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A Facile Regioselective 1,3-dipolar Cycloaddition Protocol for the Synthesis of Thiophene containing Spiro Heterocycles

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Abstract

An efficient three component synthesis of novel spiropyrrolidine compounds were obtained in good-to-excellent yields from the chemo-regio-and stereoselective reaction between α,β-unsaturated ketones with thiophene substituents and non-stabilized azomethineylides, generated in situ from acenaphthenequinone and sarcosine. This protocol has the advantages of highly efficiency, mild reaction conditions, a one-pot procedure, easy workup, short reaction times, convenient operation, and catalyst-free conditions. The synthesized compounds have been characterized by their IR, ^{1}H-NMR and ^{13}C-NMR spectral data. Single crystal analysis of compounds 5a and 5c and 2D-NMR analysis of compound 5c confirmed the structures of spiropyrrolidine derivatives.

Keywords: Multicomponent reaction**,** azomethine ylides**,** spiropyrrolidine**,** chemo-regioselectivity.

Introduction

Multicomponent reactions[1] are used to synthesis heterocyclic scaffolds that have emerged as a powerful outfit for carrying the molecular array necessary in combinatorial approaches for the synthesis of bioactive compounds. Multicomponent reactions (MCRs) have been comprehensively studied due to their highly effective one-pot procedure that has many advantages, including atom economy[2] and facile synthesis of molecules that have interesting biological properties using readily obtainable starting materials. 1, 3-dipolar cycloaddition of multicomponent reactions play a key role in the synthesis of five-membered heterocyclic compounds[3].1, 3-Dipolar cycloaddition reactions of azomethine ylides with olefinic and acetylenic dipolarophiles represent an important approach for the formation of N-heterocycles which are prevalent in a variety of biologically active compounds[4]. In current years construction of spiro compounds by 1,3-dipolar cycloaddition reactions of azomethine ylides has been well developed, and the reactions advances with high regio- and stereo selectivity[5,6].

1,3-Dipolar cycloaddition of stabilized azomethine ylides (generated *in situ* by the reaction of isatin and secondary amino acids) to C=C group, known as the Huisgen cycloaddition reaction serves as an efficient method for the formation of complex structures of spiropyrrolizidines with multiple stereogenic centres in a single concerted step[7]. Two π-electrons of the dipolarophile and four electrons of the dipolar compound participate in a strenuous, pericyclic shift. This shift is stereo conservative (suprafacial) and the reaction is therefore a [2S+4S] cycloaddition. It occurs through the interaction between HOMO of azomethine ylide and LUMO of the alkene[8]. Addition of azomethine ylide to dipolarophile with exo cyclic double bond affords the spiro-heterocycle[9-11] such as pyrrolizines, pyrrolizidines and pyrazolidines etc. which possess important biological activities[12].

Pyrrolidines have involved much attention as they append to the central framework of many alkaloids and pharmacologically active compound[13]. Spiro heterocycles, particularly spiropyrrolidines have gained significant attention due to their highly pronounced biological activities, such as antimicrobial, antitumor and antibiotic properties[14]. Some spiropyrrolidines are potential antileukemic and anticonvulsant agents and possess antiviral and local anesthetic activities[15]. Recently, spiropyrrolidine derivatives are also patented for their use against HCV and HIV infections and as modulators of chemokine receptor[16] and their syntheses have received great attention.

Derivatives of thiophene are the significant assembly of heterocyclic compounds possessing broad biological activities, such as anti-inflammatory[17], analgesic[17], antioxidant[18], antitubercular[19] antidepressant[19] sedative[20] antiamoebic[21] oral analgesic[22] anti-metabolite[23] and antineoplastic properties[24]. From the above mentioned reports, it seemed that the growth of an efficient, rapid, and clean synthetic route towards focused libraries of such compounds is of great importance to both medicinal and synthetic chemists. As a branch of our interest in 1, 3-dipolar cycloaddition reactions[25,26] to synthesis of spiropyrrolidines containing a thiophenyl moiety we account the efficient, chemo-regio-and stereoselective synthesis of novel monospiropyrrolidine derivatives enclosing a thiophenyl moiety via a multicomponent 1, 3-dipolar cycloaddition reaction of azomethine ylides.

Material and Methods

The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only strong absorption bands (reciprocal centimeters) are listed. ^{1}H NMR spectra were recorded at 400 MHz on BRUKER DRX 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz on BRUKER DRX 400 MHz spectrometer in $CDCl_3$.Microanalysis was performed on Heraeus Carlo Erba 1108 CHN analyzer. All the reagents and solvents used were of high grade and purchased from Fluka and Merck. The various substituted (*E*)-3-aryl-1-(thiophen-2-yl) prop-2-en-1-ones 4a-4k were synthesized in accordance with the literature[27].

General procedure for the synthesis of thiophenyl embedded spiropyrrolidines bearing acenaphthalene system (5a-5k): A mixture of acenaphthenequinone 1 (1 mmol), sarcosine 2 (1 mmol) and (*E*)-3-aryl-1-(thiophen-2-yl) prop-2-en-1-ones 4a-4k (1 mmol) in methanol (20 mL) was refluxed with stirring for the appropriate time (see table 2). The reaction mixture was cooled to room temperature. The precipitate obtained from the reaction was filtered and recrystallized from ethanol to afford crystalline products.

