{H}_3$), 1.34 (6H, d, $^3J_{HH}$ = 6.0 Hz, 2 CHC$\underline{H}_3$), 1.44 (3H, t, $^3J_{HH}$ = 6.0 Hz, $CH_2\underline{CH}_3$), 4.73 (2H, q, $^3J_{HH}$ = 6.0 Hz, OCH_2), 5.08 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.16 (H, sep, $^3J_{HH}$ = 6.0 Hz, OCH), 5.62 (1H, s, CH), 7.59 (2H, d, $^3J_{HH}$ = 9.0 Hz, 2 CH_{Ar}), 7.79 (2H, d, $^3J_{HH}$ = 9.0 Hz, 2 CH_{Ar}); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm) = 15.47, 21.52, 21.57, 21.73, 21.78, 60.53, 69.13, 69.58, 70.99, 84.84, 115.45, 125.25, 128.75, 128.99, 132.35, 151.72, 155.67, 160.58, 163.18, 166.02; MS *m/z* (%) = 538 (M^+, 33), 450 (58), 407 (30), 357 (25), 331 (63), 305 (20), 181 (18), 125 (18), 97 (23), 41 (68), 43 (100), 28 (88). Anal. calcd for $C_{22}H_{24}BrN_3O_6S$ (538.41): C, 49.08; H, 4.49; N, 7.80%. Found: C, 49.32; H, 4.42; N, 7.58%.

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Supplemental material

Supplemental material for this article is available online.

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