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An efficient synthesis of structurally diverse 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives under catalyst free conditions

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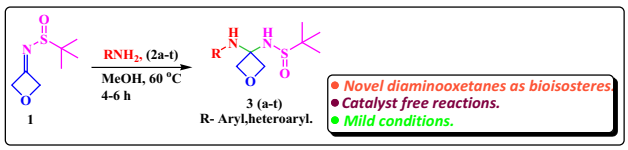
Abstract A convenient and straightforward synthesis of structurally diverse 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives from 3-oxetan-3-*tert*-butylsulfinimine and substituted aromatic amines in methanol at 60 °C temperature is described. The corresponding diaminooxetane derivatives are obtained in good to excellent yield under optimized reaction conditions. The method presented herein was found to be advantageous for diaminooxetane derivatives as emerging building block for future drug discovery. The title diaminooxetanes should be considered as bioisosteric to isopropylidenediamines and urea derivatives rather than to gem-dimethyl and carbonyl groups, respectively.

Graphical abstract



Keywords 3-Oxetan-3-*tert*-butylsulfinimine · Amine · Diaminooxetane · Catalyst-free conditions

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Introduction

In medicinal chemistry, oxetanes are a polar alternative to the geminal dimethyl group for the incorporation of bulk in drug candidates (Wuitschik et al. 2010). Oxetane scaffolds are more hydrophilic, and potentially more metabolically stable, compared to other cyclic and acyclic frameworks (Wuitschik et al. 2006a, b, 2008, 2010). The combination of a terminal amine with an aryl chain in an oxetane core revealed potential drug candidates for the treatment of phospholipidosis (Fischer et al. 2000), and for HERG channel interference (Cavalli et al. 2002). Furthermore, the oxetane ring can act as a surrogate for a carbonyl group, because both exhibit similar H-bond basicity (Berthelot et al. 1998; Besseau et al. 1998). Substitution of an oxetane for the carbonyl of a ketone has the potential to block the metabolism of the ketone (Wuitschik et al. 2010; Malapit and Howell 2015; Bull et al. 2016). Nowadays, the area of oxetane chemistry is of considerable interest as exemplified bymany efforts to explore the value of this ring to the design of potential drug candidates.

The oxetane ring system is found in many natural products (Fig. 1) such as the TAXOL® (A), an anticancer isolated from *Taxus brevifloria* (Wani et al. 1971); oxetanocin (B), a reverse transcriptase inhibitor of HIV isolated from the soil bacterium *Bacillus megaterium* NK84-0218 (Shimada et al. 1986; Hashino et al. 1987; Seki et al. 1989; Norbeck and Kramer 1988); Merrilactone A (C), a stimulator of rat neurosis isolated from *Illicium merrillianum* (Huang et al. 2000); Mitrephorone A (D), a cytotoxin isolated from *Mitrephoreglabra* (Li et al. 2005); oxetin (E), a herbicide and antibacterial isolated from *Streptomyces* sp. OM-2317 (Omura et al. 1984); and Bradyoxetin (F), an important semiochemical for *Bradyrhizobium japonicum* that is involved in symbiotic

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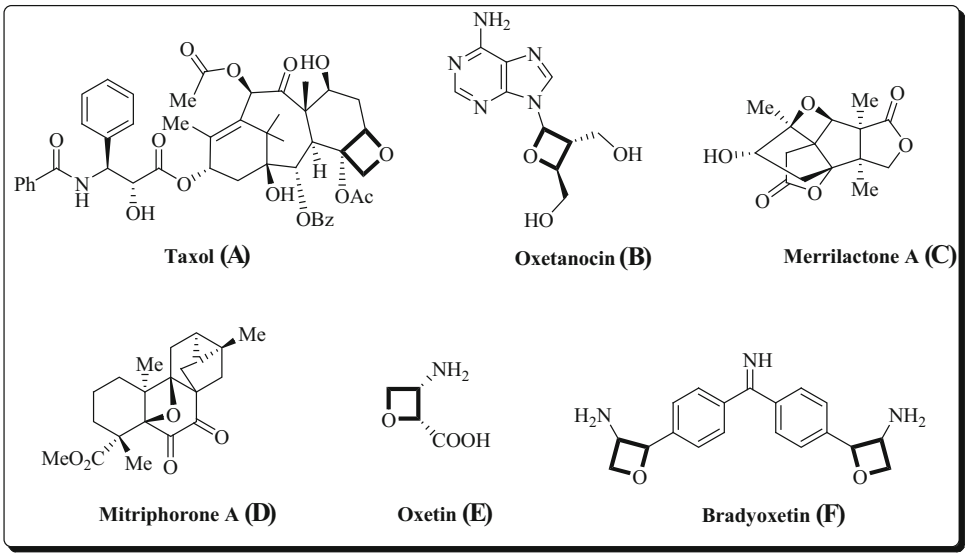


