Accepted Manuscript

Synthesis of novel five-membered endocyclic sulfoximines — 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxides

Yong Hua, Wenjie Zhang, Xin Wang, Zemei Ge, Runtao Li

PII: S0040-4020(17)30607-5

DOI: 10.1016/j.tet.2017.05.098

Reference: TET 28764

To appear in: *Tetrahedron*

Received Date: 12 April 2017

Revised Date: 28 May 2017

Accepted Date: 31 May 2017

Please cite this article as: Hua Y, Zhang W, Wang X, Ge Z, Li R, Synthesis of novel five-membered endocyclic sulfoximines — 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxides, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.05.098.

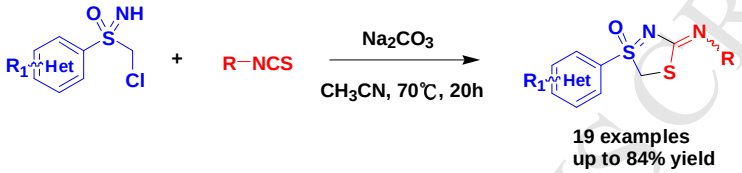
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of novel five-membered endocyclic sulfoximines — 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxides

Leave this area blank for abstract info.

Yong Hua, Wenjie Zhang, Xin Wang, Zemei Ge, Runtao Li
State Key Laboratory of Nature and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China.



Tetrahedron
journal homepage: www.elsevier.com

Synthesis of novel five-membered endocyclic sulfoximines — 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxides

Yong Hua, Wenjie Zhang, Xin Wang, Zemei Ge*, Runtao Li*

State Key Laboratory of Nature and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Five-membered endocyclic sulfoximines
Chloromethyl aryl sulfoximines
Aryl isothiocyanates
Addition/cyclization
Synthesis

ABSTRACT

A novel kind of five-membered endocyclic sulfoximines, 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2- dithiazole 1-oxides, were synthesized through addition/cyclization of chloromethyl aryl sulfoximines with aryl isothiocyanates under mild reaction conditions in moderate to good yields.

1. Introduction

In recent years, sulfoximines have gained considerable attention due to their unique structure and the entensive application in organic synthesis and medicinal chemistry.[1a-b] Many efficient methods for the synthesis of sulfoximines have been developed.[2a-e] Meanwhile, numerous sulfoximine derivatives have also been prepared, especially the endocyclic sulfoximines owing to the importance of heterocyclic compounds in medicinal chemistry.[3a-i] However, most of the methods for the synthesis of endocyclic sulfoximines focused on the six-membered or benzo-fused endocyclic sulfoximines,[4a-l] and only few on the synthesis of five-membered endocyclic sulfoximines have been reported. Donald J. Cram et al. first synthesized the five-membered endocyclic sulfoximine from the reaction of p-methylphenyl methyl sulfoximine and ethyl 2-bromoacetate in the presence of sodium hydride, but only result in 13% yield (Fig 1, a).[5] Carsten Bolm et al. found that, when treated with a combination of iodobenzene diacetate (PIDA) and potassium iodide, the unsaturated NH-sulfoximines would afford the endocyclic sulfoximine dihydro isothiazole 1-oxides in moderate to good yields (Fig 1, b).[6] More recently, Vincent Reboul et al. developed an asymmetric synthesis of five-membered endocyclic sulfoximines from the cyclization of methionine derivatives by using PIDA (Fig 1, c).[7] Herein, we report the synthesis of a new kind of five-membered endocyclic sulfoximines, 3,5-dihydro-1,4,2-dithiazole 1-oxides, through addition/ cyclization of chloromethyl aryl sulfoximines with aryl isothiocyanates under mild reaction conditions in moderate to good yields (Fig 1, d).

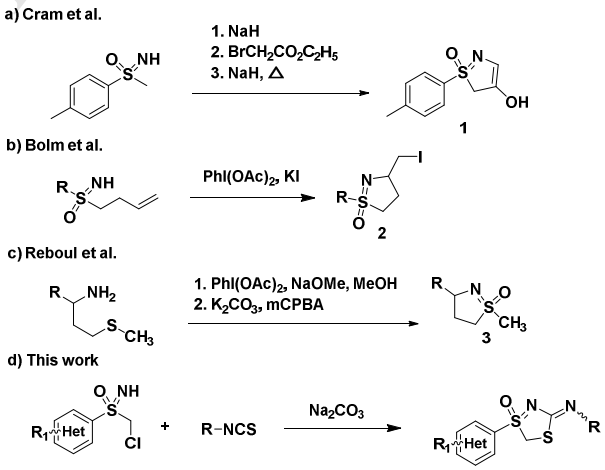


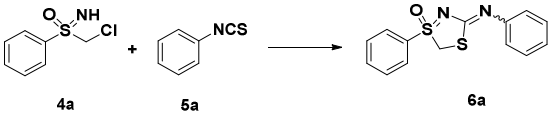
Fig 1. Preparation of five-membered endocyclic sulfoximines.

