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1,2,4-Oxadiazoles from cycloreversions of oxadiazabicyclo[3.2.0]heptenes: 1-azetines as thiocyanate equivalents

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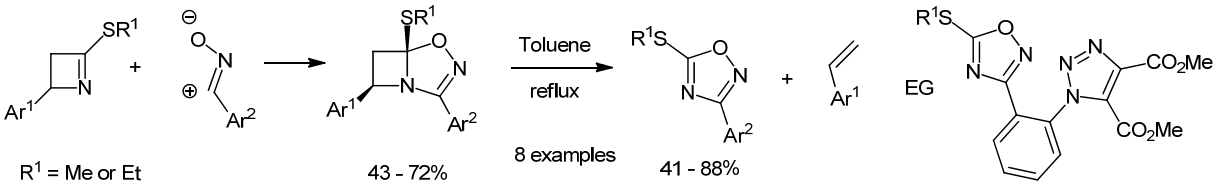

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1,2,4-Oxadiazoles from cycloreversions of oxadiazabicyclo[3.2.0]heptenes: 1-azetines as thiocyanate equivalents

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ABSTRACT

1,3-Dipolar cycloaddition of nitrile oxides to 4-aryl-2-alkylthio-1-azetines gave a series of oxadiazabicyclo[3.2.0]heptenes as single diastereoisomers. Heating these cycloadducts in toluene resulted in an overall [2+2]-cycloreversion to give 5-alkylthio-3-aryl-1,2,4-oxadiazoles. In this process, the 1-azetine behaves as a thiocyanate equivalent. When the nitrile oxide substituent was 2-azidobenzene, the azide could be converted into a 1,2,3-triazole giving a (1,2,4-oxadiazolo)-(1,2,3-triazolo)-1,2-disubstituted benzene. 1,2,4-Oxadiazoles are sought after in medicinal chemistry and materials sciences.

1. Introduction

1,2,4-Oxadiazoles have attracted attention due to their biological activity, often related to their bioisosteric nature and use in medicinal chemistry.[1] This area has been extensively reviewed[1] and a selection of recent compounds of interest is shown in Figure 1. Compound **1** is one of a series of 1,2,4-oxadiazoles that are potent EthR inhibitors that boost ethionamide activity in the treatment of multi-drug resistant tuberculosis.[2] Compound **2** is of interest as a combretastatin A-4 analogue with higher efficacy as an antimitotic agent.[3] Thiol linked 1,2,4-oxadiazoles **3** that have electron withdrawing aryl substituents show great potency towards androgen independent prostrate cancer cell-lines.[4] Compound **4** is an excellent *in vivo* sphingosine phosphate receptor-1 ($S1P_1$) selective modulator that suppresses the development of autoimmune diseases including multiple sclerosis and adjuvant-induced arthritis models.[5] Compound **5** is representative of a potent class of tankyrase (TNKS1/2) dual inhibitors that show no activity at poly(ADP-ribose) polymerase (PARP1 and 2) domains, and are inhibitors of the Wnt pathway whose dysregulation is a key priority in multiple diseases including several cancers.[6] In 2011 the first 1,2,4-oxadiazole natural products, phidianidines A (**6**, X = Br) and B (**6**, X = H), were isolated[7a] – from a marine opisthobranch source – and their synthesis reported shortly thereafter.[7b] 1,2,4-Oxadiazoles are also of interest in materials research[1] with recent examples including bent-core[8] and bent-rod liquid crystals[9] with stable liquid phases over broad temperature ranges. 3-Nitro-5-substituted-1,2,4-oxadiazoles such as compound **7** are reported as "explosophoric" energetic, insensitive high explosives.[10] Finally, the use of pyridyl-1,2,4-oxadiazoles[11] and *bis*-1,2,4-oxadiazole[12] as ligands that chelate Ni^{II}, Cu^{II}, Zn^{II} and Pd^{II} has been reported, together with a report that *bis*(pyridyl)-1,2,4-oxadiazole Cu^{II} complexes display promising activity as DNA groove binders.[13]

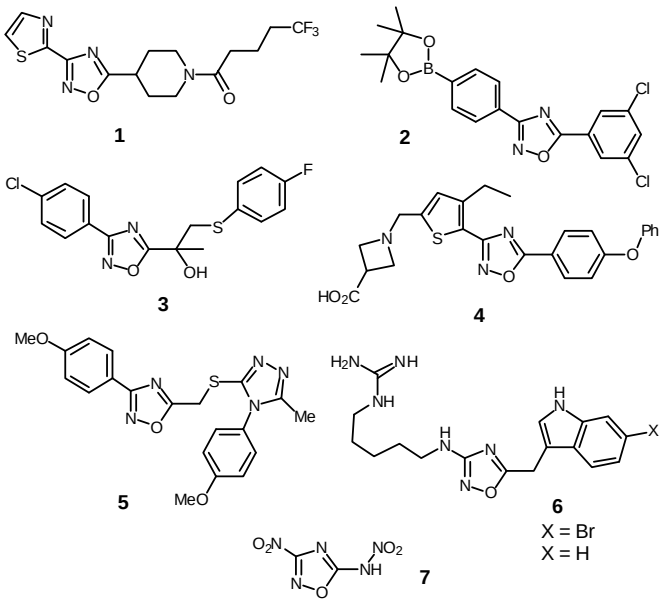
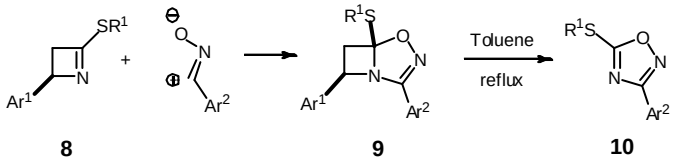