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-phenyl-pyrrolidine (5a): Reaction time 90 min, yellow solid, mp 194-196 ºC, yield 88%. Anal. Calcd. for $C_{27}H_{21}NO_2S$: C, 76.57; H, 5.00; N, 3.31%. Found: C, 76.70; H, 4.90; N, 3.35%.IR: ν_{max} (KBr, cm^{-1}) 1658, 1687. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, -NCH_3), 3.56 (H-5) (t, 1H, *J* = 8.2 Hz), 3.78 (H-5) (t, 1H, *J* = 9.4 Hz), 4.43 (H-3) (d, 1H, *J* = 9.2 Hz), 4.60-4.67 (H-4) (m, 1H), 6.43 (H-4'') (dd, 1H, *J* = 4.0, 4.8 Hz, -Ar-H), 6.88 (H-5") (dd, 1H, *J* = 1.0, 3.8 Hz, -Ar-H), 7.09 (H-3'') (dd, 1H, *J* = 1.0, 5.0 Hz, -Ar-H), 7.20-7.24 (H-3''') (m, 1H, -Ar-H), 7.33 (H-2''' and H-6''') (t, 2H, *J* = 7.6 Hz, -Ar-H), 7.53-7.59 (H-5', H-6', H-3''' and H-5''') (m, 4H, -Ar-H), 7.61-7.64 (H-2') (m, 1H, -Ar-H), 7.68 (H-4') (dd, 1H, *J* = 1.6, 7.2 Hz, -Ar-H), 7.88 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.96 (H-3') (d, 1H, *J* = 7.6 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.21 (N-**C**H_3), 44.82 (C-4), 61.21 (C-5), 64.31 (C-3), 120.70, 123.97, 124.81, 126.84, 127.05, 127.76, 128.23, 128.66, 128.86, 130.00, 131.02, 131.70, 132.04, 133.58, 136.63, 141.56, 142.32, 144.35, 190.03 (thiophenyl carbon), 208.88 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(4'-nitrophenyl) pyrrolidine (5b): Reaction time 50 min, yellow solid, mp 170-172 ºC, yield 97%. Anal. Calcd. for $C_{27}H_{20}N_2O_4S$: C, 69.22; H, 4.30; N, 5.98%. Found: C, 69.40; H, 4.35; N, 6.00%. IR: ν_{max} (KBr, cm^{-1}) 1656, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, -NCH_3), 3.59 (H-5) (t, 1H, *J* = 8.2 Hz), 3.79 (H-5) (t, 1H, *J* = 9.2 Hz), 4.36 (H-3) (d, 1H, *J* = 8.8 Hz), 4.72-4.78 (H-4) (m, 1H), 6.44 (H-4") (dd, 1H, *J* = 4.0, 4.8 Hz, -Ar-H), 6.86 (H-5") (dd, 1H, *J* = 1.2, 4.0 Hz, -Ar-H), 7.14 (H-3'') (dd, 1H,*J* = 1.2, 4.8 Hz, -Ar-H), 7.50-7.58 (H-2' and H-6') (m, 2H, -Ar-H), 7.64-7.71 (H-4' and H-5') (m, 2H, -Ar-H), 7.76 (H-2''' and H-6''') (d, 2H, *J* = 8.8 Hz, -Ar-H), 7.92 (H-1') (d, 1H, *J* = 7.2 Hz, -Ar-H), 7.99 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H), 8.20 (H-3''' and H-5''') (d, 2H, *J* = 8.8 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.12 (N-**C**H_3), 44.45 (C-4), 60.70 (C-5), 64.20 (C-3), 120.98, 123.90, 123.95, 125.10, 127.20, 127.90, 128.77, 129.18, 130.03, 131.17, 132.31, 134.07, 135.96, 142.38, 143.83, 147.04, 149.57, 189.42 (thiophenyl carbon), 208.71 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(4'-methylphenyl) pyrrolidine (5c): Reaction time 80 min, yellow solid, mp 188-190 ºC, yield 91%. Anal. Calcd. for $C_{28}H_{23}NO_2S$: C, 76.86; H, 5.30; N, 3.20%. Found: C, 76.92; H, 5.20; N, 3.25%. IR: ν_{max} (KBr, cm^{-1}) 1651, 1697. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, -NCH_3), 2.31 (s, 3H, -CH_3), 3.54 (H-5) (t, 1H, *J* = 8.2 Hz), 3.77 (H-5) (t, 1H, *J* = 9.4 Hz), 4.42 (H-3) (d, 1H, *J* = 9.2 Hz), 4.58-4.65 (H-4) (m, 1H), 6.41 (H-4") (dd, 1H, *J* = 3.8, 5.0 Hz, -Ar-H), 6.89 (H-5") (dd, 1H, *J* = 1.0, 3.8 Hz, -Ar-H), 7.07 (H-3'') (dd, 1H, *J* = 1.0, 5.0 Hz, -Ar-H), 7.14 (H-3''' and H-5''') (d, 2H, *J* = 7.6 Hz, -Ar-H), 7.48 (H-2''' and H-6''') (d, 2H, *J* = 8.0 Hz, -Ar-H), 7.55-7.68 (H-2', H-4', H-5' and H-6') (m, 4H, -Ar-H), 7.89 (H-1') (d, 1H, *J* = 6.4 Hz, -Ar-H), 7.95 (H-3') (d, 1H, *J* = 8.4 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 21.11 (-**C**H_3), 35.31 (N-**C**H_3), 44.55 (C-4), 61.31 (C-5), 64.40 (C-3), 120.77, 124.01, 124.89, 127.13, 127.84, 128.17, 128.87, 129.42, 130.04, 131.10, 131.74, 132.14, 133.67, 136.47, 136.71, 138.50, 142.36, 144.44, 190.15 (thiophenyl carbon), 208.97 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(4'-methoxyphenyl) pyrrolidine (5d): Reaction time 100 min, yellow solid, mp 199-201 ºC, yield 84%.). Anal. Calcd. for $C_{28}H_{23}NO_3S$: C, 74.15; H, 5.11; N, 3.09%. Found: C, 74.00; H, 5.15; N, 3.01%. IR: ν_{max} (KBr, cm^{-1}) 1658, 1708. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, -NCH_3), 3.52 (H-5) (t, 1H, *J* = 8.2 Hz), 3.74 (H-5) (t, 1H, *J* = 9.4 Hz), 3.78 (s, 3H, -OCH_3), 4.37 (H-3) (d, 1H, *J* = 9.2 Hz), 4.55-4.62 (H-4) (m, 1H), 6.43 (H-4") (dd, 1H, *J* = 3.6, 4.8 Hz, -Ar-H), 6.86-6.87 (H-5'') (m, 1H, -Ar-H), 6.88 (H-3"' and H-5''') (d, 2H, *J* = 8.8 Hz, -Ar-H), 7.10 (H-3'') (dd, 1H, *J* = 1.0, 5.0 Hz, -Ar-H), 7.50 (H-2''' and H-6''') (d, 2H, *J* = 8.8 Hz, -Ar-H), 7.51-7.64 (H-2', H-5' and H-6') (m, 3H, -Ar-H), 7.67 (H-4') (dd, 1H, *J* = 1.6, 7.6 Hz, -Ar-H), 7.88 (H-1') (d, 1H, *J* = 7.2 Hz, -Ar-H), 7.96 (H-3') (d, 1H,*J* = 8.4 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.22 (N-**C**H_3), 44.15 (C-4), 61.27 (C-5), 64.48 (C-3), 55.27 (-**O**CH_3), 114.10, 120.67, 123.94, 124.78, 127.05, 127.74, 128.80, 129.19, 129.99, 131.00, 131.71, 132.03, 133.54, 136.70, 142.31, 144.42, 158.55. 190.15 (thiophenyl carbon), 208.96 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(4'-fluorophenyl) pyrrolidine (5e): Reaction time 60 min,