2. Results and discussion

In our initial attempt, chloromethyl phenyl sulfoximine (**4a**) and phenyl isothiocyanate (**5a**) were selected as the model substrates, with the presence of sodium carbonate in DMF at 60°C for 20 hours to prepare the five-membered endocyclic sulfoximine **6a**. To our delight, the desired product **6a** was successfully obtained in 65% yield (Table 1 Entry 1). Encouraged by this result, further optimization of the reaction conditions was performed next. Solvents screening results showed that polar solvent was favorable

for the reaction, and acetonitrile turned out to be the best one with a yield of 78% (Table 1, Entries 2-6). In addition to sodium carbonate, both organic bases and several other inorganic bases were tested. However, none of them showed better results than sodium carbonate (Table 1, Entries 7-10). A survey of the feeding ratio of isothiocyanate (**5a**) indicated that 1.1 equivalent was the best choice to afford **6a** in 78% yield (Table 1, Entries 10-12). Finally, the effect of reaction temperature on the reaction was examined and the best yield of **6a** was achieved at reaction temperature of 70 °C (Table 1, entries 12-14).

Table 1. Screening of Reaction Conditions.[a]



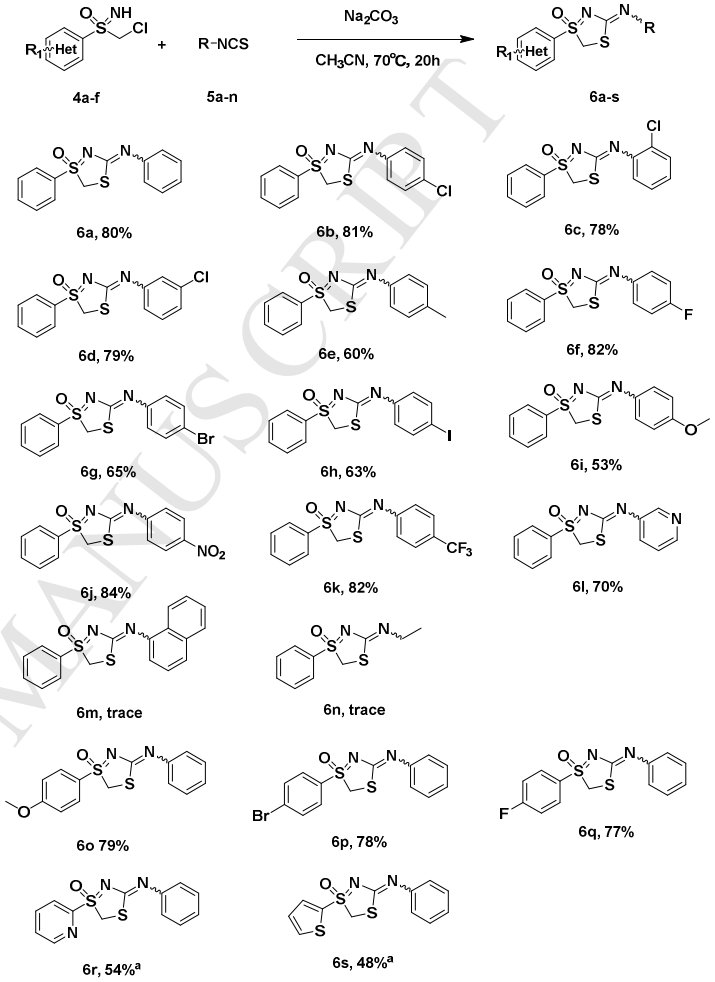
Entry	Solvent	Base	Temp (℃)	Ratio (**4a**:**5a**)	Yield (%)[b]
1	DMF	Na_2CO_3	60	1:1.2	65
2	toluene	Na_2CO_3	60	1:1.2	trace
3	THF	Na_2CO_3	60	1:1.2	54
4	CH_3CN	Na_2CO_3	60	1:1.2	78
5	acetone	Na_2CO_3	reflux	1:1.2	52
6	DMSO	Na_2CO_3	60	1:1.2	63
7	CH_3CN	TEA	60	1:1.2	71
8	CH_3CN	$NaHCO_3$	60	1:1.2	77
9	CH_3CN	DBU	60	1:1.2	trace
10	CH_3CN	Cs_2CO_3	60	1:1.2	trace
11	CH_3CN	Na_2CO_3	60	1:1.1	78
12	CH_3CN	Na_2CO_3	60	1:1.0	75
13	CH_3CN	Na_2CO_3	70	1:1.1	80
14	CH_3CN	Na_2CO_3	reflux	1:1.1	77

[a] Reaction was conducted with **4a** (0.2 mmol) in solvent (1 mL) under corresponding temperature.

