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Heteroaromatic annulation studies on 10,11-dihydro-11-[bis(methylthio)methylene]dibenzoxepin-10-one: a facile access to novel dibenzoxepino[4,5]-fused heterocycles

Sarvesh Kumar, Hiriyakkanavar Ila* and Hiriyakkanavar Junjappa

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

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Dedicated to Professor Nouria A. Al-Awadi on her 55th birthday

Abstract—10,11-Dihydro-11-[bis(methylthio)methylene]dibenzoxepin-10-one has been shown to be a useful three carbon synthon for the efficient regiospecific annulation of a variety of five- (pyrazoles, isoxazoles, thiophene, and γ-lactone) and six-membered (pyrimidines, pyridone and pyridines) heterocycles by cyclocondensation with heterobinucleophiles such as hydrazine, hydroxylamine, dimethylsulfonium methylide, guanidine, thiourea, cyanoacetamide, and substituted β-lithioaminoacrylonitrile.

1. Introduction

A number of dibenzoxepine derivatives containing a fused heterocyclic ring at the 4,5-position are known to display a wide range of biological activity, and have proven to be lead compounds for psychoactive drugs for the treatment of anxiety disorder, depression, and in particular schizophrenic psychoses.[1,2] Thus, a few of the azepino- (maroxepine, savoxepine),[3] piperidino- (ORG 4428, beloxepin)[1a,4] and pyrrolidino-fused (ORG 5222)[1a,4] dibenzoxepine derivatives are shown to be a new class of emerging potential antianxiety and antidepressant agents, displaying improved activity and tolerance in comparison to the existing classical psychoactive drugs. Therefore, such dibenzoxepino-fused heterocycles have attracted considerable attention from both medicinal and synthetic organic chemists in recent years because of their broad pharmacological applications as indicated by large number of publications and patents in this field.[1,5] As a part of our ongoing research program on aromatic and heteroaromatic annulation studies on α-oxoketene dithioacetals as three carbon 1,3-electrophilic components,[6,7] we became interested in elaborating this strategy for the synthesis of dibenzoxepino[4,5]-fused five- and six-membered heterocycles in view of the unique biological activity displayed by this class of compounds. The corresponding 10,11-dihydro-11-[bis(methylthio)methylene]-dibenzoxepin-10-one **2** was selected as a model substrate for our heteroannulation studies and the results are reported herein.

2. Results and discussion

The desired α-oxoketene dithioacetal **2** was prepared in high yield by the treatment of 10,11-dihydrodibenzoxepin-10-one **1**[8] with sodium hydride and carbon disulfide in THF at 0 °C followed by alkylation with methyl iodide (Scheme 1).[9] The corresponding β-oxodithioester **3** was also synthesized as a useful precursor for various heterocycles by reacting the ketone **1** with dimethyl trithiocarbonate in the presence of NaH in refluxing benzene according to our earlier reported procedure.[10] Syntheses of dibenzoxepino[4,5]-fused five-membered heterocycles were undertaken first (Schemes 2–4). Thus, when **2** was reacted with hydrazine hydrate in refluxing ethanol, the corresponding 3-(methylthio)-2*H*-dibenzoxepino[4,5-*c*]pyrazole **4** was obtained in 73% yield (Scheme 2).[11] Similarly, the treatment of the ketene dithioacetal **2** with phenylhydrazine in the presence of potassium *tert*-butoxide in refluxing *tert*-butanol furnished 3-(methylthio)-2-phenyldibenzoxepino[4,5-*c*]pyrazole **5** in 63% yield.[12] The corresponding regioisomeric 3-(methylthio)-1-phenyldibenzoxepin[4,5-*d*]pyrazole **6a** could also be prepared in good yield by treating β-oxodithioester **3** with phenylhydrazine in refluxing ethanol.[12a] The structures and regiochemistry of products **5** and **6** were established with the help of spectral and analytical data, and also by desulfurization of the pyrazole **6a** to the known dethiomethylated pyrazole **6b**[1a] with Raney-Ni in refluxing ethanol.