Fig. 1 Natural products containing oxetane core

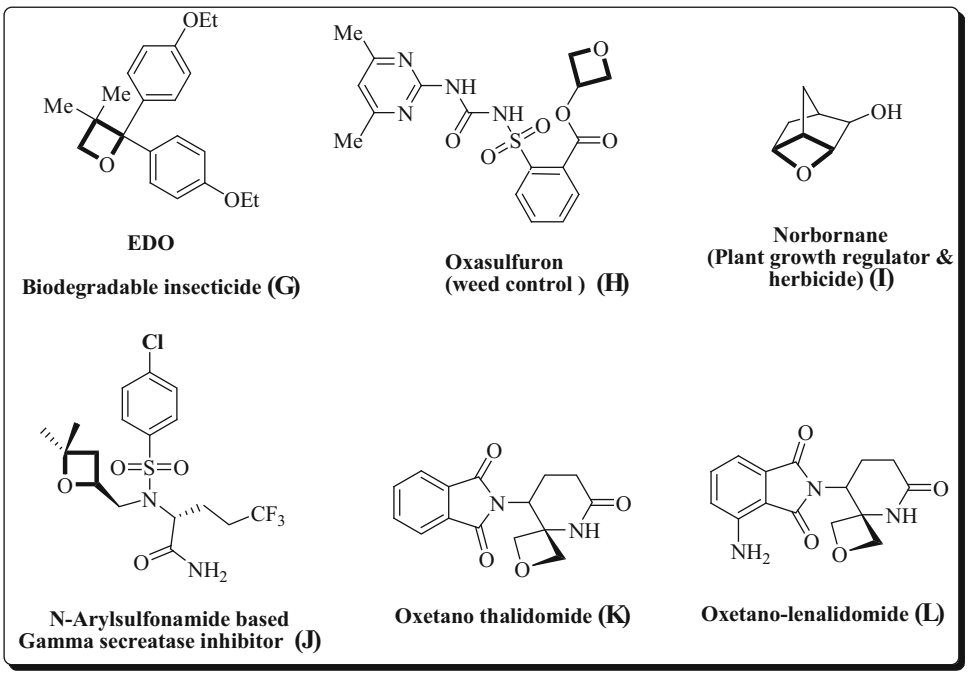
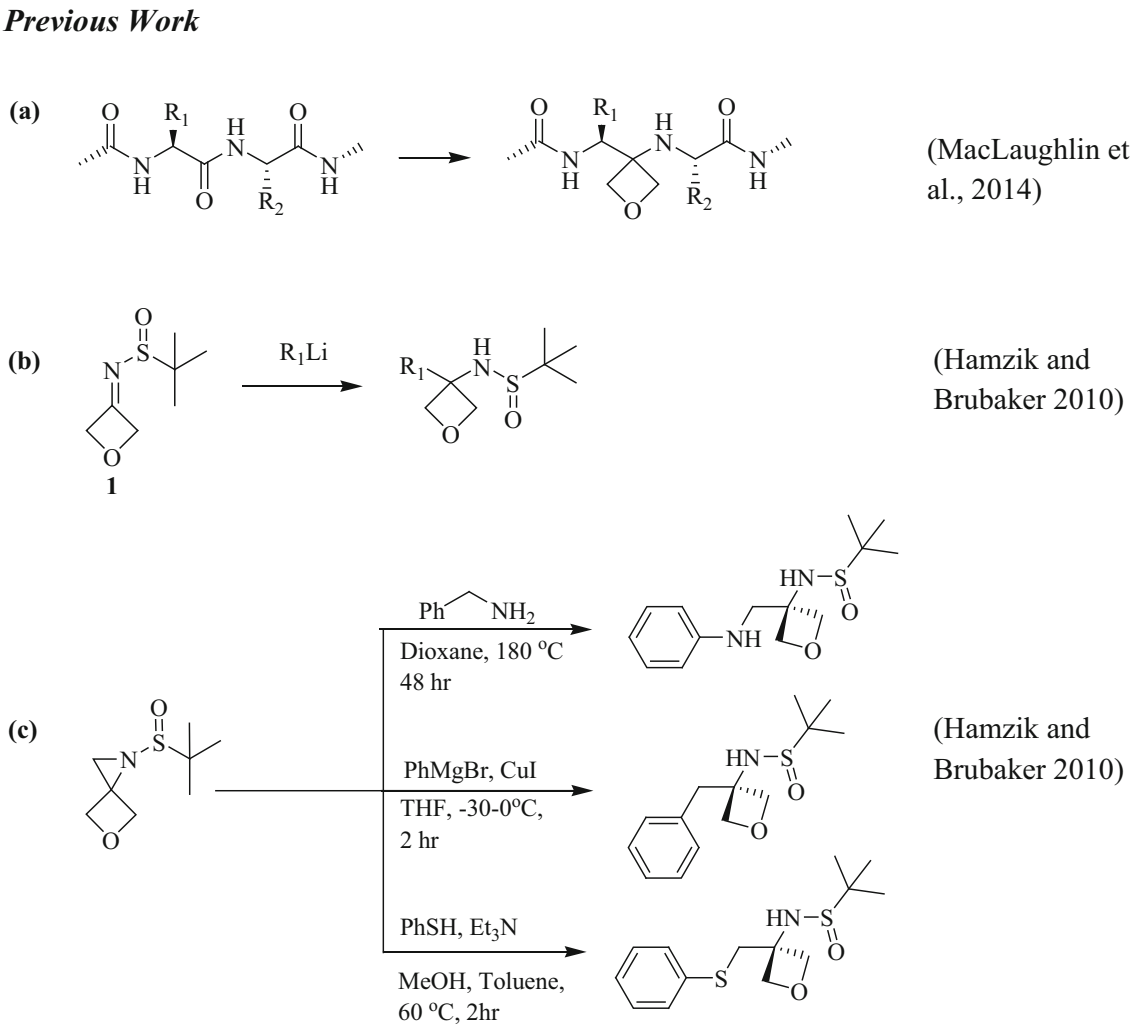


Fig. 2 Biologically active oxetane analogues

gene regulation in the soybean plant (Loh et al. 2002). Some synthetic oxetane derivatives have agrochemical applications (Fig. 2). EDO(**G**, 2,2-bis(4-ethoxyphenyl)-3,3-dimethyloxetane) is an insecticide that is 25 times more potent than DDT (Holan 1971). Oxasulfuron (H) is useful for weed control (Mayer and Ciba-Geigy 1992). Norbornane derivative I is a herbicide and plant growth regulator (Soloway et al. 1986). Recently, Stephan et al. (Stephan et al. 2011) studied the metabolism-based optimization of *N*-arylsulfonamide-based gamma-secretase inhibitors of structure (J). Burkhard et al. (2013) studied the metabolic stability of an oxetane analogue (K) of thalidomide and of lenalidomide (L) (Burkhard et al. 2013).