Figure 1: A selection of 1,2,4-oxadiazoles of recent interest

1,2,4-Oxadiazoles are most commonly constructed using 1,3-dipolar cycloadditions between nitrile oxides and nitriles[1,14] or from the reactions of a nitrile-derived amidoxime with a carboxylic acid derivative.[1,15] In this report, we show that 5-alkylthio-1,2,4-oxadiazoles **10** can be obtained from a formal [2+2]-cycloreversion of the oxadiazabicyclo[3.2.0]heptenes **9** [Scheme 1] which in turn are readily constructed from the 1,3-dipolar cycloaddition of a nitrile oxide to a 4-aryl-1-azetine **8**. In this process, the 1-azetine acts as an equivalent for the nitrile species $R^1S–CN$, known as either an alkyl thiocyanate or an alkyl thiocyanic ester.[16]

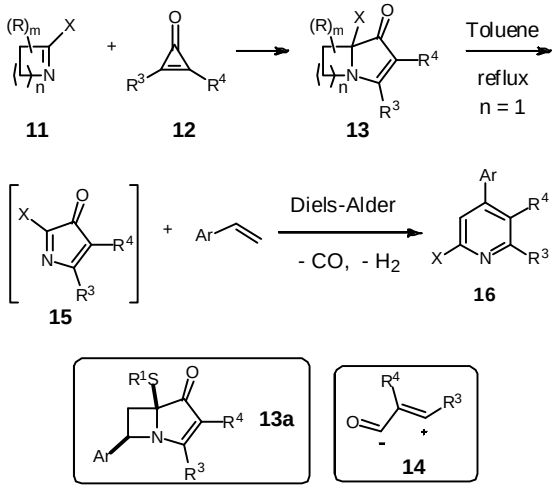


8 **9** **10**

Scheme 1: Synthesis of 1,2,4-oxadiazoles from 1-azetines

2. Results and Discussion

This work has its origins in our studies [Scheme 2] that focused upon the synthesis of azabicycles **13** from the reaction of cyclic imines **11** with cyclopropenones **12**, where the latter function as all-carbon 1,3-dipole equivalents **14**.[17] When the imine **11** was a 4-aryl-1-azetine the intermediate bicycles **13a** (n = 1) gave the tetra-substituted pyridines **16**.[18] We postulated that this transformation proceeded through a [2+2] cycloreversion to give a non-isolable, high-energy azacyclopentadienone **15** and a styrene. The styrene and intermediate **15** then recombine by Diels-Alder reaction, followed by chelotropic extrusion of carbon monoxide and aromatisation to yield the pyridine, paralleling the synthesis of benzenes from cyclopentadienones. The ease with which this process produced the proposed intermediate **15** led us look at this as a route for the formation of 1,2,4-oxadiazoles, which we anticipated would be isolable and not undergo further reaction.

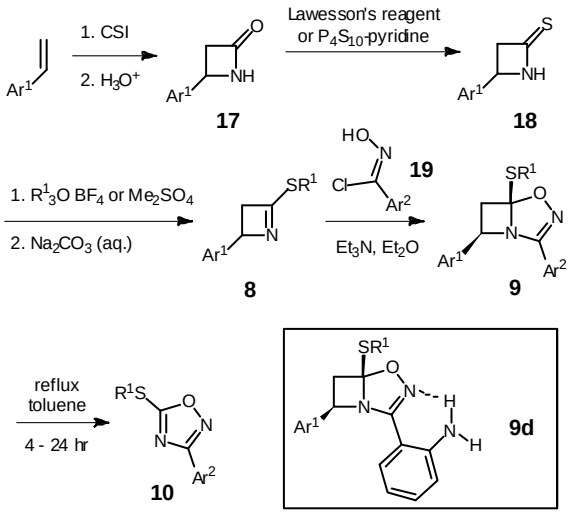


11 **12** **13** **15** **16** **13a** **14**

Scheme 2: Pyridines from azacyclopentadienones[19]

As shown in Scheme 3 and Table 1, the 1-azetines **8** required for this study were synthesised from the alkylation of the corresponding thio-β-lactams **18** with Meerwein's salts or dimethyl sulfate. The thio-β-lactams were obtained from the reaction of the β-lactam **17** with either Lawesson's reagent,[19] or the much more convenient and odour-free P_4S_{10}-pyridine complex developed by Bergman.[20] The β-lactams **17** were easily available from the reaction of chlorosulfonyl isocyanate (CSI) with the relevant styrene.[21] The nitrile oxides were generated by the standard route[22] of dehydrochlorination of the chloro-oximes **19**. This approach produced seven examples, **9a – c** and **9e – h**, of the desired oxadiazabicycles **9** as summarised in Table 1. As seen in Table 1, the oxadiaza[3.2.0]bicycles **9** were produced in yields of 43 – 72%. It is worth noting that each of the adducts **9** was a single diastereoisomer with (nOesy) *cis* stereochemistry between the Ar^1 and SR^1 groups, presumably a result of the incoming 1,3-dipole approaching *trans* to the existing Ar^1 group, thus forcing the SR^1 group *cis* to the Ar^1 substituent. The treatment of the azido compound **9a** (Ar^2 = 2-N_3-C_6H_4) with triphenylphosphine followed by hydrolysis gave the corresponding amino species **9d** (Ar^2 = 2-NH_2-C_6H_4) in 70% overall yield, giving us access to an eighth example of an oxadiaza[3.2.0]bicycle.

When heated to reflux in toluene, all but one of the oxadiazabicycles **9a-h** formed the 5-alkylthio-1,2,4-oxadiazole **10** (Scheme 3), in good to excellent yields (see Table 1). The one exception was compound **9d** which proved to be stable, possibly as a result of increased stability resulting from intramolecular hydrogen bonding between the amino group and *N*-2 or *N*-4 of the oxadiazolidine ring (as shown for *N*-2 in Scheme 3). The products of these reactions, 5-alkylthio-1,2,4-oxadiazoles **10**, are a class of 1,2,4-oxadiazole that have attracted no other synthetic approaches to our knowledge.[1] We are currently exploring the synthetic utility of the 5-alkylthio-1,2,4-oxadiazoles **10**.