[b] Isolated yields.

The generality of this reaction was further explored with the optimized conditions. As exhibited in Scheme 1, chloromethyl phenyl sulfoximine (**4a**) could smoothly react with various aryl isothiocyanates （**5**） to afford the corresponding five-membered endocyclic sulfoximines (**6a-6l)** in moderate to good yields (53-84%). The position of the substituent at the benzene ring does not have significant effect on the reactions (**6b-6d,** 78-81% yields). However, the electronic properties of the substituents on the benzene ring have obviously effect the reactions. The electron-withdrawing substitutes (**6j**, 4-NO_2, 84% yield; **6k**, 4-CF_3, 82% yield) are more favorable for the reactions than the electron-donating substitutes (**6e**, 4-Me, 60% yield; **6i**, 4-OMe, 53% yield). 3-Pyridyl isothiocyanate also got a good yield (**6l**, 70%). However, ethyl isothiocyanate and 1-naphthyl isothiocyanate only gave a trace of the desired products (**6m** and **6n)**, which maybe due to the low reactivity and large steric effect respectively. Subsquently, representative substituted aryl or heteroaryl chloromethyl sulfoximines (**4-a-f**) were allowed to react with phenyl isothiocyanate (**5a)** under the optimized reaction conditions. All of them worked well and the desired products (**6o-6s**) were formed in 48-80% yields. Additionally, all the products **6** are the mixtures of cis- and trans- isomers according to their ^{1}H-NMR and ^{13}C-NMR spectra (See supporting information), and the ratio of cis-trans isomers is related to the kinds and positions of substituents.[8]

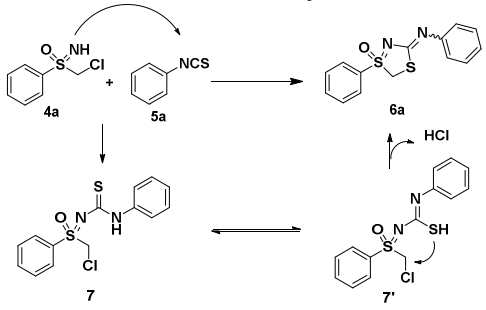
Scheme 1. Synthesis of 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxides.



[a] Reaction was conducted for 48 h.

Based on our experimental results, a possible pathway for this reaction is proposed in Scheme 2.[9a-c] First, the nucleophilic addition between sulfoximine **4a** and isothiocyanate **5a** takes place, forming the thiourea derivatives of sulfoximine (**7**), which is a pair of tautomer with **7'**. Subsequently, the product **6a** is generated through the intramolecular nucleophilic substitution of **7'.**

Scheme 2. Possible Reaction Pathway.



3. Conclusion

In summary, we have developed an efficient method for the synthesis of a novel five-membered endocyclic sulfoximines through addition/cyclization of chloromethyl aryl sulfoximines with aryl isocyanates. A series of 1-aryl-3-(arylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxides were prepared in moderate to good yields by this method. Due to the unique properties of sulfoximine group and the importance of heterocyclic compounds in medicinal chemistry, this novel kind of endocyclic sulfoximines will be of great interest to medicinal chemists. The biological activities of these compounds are currently under investigation in our laboratory.

4. Experimental section

4.1 General

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AVANCE 400 MHz and 600 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. The ^{1}H-NMR chemical shifts (in ppm) were referenced to tetramethylsilane. The ^{13}C-NMR chemical shifts were given using solvent ($CDCl_3$ or DMSO-d_6) as the internal standard. High resolution mass spectra were recorded using LCMS–IT–TOF technique (Shimadzu). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Column chromatography was carried out on silica gel (particle size 200-300 mesh ASTM).

*4.2 Preparation of chloromethyl aryl sulfoximines (**4a-4d**)*

Typical procedure:[2e] Chloromethyl phenyl sulfide (10 mmol) was dissolved in methanol (25 mL), and $PhI(OAc)_2$ (25 mmol), NH_2COONH_4 (20 mmol) was added. The mixture was reacted at room temperature for 3 hours. After completion, the solvent was evaporated and then 20 mL of water was added. The mixture was extracted with DCM and the combined organic phase were dried over anhydrous Na_2SO_4. After removal of solvents, the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (4:1) to afford the desired product (Chloromethyl)(imino)(phenyl)-λ^6-sulfanone (**4a**) as a pale yellow oil (1.57 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 4.59 (s, 2H), 3.18 (s, 1H).