Prior research has focused on the synthesis and metabolism of 3-aminooxetanes (Scheme 1). In one previous report, MacLaughlin et al. reported the synthesis of an oxetanyl peptidomimetic (MacLaughlin et al. 2014). Brubaker and Hamzik reported the preparation of 3-aminooxetanes by the reaction of an oxetane-derived sulphinylimine (**1**) with organolithiums, and the ring opening of *N*-sulfinyl spiroaziridines with thiols, RMgX, and amines (Hamzik and Brubaker 2010). Much less attention has been given to the study of diaminooxetanes. As a part of our ongoing research on the synthesis of bioactive compounds and the exploration of new building blocks for medicinal chemistry (Gholap et al. 2012, 2014;



Scheme 1 Previous reports on the synthesis of 3-aminooxetane derivatives

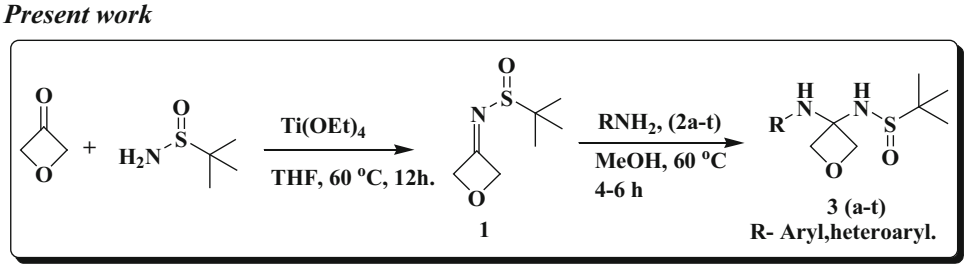
Gholap and Deshmukh 2013; Gholap 2016, Gholap and Gunjal 2016, 2017), we report herein the synthesis of some 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives as potential pharmacophores. To the best of our knowledge, there is no prior report on the catalyst-free synthesis of diaminooxetane derivatives.

Result and discussion

The synthesis of 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives was conducted using previously reported method (Hamzik and Brubaker 2010). The synthesis of key 3-oxetan-3-*tert*-butylsulfinylimine (**1**) was performed starting with commercially available *tert*-butylsulfinimide and 3-oxetanone, using titanium tetraethoxide, in THF at 60 °C (Scheme 2) (Liu et al. 1999; Cogan et al. 1999). The desired oxetane-3-*tert*-butyl sulfinimine was obtained as thick oil.

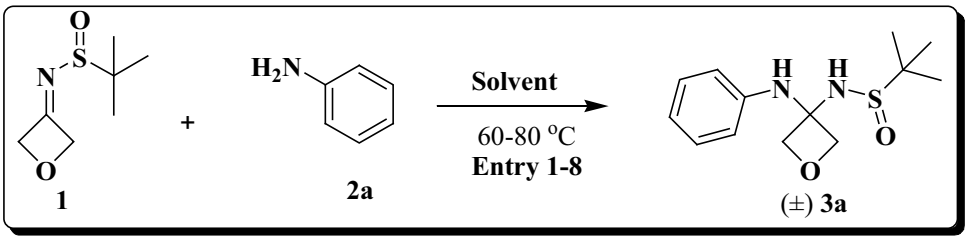
Initially for optimization of reaction conditions, the reaction of sulfinimine (**1**) and aniline was conducted in various solvents such as DMSO, THF, 1,4-dioxane, ethanol, acetonitrile and methanol. The results obtained were summarized in Table 1. It has been found that when reaction 3-oxetan-3-*tert*-butylsulfinimine (**1**) and aniline was conducted in methanol at 60 °C under catalyst free condition, the product '**3a**' was obtained in 68% yield (entry 8, Table 1). Further increase in temperature did not show satisfactory improvement in the yield of the final product. Hence above reaction condition was chosen as optimized condition for all later studies.

Encouraged by above results, several structurally diverse aniline derivatives were selected as nucleophiles and results obtained were collected in Table 2. It has been observed that donating substituent located at the para position of the aniline moiety slightly accelerates the reaction and desired products were obtained in good to excellent yields (entries 2, 8 and 13, Table 2). However,



Scheme 2 Synthesis of 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives

Table 1 The synthesis of 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide (**3a**) in various solvents



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DMSO	80	12	20
2	THF	60	18	15
3	1,4-Dioxane	70	18	10
4	Ethanol	70	12	25
5	Toluene	80	8	0
6	Acetonitrile	80	12	12
7	Methanol	50	12	35
8	Methanol	60	5	68

ortho, meta and para nitroanilines are unreactive even after prolonged heating (10 h at 60 °C) and unreacted starting material was recovered.

Experimental section

General

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. All the reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates. Visualization was accomplished with either UV light, by immersion in ninhydrin solution or I_2 adsorption as visualized on the silica gel after heating with a heat gun for $\sim$15 s. The column chromatography was performed on silica gel (100–200 or 230–400 mesh). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 400 MHz spectrometer. Coupling constants were given in Hertz. All chemical shifts were quoted in ppm, relative to DMSO using the residual solvent peak as a reference standard. HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film.