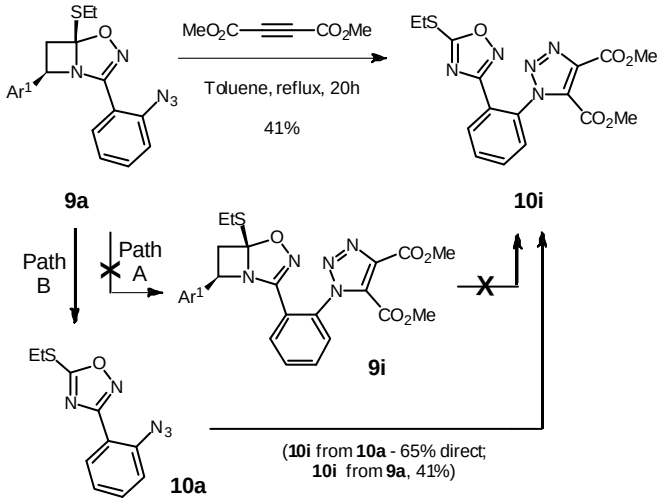


17 **18** **19** **8** **9** **10** **9d**

Scheme 3: The synthesis of 5-alkylthio-1,2,4-oxadiazoles **10**

A further example of a 5-alkylthio-1,2,4-oxadiazole, the aryltriazole compound **10i** (Scheme 4), was obtained by reacting the azido compound **9a** with dimethylacetylene dicarboxylate (DMAD) in toluene for 20 hours at reflux. The product presumably forms through consecutive [2+2]-cycloreversion and azide 1,3-dipolar cycloaddition. The presumed intermediate of the cycloaddition-first pathway (Pathway A, Scheme 4), compound **9i**, could not be detected, whereas TLC indicated that the 1,2,4-oxadiazole **10a** was present in small amounts, implying that the cycloreversion-first pathway (Pathway B, Scheme 4) represents the correct sequence of events. Compound **10i** could be obtained in 65% yield by treating 1,2,4-oxadiazole **10a** with DMAD in toluene for 4 hours at reflux confirming that it can act

as a credible precursor for the formation of 1,2,4-oxadiazole **10i**.



Scheme 4: Routes to the 3-(triazoloaryl)-1,2,4-oxadiazole **10i**

3. Conclusions

1,3-Dipolar cycloadditions of nitrile oxides to 4-aryl-2-alkylthio-1-azetines gave oxadiazabicyclo[3.2.0]heptenes that underwent a formal [2+2]-cycloreversion and loss of a styrene to furnish 5-alkylthio-3-aryl-1,2,4-oxadiazoles. The use of 2-azido-benzonitrile oxide allowed subsequent 1,3-dipolar cycloaddition of DMAD to the azide ("click" reaction) in order to furnish the 1-(1,2,4-oxadiazolo)-2-(1,2,3-triazolo)-substituted benzenes **10i**. In these processes, a 2-alkylthio-1-azetine functions as an equivalent of the alkyl thiocyanate or alkyl thiocyanic ester functional group. We are currently exploring the properties and synthetic utility of the 5-alkylthio-1,2,4-oxadiazoles **10**, and are also extending our studies to look at other nitrilium betaines and other 1-azetines. As part of a recently initiated programme of study[23] focused upon 1,2,4-oxadiazoles as ligands in supramolecular coordination chemistry, we are also exploring the ligand properties of compound **10i**.

Table 1. 1-Azetines **8**, oxadiaza[3.2.0]bicycles **9** and 1,2,4-oxadiazoles **10** produced as per Scheme 3

Entry	Ar^1	Yield of **17** (%)	Yield of **18** (%)	Yield of **8** (%)	R^1	Ar^2	Yield of **9** (%)	Yield of **10** (%)
a	Ph	75 – 77[a]	63 – 86[a]	46 – 61[a]	Et	2-N_3-C_6H_4	63	51
b	2-Naphth	64	73	40	Me	2-N_3-C_6H_4	44	68
c	Ph	75 – 77[a]	63 – 86[a]	46 – 61[a]	Et	Ph	60	83
d	Ph	-[b]	-[b]	-[b]	Et	2-NH_2-C_6H_4	70[b]	-[c]
e	Ph	75 – 77[a]	63 – 86[a]	43	Me	4-MeO-C_6H_4	43	88
f	4-Me-C_6H_4	83	82	41	Me	4-MeO-C_6H_4	72	82
g	4-Me-C_6H_4	83	82	39	Et	4-MeO-C_6H_4	48	81
h	2-Naphth	64	73	40	Me	4-MeO-C_6H_4	44	87
i	-[d]	-[d]	-[d]	-[d]	Et	See Scheme 4	Not formed[d]	41[d]

[a]The sequence of reactions leading to 1-azetine **8a** (R^1 = Et, Ar^1 = Ph) was performed more than once, hence giving a range of yields. [b]Produced by Staudinger reaction and subsequent hydrolysis of compound **9a**. [c] The adduct **9d** was stable. [d]Compound **10i** was formed directly from compound **9a** – see Scheme 4.