Keywords: Heteroaromatic annulation; α-Oxoketene dithioacetal; Dibenzoxepine; Heterocycles.
* Corresponding author. Tel.: +91 512 2597870; fax: +91 512 2597436; e-mail: hila@iitk.ac.in

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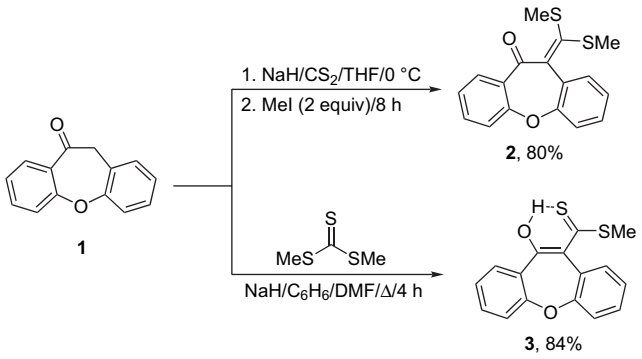
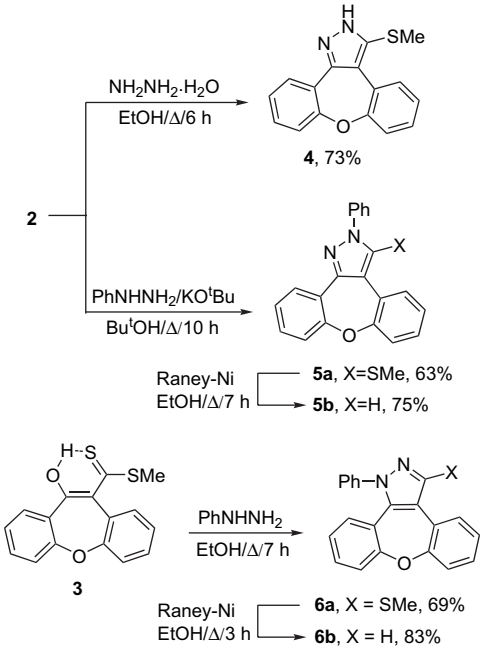
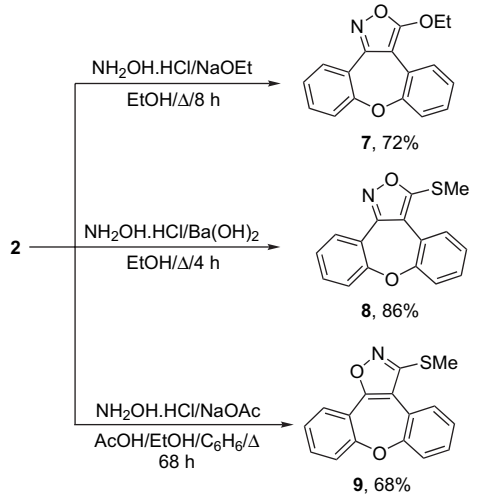


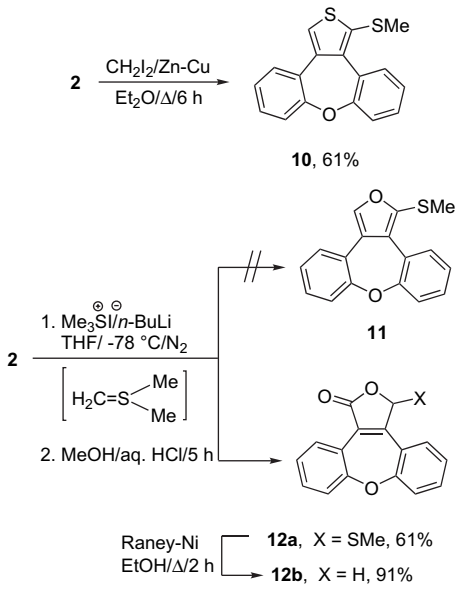
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