With the same method, (Chloromethyl)(imino)(4-methoxyphenyl)- λ^6-sulfanone (**4b**) was afforded as a pale yellow oil (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 4.55 (s, 2H), 3.90 (s, 3H), 3.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 131.6, 128.7, 114.5, 61.5, 55.8;

(4-Bromophenyl)(chloromethyl)(imino)-λ^6-sulfanone (**4c**) was afforded as a pale yellow oil (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.77 – 7.68 (m, 2H), 4.57 (s, 2H), 3.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 132.6, 131.0, 129.7, 61.1;

(Chloromethyl)(4-fluorophenyl)(imino)-λ^6-sulfanone (**4d**) was afforded as a pale yellow oil (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 7.82 (m, 2H), 7.45 – 6.98 (m, 2H), 4.58 (s, 2H), 3.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 165.0, 133.5, 133.4, 132.4, 132.3, 116.7, 116.4, 61.3;

(Chloromethyl)(imino) (pyridin-2-yl)-λ^6-sulfanone **(4e)** was afforded as a pale yellow oil (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.4 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.00 (t, *J* = 7.8 Hz, 1H), 7.59 (dd, *J* = 7.0, 5.3 Hz, 1H), 4.95 (q, *J* = 11.9 Hz, 2H), 3.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.83, 150.33, 138.21, 127.47, 123.82, 57.93.

(Chloromethyl)(imino)(thiophen-2-yl)-λ^6-sulfan-one **(4f)** was afforded as a pale yellow oil (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H), 7.20 (t, *J* = 4.3 Hz, 1H), 4.74 – 4.65 (m, 2H), 3.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.06, 135.93, 135.68, 128.26, 62.00.

*4.3 General procedure for the preparation of compounds (**6a-6s**)*

To a solution of chloromethyl aryl sulfoximine **4** (0.2 mmol) in acetonitrile (1 mL) was added Na_2CO_3 (0.22 mmol) and isothiocyanate **5** (0.22 mmol). The resulting mixture was stirred at 70 °C for 20 hours. After completion of the reaction, the solvent was evaporated and then 10 mL of water was added. The mixture was extracted with DCM. The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4. filtered and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate to give the desired product (**6a-6s**).

*4.3.1 1-Phenyl-3-(phenylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6a**)*

White solid, R_f=0.24 (EtOAc 1:2 Hex); Yield 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H,), 7.75 (t, *J* = 7.5 Hz, 0.5H), 7.67 (t, *J* = 7.9 Hz, 2H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H,), 7.33 – 7.27 (m, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 2.5H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 0.5H), 4.56 (d, *J* = 11.5 Hz, 0.5H), 4.50 (d, *J* = 11.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 159.0, 150.1, 148.6, 135.4, 135.4, 135.3, 134.8, 130.0, 129.9, 129.2, 129.1, 128.8, 128.5, 124.3, 123.8, 123.0, 121.6, 58.9, 57.1; ES-HRMS: Calcd for $C_{14}H_{13}N_2OS_2$ $[M+H]^+$, 289.0464, Found 289.0470.

*4.3.2. 3-((4-Chlorophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6b**)*

White solid, R_f=0.22 (EtOAc 1:2 Hex); Yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 7.8 Hz, 1.48H), 7.83 – 7.76 (m, 1.74H), 7.72 – 7.63 (m, 3.48H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 1.48H), 7.24 (d, *J* = 8.8 Hz, 1.48H), 6.99 (d, *J* = 8.5 Hz, 2H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 0.74H), 4.56 (d, *J* = 11.5 Hz, 0.74H), 4.52 (d, *J* = 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 148.6, 147.2, 135.6, 135.6, 135.3, 134.7, 130.1, 130.1, 129.6, 129.3, 129.2, 129.0, 128.9, 128.6, 124.5, 123.1, 59.0, 57.2; ES-HRMS: Calcd for $C_{14}H_{12}ClN_2OS_2$ $[M+H]^+$, 323.0074, Found 323.0073.

*4.3.3. 3-((2-Chlorophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6c**)*

White solid, R_f=0.22 (EtOAc 1:2 Hex); Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 2H), 7.97 (d, *J* = 7.8 Hz, 1.6H), 7.83 – 7.72 (m, 1.8H), 7.70 –7.60 (m, 3.6H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 0.8H), 7.25 – 7.14 (m, 2.6H), 7.10 – 7.04 (m, 2H), 6.99 – 6.93 (m, 0.8H), 4.80 (d, *J* = 11.6 Hz, 1.8H), 4.64 (d, *J* = 11.6 Hz, 0.8H), 4.58 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 147.3, 147.1, 135.6, 135.5, 135.2, 135.0, 130.2, 130.1, 123.0, 129.5, 129.2, 129.1, 128.9, 128.6, 127.4, 127.0, 126.8, 126.5, 125.3, 124.4, 123.3, 123.1, 59.2, 58.1; ES-HRMS: Calcd for $C_{14}H_{12}ClN_2OS_2$ $[M+H]^+$, 323.0074, Found 323.0070.