General procedure for the synthesis of 2-methyl-propane-2-sulfinic acid (3-arylamino-oxetan-3-yl)-amide derivatives

To a stirred solution of substituted aniline (1 eq) in methanol (3 mL), oxetan-3-*tert*-butylsulfinimine (1.5 eq) was added under argon atmosphere. Reaction mixture was

Table 2 Synthesis of some 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives (**3**) in MeOH at 60 °C under catalyst free conditions

Entry	Amine (**2**)	Product (**3**)	Time (h)	Yield (%)[a,b]
1	$C_6H_5NH_2$	**3a**	5	68
2	4-$MeC_6H_4NH_2$	**3b**	6	71
3	3-$MeC_6H_4NH_2$	**3c**	5	57
4	4-$ClC_6H_4NH_2$	**3d**	5	65
5	3-$ClC_6H_4NH_2$	**3e**	6	52
6	4-$FC_6H_4NH_2$	**3f**	5.5	59
7	2-$FC_6H_4NH_2$	**3g**	5	62
8	4-$MeOC_6H_4NH_2$	**3h**	6	70
9	3-$MeOC_6H_4NH_2$	**3i**	5.2	68
10	4-$CF_3C_6H_4NH_2$	**3j**	5.6	71
11	3-$CF_3C_6H_4NH_2$	**3k**	6	64
12	3-$CF_3OC_6H_4NH_2$	**3l**	6	57
13	4-$CF_3OC_6H_4NH_2$	**3m**	6	78
14	3-t-Butyl$C_6H_4NH_2$	**3n**	5	68
15	4-$BrC_6H_4NH_2$	**3o**	5	60
16	3,5-Di-$MeC_6H_3NH_2$	**3p**	5	63
17	2,3-Di-$MeC_6H_3NH_2$	**3q**	5	75
18	2-Br,4-Me $C_6H_3NH_2$	**3r**	6	62
19	2-Me,4-F $C_6H_3NH_2$	**3s**	5.5	70
20	4-$CNC_6H_4NH_2$	**3t**	6	67

[a] Isolated yields of the product

[b] All products were characterized by IR, ^{1}H-NMR, HRMS and ^{13}C-NMR

heated at 60 °C for appropriate time (Table 2). After the completion of reaction (TLC), reaction mixture was then concentrated. To the resulting residue water was added and then extracted with ethyl acetate (2 × 3 mL). Organic layer was then dried over anhydrous sodium sulphate and filtered. Solvent was removed under reduced pressure. The resulting products were then purified by chromatography using *n*-hexane–ethyl acetate (7:3) to afford pure 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives. All synthesized compounds were characterized by IR, ^{1}H-NMR, HRMS and ^{13}C-NMR spectroscopic techniques.

Synthesis of (±)2-methyl-propane-2-sulfinic acid (3-phenylamino-oxetan-3-yl)-amide (3a)

Off white solid (182 mg, 68%); ^{1}H NMR (400 MHz, DMSO) δ: 7.08–7.02 (m, 3H, Ar–H and –NH), 6.58–6.61 (t, J = 7.2 Hz, 1H, Ar–H), 6.51 (d, J = 7.6 Hz, 2H, Ar–H), 6.19 (s, 1H, –NH), 4.88 (d, J = 4.0 Hz, 1H, O–CH), 4.81 (d, J = 6.4 Hz, 1H, O–CH), 4.67 (d, J = 6.4 Hz, 1H, O–CH), 4.52 (d, J = 6.0 Hz, 1H, O–CH), 1.03 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 144.0, 128.5, 117.0, 113.9, 82.6, 81.2, 69.7, 54.3, 22.6. IR (film, KBr) cm^{-1}: 3175, 2956, 2878, 1603, 1266, 1052, 961,749. HRMS (ESI, H) m/z calc'd for $C_{13}H_{20}N_2O_2S$. $[M + Na]^+$ 291.1142 found 291.1137.

Synthesis of (±)2-methyl-propane-2-sulfinic acid (3-*p*-tolylamino-oxetan-3-yl)-amide (3b)

White solid (200 mg, 71%); ^{1}H NMR (400 MHz, DMSO) δ: 6.88 (d, J = 7.6 Hz, 2H, Ar–H), 6.83 (S, 1H, –NH), 6.43 (d, J = 7.6 Hz, 2H, Ar–H), 6.14 (S, 1H, –NH), 4.88 (d, J = 6.4 Hz, 1H, O–CH), 4.79 (d, J = 6.0 Hz, 1H, O–CH), 4.65 (d, J = 6.0 Hz, 1H, O–CH), 4.49 (d, J = 6.4 Hz, 1H, O–CH–), 2.13 (s, 3H, CH_3), 1.03 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 141.7, 129.2, 125.6, 114.1, 82.9, 81.3, 69.9, 54.4, 22.8, 20.2. IR (film, KBr) cm^{-1}: 3368, 2919, 2876, 1617, 1518, 1264, 962, 812. HRMS (ESI, H) m/z calc'd for $C_{14}H_{22}N_2O_2NaS$ $[M + Na]^+$ 305.1299 found 305.1294.