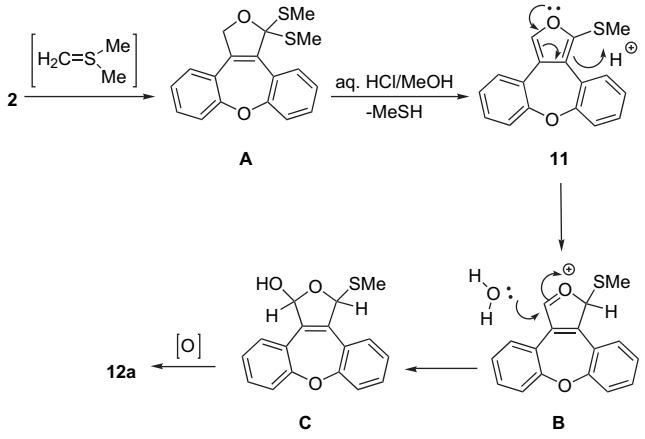
The ketene dithioacetal **2** was next reacted with hydroxylamine hydrochloride with a view to synthesize dibenzoxepino-fused isoxazoles as shown in the Scheme 3.[13] Thus, when **2** was exposed to $NH_2OH\cdot HCl$ in the presence of sodium ethoxide in refluxing ethanol, the product isolated was characterized as 3-ethoxydibenzoxepino[4,5-*c*]isoxazole **7** in which the methylthio group was replaced by the ethoxy group as observed earlier in our previous studies.[9b] On the other hand, treatment of **2** with $NH_2OH\cdot HCl$ in the presence of a non-nucleophilic base such as barium hydroxide afforded the corresponding 3-(methylthio)dibenzoxepino-[4,5-*c*]isoxazole **8** in 86% yield.[13] Similarly, the reaction of **2** with $NH_2OH\cdot HCl$ in the presence of sodium acetate–acetic acid buffer furnished regioisomeric 3-(methylthio)-dibenzoxepino[4,5-*d*]isoxazole **9** in good yield (Scheme 3). These observations are in conformity with our earlier report[13] on the formation of regioisomeric isoxazoles under varying pH conditions.

The ketene dithioacetal **2** was next subjected to treatment with methylene iodide and Zn–Cu couple yielding the corresponding 1-(methylthio)thieno[3,4-*d*]dibenzoxepine **10** (61%), in line with our earlier observations on Simmons–Smith reaction on α-oxoketene dithioacetals.[14]

Interestingly, attempted preparation of dibenzoxepino-fused methylthiofuran **11** by reacting ketene dithioacetal **2** with dimethylsulfonium methylide followed by acid work-up[15] yielded an unexpected product, which was characterized as 3-(methylthio)-1,3-dihydro-1-oxo-furo-[3,4-*d*]dibenzoxepine **12a**, instead of **11** on the basis of its spectral and analytical data and also by Raney-Ni mediated desulfurization of **12a** to **12b** (Scheme 4).

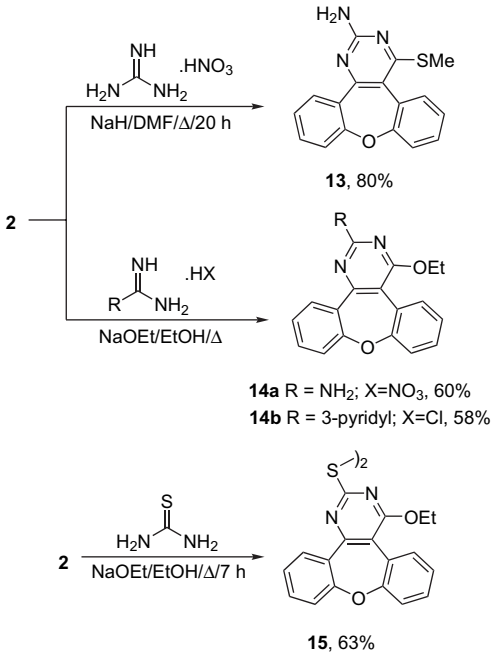
The probable mechanism for the formation of the lactone **12a** from **2**, which involves an oxidative step at some stage of the transformation, is shown in Scheme 5. The initial fused dihydrofuran intermediate **A** affords the furan **11** on treatment with aqueous HCl. However, the furan **11** appears

to be unstable under the present reaction condition and undergoes acid-induced hydration and subsequent oxidation of the hydrated intermediate **C** to furnish the lactone **12a**. Our attempts to isolate furan **11** under varying conditions were unsuccessful.