*4.3.4. 3-((3-Chlorophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6d**)*

White solid, R_f=0.22 (EtOAc 1:2 Hex); Yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 2H), 7.97 (d, *J* = 7.5 Hz, 1.4H), 7.83 – 7.76 (m, 1.7H), 7.72 – 7.63 (m, 3.4H), 7.36 – 7.34 (m, 0.7H),7.30 – 7.24 (m, 1.4H), 7.22 – 7.18 (m, 1H), 7.14 – 7.09

(m, 1H), 7.06 (t, *J* = 1.9 Hz, 1H), 7.02 (dt, *J* = 7.1, 2.0 Hz, 0.7H), 6.94 (d, *J* = 7.9 Hz, 1H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 0.7H), 4.57 (d, *J* = 11.5 Hz, 0.7H), 4.53 (d, *J* = 11.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 151.3, 135.6, 135.5, 134.7, 134.5, 134.0, 130.2, 130.1, 130.1, 129.5, 129.3, 128.9, 124.4, 123.9, 123.2, 122.0, 121.5, 120.0, 59.1, 57.2; ES-HRMS: Calcd for $C_{14}H_{12}ClN_2OS_2$ $[M+H]^+$, 323.0074, Found 323.0069.

*4.3.5. 1-Phenyl-3-(p-tolylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6e**)*

White solid, R_f=0.23 (EtOAc 1:2 Hex); Yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.4 Hz, 2H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.85 – 7.75 (m, 1.5H), 7.72 – 7.62 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 4.80 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 0.5H), 4.56 (d, *J* = 11.4 Hz, 0.5H), 4.51 (d, *J* = 11.4 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 1.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 158.7, 147.7, 146.2, 135.5, 135.4, 135.4, 134.9, 133.9, 133.4, 130.0, 129.7, 129.3, 129.2, 128.9, 122.8, 121.4, 58.9, 57.1, 21.0; ES-HRMS: Calcd for $C_{15}H_{15}N_2OS_2$ $[M+H]^+$, 303.0620, Found 303.0616.

*4.3.6. 3-((4-Fluorophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6f**)*

White solid, R_f=0.22 (EtOAc 1:2 Hex); Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 1.4H), 7.85 – 7.77 (m, 1.7H), 7.73 – 7.65 (m, 3.4H), 7.36 – 7.32 (m, 1.4H), 7.09 – 6.95 (m, 5.4H), 4.82 (d, *J* = 11.4 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 0.7H), 4.58 (d, *J* = 11.5 Hz, 0.7H), 4.53 (d, *J* = 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.7, 146.3, 144.6, 135.6, 135.5, 135.4, 134.8, 130.1, 130.0, 129.3, 128.9, 124.5, 124.4, 123.0, 122.9, 115.9, 115.7, 115.2, 115.0, 59.0, 57.1; ES-HRMS: Calcd for $C_{14}H_{12}FN_2OS_2$ $[M+H]^+$, 307.0370, Found 307.0370.

*4.3.7. 3-((4-Bromophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6g**)*

Yellow solid, R_f=0.23 (EtOAc 1:2 Hex); Yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 7.9 Hz, 1.46H), 7.85 – 7.75 (m, 1.73H), 7.72 – 7.63 (m, 3.46H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 1.46H), 7.21 (d, *J* = 8.6 Hz, 1.46H), 6.93 (d, *J* = 8.5 Hz, 2H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 0.73H), 4.56 (d, *J* = 11.5 Hz, 0.73H), 4.52 (d, *J* = 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 149.1, 147.8, 135.6, 135.6, 135.3, 134.7, 132.2, 131.5, 130.1, 130.1, 129.3, 128.9, 124.9, 123.5, 117.4, 116.9, 59.0, 57.2; ES-HRMS: Calcd for $C_{14}H_{12}BrN_2OS_2$ $[M+H]^+$, 366.9569, Found 366.9568.

*4.3.8. 3-((4-Iodophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6h**)*

Yellow solid, R_f=0.23 (EtOAc 1:2 Hex); Yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1.48H), 7.84 – 7.74 (m, 1.74H), 7.72 – 7.65 (m, 3.48H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 1.48H), 7.08 (d, *J* = 8.3 Hz, 1.48H), 6.82 (d, *J* = 8.2 Hz, 2H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 0.74H), 4.56 (d, *J* = 11.6 Hz, 0.74H), 4.52 (d, *J* = 11.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 159.4, 149.7, 148.5, 138.1, 137.5, 135.6, 135.2, 134.7, 130.1, 130.1, 129.3, 128.9, 125.3, 123.9, 88.2, 87.8, 59.0, 57.2; ES-HRMS: Calcd for $C_{14}H_{12}IN_2OS_2$ $[M+H]^+$, 414.9430, Found 414.9425.