Acknowledgments

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4. Experimental Section

All reactions were conducted using oven-dried glassware under nitrogen dried through 4 Å molecular sieves and delivered through a gas manifold. Work-up procedures were carried out in air. All solvents were purchased from Fisher Chemicals and were of analytical grade. Anhydrous grade solvents were freshly distilled using a continuous still under nitrogen. Acetone was dried overnight over 3 Å molecular sieves (10% w/v), and then distilled over freshly activated 3 Å molecular sieves over 3-4 h. Chloroform was dried over 4 Å molecular sieves or distilled over phosphorus pentoxide (3% w/v). Dichloromethane, ethyl acetate and toluene were distilled over calcium hydride (5% w/v) over 4-6 h. Diethyl ether and THF were pre-dried over sodium wire, and then distilled over sodium wire (1-2% w/v) with benzophenone (0.2-0.3% w/v) as an indicator. Any other anhydrous solvents were purchased from Acros or Sigma-Aldrich. All reactions were monitored by TLC, which was carried out on 0.20 mm Macherey-Nagel Alugram® Sil G/UV_{254} silica gel-60 F_{254} precoated aluminium plates and visualisation was achieved using UV light and / or vanillin stain. Column chromatography was performed on Merck silica gel (0.063-0.200 mm, 60 Å). NMR spectra were recorded on a Bruker DPX-400 instrument or on a Bruker Avance 500. IR spectra were recorded on a Nicolet 380 FT-IR instrument as a thin film for oils, a drop for liquids or neat for solids. Mass spectra were recorded on a Bruker Daltonics micrOTOF mass spectrometer operating at a positive ion mode under an electrospray ionisation (ESI +) method. High resolution mass spectra were recorded on a Finnegan MAT 900 XTL instrument operated by the EPSRC National Mass Spectrometry service at the University of Swansea. Melting points were recorded on a Gallenkamp apparatus. 1-Azetines **8a-h** were

synthesised as reported previously,[18] and gave consistent spectroscopic data.

*4.1. 2-(2-Azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene **9a***

To 2-ethylthio-4-phenyl-1-azetine (**8a**)[18] (176 mg, 0.920 mmol) and 2-azidobenzohydroximoyl chloride[24] (**19a**) (181 mg, 0.921 mmol) was added triethylamine (0.153 mL, 112 mg, 1.10 mmol) diluted in diethyl ether (5 mL) dropwise over 5 hours at room temperature. The mixture was stirred overnight under an inert atmosphere. The solution was filtered and the solvent was removed *in vacuo* to give the crude product as an orange oil which was purified by gravity silica chromatography (R_f = 0.3; PE 40-60 ºC / EtOAc: 9/1) to give the product as a single diastereoisomer as a yellow oil (206 mg, 63%).

IR υ_{max} (cm^{-1}) 2928 (w), 2114 (s), 1683 (m), 1592 (m), 1577 (m), 1498 (m), 1455 (m), 1293 (m), 1164 (m), 1090 (m), 1054 (m), 749 (s), 698 (s).

^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.57 (2H, d, *J*=7.1 Hz, Ph), 7.43-7.33 (5H, m, Ph), 7.24 (1H, d, *J*=7.4 Hz, Ph), 6.87 (1H, t, *J*=7.6 Hz, Ph), 4.81 (1H, dd, *J*=9.3 and 5.4 Hz, PhC*H*N), 3.69 (1H, dd, *J*=13.1 and 9.3 Hz, PhCH*C*H_2), 2.86 (1H, dq, *J*=12.6 and 7.5 Hz, S*C*$H_2$$CH_3$), 2.75 (1H, dq, *J*=12.6 and 7.5 Hz, S*C*$H_2$$CH_3$), 2.72 (1H, dd, *J*=13.1 and 5.4 Hz, PhCH*C*H_2), 1.36 (3H, t, *J*=7.5 Hz, SCH_2*C*H_3).

^{13}C NMR δ (100 MHz, $CDCl_3$) 158.6 (N-*C*=N), 140.5 (*C*, Ar), 138.8 (*C*, Ar), 131.7 (*CH*, Ar), 131.6 (*C*, Ar), 130.8 (*CH*, Ar), 128.6 (*CH*, Ar), 128.0 (*CH*, Ar), 126.1 (*CH*, Ar), 124.6 (*CH*, Ar), 119.4 (*CH*, Ar), 110.9 (*C*-SEt), 66.8 (*CH*), 45.2 (S*C*$H_2$$CH_3$), 22.5 (*C*$H_2$), 14.6 ($SCH_2$*C*$H_3$).

MS (*m/z*) 352.1 $[M+H]^+$, 374.1 $[M+Na]^+$, 725.2 $[M_2 + Na]^+$.

HRMS (*m/z*) $[M]^+$ for $C_{18}H_{17}N_5OS$ calculated 351.1148 measured 351.1145.

*4.2. 2-(2-Azidophenyl)-5-methylthio-7-(2'-naphthyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene **9b***

Obtained as per the method for compound **9a** as a clear yellow oil (74 mg, 44%) from 2-methylthio-4-(2'-naphthyl)-1-azetine (**8b**)[18] (100 mg, 0.440 mmol) and 2-azidobenzohydroximoyl chloride (**19a**) (100 mg, 0.509 mmol); R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 2968 (m), 2918 (m), 2128 (s), 1597 (m), 1581 (m), 1447 (m), 1300 (m), 751 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.95-7.85 (2H, m, Ar), 7.82 (1H, dd, *J*=7.0 and 1.5 Hz, Ar), 7.58-7.50 (2H, m, Ar), 7.44-7.38 (2H, m, Ar), 7.28-7.23 (2H, m, Ar), 7.18 (1H, d, *J*=8.0 Hz, Ar), 6.96 (1H, td, *J*=1.0 and 7.0 Hz, Ar), 5.01 (1H, dd, *J*=9.3 and 5.5 Hz, Ar*CH*N), 3.74 (1H, dd, *J*=13.0 and 9.3 Hz, ArCH*C*H_2), 2.82 (1H, dd, *J*=13.0 and 5.5 Hz, ArCH*C*H_2) 2.3 (3H, s, SCH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 158.8 (N=C-N), 139.1 (C, Ar), 137.9, (C, Ar), 133.2 (C, Ar), 132.2 (C, Ar), 132.0 (CH, Ar), 131.0 (CH, Ar), 130.2 (CH, Ar), 128.9 (CH, Ar), 128.4 (CH, Ar), 128.0 (CH, Ar), 126.4 (CH, Ar), 126.3 (CH, Ar), 124.8 (CH, Ar), 124.0 (CH, Ar), 119.6 (CH, Ar), 118.8 (C, Ar), 116.1 (*C*-SMe), 66.8 (*CH*), 22.7 (*C*H_2), 10.8 (*C*H_3).