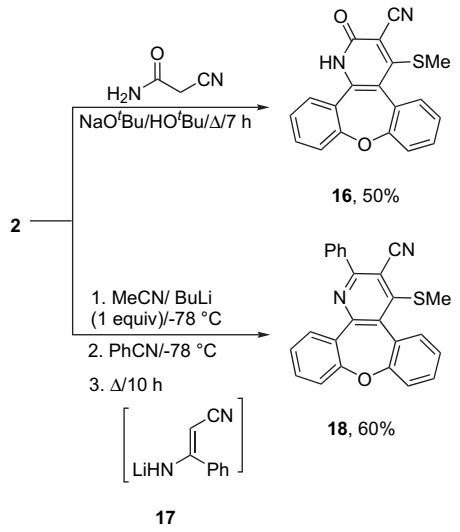


Scheme 5.

Cyclocondensation of **2** with 1,3-heterobinucleophiles was next examined with a view to synthesize dibenzoxepino-fused six-membered heterocycles (Schemes 6 and 7). Thus, heterocyclization of **2** with guanidine nitrate in the presence of sodium hydride in DMF afforded the corresponding 2-amino-4-(methylthio)dibenzoxepino[4,5-*d*]-pyrimidine **13** in 80% yield.[9] On the other hand, a similar reaction when conducted in the presence of sodium ethoxide in refluxing ethanol gave 2-amino-4-ethoxydibenzoxepino[4,5-*d*]pyrimidine **14a** (60%) in accordance with our earlier reported alkoxypyrimidine synthesis from α-oxoketene dithioacetals.[9b] Similarly, treatment of **2** with 2-(3-pyridyl)amidine hydrochloride under identical conditions



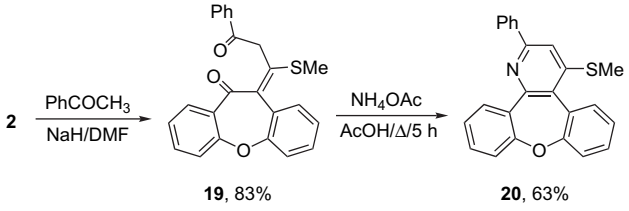
Scheme 6.



Scheme 7.

furnished 4-ethoxy-2-(3-pyridyl)dibenzoxepino[4,5-*d*]-pyrimidine **14b** in 58% yield (Scheme 6). Cyclocondensation of **2** with thiourea using sodium ethoxide in refluxing ethanol furnished the dimeric compound bis(4-ethoxydibenzoxepino[4,5-*d*]pyrimidin-2-yl)disulfide **15** resulting via oxidative dimerization of the initially formed 4-ethoxy-2-mercaptodibenzoxepino[4,5-*d*]pyrimidine (Scheme 6).

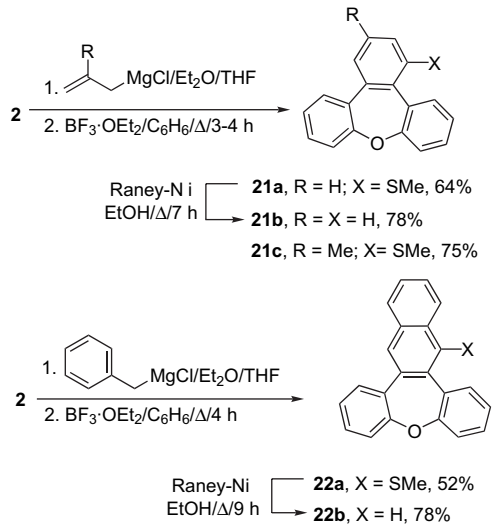
The versatility of our heteroaromatic annulation strategy was further demonstrated by the synthesis of a few pyrido-fused dibenzoxepines as shown in Schemes 7 and 8. Thus, the reaction of **2** with cyanoacetamide in the presence of sodium *tert*-butoxide in *tert*-butanol afforded the highly functionalized 3-cyano-4-(methylthio)-1*H*-dibenzoxepino-[4,5-*b*]pyridine-2-one **16** in a moderate yield of 50%.[16] Similarly, the cyclocondensation of **2** with β-phenyl-β-lithioaminoacrylonitrile **17** (generated in situ according to earlier reported method)[17] yielded 4-(methylthio)-2-phenyl-dibenzoxepino[4,5-*b*]pyridine-3-carbonitrile **18** in 60% yield (Scheme 7). In another strategy for pyridine annulation, the ketene dithioacetal **2** was subjected to conjugate addition–elimination with acetophenone enolate affording the conjugate adduct **19**, which in the presence of ammonium acetate–acetic acid provided the corresponding 4-(methylthio)-2-phenyldibenzoxepino[4,5-*b*]pyridine **20** in 63% yield (Scheme 8).[18]



Scheme 8.