yellow solid, mp 184-186 ºC, yield 95%. Anal. Calcd. for $C_{27}H_{20}FNO_2S$: C, 73.45; H, 4.57; N, 3.17%. Found: C, 73.50; H, 4.65; N, 3.23%. IR: ν_{max} (KBr, cm^{-1}) 1656, 1705. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, -NCH_3), 3.54 (H-5) (t, 1H, *J* = 8.2 Hz), 3.74 (H-5) (t, 1H, *J* = 9.4 Hz), 4.35 (H-3) (d, 1H, *J* = 9.2 Hz), 4.58-4.65 (H-4) (m, 1H), 6.43 (H-4") (dd, 1H, *J*= 3.8, 5.0 Hz, -Ar-H), 6.87 (H-5'') (dd, 1H, *J* = 1.0, 3.8 Hz, -Ar-H), 7.01 (H-3''' and H-5''') (t, 2H, *J* = 8.6 Hz), 7.11 (H-3'') (dd, 1H, *J* =1.0, 5.0 Hz, -Ar-H), 7.52-7.53 (H-5' and H-6')(m, 2H, -Ar-H), 7.55 (H-2''' and H-6''') (d, 2H, *J* = 8.0 Hz, -Ar-H), 7.61-7.65 (H-2') (m, 1H, -Ar-H), 7.68 (H-4') (dd, 1H, *J* = 1.2, 7.6 Hz, -Ar-H), 7.89 (H-1') (d, 1H, *J* = 7.2 Hz, -Ar-H), 7.97 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.18 (N-**C**H_3), 44.05 (C-4), 61.17 (C-5), 64.43 (C-3), 115.45 (d, J_{CF} = 21.0 Hz), 120.79, 123.91, 124.89, 127.10, 127.80. 128.79, 129.70 (d, J_{CF} = 8.0 Hz), 129.98, 131.04, 131.59, 132.14, 133.74, 136.42, 137.24, 142.33, 144.21, 161.85 (d, J_{CF} = 244.0 Hz), 189.94 (thiophenyl carbon), 208.93 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(4'-chlorophenyl) pyrrolidine (5f): Reaction time 70 min, yellow solid, mp 200-202ºC, yield 94%. Anal. Calcd. for $C_{27}H_{20}ClNO_2S$: C, 70.81; H, 4.40; N, 3.06%. Found: C, 70.90; H, 4.32; N, 3.00%. IR: ν_{max} (KBr, cm^{-1}) 1658, 1707. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, -NCH_3), 3.54 (H-5) (t, 1H, *J* = 8.2 Hz), 3.74 (H-5) (t, 1H, *J* = 9.4 Hz), 4.35 (H-3) (d, 1H, *J* = 9.2 Hz), 4.58-4.64 (H-4) (m, 1H), 6.43 (H-4") (t, 1H, *J* = 4.4 Hz, -Ar-H), 6.87 (H-5'') (dd, 1H, *J* = 0.8, 4.0 Hz, -Ar-H), 7.11 (H-3'') (d, 1H, *J* = 4.8 Hz, -Ar-H), 7.29 (H-2''' and H-6''') (d, 2H, *J* = 8.4 Hz, -Ar-H), 7.52 (H-3''' and H-5''') (d, 2H, *J* = 8.4 Hz, -Ar-H), 7.53-7.69 (H-2', H-4', H-5' and H-6') (m, 4H, -Ar-H), 7.89 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.96 (H-3') (d, 1H, *J* = 8.4 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 34.28 (N-**C**H_3), 43.26 (C-4), 60.09 (C-5), 63.43 (C-3), 119.92, 123.00, 124.03, 126.24, 126.93, 127.90, 128.72, 129.09, 130.18, 130.66, 131.28, 131.72, 132.92, 135.45, 139.22, 141.43, 143.23, 188.93 (thiophenyl carbon), 207.97 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(4'-bromophenyl) pyrrolidine (5g): Reaction time 75 min, yellow solid, mp 220-222 ºC, yield 96%. Anal. Calcd. for $C_{27}H_{20}BrNO_2S$: C, 64.55; H, 4.01; N, 2.79%. Found: C, 64.45; H, 3.92; N, 2.70%. IR: ν_{max} (KBr, cm^{-1}) 1656, 1707. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, -NCH_3), 3.54 (H-5) (t, 1H, *J* = 8.2 Hz), 3.73 (H-5) (t, 1H, *J* = 9.4 Hz), 4.34 (H-3) (d, 1H, *J* = 9.2 Hz), 4.56-4.60 (H-4) (m, 1H), 6.43 (H-4") (dd, 1H, *J* = 4.0, 4.8 Hz, -Ar-H), 6.86-6.87 (H-5'') (m, 1H, -Ar-H), 7.11 (H-3'') (dd, 1H, *J* = 0.8, 4.8 Hz, -Ar-H), 7.41-7.49 (H-2''', H-3''', H-5''' and H-6''') (m, 4H, -Ar-H), 7.51-7.57 (H-5' and H-6') (m, 2H, -Ar-H), 7.61-7.65 (H-2') (m, 1H, -Ar-H), 7.68 (H-4') (d, 1H, *J* = 7.6 Hz, -Ar-H), 7.89 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.96 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.16 (N-**C**H_3), 44.23 (C-4), 60.93 (C-5), 64.31 (C-3), 120.73, 120.80, 123.91, 124.91, 127.12, 127.81, 128.78, 130.00, 131.07, 131.59, 131.76, 132.15, 133.78, 136.35, 140.67, 142.33, 144.14, 189.80 (thiophenyl carbon), 208.84 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one–3-thiophenoyl – 4 - (4'-benzyloxyphenyl) pyrrolidine (5h): Reaction time 80 min, yellow solid, mp 235-237 ºC, yield 83%. Anal. Calcd. for $C_{34}H_{27}NO_3S$: C, 77.10; H, 5.14; N, 2.64%. Found: C, 77.20; H, 5.18; N, 2.70%. IR: ν_{max} (KBr, cm^{-1}) 1656, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, -NCH_3), 3.52 (H-5) (t, 1H, *J* = 8.2 Hz), 3.74 (H-5) (t, 1H, *J* = 9.4 Hz), 4.37 (H-3) (d, 1H, *J* = 9.2 Hz), 4.55-4.62 (H-4) (m, 1H), 5.03 (s, 2H, -OCH_2-), 6.42 (H-4") (dd, 1H, *J* = 4.0, 4.8 Hz, -Ar-H), 6.87 (H-5'') (dd, 1H, *J* = 1.0, 3.8 Hz, -Ar-H), 6.94 (H-3''' and H-5''') (d, 2H, *J* = 8.8 Hz, -Ar-H), 7.09 (H-3'') (dd, 1H, *J* = 1.0, 5.0 Hz, -Ar-H), 7.28-7.32 (H-4'''') (m, 1H, -Ar-H), 7.34-7.38 (H-5' and H-6') (m, 2H, -Ar-H), 7.41 (H-3'''' and H-5'''') (d, 2H, *J* = 8.4 Hz, -Ar-H), 7.49 (H-2'''' and H-6'''') (d, 2H, *J* = 8.4 Hz, -Ar-H), 7.54 (H-2''' and H-6''') (d, 2H, *J* = 8.4 Hz, -Ar-H), 7.57-7.63 (H-2') (m, 1H, -Ar-H), 7.67 (H-4') (dd, 1H, *J* = 1.8, 7.4 Hz, -Ar-H), 7.88 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.95 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.22 (N-**C**H_3), 44.14 (C-4), 61.26 (C-5), 64.44 (C-3), 70.07 (-O**C**H_2-), 115.04, 120.69, 123.93, 124.80, 127.06, 127.47, 127.76, 127.90, 128.57, 128.80, 129.23, 129.98, 131.02, 131.69, 132.05, 133.57, 133.83, 136.67, 137.16, 142.31, 144.39, 157.80, 190.15 (thiophenyl carbon), 208.97 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(3',4'-dimethoxy phenyl) pyrrolidine (5i): Reaction time 100 min, yellow solid, mp 205-207 ºC, yield 80%. Anal. Calcd. for $C_{29}H_{25}NO_4S$: C, 72.03; H, 5.21; N, 2.90%. Found: C, 72.20; H, 5.15; N, 2.95%. IR: ν_{max} (KBr, cm^{-1}) 1653, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, -NCH_3), 3.55 (H-5) (t, 1H, *J* = 8.2 Hz), 3.76 (H-5) (t, 1H, *J* = 9.4 Hz), 4.39 (H-3) (d, 1H, *J* = 8.8 Hz), 4.55-4.61 (H-4) (m, 1H), 6.45 (H-4") (dd, 1H, *J* = 3.8, 5.0 Hz, -Ar-H), 6.83 (H-5'') (d, 1H, *J* = 8.4 Hz -Ar-H), 6.89 (H-3'') (dd, 1H, *J* = 1.0, 3.8 Hz, -Ar-H), 7.09-7.17 (H-2''', H-3''' and H-6''') (m, 3H, -Ar-H), 7.53-7.67 (H-2', H-5' and H-6') (m, 3H, -Ar-H), 7.69 (H-4') (dd, 1H, *J* = 1.2, 6.0 Hz, -Ar-H), 7.88 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.97 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.24 (N-**C**H_3), 44.59 (C-4), 55.93 (-O**C**H_3), 55.98 (-O**C**H_3), 61.22 (C-5), 64.46 (C-3), 111.35, 111.45, 120.15, 120.73, 123.93, 124.84, 127.12, 127.77, 128.78, 130.01, 131.08, 131.64, 132.11, 133.65, 142.30, 144.39, 147.94, 149.10, 190.22 (thiophenyl carbon), 208.10 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(3'-bromophenyl) pyrrolidine (5j): Reaction time 75 min, yellow solid, mp 210-212 ºC, yield 93%. Anal. Calcd. for $C_{27}H_{20}BrNO_2S$: C, 64.55; H, 4.01; N, 2.79%. Found: C, 64.45; H, 3.92; N, 2.70%. IR: ν_{max} (KBr, cm^{-1}) 1658, 1708. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, -NCH_3), 3.54 (H-5) (t, 1H, *J* = 8.2 Hz), 3.74 (H-5) (t, 1H, *J* = 9.2 Hz), 4.36 (H-3) (d, 1H, *J* =