HRMS (*m/z*) $[M + Na]^+$ for $C_{21}H_{17}N_5NaOS$ calculated 410.1046, measured 410.1046.

*4.3. 2,7-Diphenyl-5-ethylthio-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene **9c***

Obtained as per the method for compound **9a** as a clear yellow oil (197 mg, 60%) from 2-ethylthio-4-phenyl-1-azetine (**8a**)[18] (200 mg, 1.05 mmol) and benzohydroximoyl chloride (**19c**) (160 mg, 1.05 mmol); R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 3054 (w), 1592 (m), 1421.9 (m), 1265.3 (s), 1167 (m), 1092 (m), 1060 (m), 750 (s), 701 (s) .

^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.50-7.46 (6H, m, Ar-H), 7.44-7.40 (4H, m, Ar-H), 4.85 (1H, dd, *J* = 9.2, 5.4 Hz, C*H*Ph), 3.72 – 3.68 (1H, m, PhCHC*H*$_2$), 2.89 (1H, dq, *J*=12.6, 7.8 Hz, SC*H*$_2$), 2.78-2.76 (2H, m, 1×SC*H*$_2$ + 1×PhCHC*H*$_2$), 1.37 (3H, t, *J* = 7.8 Hz, C*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$) 192.2 (C=N), 160.7 (C, Ar), 156.1 (C, Ar), 140.5 (Ar, CH), 130.9 (Ar, CH), 128.9 (Ar, CH), 128.8 (Ar, CH), 128.7 (Ar, CH), 128.1 (Ar, CH), 117.2 (*C*-SEt), 66.7 (CH), 45.4 (CH_2), 22.5 (CH_2), 14.7 (CH_3).

HRMS (*m/z*) $[M+H]^+$ calculated for $C_{18}H_{19}N_2OS$ 311.1213, measured = 311.1214.

*4.4. 2-(2'-Aminophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene **9d***

2-(2'-Azidophenyl)-5-(ethylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene **9a** (0.0468 g, 0.133 mmol) and triphenylphosphine (0.039 g, 0.149 mmol), were dissolved in tetrahydrofuran (5 mL) and stirred for 24 hours at room temperature under an atmosphere of nitrogen. Water (0.250 mL) was then added in one portion and the reaction was heated at reflux for a further 24 hours. The sample was concentrated under vacuum purified by silica column chromatography (eluent: petroleum ether: ethyl acetate, 6:1) to yield the amine (**9d**; 0.030 g, 70% yield) as a yellow oil; R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 3448 (m, broad), 2977 (m), 2847 (m), 1593 (s), 1412 (m), 1390 (m), 1302 (m), 1178 (m).

^{1}H NMR δ (500 MHz, $CDCl_3$) 7.50 – 7.60 (2H, m, Ar-H), 7.38 – 7.32 (2H, m, Ar-H), 7.31 – 7.28 (1H, m, Ar-H), 7.01 – 7.13 (1H, m, Ar-H), 6.89 (1H, dd, *J*=5.0, 1.0 Hz, Ar-H), 6.63 (1H, dd, *J*=8.1, 1.0 Hz, Ar-H), 6.31 – 6.42 (1H, m, Ar-H), 5.39 (2H, s, NH_2), 4.75 (1H, dd, *J*=10.0, 5.0 Hz, PhC*H*), 3.55 – 3.59 (1H, m, PhCHC*H*$_2$), 2.74 – 2.78 (1H, m, PhCHC*H*$_2$), 2.71 – 2.63 (2H, m, CH_3C*H*$_2$), 1.27 (3H, t, *J*=7.5 Hz, CH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 161.9 (C=N), 147.1 (Ar, C), 140.7 (Ar, C), 131.6 (Ar, CH), 129.7 (Ar, CH), 128.8 (Ar, CH), 128.4 (Ar, CH), 126.7 (Ar, CH), 116.6 (Ar, CH), 115.7 (Ar, CH), 110.0 (Ar, C), 106.9 (*C*SEt), 67.4 (CH), 45.2 (CH_2), 29.7 (CH_2), 14.8 (CH_3).

HRMS (*m/z*) $[M]^+$ for $C_{18}H_{19}N_3OS$ calculated = 325.1243, measured = 325.1245.

*4.5. 2-(4'-Methoxyphenyl)-5-methylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene **9e***

Obtained as per the method for compound **9a** as a clear yellow oil (140 mg, 43%) from 2-methylthio-4-phenyl-1-azetine (**8e**)[18] (180 mg, 0.984 mmol) and 4-methoxybenzohydroximoyl chloride (**19e**) (182 mg, 0.981 mmol); R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 2905 (w), 1606 (s) 1510 (s), 1421 (m), 1347 (m), 1305 (m), 1256 (s), 1172 (m), 1026 (m), 836 (m), 753 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.64-7.38 (5H, m, Ph), 6.97 (2H, d, *J*=7.0 Hz, Ar), 6.82 (2H, d, *J*=7.0 Hz, Ar), 4.83 (1H, dd, *J*=5.5, 9.3 Hz, PhC*H*), 3.82 (3H, s, OCH_3), 3.67 (1H, dd, *J*=9.3,

13.0 Hz, PhCHCH_2), 2.72 (1H, dd, *J*=13.0 and 5.5 Hz, PhCHCH_2), 2.17 (3H, s, SCH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 161.7 (N=C-N), 160.6 (C, Ar), 140.6 (C, Ar), 137.5 (C, Ar), 133.9 (CH, Ar), 128.7 (CH, Ar), 128.6 (CH, Ar), 126.9 (CH, Ar), 114.6 (CH, Ar), 114.4 (*C*-SMe), 66.5 (CH), 55.3 (OCH_3), 44.6 (CH_2), 10.3 (SCH_3).