Finally, we also investigated benzo- and naphtho-annulation of **2** with allyl and benzyl Grignard reagents with a view to synthesize [4,5]-benzo- and naphtho-fused dibenzoxepines, as well as to show the generality and scope of our aromatic

annulation protocol.[6b,19] Thus, 1,2-addition of **2** with either allyl or methallyl magnesium halide followed by the cycloaromatization of the resulting carbinol acetal in the presence of $BF_3 \cdot OEt_2$ at reflux in benzene proceeded smoothly affording the respective tribenzoxepine **21a** or **21c** in overall good yield.[20] 1-(Methylthio)tribenzoxepine **21a** was converted into the parent **21b**[21] in 78% yield by reductive dethiomethylation with Raney-Ni (Scheme 9). Similarly, the treatment of **2** with benzylmagnesium chloride under previously reported conditions afforded only 1,2-carbinol adduct, which was transformed into the 5-(methylthio)naphtho[2,3-*d*]dibenzoxepine **22a** through $BF_3 \cdot OEt_2$ promoted cycloaromatization under standard reaction conditions.[22] Subsequent Raney-Ni dethiomethylation of **22a** gave the parent **22b** in 78% yield (Scheme 9).



Scheme 9.

3. Conclusion

In summary, overall work presented in this paper further demonstrates the versatility of our heteroaromatic/aromatic annulation protocol via α-oxoketene dithioacetal for generating a wide range of novel hitherto unreported condensed polycyclic heteroaromatics, which cannot be prepared easily by traditional classical methods. In view of the wide range of biological activities displayed by dibenzoxepino-fused heterocycles, especially, as psychoactive drugs, these newly synthesized heterocycles will prove useful for preliminary pharmacological evaluations.

4. Experimental

4.1. General

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Jeol JNM Lambda Spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as an internal standard. Melting points were measured using Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1320 spectrometer. Mass spectra were recorded on Jeol SX 102/DA-6000 Mass Spectrometer/Data System. Elemental analyses were carried out on an Elementar Vario EL III analyzer.

Column chromatography was carried out using silica gel (100–200 mesh). THF was distilled over sodium benzophenone ketyl prior to use. DMF was distilled over calcium hydride and stored over molecular sieves. *n*-BuLi was purchased from Aldrich company.

4.1.1. Synthesis of 10,11-dihydro-11-[bis(methylthio)-methylene]dibenz[*b*,*f*]oxepin-10-one (2). To a stirred suspension of NaH (60%, 0.2 g, 4.8 mmol) in dry DMF (10 mL) under a nitrogen atmosphere was added dropwise a DMF solution (10 mL) of 10,11-dihydro-dibenzoxepin-10-one **1** (0.4 g, 1.9 mmol) and carbon disulfide (0.13 mL, 2.2 mmol) at 0 °C. The resulting anion was stirred at the same temperature for 30 min, followed by stirring at room temperature overnight (12 h). Methyl iodide (0.9 mL, 3.8 mmol) was added dropwise at 0 °C followed by stirring of the reaction mixture at room temperature for 8 h (monitored by TLC). The reaction mixture was poured into ice-cold water (50 mL) and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with water (3×40 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was recrystallized from hexane–chloroform to yield **2** as yellow crystals (0.48 g, 80%); R_f 0.2 (49:1 hexane–EtOAc); mp 132–133 °C; IR cm^{-1} (KBr): 3062, 2920, 1632, 1464, 1443, 1299; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, J=8.04, 1.72 Hz, 1H, ArH), 7.49 (ddd, J=7.44, 7.44, 1.96 Hz, 1H, ArH), 7.45 (d, J=7.32, 1H, ArH), 7.29–7.25 (m, 3H, ArH), 7.22–7.17 (m, 2H, ArH), 2.44 (s, 3H, SMe), 2.15 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.7, 160.0, 156.6, 152.7, 137.4, 134.5, 131.4, 131.3, 130.1, 128.9, 127.4, 125.7, 124.2, 121.0, 120.7, 18.5, 17.9; MS *m*/*z* (%): 315 (M^++1, 100), 314 (M^+, 80), 267 (58). Anal. Calcd for $C_{17}H_{14}O_2S_2$: C, 64.94%; H, 4.49%. Found: C, 64.83%; H, 4.57%.