*4.3.9. 3-((4-Methoxyphenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6i**)*

White solid, R_f=0.24 (EtOAc 1:2 Hex); Yield 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 7.8 Hz, 1.2H), 7.83 –7.74 (m, 1.6H), 7.71 – 7.62 (m, 3.2H), 7.36 (d, *J* = 8.4 Hz, 1.2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 1.2H), 4.78 (d, *J* = 11.3 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 0.6H), 4.53 (d, *J* = 11.3 Hz, 0.6H), 4.49 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 1.8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.2, 143.6, 141.8, 135.6, 135.4, 135.4, 134.9, 130.0, 130.0, 129.3, 128.9, 124.3, 122.6, 114.3, 113.7, 58.8, 57.0, 55.5, 55.4; ES-HRMS: Calcd for $C_{15}H_{15}N_2O_2S_2$ $[M+H]^+$, 319.0569, Found 319.0568.

*4.3.10. 3-((4-Nitrophenyl)imino)-1-phenyl-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6j**)*

Yellow solid, R_f=0.21 (EtOAc 1:2 Hex); Yield 84%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.16 (s, 2H), 8.07 (s, 2H), 7.91 (t, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.4 Hz, 2H), 7.33 (s, 1H), 7.19 (s, 1H), 5.44 (d, *J* = 12.2 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.2, 160.1, 156.3, 155.5, 143.3, 142.6, 135.8, 133.8, 130.1, 129.0, 125.1, 124.9, 124.5, 123.4, 122.4, 57.3, 55.7; ES-HRMS: Calcd for $C_{14}H_{12}N_3O_3S_2$ $[M+H]^+$, 334.0315, Found 334.0313.

*4.3.11. 1-Phenyl-3-((4-(trifluoromethyl)phenyl)imino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6k**)*

White solid, R_f=0.22 (EtOAc 1:2 Hex); Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 2H), 7.99 (d, *J* = 7.6 Hz, 1.7H), 7.87 – 7.78 (m, 1.85H), 7.75 – 7.65 (m, 3.7H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 1.7H), 7.38 (d, *J* = 7.9 Hz, 1.7H), 7.16 (d, *J* = 7.7 Hz, 2H), 4.85 (d, *J* = 11.9 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 0.85H), 4.61 (d, *J* = 12.0 Hz, 0.85H), 4.57 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 152.0, 141.3, 135.7, 135.1, 134.5, 130.2, 130.1, 129.3, 128.8, 126.4, 126.4, 125.8, 125.8, 123.1, 121.9, 59.1, 57.3; ES-HRMS: Calcd for $C_{15}H_{12}N_2F_3OS_2$ $[M+H]^+$, 357.0338, Found 357.0341.

*4.3.12. 1-Phenyl-3-(pyridin-3-ylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6l**)*

White solid, R_f=0.20 (EtOAc); Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.35 (d, *J* = 4.7 Hz, 1H), 8.33 (s, 1H), 8.23 (d, *J* = 4.7 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.77 (dd, *J* = 17.8, 7.8 Hz, 2H), 7.71 – 7.59 (m, 5H), 7.38 – 7.32 (m, 1H), 7.26 (dd, *J* = 10.1, 5.3 Hz, 1H), 7.18 (dd, *J* = 8.1, 4.8 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.66 – 4.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.44, 160.69, 146.15, 145.44, 145.42, 144.90, 144.70, 143.44, 135.70, 135.69, 134.92, 134.40, 130.14, 130.10, 129.87, 129.20, 129.00, 128.79, 123.63, 123.27, 59.10, 57.31; ES-HRMS: Calcd for $C_{13}H_{12}N_3OS_2$ $[M+H]^+$, 290.0422, Found 290.0417.

*4.3.13. 1-(4-Methoxyphenyl)-3-(phenylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6o**)*

White solid, R_f=0.24 (EtOAc 1:2 Hex); Yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.9 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.17 – 7.03 (m, 6.5H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 0.5H), 4.50 (d, *J* = 11.3 Hz, 0.5H), 4.45 (d, *J* = 11.3 Hz, 1H), 3.93 (s, 1H), 3.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.2, 131.7, 131.3, 129.1, 128.5, 125.0, 124.3, 123.8, 123.1, 121.7, 115.3, 59.1, 58.4, 57.4, 56.0; ES-HRMS: Calcd for $C_{15}H_{15}N_2O_2S_2$ $[M+H]^+$, 319.0569, Found 319.0570.

*4.3.14. 1-(4-Bromophenyl)-3-(phenylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6p**)*

Yellow solid, R_f=0.23 (EtOAc 1:2 Hex); Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.83 – 7.73 (m, 3.84H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.27 (m, 1.84H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.08 – 7.04 (m, 0.46H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 0.46H), 4.55 (d, *J* = 11.5 Hz, 0.46H), 4.49 (d, *J* = 11.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 158.7, 150.0, 148.6, 133.4, 131.4, 130.8, 130.4, 129.2, 128.6, 124.5, 124.0, 123.0, 121.6, 59.0, 57.2; ES-HRMS: Calcd for $C_{14}H_{12}B_rN_2OS_2$ $[M+H]^+$, 366.9569, Found 366.9575.