Synthesis of (±)2-methyl-propane-2-sulfinic acid (3-*m*-tolylamino-oxetan-3-yl)-amide (3c)

Off white solid (160 mg, 57%); ^{1}H NMR (400 MHz, DMSO) δ: 6.94 (dd, J = 4.0 Hz 2H, Ar–H), 6.43 (d, J = 7.6 HZ, 1H, Ar–H), 6.33 (s, 1H, –NH), 6.31 (d, J = 8.0 Hz, 1H, Ar–H), 6.16 (s, 1H, –NH), 4.89 (d, J = 6.0 Hz, 1H, O–CH), 4.80 (d, J = 6.4 Hz, 1H, O–CH), 4.67 (d, J = 6.4 Hz, 1H, O–CH–), 4.50 (d, J = 6.0 Hz, 1H, O–CH–), 2.15 (s, 3H, CH_3), 1.07 (s, 9H, t-Bu). ^{13}C-NMR (100 MHz, DMSO) δ: 144.0, 137.5, 128.4, 117.9, 114.7, 111.2, 82.8, 81.3, 69.7, 54.3, 22.6, 21.3. IR (film, KBr) cm^{-1}: 3372, 3124, 2956, 1607, 1272, 1049, 958, 852. HRMS (ESI, H) m/z calc'd for $C_{14}H_{22}N_2O_2S$ $[M + Na]^+$ 305.1299 found 305.1294.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-chloro-phenylamino)-oxetan-3-yl]-amide (3d)

Off white solid (196 mg, 65%); ^{1}H NMR (400 MHz, DMSO) δ: 7.26 (S, 1H, –NH), 7.11 (d, J = 8.8 Hz, 2H, Ar–H), 6.51 (d, J = 8.8 Hz, 2H, Ar–H), 6.24 (s, 1H, –NH), 4.89 (d, J = 6.0 Hz, 1H, O–CH), 4.81 (d, J = 6.4 Hz, 1H, O–CH), 4.65 (d, J = 6.0 Hz, 1H, O–CH), 4.50 (d, J = 6.0 Hz, 1H, O–CH), 1.07 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 143.0, 128.6, 120.6, 115.4, 82.5, 81.1, 69.6, 54.4, 22.6. IR (film, KBr) cm^{-1}: 3300, 3222, 2964, 1607, 1527, 1329, 1173, 1044, 956, 834. HRMS (ESI, H) m/z calc'd for $C_{13}H_{19}ClN_2O_2S$ $[M + Na]^+$ 325.0753 found 325.0748.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(3-chloro-phenylamino)-oxetan-3-yl]-amide (3e)

Off white solid (157 mg, 52%); ^{1}H NMR (400 MHz, DMSO) δ: 7.39 (S, 1H, NH), 7.09 (dd, $J = 8.8$ Hz, 1H, Ar–H), 6.63 (dt, $J = 1.2$ Hz, 1H, Ar–H), 6.49 (dd, $J = 1.6$ Hz, 2H, Ar–H), 6.28 (s, 1H, –NH), 4.91 (d, $J = 6.4$ Hz, 1H, O–CH), 4.82 (d, $J = 6.4$ Hz, 1H, O–CH), 4.66 (d, $J = 6.4$ Hz, 1H, O–CH), 4.52 (d, $J = 6.4$ Hz, 1H, O–CH), 1.05 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 145.6, 133.1, 130.1, 116.6, 113.2, 112.8, 82.2, 81.1, 69.5, 54.4, 22.6. IR (film, KBr) cm^{-1}: 3381, 3225, 2961, 1598, 1481, 1261, 1049, 961, 854,773. HRMS (ESI, H) *m/z* calc'd for $C_{13}H_{19}ClN_2O_2S$ $[M + Na]^+$ 325.0753 found 325.0748.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-fluoro-phenylamino)-oxetan-3-yl]-amide (3f)

White solid (168 mg, 59%); ^{1}H NMR (400 MHz, DMSO) δ: 6.98 (S, 1H, NH), 6. 89 (dd, $J = 8.8$ Hz, 2H, Ar–H), 6.47–6.44 (m, 2H, Ar–H), 6.17 (s, 1H, –NH), 4.86 (d, $J = 6.0$ Hz, 1H, O–CH), 4.78 (d, $J = 6.0$ Hz, 1H, O–CH), 4.62 (d, $J = 6.0$ Hz, 1H, O–CH), 4.47 (d, $J = 6.0$ Hz, 1H, O–CH), 1.00 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 156.3 (d, $^{1}J_{C-F} = 231$ Hz), 140.7, 115.3 (d, $J_{C-F} = 22$ Hz), 115.07 (d, $J_{C-F} = 7$ Hz), 82.8, 81.3, 69.9, 54.5, 22.7. IR (film, KBr) cm^{-1}: 3368, 3199, 2954, 1620, 1521, 1044, 983, 869, 761. HRMS (ESI, H) *m/z* calc'd for $C_{13}H_{19}FN_2O_2S$ $[M + Na]^+$ 309.1048 found 309.1043.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(2-fluoro-phenylamino)-oxetan-3-yl]-amide (3g)

White solid (177 mg, 62%); ^{1}H NMR (400 MHz, DMSO) δ: 7.05–7.02 (m, 1H, Ar–H), 6.9 (dd, $J = 7.2$ Hz, $J = 7.6$ Hz, 1H, Ar–H), 6.81 (s, 1H, NH), 6.65–6.60 (m, 1H, Ar–H), 6.46–6.41 (m, $J = 8$ Hz, 1H, Ar–H), 6.25 (s, 1H, –NH), 4.91 (dd, $J = 6.4$ Hz, 2H, O–CH_2), 4.82 (d, $J = 6.4$ Hz, 1H, O–CH), 4.61 (d, $J = 6.0$ Hz, 1H, O-CH), 1.00 (s, 9H, t-Bu). ^{13}C NMR (100 MHz,DMSO) δ: 152.4 (d, $^{1}J_{C-F} = 238$ Hz), 132.0 (d, $^{2}J_{C-F} = 11$ Hz), 123.9 (d, $^{4}J_{C-F} = 3$ Hz), 117.3 (d, $^{3}J_{C-F} = 7$ Hz), 114.9 (d,$^{3-}J_{C-F} = 3$ Hz), 114.8 (d, $^{2}J_{C-F} = 19$ Hz), 81.9, 81.5, 69.6, 54.5, 22.5. IR (film, KBr) cm^{-1}: 3369, 3200, 2955, 1620, 1519, 1269, 1044, 983, 869, 761. HRMS (ESI, H) *m/z* calc'd for $C_{13}H_{19}FN_2O_2S$ $[M + Na]^+$ 309.1048 found 309.1043.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-methoxy-phenylamino)-oxetan-3-yl]-amide (3h)