MS (*m/z*) 349.1 $[M+Na]^+$, 675.2 $[M_2 + Na]^+$.

HRMS (*m/z*) $[M+Na]^+$ for $C_{18}H_{18}N_2NaO_2S$ calculated = 349.0164, measured = 349.0159.

4.6. 2-(4'-Methoxyphenyl)-5-methylthio-7-(4'-tolyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene ***9f***

Obtained as per the method for compound **9a** as a clear yellow oil (140 mg, 72%) from 2-methylthio-4-(4'-tolyl)-1-azetine (**8f**)[18] (110 mg, 0.571 mmol) and 4-methoxybenzohydroximoyl chloride (**19e**) (107 mg, 0.574 mmol); R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 2893 (w), 1608 (s) 1512 (s), 1346 (s), 1306 (m), 1255 (s), 1172 (s), 1051 (m), 1031 (m), 838 (m), 753 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.42-7.39 (4H, m, 2 × Ar^1, 2 × Ar^2), 7.14 (2H, d, *J*=8.0 Hz, Ar^1), 6.71 (2H, d, *J*=7.2 Hz, Ar^2), 4.68 (1H, dd, *J*=5.4 and 9.4 Hz, Ar^1CH), 3.68 (3H, s, OCH_3), 3.54 (1H, dd, *J*=9.4 and 13.3 Hz, Ar^1CHCH_2), 2.61 (1H, dd, *J*=5.4 and 13.3 Hz, Ar^1CHCH_2), 2.30 (3H, s, SCH_3), 2.13 (3H, s, CH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 161.8 (N=C-N), 160.7 (C, Ar), 138.1 (C, Ar), 137.9 (C, Ar), 129.1 (CH, Ar), 128.7 (CH, Ar), 126.4 (CH, Ar), 116.9 (C, Ar), 114.7 (CH, Ar), 111.2 (*C*-SMe), 66.5 (CH), 55.4 (OCH_3), 44.7 (CH_2), 21.1 ($ArCH_3$), 10.4 (SCH_3).

MS (*m/z*) 341.1 $[M+H^+]$, 363.1 $[M+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{19}H_{21}N_2O_2S$ calculated = 341.0501, measured = 341.0503.

4.7. 2-(4'-Methoxyphenyl)-5-ethylthio-7-(4'-tolyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene ***9g***

Obtained as per the method for compound **9a** as a clear yellow oil (83 mg, 48%) from 2-ethylthio-4-(4'-tolyl)-1-azetine (**8g**)[18] (100 mg, 0.485 mmol) and 4-methoxybenzohydroximoyl chloride (**19e**) (100 mg, 0.539 mmol); R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 2915 (w), 1608 (s), 1590 (m), 1512 (s), 1345 (m), 1256 (s), 1173 (m), 1030 (m), 838 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.54-7.49 (2H, m, ArH), 7.29-7.24 (2H, m, ArH), 6.95 (2H, dd, *J*=2.4 and 8.1 Hz, ArH), 6.83 (2H, d, *J*=7.2 Hz, ArH), 4.80 (1H, dd, *J*=5.3 and 9.3 Hz, ArC*H*), 3.8 (3H, s, OCH_3), 3.62 (1H, dd, *J*=9.3 and 13.0 Hz, $ArCHCH_2$), 2.92-2.75 (2H, m, SCH_2CH_3), 2.71 (1H, dd, *J*=5.3 and 13.0 Hz, $ArCHCH_2$), 2.42 (3H, s, Ar-CH_3), 1.36 (3H, t, *J*=7.0, SCH_2CH_3).

^{13}C NMR: δ (125 MHz, $CDCl_3$) 161.8 (N=C-N), 160.7 (C, Ar), 138.0 (C, Ar), 137.8 (C, Ar), 129.4 (CH, Ar), 129.0 (CH, Ar), 126.4 (C, Ar), 114.4 (CH, Ar), 114.2 (CH, Ar), 111.5 (C, *C*SEt), 66.77 (CH), 55.3 (OCH_3), 45.4 ($ArCHCH_2$), 22.7 (SCH_2), 21.1 ($ArCH_3$), 14.8 (SCH_2CH_3).

MS (*m/z*) 377.1 $[M+Na]^+$, 731.2 $[M_2 + Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{20}H_{23}N_2O_2S$ calculated = 355.0657, measured = 355.0657.

4.8. 2-(2'-Methoxyphenyl)-5-methylthio-7-(2'-naphthyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene ***9h***

Obtained as per the method for compound **9a** as a clear yellow oil (72 mg, 44%) from 2-methylthio-4-(2'-naphthyl)-1-azetine (**8b**)[18] (100 mg, 0.440 mmol) and 4-methoxybenzohydroximoyl chloride (**19e**) (100 mg, 0.539 mmol); R_f = 0.3 (PE 40-60 ºC / EtOAc: 10/1).