4.1.2. Synthesis of methyl(10,11-dihydro-10-oxodibenz[*b*,*f*]oxepine)-11-dithioate (3). A solution of ketone **1** (1.0 g, 4.8 mmol) in benzene (20 mL) was added dropwise to a stirred suspension of NaH (60%, 0.48 g, 12.0 mmol) and dimethyl trithiocarbonate (0.8 g, 5.7 mmol) in a solution of benzene (40 mL) and DMF (4 mL) at reflux temperature over a period of 40 min. After addition was over, the refluxing was continued for 4 h (monitored by TLC). The reaction mixture was cooled to room temperature and poured into saturated aqueous ammonium chloride solution (40 mL). The organic layer was separated and washed with water (3×40 mL), brine (1×40 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (24:1) as eluant to give **3** as a viscous yellow liquid (1.2 g, 84%); R_f 0.6 (49:1 hexane–EtOAc); IR cm^{-1} (neat): 2920, 1679, 1527, 1443, 1219, 968; ^{1}H NMR (400 MHz, $CDCl_3$) (4:5 mixture of keto–enol tautomers): δ 8.12 (dd, J=7.92, 1.84 Hz, 0.45H, ArH, keto), 7.87 (dd, J=8.16, 1.84 Hz, 0.55H, ArH, enol), 7.88–7.39 (m, 2.45H, ArH, keto+enol), 7.34–7.19 (m, 4H, ArH, keto+enol), 7.11 (ddd, J=8.06, 6.10, 2.39 Hz, 0.55H, ArH, enol), 4.98 (s, 0.45H, CH, keto), 2.61 (s, 3×0.55H, SMe, enol), 2.55 (s, 3×0.45H, SMe, keto); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 230.8, 222.3, 187.8, 163.9, 161.1, 160.0, 158.0, 156.6, 134.9, 133.9, 133.3, 131.8, 131.52, 130.56, 130.5, 129.5, 128.1, 127.9, 127.2, 126.4, 125.1, 124.9, 124.2, 124.0, 121.8, 121.6, 121.1, 120.9, 120.5, 29.7, 19.7, 19.3; MS *m/z* (%): 301 (M^++1, 78), 300 (M^+, 69), 299 (M^+−1, 56), 267 (35), 253 (100), 252 (72). Anal. Calcd for $C_{16}H_{12}O_2S_2$: C, 63.97%; H, 4.03%. Found: C, 64.06%; H, 4.07%.

4.1.3. Synthesis of 3-(methylthio)-2*H*-dibenz[*b*,*f*]oxepino[4,5-*c*]pyrazole (4). To a stirred solution of **2** (0.45 g, 1.5 mmol) in ethanol (20 mL), hydrazine hydrate (80%, 0.14 mL, 2.25 mmol) was added and the reaction mixture was refluxed for 6 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was dissolved in chloroform (20 mL). The chloroform layer was washed with water (2×20 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluant to give **4** as a white solid (0.32 g, 73%); R_f 0.3 (9:1 hexane–EtOAc); mp 163–164 °C; IR cm^{-1} (KBr): 3257, 1524, 1445, 1240, 1135, 990, 938, 760, 737; ^1H NMR (400 MHz, $CDCl_3$): 7.90 (dd, *J*=7.68, 1.36 Hz, 1H, ArH), 7.57 (d, *J*=7.32, 1H, ArH), 7.32–7.23 (m, 4H, ArH), 7.19 (ddd, *J*=7.88, 7.88, 1.64 Hz, 1H, ArH), 7.08 (ddd, *J*=6.96, 6.96, 2.20 Hz, 1H, ArH), 2.47 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 156.1, 130.6, 128.4, 127.7, 126.5, 125.3, 125.2, 124.0, 121.8, 121.7, 116.6, 17.0; MS *m/z* (%): 281 (M^++1, 100), 280 (M^+, 80), 234 (40). Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55%; H, 4.31%; N, 9.99%. Found: C, 68.71%; H, 4.28%; N, 10.02%.