Off white solid (208 mg, 70%); ^{1}H NMR (400 MHz, DMSO) δ: 6.71–6.66 (m, 3H, Ar–H), 6.47 (dd, $J = 3.6$ Hz, $J = 1.5$ Hz, 2H, Ar–H), 6.13 (s, 1H, –NH), 4.87 (d, $J = 6.0$ Hz, 1H, O–CH), 4.79 (d, $J = 6.4$ Hz, 1H, O–CH), 4.63 (d, $J = 6.0$ Hz, 1H, O–CH), 4.48 (d, $J = 6.0$ Hz, 1H, O–CH), 3.62 (s, 3H, CH_3), 1.03 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 151.4, 137.9, 114.9, 114.2, 82.7, 81.0, 70.2, 55.1, 54.2, 22.6. IR (film, KBr) cm^{-1}: 3143, 3335, 3167, 1509, 1249, 1007, 861, 822. HRMS (ESI, H) *m/z* calc'd for $C_{14}H_{22}N_2O_3S$ $[M + Na]^+$ 321.1248 found 321.1243.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(3-methoxy-phenylamino)-oxetan-3-yl]-amide (3i)

Off white solid (202 mg, 68%); ^{1}H NMR (400 MHz, DMSO) δ: 7.04 (s, 1H, –NH), 6.96 (t, $J = 8$ Hz, 1H, Ar–H), 6.20–6.18 (m, 2H, Ar–H), 6.14 (dd, $J = 1.6$ Hz, 1H, Ar–H), 6.06 (m, 1H, Ar–H), 4.88 (d, $J = 6.0$ Hz, 1H, O–CH), 4.79 (d, $J = 6.4$ Hz, 1H, O–CH), 4.66 (d, $J = 6.4$ Hz, 1H, O–CH), 4.51 (d, $J = 6.4$ Hz, 1H, O–CH–), 1.05 (s, 9H, t-Bu). ^{13}C NMR (100 MHz. DMSO) δ: 160.0, 145.5, 129.5, 107.1, 102.7, 99.9, 82.8, 81.3, 69.8, 54.5, 22.7. IR (thin film, KBr) cm^{-1}: 3401, 3355, 3153, 1615, 1528, 1216, 1011, 968, 844. HRMS (ESI, H) *m/z* calc'd for $C_{14}H_{22}N_2O_3S$ $[M + Na]^+$ 321.1248 found 321.1243.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-trifluoromethyl-phenylamino)-oxetan-3-yl]-amide(3j)

Off white solid (238 mg, 71%); ^{1}H NMR (400 MHz, DMSO) δ: 7.75 (s, 1H, –NH), 7.41 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.63 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.36 (s, 1H, –NH), 4.93 (d, $J = 6.0$ Hz, 1H, O–CH), 4.84 (d, $J = 6.4$ Hz, 1H, O–CH), 4.70 (d, $J = 6.4$ Hz, 1H, O–CH), 4.54 (d, $J = 6.4$ Hz, 1H, O–CH), 1.04 (s, 9H, t-Bu). ^{13}C NMR (100 MHz. DMSO) δ: 147.4, 126.4, 125.9, 117.5 (q, 4-CF_3, $J_{C-F} = 95$ Hz), 113.6, 82.3, 81.1, 69.4, 54.4, 22.5. IR (film, KBr) cm^{-1}: 3376, 3227, 2967, 1618, 1332, 1112, 1047, 957, 832. HRMS (ESI, H) *m/z* calc'd for $C_{14}H_{19}F_3N_2O_2S$ $[M + Na]^+$ 359.1016 found 359.1012.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(3-trifluoromethyl-phenylamino)-oxetan-3-yl]-amide (3k)

Faint brown solid (215 mg, 64%); ^{1}H NMR (400 MHz, DMSO) δ: 7.58 (s, 1H, –NH), 7.30 (dd, $J = 8$ Hz, 1H, Ar–H), 6.93 (d, $J = 7.6$ Hz, 1H, Ar–H), 6.81 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 6.32 (s, 1H, –NH), 4.94 (d, $J = 6.4$ Hz, 1H, O–CH–), 4.84 (d, $J = 6.4$ Hz, 1H, O–CH–), 4.68 (d, $J = 6.4$ Hz, 1H, O–CH–), 4.52 (d, $J = 6.8$ Hz, 1H, O–CH–), 1.03 (s, 9H, t-Bu). ^{13}C NMR

(100 MHz. DMSO) δ: 149.1, 130.1, 129.6, 121.3 (q, 3-CF_3, $J_{C-F} = 271$ Hz), 117.8, 113.2, 109.7, 82.6, 81.1, 69.6, 54.4, 22.5. IR (film, KBr) cm^{-1}: 3290, 3243, 2981, 1613, 1447, 1163, 1042, 931, 857. HRMS (ESI, H) *m/z* calc'd for $C_{14}H_{19}F_3N_2O_2S$ $[M + Na]^+$ 359.1016 found 359.1012.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(3-trifluoromethoxy-phenylamino)-oxetan-3-yl]-amide (3l)