IR υ_{max} (cm^{-1}) 2928 (w), 1608 (s), 1511 (s), 1404 (m), 1349 (m), 1256 (s), 1172 (m), 1028 (m), 836 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.98 (2H, d, *J*=8.8 Hz, 4-MeOAr), 7.94-7.85 (2H, m, naphth), 7.57-7.47 (3H, m, naphth), 7.0-6.95 (2H, m, naphth), 6.80 (2H, d, *J*=8.8 Hz, 4-MeOAr), 5.0 (1H, dd, *J*=5.5 and 9.5 Hz, naphthC*H*), 3.77 (3H, s, OCH_3), 3.74 (1H, dd, *J*=9.5 and 13.5 Hz, $naphthCHCH_2$), 2.82 (1H, dd, *J*=13.5 and 5.5 Hz, $naphthCHCH_2$), 2.30 (3H, s, SCH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 161.8 (N=C-N), 138.1 (C, Ar), 133.3 (C, Ar), 133.2 (C, Ar), 130.2 (C, Ar), 130.0 (CH, Ar), 129.0 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 126.8 (CH, Ar), 126.4 (CH, Ar), 125.2 (CH, Ar), 123.9 (CH, Ar), 116. 8 (CH, Ar), 114.4 (C, Ar), 111.3 (*C*-SMe), 66.6 (*C*H), 55.3 (OCH_3), 44.7 (CH_2), 10.4 (SCH_3).

HRMS (*m/z*) $[M + Na]^+$ for $C_{22}H_{20}N_2NaO_2S$ calculated 399.1138 measured 399.1142.

4.9. 3-(2-Azidophenyl)-5-ethylthio-1,2,4-oxadiazole ***10a***

2-(2-Azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**9a**) (100 mg, 0.284 mmol) was dissolved in toluene (5 mL) and heated at reflux for 47 h. The solvent was removed *in vacuo* and the crude product was purified by gravity silica chromatography (R_f = 0.4; PE 40-60 ºC / EtOAc : 7/1) to yield the title product as an orange oil (36 mg, 51%).

IR υ_{max} (cm^{-1}) 2930 (w), 2130-2100 (s), 1582 (m), 1520 (m), 1505 (m), 1470 (m), 1339 (s), 1304 (m), 1271 (m), 1187 (m), 750 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$) 7.99 (1H, dd, *J*=7.7 and 1.6 Hz, ArH), 7.55 (1H, ddd, *J*=8.1, 7.4 and 1.6 Hz, ArH), 7.27 (1H, dd, *J*=8.1 and 0.8 Hz, ArH), 7.19 (1H, td, *J*=7.7 and 0.8 Hz, ArH), 3.34 (2H, q, *J*=7.4 Hz, SCH_2CH_3), 1.54 (3H, t, *J*=7.4 Hz, SCH_2CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$) 177.6 (S-*C*=N), 166.7 (N-*C*=N), 138.9 (C**,** Ar), 132.1 (CH, Ar), 131.6 (CH, Ar), 124.9 (CH, Ar), 119.3 (CH, Ar), 118.2 (C, Ar), 27.3 (SCH_2CH_3), 14.8 (SCH_2CH_3).

MS (*m/z*) 248.1 $[M+H]^+$, 270.0 $[M+Na]^+$, 517.1 $[M_2+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{10}H_{10}N_5OS$ calculated 248.0601 measured 248.0603.

4.10. 3-(2-Azidophenyl)-5-methylthio-1,2,4-oxadiazole ***10b***

Obtained as a clear, yellow oil (41 mg, 68% yield) as per the method for compound **10a** from 2-(2-azidophenyl)-7-(2'-naphthyl)-5-methylthio-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (**9b**, 100 mg) after silica chromatography (R_f = 0.2; eluent: petroleum ether: ethyl acetate, 16:1).

IR υ_{max} (cm^{-1}) 2966 (w), 2128 (s), 1597 (m), 1578 (m), 1501 (m), 1300 (m), 750 (m).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 7.97 (1H, dd, *J*=2.0 and 8.0 Hz, ArH), 7.55-7.45 (1H, m, ArH), 7.37 (1H, dd, *J*=2.0 and 8.0 Hz, ArH), 7.27-7.22 (1H, m, ArH), 2.73 (3H, s, SCH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 178.0 (C, oxadiazole), 166.7 (C, oxadiazole), 138.8 (C, Ar), 132.1 (CH, Ar), 131.0 (CH, Ar), 124.9 (CH, Ar), 119.3 (CH, Ar), 118.9 (C, Ar), 15.3 (S*C*H_3).

HRMS (*m/z*) $[M+Na]^+$ for $C_9H_7N_5NaOS$ calculated 256.0264 measured 256.0273.

4.11. 3-(Phenyl)-5-ethylthio-1,2,4-oxadiazole ***10c***

Obtained as a clear, yellow oil (72 mg, 83% yield) as per the method for compound **10a** from 2,7-diphenyl-5-ethylthio-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (**9c**, 130 mg) after silica chromatography (R_f = 0.2; eluent: petroleum ether: ethyl acetate, 16:1).

IR υ_{max} (cm^{-1}) 2935 (m), 1544 (m), 1522 (s), 1474 (m), 1359 (m), 1266 (s), 1195 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$) 7.27-7.33 (3H, m, Ar-H), 7.23-7.13 (2H, m, Ar-H), 3.38 (2H, q, *J*=7.5 Hz, SCH_2), 1.56 (3H, t, *J*=7.5 Hz, CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$) 176.9 (C), 137.8 (C), 130.9 (CH, Ar), 128.9 (CH, Ar), 126.1 (C), 125.3 (CH, Ar), 28.9 (CH_2), 21.4 (CH_3).

HRMS (*m/z*) $[M+H]^+$ for $C_{10}H_{10}N_2OS$ calculated = 207.1404, measured = 207.1407.