*4.3.15. 1-(4-Fluorophenyl)-3-(phenylimino)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6q**)*

White solid, R_f=0.22 (EtOAc 1:2 Hex); Yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.6, 4.9 Hz, 2H), 7.99 (dd, *J* = 8.6, 4.8 Hz, 0.92H), 7.38 – 7.28 (m, 6.76H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 0.46H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.80 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 0.46H), 4.55 (d, *J* = 11.5 Hz, 0.46H), 4.49 (d, *J* = 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.8, 158.7, 150.0, 148.7, 132.5, 132.4, 132.1, 132.0, 130.5, 130.5, 129.1, 128.6, 124.4, 124.0, 123.0, 121.6, 117.6, 117.4, 110.0, 59.1, 57.3; ES-HRMS: Calcd for $C_{14}H_{12}FN_2OS_2$ $[M+H]^+$, 307.0370, Found 307.0365.

*4.3.16. 3-(Phenylimino)-1-(pyridin-2-yl)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6r**)*

White solid, R_f=0.50 (EtOAc); Yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.5 Hz, 1H), 8.78 (d, *J* = 4.5 Hz, 0.47H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 0.47H), 8.08 (t, *J* = 7.8 Hz, 1H), 8.03 (t, *J* = 7.8 Hz, 0.47H), 7.69 – 7.58 (m, 1.47H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.23 (m, 1.88H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 2.47H), 5.35 – 5.29 (m, 1.47H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 0.47H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.74, 158.45, 154.44, 154.37, 150.91, 150.81, 150.06, 148.84, 138.85, 138.73, 129.05, 128.47, 128.42, 128.38, 124.31, 123.92, 123.81, 123.76, 122.94, 121.70, 54.12, 52.44; ES-HRMS: Calcd for $C_{13}H_{12}N_3OS_2$ $[M+H]^+$, 290.0422, Found 290.0420.

*4.3.17. 3-(Phenylimino)-1-(thiophen-2-yl)-3,5-dihydro-1,4,2-dithiazole 1-oxide (**6s**)*

Yellow solid, R_f=0.25 (EtOAc 1:2 Hex); Yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 3.5 Hz, 1H), 7.94 (d, *J* = 4.9 Hz, 1H), 7.90 (d, *J* = 4.9 Hz, 0.45H), 7.85 (d, *J* = 3.4 Hz, 0.45H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31 –7.27 (m, 2.8H), 7.24 (t, *J* = 4.0 Hz, 0.45H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.09 –7.06 (m, 0.45H), 7.04 (d, *J* = 7.8 Hz, 2H), 4.88 (d, *J* = 11.3 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 0.45H), 4.69 (d, *J* = 11.2 Hz, 0.45H), 4.63 (d, *J* = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.71, 157.50, 149.91, 148.67, 137.97, 137.84, 137.77, 137.31, 135.13, 134.36, 129.17, 129.13, 128.57, 124.45, 124.00, 122.93, 121.57, 59.98, 58.35; ES-HRMS: Calcd for $C_{12}H_{11}N_2OS_3$ $[M+H]^+$, 295.0034, Found 295.0031.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (No. 81673287).