Off white solid (200 mg, 57%); ^1H NMR (400 MHz, DMSO) δ: 7.57 (s, 1H,–NH), 7.30 (dd, $J_1 = 7.6$ Hz, $J_2 = 8$ Hz, 1H, Ar–H), 6.93 (d, $J = 7.6$ Hz, 1H, Ar–H), 6.81 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 6.31 (s, 1H, –NH), 4.94 (d, $J = 6.0$ Hz, 1H, O–CH–), 4.84 (d, $J = 6.4$ Hz, 1H, O–CH), 4.68 (d, $J = 6.4$ Hz, 1H, O–CH), 4.52 (d, $J = 60$ Hz, 1H, O–CH–), 1.03 (s, 9H, t-Bu). ^{13}C NMR (100 MHz. DMSO) δ: 149.5, 146.9, 130.2, 121.4 (q, 3-OCF_3, $J_{C-F} = 254$ Hz), 113.2, 108.7, 105.7, 83.0, 81.0, 54.6, 22.5. IR (film, KBr) cm^{-1}: 3375, 3266, 2966, 1617, 1490, 1267, 1048, 959, 856. HRMS (ESI, H) *m/z* calc'd for $C_{14}H_{19}F_3N_2O_3S$ $[M + Na]^+$ 375.0965 found 375.0961.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-trifluoromethoxy-phenylamino)-oxetan-3-yl]-amide (3m)

Off white solid (274 mg, 78%); ^1H NMR (400 MHz, DMSO) δ: 7.33 (s, 1H, –NH), 7.08 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.554 (d, $J = 8.8$ Hz, 2H, Ar–H), 6.26 (s, 1H, –NH), 4.90 (d, $J = 6.4$ Hz, 1H, O–CH), 4.82 (d, $J = 6.4$ Hz, 1H, O–CH), 4.66 (d, $J = 6.4$ Hz, 1H, O–CH), 4.53 (d, $J = 6.0$ Hz, 1H, O–CH), 1.03 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 143.4, 139.5, 122.0 (q, 4-OCF_3, $J_{C-F} = 21$ Hz), 119.1, 114.6, 82.5, 81.2, 69.7, 54.4, 22.6. IR (film, KBr) cm^{-1}: 3375, 3263, 2926, 1617, 1522, 1282, 1050, 963, 837. HRMS (ESI, H) *m/z* calc'd for $C_{14}H_{19}F_3N_2O_3S$ $[M + Na]^+$ 375.0965 found 375.0961.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-*tert*-butyl-phenylamino)-oxetan-3-yl]-amide (3n)

Off white solid (220 mg, 68%); ^1H NMR (400 MHz, DMSO) δ: 7.10 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.84 (s, 1H, –NH), 6.47 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.13 (S, 1H, –NH), 4.86 (d, $J = 6.0$ Hz, 1H, O–CH–),4.79 (d, $J = 6.0$ Hz, 1H, O–CH–), 4.65 (d, $J = 6.0$ Hz, 1H, O–CH–), 4.50 (d, $J = 6.0$ Hz, 1H, O–CH), 1.19 (s, 9H, t-Bu), 1.04 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 141.6, 139.1, 125.1, 113.7, 82.7, 81.3, 69.8, 54.2, 33.5, 31.4, 22.6. IR (film, KBr) cm^{-1}: 3376, 3178, 2960, 1624, 1522, 1266, 1041,967, 824. HRMS (ESI, H) *m/z* calc'd for $C_{17}H_{28}N_2O_2S$ $[M + Na]^+$ 347.1758 found 347.1764.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-bromo-phenylamino)-oxetan-3-yl]-amide (3o)

White solid (207 mg, 60%), ^1H NMR (400 MHz,DMSO) δ: 7.28 (S, 1H, –NH), 7.23 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.46 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.25 (s, 1H, –NH), 4.89 (d, $J = 6.0$ Hz, 1H, O–CH), 4.81 (d, $J = 6.4$ Hz, 1H, O–CH), 4.65 (d, $J = 6.4$ Hz, 1H, O–CH), 4.50 (d, $J = 6.0$ Hz, 1H, O–CH), 1.03 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 143.4, 131.1, 115.9, 108.1, 82.5, 81.1, 69.5, 54.4, 22.6. IR (film, KBr) cm^{-1}: 3322, 3235, 2966, 1593, 1488, 1045, 974, 820. HRMS (ESI, H) *m/z* calc'd for $C_{13}H_{19}BrN_2O_2S$ $[M + Na]^+$ 369.0244 found 369.0248 and 371.0243.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(3,5-dimethyl-phenylamino)-oxetan-3-yl]-amide (3p)

Off white solid (186 mg, 63%); ^1H NMR (400 MHz, DMSO) δ: 6.85 (s, 1H, –NH), 6.24 (s, 1H, –NH), 6.14 (s, 1H, Ar–H), 4.87 (d, $J = 6.0$ Hz, 1H, O–CH–), 4.78 (d, $J = 6.0$ Hz, 1H, O–CH), 4.66 (d, $J = 6.4$ Hz, 1H, O–CH), 4.49 (d, $J = 6.0$ Hz, 1H, O–CH, 2.10 (s, 6H, CH_3), 1.05 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 148.3, 143.9, 137.3, 119., 117.7, 112.0, 82.9, 81.4, 69.8, 54.3, 22.6, 21.2. IR (film, KBr) cm^{-1}: 3335, 3191, 2957, 1606, 1254, 1038, 982, 829. HRMS (ESI, H) *m/z* calc'd for $C_{15}H_{24}N_2O_2S$ $[M + Na]^+$ 319.1442 found 319.1451.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(2,3-dimethyl-phenylamino)-oxetan-3-yl]-amide (3q)