4.12. 3-(4-Methoxyphenyl)-5-methylthio-1,2,4-oxadiazole ***10e/f/h***

Obtained as a clear, yellow oil (45 mg, 88% yield), (52 mg, 82% yield) and (34 mg, 87% yield), as per the method for compound **10a**, from 2-(4'-methoxyphenyl)-5-methylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**9e**, 80 mg) or 2-(4'-methoxyphenyl)-5-methylthio-7-(4'-tolyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**9f**, 100 mg), or 2-(4'-methoxyphenyl)-5-methylthio-7-(2'-naphthyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**9h**, 70 mg), respectively, after silica chromatography (eluent: petroleum ether: ethyl acetate, 16:1); R_f = 0.5 (PE 40-60 ºC / EtOAc : 10/1).

IR υ_{max} (cm^{-1}) 2919 (m), 1611 (s), 1509 (s), 1466 (m), 1422 (m), 1346 (m), 1297 (m), 1250 (s), 1198 (m), 1117 (m), 1027 (m), 833 (s), 758 (s).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$) 7.99 (2H, d, *J*=8.0, ArH), 6.98 (2H, d, *J*=8.0, ArH), 3.85 (3H, s, OMe), 2.78 (3H, s, SMe).

^{13}C NMR: δ_C (125 MHz, $CDCl_3$) 178.1 (C, oxadiazole), 168.3 (C, oxadiazole), 162.0 (C, Ar), 129.1 (CH, Ar), 119.0 (C, Ar), 114.2 (CH, Ar), 55.4 (O-*C*H_3), 14.2 (S-*C*H_3).

HRMS (*m/z*) $[M+Na]^+$ for $C_{10}H_{10}N_2NaO_2S$ calculated = 245.0355, measured = 245.0350.

4.13. 3-(4-Methoxyphenyl)-5-ethylthio-1,2,4-oxadiazole ***10g***

Obtained as a clear, yellow oil (40 mg, 81% yield) as per the method for compound **10a** from 2-(4'-methoxyphenyl)-5-ethylthio-7-(4'-tolyl)-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**9g**, 80 mg) after silica chromatography (eluent: petroleum ether: ethyl acetate, 16:1); R_f = 0.5 (PE 40-60 ºC / EtOAc : 10/1).

IR υ_{max} (cm^{-1}) 2920 (w), 1611 (s), 1505 (s), 1420 (m), 1348 (s), 1299 (m), 1250 (s), 1171 (m), 1028 (m), 838 (m), 753 (m).

^{1}H NMR: δ_H (500 MHz, $CDCl_3$): 7.98 (2H, d, *J*=8.1 Hz, ArH), 6.96 (2H, d, *J*=8.1 Hz, ArH), 3.86 (3H, s, OMe), 3.32 (2H, q, *J*=7.9 Hz, CH_2CH$_3$), 1.52 (3H, t, *J*=7.9 Hz, CH$_2$CH_3).

^{13}C NMR δ (125 MHz, $CDCl_3$): 177.6 (C, oxadiazole), 168.3 (C, oxadiazole), 162.0 (C, Ar), 129.0 (CH, Ar), 119.0 (C, Ar), 114.2 (CH, Ar), 55.4 (O-*C*H_3), 27.3 (S-*C*H_2), 14.8 (S-CH$_2$*C*H_3).

MS (*m/z*) 259.0 $[M+Na]^+$, 731.2 $[M_2 + Na]^+$.

HRMS (*m/z*) $[M+Na]^+$ for $C_{11}H_{12}N_2NaO_2S$ calculated = 259.0511, measured = 259.0518.

4.14. Synthesis of 1,2,3-triazole ***10i****: Reaction of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]-hept-2-ene with DMAD*

2-(2-Azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiaza bicyclo[3.2.0]hept-2-ene (**9a**) (110 mg, 0.313 mmol) and dimethylacetylene dicarboxylate (DMAD) (42 µL, 49 mg, 0.34 mmol, 1 eq.) were dissolved in toluene (5 mL) and the solution was heated at reflux under nitrogen overnight. The solvent was removed in vacuo to give the crude product as an orange oil, which was purified by gravity silica chromatography (R_f = 0.3; PE 40-60 ºC/EtOAc: 10/1) to give the triazole derivative **10i** as a yellow oil (50 mg, 41%).

IR υ_{max} (cm^{-1}) 2954 (w), 1735 (s, C=O), 1557 (w), 1507 (m), 1474 (m), 1448 (m), 1358 (s), 1290 (m), 1232 (m), 1181 (m), 1105 (m), 1078 (m), 1004 (w), 963 (w), 826 (w), 809 (w), 777 (w), 758 (m), 669 (w).

^{1}H NMR δ (500 MHz, $CDCl_3$) 8.25 (1H, dd, *J*=7.1 and 2.2 Hz, ArH), 7.68 – 7.74 (2H, m, ArH), 7.54 (1H, dd, *J*=7.4 and 1.6 Hz, ArH), 4.02 (3H, s, CO_2*Me*), 3.76 (3H, s, CO_2*Me*), 3.09 (2H, q, *J*=7.4 Hz, S*C*H_2CH$_3$), 1.36 (3H, t, *J*=7.4 Hz, SCH$_2$*C*H_3).

^{13}C NMR δ (125 MHz, $CDCl_3$) 178.9 (EtS-*C*=N), 165.5 (N-C=N), 160.4 (C=O), 158.1 (C=O), 139.1 (C, Ar), 133.8 (*C*=C), 133.1 (C=*C*), 131.6 (*C*H, Ar), 131.4 (*C*H, Ar), 130.1 (*C*H, Ar), 128.7 (*C*H, Ar), 124.2 (C, Ar), 53.3 (CO_2*C*H_3), 52.7 (CO_2*C*H_3), 27.4 (S*C*H_2CH$_3$), 14.5 (SCH$_2$*C*H_3).

MS (*m/z*) 390.1 $[M+H]^+$, 412.1 $[M+Na]^+$, 779.2 $[M_2+H]^+$, 801.1 $[M_2+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{16}H_{16}N_5O_5S$ calculated 390.0867 measured 390.0867.

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