9.2 Hz), 4.56-4.63 (H-4) (m, 1H), 6.43 (H-4") (dd, 1H, *J* = 4.0, 4.8 Hz, -Ar-H), 6.88 (H-5'') (dd, 1H, *J* = 0.8, 4.0 Hz, -Ar-H), 7.11 (H-3'') (dd, 1H, *J* = 1.0, 5.0 Hz, -Ar-H), 7.20 (H-2''') (t, 1H, *J* = 7.8 Hz, -Ar-H), 7.34-7.37 (H-3''') (m, 1H, -Ar-H), 7.50-7.69 (H-2', H-5', H-6', H-4''' and H-6''') (m, 5H, -Ar-H), 7.72-7.73 (H-4') (m, 1H, -Ar-H), 7.89 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.96 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.15 (N-**C**H_3), 44.39 (C-4), 60.94 (C-5), 64.14 (C-3), 120.82, 122.72, 123.91, 124.92, 126.99, 127.10, 127.81, 128.78, 129.99, 130.06, 130.25, 131.12, 131.26, 131.59, 132.14, 133.79, 136.34, 142.33, 144.02, 144.10, 189.71 (thiophenyl carbon), 208.75 (acenaphthenequinone ring carbonyl).

1-*N*-methyl-spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(3'-chlorophenyl) pyrrolidine (5k): Reaction time 70 min, yellow solid, mp 208-210 ºC, yield 92%. Anal. Calcd. for $C_{27}H_{20}ClNO_2S$: C, 70.81; H, 4.40; N, 3.06%. Found: C, 70.90; H, 4.32; N, 3.00%. IR: ν_{max} (KBr, cm^{-1}) 1656, 1707. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H, -NCH_3), 3.54 (H-5) (t, 1H, *J* = 8.2 Hz), 3.75 (H-5) (t, 1H, *J* = 9.4 Hz), 4.37 (H-3) (d, 1H, *J* = 9.2 Hz), 4.58-4.64 (H-4) (m, 1H), 6.42 (H-4") (t, 1H, *J* = 4.4 Hz, -Ar-H), 6.88 (H-5'') (d, 1H, *J* = 3.2 Hz, -Ar-H), 7.10 (H-3'') (d, 1H, *J* = 4.8 Hz, -Ar-H), 7.18-7.27 (H-2''' and H-4''') (m, 2H, -Ar-H), 7.46-7.68 (H-2', H-5', H-6', H-3''' and H-6''') (m, 5H, -Ar-H), 7.67 (H-4') (d, 1H, *J* = 8.0 Hz, -Ar-H), 7.90 (H-1') (d, 1H, *J* = 6.8 Hz, -Ar-H), 7.96 (H-3') (d, 1H, *J* = 8.0 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$)δ: 35.15 (N-**C**H_3), 44.41 (C-4), 60.92 (C-5), 64.12 (C-3), 120.83, 123.90, 124.94, 126.51, 127.11, 127.83, 128.35, 128.78, 129.95, 129.99, 131.12, 131.59, 132.15, 133.81, 134.44, 136.35, 142.33, 143.72, 144.10, 189.73 (thiophenyl carbon), 208.75 (acenaphthenequinone ring carbonyl).

X-ray crystallography, X-ray data collection, structure determination and refinement of compound (5c): Single crystals suitable for diffraction were obtained by the slow evaporation of a solution of the compound in methanol. The yellow colour crystal of the compound **5c** having appropriate dimensions of 0.45 × 0.25 × 0.20 mm was mounted on a glass fiber with epoxy cement for the X-ray crystallographic study. Brukeraxs kappa apex2 CCD diffractometer equipped with graphite mono chromated Mo Kα (λ = 0.71073 Å) radiation was used for the measurement of data. The collected data were reduced using the SAINT program and structural refinement was carried out by Full-matrix least-squares on F^2 (SHELXL-97) [28]. Molecular graphics employed include ORTEP and PLATON[29]. The ORTEP view of the compound with atomic numbering is shown in figure-2.

Results and Discussion

To accelerate the cycloaddition reaction, various solvents, such as acetonitrile, ethanol, dioxane, methanol, isopropyl alcohol , *t*-butyl alcohol, toluene and DMF were examined and were shown to have a considerable impact on the yield of the reaction.The desired product was obtained in fairly good yields with high purity up to 87-91% when the reaction was carried out in methanol or ethanol (table-1, entries 1-2). Moderate yields were observed when toluene, and dioxane were used (table-1, entries 3-4). The yield decreased and a longer reaction time was required to progress the reaction with *i*-propanol, *t*-butanol, acetonitrile and dimethylformide (table-1, entries 5-8). This can be attributed to the diminished stabilization of the polar transition states and/or intermediate involved in this reaction. Consequently, methanol was used as the solvent of choice. It gives a maximum yield within lesser reaction time, the cycloaddition reaction of acenaphthenequinone1, sarcosine 2 and thiophenyl grafted dipolarophile 4c was carried out.