Off white solid (222 mg, 75%); ^1H NMR (400 MHz, DMSO) δ: 6.80 (dd, $J = 7.6$ Hz, 1H, Ar–H), 6.49 (d, $J = 7.4$ Hz, 1H, Ar–H), 6.13 (s, 1H, –NH), 6.12 (d, $J = 8.4$ Hz, 1H, Ar–H), 5.91 (s, 1H, –NH), 4.89 (dd, $J = 6.0$ Hz, 2H, O–CH_2), 4.82 (d, $J = 6.4$ Hz, 1H, O–CH), 4.59 (d, $J = 6.0$ Hz, 1H, O-CH), 2.18 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.01 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 141.4, 136.0, 124.8, 121.3, 119.5, 110.8, 82.5, 81.6, 70.1, 54.5, 22.6, 20.5, 13.0. IR (film, KBr) cm^{-1}: 3341, 3239, 2956, 1590, 1476, 1064, 979, 887,761. HRMS (ESI, H) *m/z* calc'd for $C_{15}H_{24}N_2O_2S$ $[M + Na]^+$ 319.1442 found 319.1451.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(2-bromo-4-methyl-phenylamino)-oxetan-3-yl]-amide (3r)

White solid (223 mg, 62%); ^1H NMR (400 MHz, DMSO) δ: 7.29 (d, $J = 4.0$ Hz, 1H, Ar–H), 6.93 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.31 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.27 (S, 1H, –NH), 5.93 (S, 1H, –NH), 4.91 (d, $J = 6.4$ Hz, 1H, O–CH), 4.88 (dd, $J = 6.8$ Hz, $J = 8$ Hz, 2H, O–CH), 4.84 (d,

J = 6.8 Hz, 1H, O–CH),4.60 (d, J = 6.4 Hz, 1H), 2.15 (s, 3H, CH_3), 1.01 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 138.3, 132.8, 128.3, 128.0, 114.2, 109.3, 82.0, 81.3, 69.9, 54.7, 22.5, 19.5. IR (film, KBr) cm^{-1}: 3343, 3215, 2961, 1611, 1515, 1238, 1045, 963, 870. HRMS (ESI, H) m/z calc'd for $C_{14}H_{21}BrN_2O_2S$ $[M + Na]^+$ 383.0399 found 383.0404 and 385.0373.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-fluoro-2-methyl-phenylamino)-oxetan-3-yl]-amide (3s)

Pink solid (210 mg, 70%); ^{1}H NMR (400 MHz, DMSO) δ: 6.89–6.86 (dd, J = 2.4 Hz, 1H, Ar–H), 6.77–6.72 (m, 1H, Ar–H), 6.20 (s, 1H, –NH), 6.17 (t, J = 5.2 Hz, 2H, Ar–H), 5.93 (s, 1H, –NH), 4.91–4.87 (dd, J = 6 Hz, 2H, O–CH_2), 4.82 (d, J = 6.4 Hz, 1H, O–CH), 4.59 (d, J = 6.0 Hz, 1H, O-CH), 2.15 (s, 3H, CH_3), 1.00 (s, 9H, t-Bu). ^{13}C NMR (100 MHz, DMSO) δ: 155.9 (d, $^1J_{C–F}$ = 231 Hz), 138.1, 125.3 (d, $^3J_{C–F}$ = 7 Hz), 116.7 (d, $^2J_{C–F}$ = 22 Hz), 113.2(d, $^3J_{C–F}$ = 7 Hz), 111.7 (d, $^2J_{C–F}$ = 22 Hz), 82.3, 81.5, 70.0, 54.5, 22.5, 17.9. IR (film, KBr) cm^{-1}: 3376, 3218, 2960, 1522, 1255, 1043, 982, 861. HRMS (ESI, H) m/z calc'd for $C_{14}H_{21}FN_2O_2S$ $[M + Na]^+$ 323.1192 found 323.1200.

Synthesis of (±)2-methyl-propane-2-sulfinic acid [3-(4-cyano-phenylamino)-oxetan-3-yl]-amide(3t)

Off white solid (196 mg, 67%); ^{1}H NMR (400 MHz, DMSO) δ: 8.00 (S, 1H, –NH), 7.51 (d, J = 8.8 Hz, 2H, Ar–H), 6.59 (d, J = 8.4 Hz, 2H, Ar–H), 6.39 (s, 1H, –NH), 4.93 (d, J = 6.4 Hz, 1H, O–CH), 4.84 (d, J = 6.4 Hz, 1H, O–CH), 4.70 (d, J = 6.8 Hz, 1H, O–CH), 4.54 (d, J = 6.4 Hz, 1H, O–CH), 1.03 (s, 9H, t-Bu). ^{13}C-NMR (100 MHz, DMSO) δ:148.1, 133.1, 120.2, 114.2, 98.0, 82.2, 81.1, 69.3, 54.7, 22.6. IR (film, KBr) cm^{-1}: 3337, 3101, 2954, 1598, 1491, 1262, 1009, 963, 823. HRMS (ESI, H) m/z calc'd for $C_{14}H_{19}N_3O_2S$ $[M + Na]^+$ 316.1095 found 316.1090.

Conclusion

In conclusion, a convenient and straightforward synthesis of the structurally diverse 2-methyl-*N*-[(3-phenylamino)oxetan-3-yl]-2-propanesulfinamide derivatives was conducted under catalyst-free conditions from 3-oxetan-3-*t*-butyl sulfinimine and substituted aromatic amines. The corresponding derivatives are obtained in good to excellent yield under optimized reaction conditions. The method presented herein was found to be efficient for the synthesis of oxetanyl heterocycles as emerging building blocks for future drug discovery and to be considered as alternative for gem-dimethyl group as well as carbonyl group as bioisostere.

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