References

1. (a) Lucking, U. *Angew Chem Int Ed Engl.* **2013**, *52(36)*, 9399-9408; (b) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. *Eur J Med Chem*. **2017**, *126*, 225-245.
2. (a) Whitehead, J. K. and Bentley, H. R. *J Chem Soc*. **1952**, 1572-1574; (b) Misani, F.; Fair, T. W. and Reiner, L. *J Am Chem Soc*. **1951**, *73*, 459; (c) Zenzola, M; Doran, R; Degennaro, L; Luisi, R.; Bull, J. A. *Angew Chem Int Ed Engl*. **2016**, *55*, 7203-7207; (d) Mancheno, O. G.; Bistri, O.; Bolm, C. *Org Lett*. **2007**, *9(19)*, 3809-3811; (e) Tota, A.; Zenzola, M.; Chawner, S. J.; St John-Campbell, S.; Carlucci, C.; Romanazzi, G.; Degennaro, L.; Bull, J. A.; Luisi, R. *Chem Commun*. **2017**, *53(2)*, 348-351.
3. (a) Siemeister, G.; Lücking, U.; Wengner, A. M.; Lienau, P.; Steinke, W.; Schatz, C.; Mumberg, D.; Ziegelbauer, K. *Mol Cancer Ther*. **2012**, *11*, 2265; (b) Satzinger, G. *Drug News Perspect*. **2001**, 14, 197-207; (c) Bartoszyk, G. D.;Dooley, D. J.; Barth, H.; Hartenstein, J.; Satzinger, G. *J Pharm Pharmacol*. **1987**, *39*, 407-408; (d) Barnes, A. C.; Hairsine, P. W.; Matharu, S. S.; Ramm, P. J.; Taylor, J. B. *J Med Chem*. **1979**, *22*, 418-424; (e) Lu, D.; Vince, R. *Bioorg Med Chem Lett*. **2007**, *17*, 5614-5619; (f) Siemeister, G.; Lücking, U.; Wengner, A. M.; Lienau, P.; Steinke, W.; Schatz, C.; Mumberg, D.; Ziegelbauer, K. *Mol Cancer Ther*. **2012**, *11*, 2265-2273; (g)Nishimura, N.; Norman, M. H.; Liu, L.; Yang, K. C.; Ashton, K. S.; Bartberger, M. D.; Chmait, S.; Chen, J.; Cupples, R.; Fotsch, C.; Helmering, J.; Jordan, S. R.; Kunz, R. K.; Pennington, L. D.; Poon, S. F.; Siegmund, A.; Sivits, G.; Lloyd, D. J.; Hale, C.; St Jean, D. J. *J Med.Chem*. **2014**, *57*, 3094-3116; (h) Gutmann, B.; Elsner, P.; O'Kearney-McMullan, A.; Goundry, W.; Roberge, D. M.; Kappe, C. O. *Org Process Res Dev*. **2015**, *19*, 1062-1067; (i) Oost, T.; Fiegen, D.; Gnamm, C. WO2014/029830, 2014.
4. (a) Harmata, M.; Pavri, N. *Angew Chem Int Ed Engl.* **1999**, *38(16)*, 2419-2421; (b) Dong, W. R.; Wang, L.; Parthasarathy, K.; Pan, F. F.; Bolm, C. *Angew Chem Int Ed Engl.* **2013**, *52(44)*, 11573-11576; (c) Chinnagolla, R. K.; Vijeta, A.; Jeganmohan, M. *Chem Commun.* **2015**, *51(65)*, 12992-12995; (d) Cheng, Y. and Bolm, C. *Angew Chem Int Ed Engl*. **2015**, *54(42)*, 12349-12352; (e) Harmata, M. and Hong, X. C. *J Am Chem Soc*. **2003**, *125(19)*, 5754-5756; (f) Cheng, Y.; Dong, W. R.; Parthasarathy, K.; Bolm, C. *Org Lett*. **2017**, *19(3)*, 726-729; (g) Bohmann, R. A.; Unoh, Y.; Miura, M.; Bolm, C. *Chem–Eur J*. **2016**, *22(20)*: 6783-6786; (h) Harmata, M.; Cai, Z. X.; Chen, Y. G. *J Org Chem*. **2009**, *74(15)*, 5559-5561; (i) Le, T. N.; Diter, P.; Pegot, B.; Bournaud, C.; Toffano, M.; Guillot, R.; Giang, V. T.; Magnier, E. *Org Lett*. **2016**, *18(19)*, 5102-5105; (j) Battula, S. R. K.; Subbareddy, G. V.; Chakravarthy, I. E.; Saravanan, V. *RSC Adv.* **2016**, *6(61)*, 55710-55714; (k) Kuhl, J.; Reggelin, M. *Synthesis-Stuttgart*. **2017**, *49(2)*: 403-408; (l) Bizet, V.; Hendriks, C. M. M.; Bolm, C. *Chem Soc Rev*. **2015**, *44*, 3378–3390.
5. Williams, T. R.; Cram, D. J. *J Am Chem Soc*. **1971**, *93(26)*, 7333-7335.
6. Wang, H.; Frings, M.; Bolm, C. *Org Lett*. **2016**, *18(10)*, 2431-2434.
7. Marzag, H.; Schuler, M.; Tatibouet, A.; Reboul, V. *Eur J Org Chem*. **2017**, *4*, 896-900.
8. Lanyon-Hogg, T.; Ritzefeld, M.; Masumoto, N.; Magee, A. I.; Rzepa, H. S.; Tate, E. W. *J Org Chem*. **2015**, *80(9)*, 4370-4377.
9. (a) Fortin, S.; Wei, L. H.; Moreau, E.; Lacroix, J.; Cote, M. F.; Petitclerc, E.; Kotra, L. P.; C-Gaudreault, R. *J Med Chem*. **2011** *54(13)*, 4559-4580; (b) Le, T. N.; Diter, P.; Pegot, B.; Bournaud, C.; Toffano, M.; Guillot, R.; Vo-Thanh, G.; Yagupolskii, Y.; Magnier, E. *J Fluorine Chem*. **2015**, *179*, 179-187; (c) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J Org Chem*. **2009**, *74(22)*, 8719-8725.