Table-1
Reaction optimization for the formation of 5c

Entry	Temp.˚C	Solvent	Time (min)	Yield(%)[a,b]
1	Reflux	Ethanol	80	87
2	Reflux	Methanol	80	91
3	Reflux	Toluene	110	66
4	Reflux	Dioxane	100	71
5	Reflux	Acetonitrile	80	58
6	Reflux	*i*-PrOH	160	65
7	Reflux	*i*-BuOH	140	60
8	Reflux	DMF	130	55

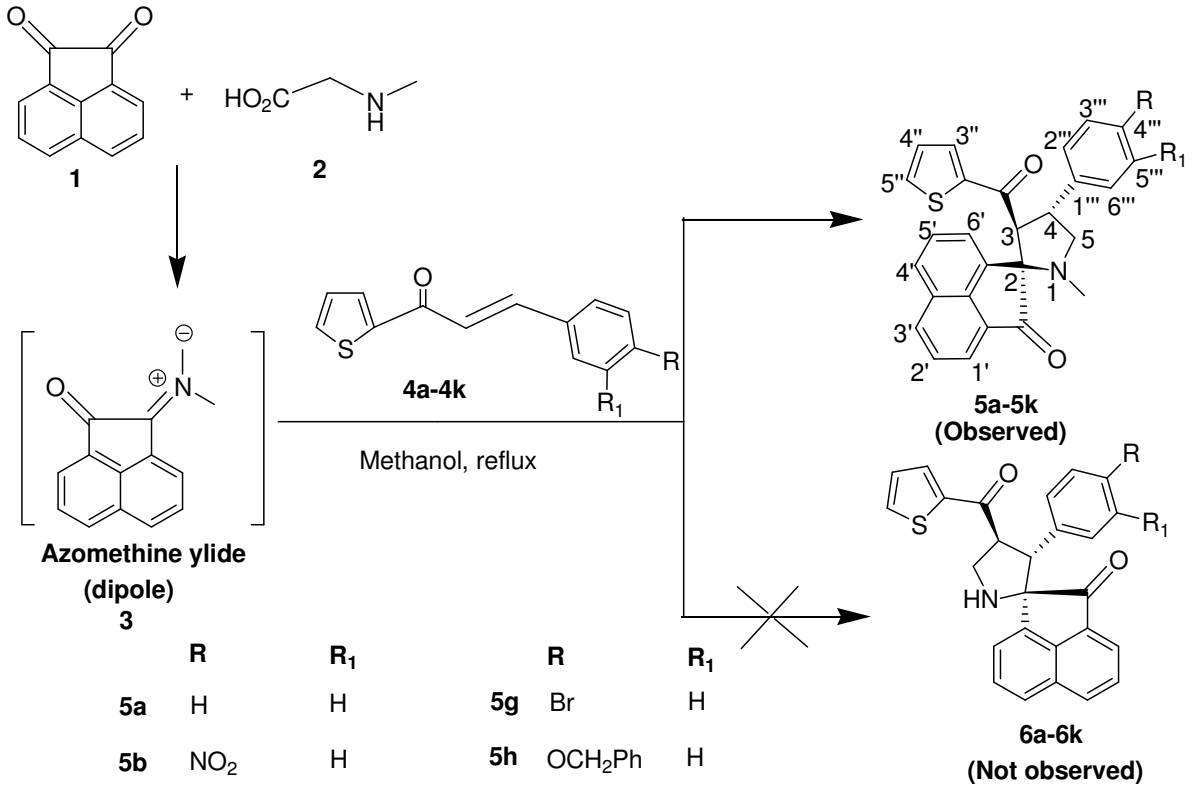
[a]Isolated yield. [b]Amount of materials in all reactions: acenaphthenequinone 1 (1 mmol), sarcosine 2 (1 mmol) and thiophenyl grafted dipolarophile 4c (1 mmol).

In the present investigation, the dipolarophiles (*E*)-3-aryl-1-(thiophen-2-yl) prop-2-en-1-ones 4a-4k were achieved by the route as described in the literature[25]. The azomethine ylides generated by acenaphthenequinone 1 and sarcosine 2 were treated with dipolarophiles 4a-4k to afford a series of novel thiophenyl grafted spiropyrrolidines 5a-5k in good-to-excellent yields (scheme-1, table-2).

All the reactions proceed chemoselectively as the nucleophilic methylene carbon (electron rich carbon) of the dipole prefers to react with C=C and not with C=O bond of 4a-4k furnishing exclusively the spiropyrrolidines 5a-5k. This reaction is regioselective with the addition of the electron rich carbon of the dipole to the β-carbon of 4a-4k and stereoselective affording only one isomer in good-to-excellent yields, *albeit* four stereo centers are present in these cycloadducts. The atom-economy of the reaction is also very high, viz. 80–97% as water and carbon dioxide alone are generated as waste.

The comprehensive mechanism of the above reaction is not fully established, the formation of regioisomer 5c could be explained as via decarboxylative condensation of acenaphthenequinone1 with sarcosine 2 furnishes the azomethine ylide 3 (dipole) which then undergoes a regioselective1,3-dipolar cycloaddition reaction with dipolarophile 4c as shown in scheme 2. The regioselectivity could be explained by considering the secondary orbital

interaction (SOI) of the orbital of the carbonyl group of dipolarophile4c with those of the azomethine ylide 3. As an end result, the path A is more favorable than path B due to the SOI. Hence, only one regioisomer 5c was formed as evidenced by single crystal analysis.



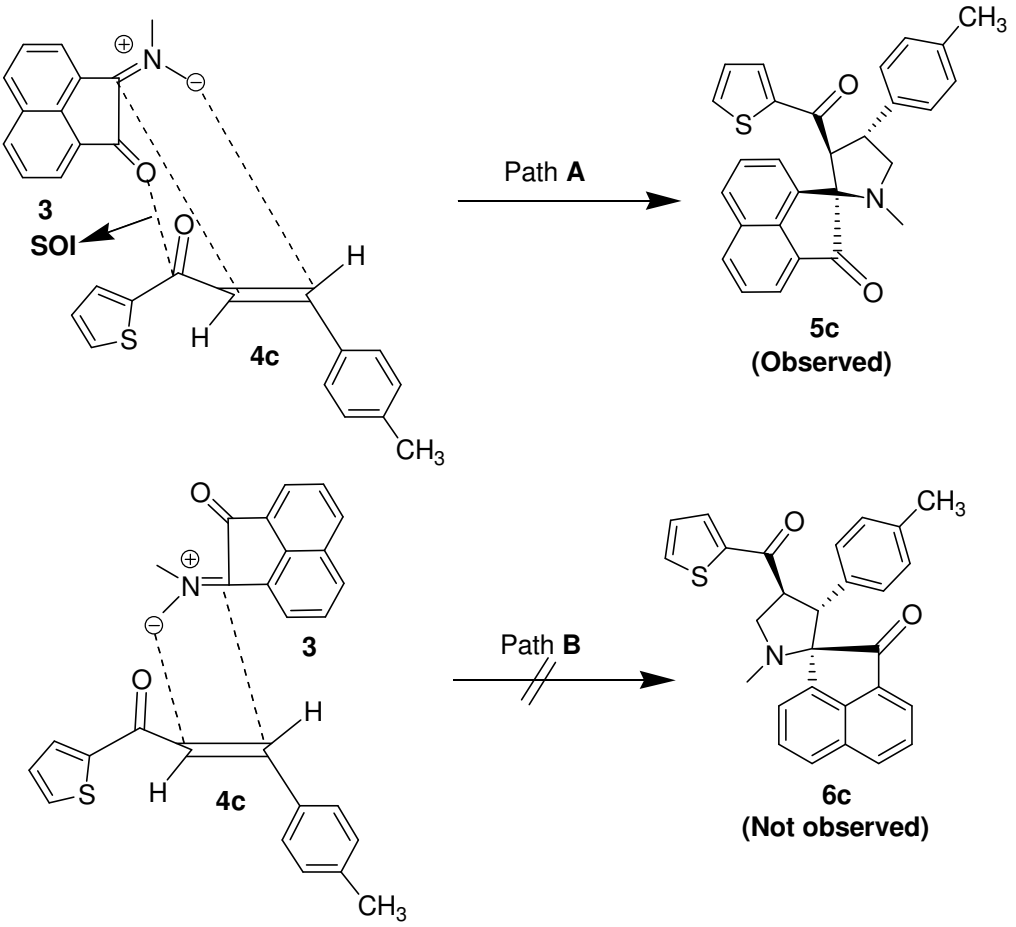
	R	R_1		R	R_1
5a	H	H	**5g**	Br	H
5b	NO_2	H	**5h**	OCH_2Ph	H
5c	CH_3	H	**5i**	OCH_3	OCH_3
5d	OCH_3	H	**5j**	H	Br
5e	F	H	**5k**	H	Cl
5f	Cl	H			

Scheme-1
Synthesis of thiophenyl grafted spiropyrrolidines 5a-5k

Table-2
Synthesis of acenaphthalene fused thiophenyl grafted spiropyrrolidines 5a-5k

Entry	Substrate	R	R_1	Amino acid	Time (min)	Yield(%)[a,b]
1	5a	H	H	2	90	88
2	5b	NO_2	H	2	50	97
3	5c	CH_3	H	2	80	91
4	5d	OCH_3	H	2	100	84
5	5e	F	H	2	60	95
6	5f	Cl	H	2	70	94
7	5g	Br	H	2	75	96
8	5h	OCH_2Ph	H	2	80	83
9	5i	OCH_3	OCH_3	2	100	80
10	5j	H	Br	2	75	93
11	5k	H	Cl	2	70	92

[a]Isolated yield. [b]Reaction conditions: acenaphthenequinone 1 (1 mmol), sarcosine 2 (1 mmol) and thiophenyl grafted dipolarophile 4a-4k (1 mmol) for the formation of cycloadducts 5a-5k



Scheme-2
Mode of approach of azomethine ylide 3

The starting precursor (*E*)-3-aryl-1-(thiophen-2-yl) prop-2-en-1-ones 4a-4k as well as the products was purified by recrystallization. The structures of all the products are in good agreement with their 1D and 2D NMR spectroscopic data. For instance, the IR spectrum of spiro-pyrrolizidine 5c showed peak at 1651 cm^{-1} due to thiophenyl carbonyl whereas the acenaphthenequinone ring carbonyl resonated at 1697 cm^{-1}. In the ^1H NMR spectrum of 5c displayed multiplet in the region δ 4.58–4.65 is due to benzylic proton (H-4) of pyrrolidine ring. A sharp singlet, which appeared at δ 2.15, was accounted for *N*-methyl protons. The aromatic methyl protons appeared at δ 2.31 as a singlet. Two triplets appeared at δ3.54 and 3.77 were attributed to diastereotopic "CH_2" functions (H-5) and a doublet at δ 4.42 is accountable for H-3 proton of pyrrolidine ring, which explains the observed regiochemistry of the product. In ^{13}C NMR spectra acenaphthenequinone and thiophenoyl C=O group occurred at δ 208.97 and 190.15 ppm, respectively. The quaternary spirocarbon (C-2) appeared at δ77.61 ppm. This is also supported by their DEPT-135 method, where the spirocarbon did not show any predictable peak. The N–CH_3 protons (δ2.15) showed HMBC correlation with C-2 (δ77.61) and C-5 (δ 61.31). From the ^1H–^1H-COSY correlation, the triplets at δ3.54 and 3.77 were assigned to the C-5 methylene protons and the triplet at δ 3.54 which showed HSQC correlation with C-5 (δ61.31) and HMBC correlation with *N*-CH_3 (δ 35.31), C-4 (δ 44.55) and C-1''' (δ 138.50). The triplet at δ3.77 showed HSQC correlation with C-5 (δ61.31) and HMBC correlation with C-2 (δ77.61) and C-3 (δ 64.30). The doublet at δ4.42 showed HSQC correlation with C-3 (δ64.40) and HMBC correlation with C-2 (δ77.61), C-1'''(δ 138.50), thiophenyl C=O group (δ190.15) and acenaphthenequinone C=O group (δ208.97), respectively. The multiplet in the region δ 4.58-4.65 showed ^1H–^1H-COSY correlation with H-5 (δ3.54 and 3.77) and HMBC correlation with C-3 (δ 64.30) and C-2'''and C-6''' (δ128.17), respectively. The aromatic protons appeared as multiplets at δ 6.41–7.95 ppm. The ^1H and ^{13}C chemical shift as well as the HMBC correlation patterns are also shown in figure-1. The structure determined from an X-ray crystallographic study of the single crystal of 5c is in accord with the structure deduced from NMR spectroscopic data (figure-2 and 3) [27].

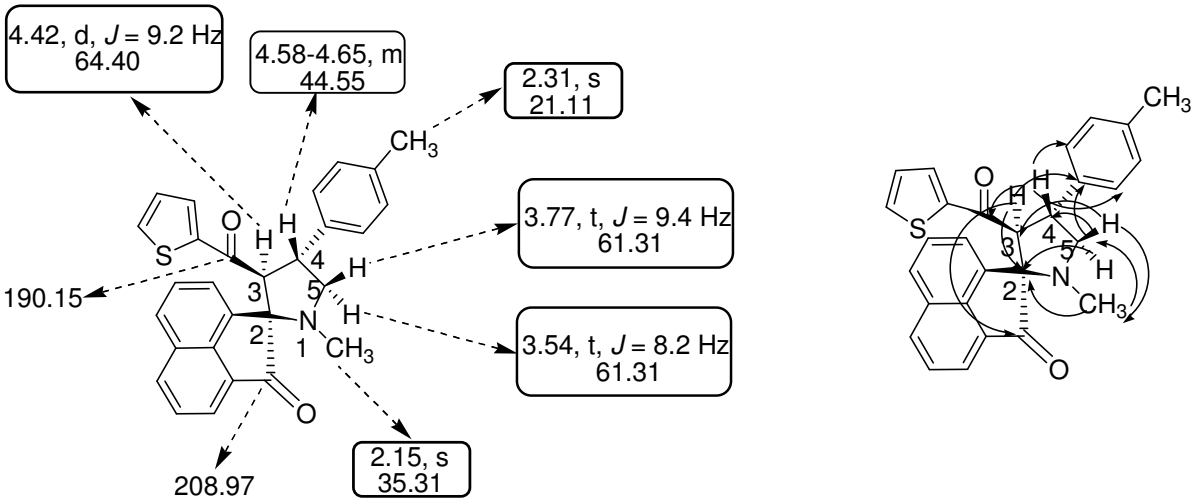


Figure-1
Selected ^{1}H, ^{13}C chemical shifts and HMBC correlations of 5c

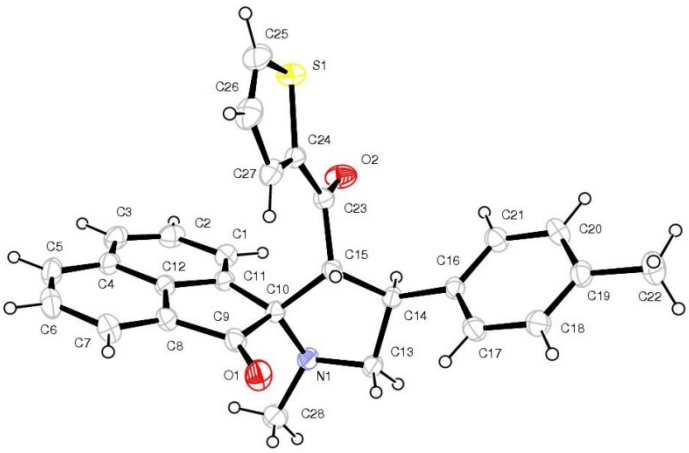


Figure-2
ORTEP diagram of compound 5c

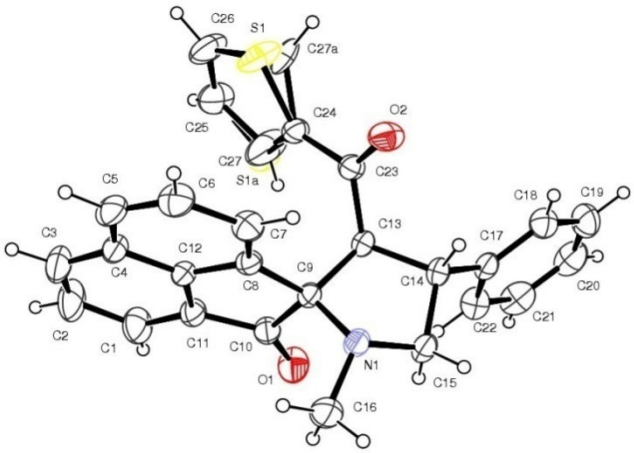


Figure-3
ORTEP diagram of compound 5a

Conclusion

In conclusion, we have build up an efficient synthesis of spiropyrrolidine derivatives by one-pot, three-component reaction of azomethine ylides with different (*E*)-3-aryl-1-(thiophen-2-yl)prop-2-en-1-ones 4a-4k. This method has the advantages of operation simplicity, high atom economy, good-to-excellent yields in short reaction times, easy workup, mild reaction conditions and catalyst-free conditions (environmental friendliness, because no transition metals are needed). The reactions proceed with excellent chemo-regio-and stereoselectivity.

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27. (a) The crystal structure has been deposited at the Cambridge Crystallographic Data centre CCDC number : 1004671, molecular formula: $C_{28}H_{23}NO_2S$, unit cell

parameters: a 9.6859(3), b 9.8620(3), c 12.9293(4), β76.6380 (10), space group P-1. Data acquisition: The Cambridge Crystallographic Data Center; deposit @ ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk/deposit, **(2014)** (b)The crystal structure has been deposited at the Cambridge Crystallographic Data centre CCDC number: 1004647, molecular formula: $C_{27}H_{21}NO_2S$, unit cell parameters: a 13.0132(6), b 9.8726(5), c 17.8545(8), β 108.882(2), space group P2(1)/c. Data acquisition: The Cambridge Crystallographic Data Center; deposit@ ccdc.cam.ac.uk, http: // www.ccdc.cam.ac.uk / deposit, **(2014)**

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