4.1.4. Synthesis of 3-(methylthio)-2-phenyldibenz[*b*,*f*]oxepino[4,5-*c*]pyrazole (5a). A solution of α-oxoketene dithioacetal **2** (0.2 g, 0.64 mmol), phenylhydrazine (0.94 mL, 0.96 mmol), and Bu^{t}OK (0.14 g, 1.28 mmol) in Bu^{t}OH (5 mL) was refluxed for 10 h (monitored by TLC) with constant stirring. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform (30 mL). The chloroform layer was washed with water (2×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluant to give **5** as a white solid (0.14 g, 63%); R_f 0.6 (9:1 hexane–EtOAc); mp 172–173 °C; IR cm^{-1} (KBr): 1440, 1194, 773, 749; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J*=7.56, 1.72 Hz, 1H, ArH), 7.88 (dd, *J*=7.80, 1.24 Hz, 1H, ArH), 7.68 (d, *J*=8.08 Hz, 2H, ArH), 7.52 (t, *J*=7.56 Hz, 2H, ArH), 7.47 (t, *J*=6.08 Hz, 1H, ArH), 7.37–7.28 (m, 4H, ArH), 7.26–7.18 (m, 2H, ArH), 2.10 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 156.9, 148.2, 139.3, 132.8, 130.1, 128.9, 128.5, 128.2, 127.5, 126.1, 125.3, 125.2, 121.8, 121.3, 120.7, 18.6; MS *m/z* (%): 357 (M^++1, 100), 356 (M^+, 80). Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13%; H, 4.52%; N, 7.86%. Found: C, 74.08%; H, 4.58%; N, 7.79%.

4.1.5. Synthesis of 3-(methylthio)-1-phenyldibenz[*b*,*f*]oxepino[4,5-*d*]pyrazole (6a). A solution of β-oxodithioester **3** (0.28 g, 0.93 mmol) and phenylhydrazine (0.13 mL, 1.34 mmol) in absolute ethanol (10 mL) was refluxed for 7 h (monitored by TLC). The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (24:1) as eluant to give **6a** as a white solid (0.23 g, 69%); R_f 0.4 (49:1 hexane–EtOAc); mp 172–173 °C; IR cm^{-1} (KBr): 1506, 1390, 1223, 764, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J*=7.46, 1.58 Hz, 1H, ArH), 7.46–7.22 (m, 10H, ArH), 6.90 (ddd, *J*=7.50, 7.50, 1.32 Hz, 1H, ArH), 6.77 (dd, *J*=8.04, 1.48 Hz, 1H, ArH), 2.64 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 156.2, 145.7, 139.7, 137.9, 130.4, 129.1, 128.8, 128.6, 127.9, 127.8, 125.29, 125.27, 124.6, 122.7, 122.0, 121.3, 117.6, 15.3; MS *m/z* (%): 357 (M^++1, 100), 356 (M^+, 72). Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13%; H, 4.52%; N, 7.86%. Found: C, 74.05%; H, 4.59%; N, 8.03%.

4.1.6. Synthesis of 3-ethoxydibenz[*b*,*f*]oxepino[4,5-*c*]isoxazole (7). Hydroxylamine hydrochloride (0.28 g, 4 mmol) was added to a stirred solution of sodium ethoxide (6 mmol, prepared in situ from 0.14 g of sodium metal and 2 mL of ethanol) in ethanol (10 mL) at room temperature. After 10 min, ketene dithioacetal **2** (0.31 g, 1.0 mmol) was added at the same temperature and the reaction mixture was refluxed for 8 h (monitored by TLC). Solvent was evaporated under reduced pressure and the residue was treated with water (20 mL). Extraction was done with chloroform (2×30 mL). The combined organic extracts were washed with water (2×20 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluant to give a white solid (**7**) (0.20 g, 72%); R_f 0.5 (9:1 hexane–EtOAc); mp 149–150 °C; IR cm^{-1} (KBr): 2986, 1641, 1526, 1445, 1383, 1224, 1041, 752, 737; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J*=7.56, 1.72 Hz, 1H, ArH), 7.70 (dd, *J*=7.58, 1.70 Hz, 1H, ArH), 7.47 (ddd, *J*=7.75, 7.75, 1.62 Hz, 1H, ArH), 7.34–7.19 (m, 5H, ArH), 4.51 (q, *J*=7.08 Hz, 2H, OCH_2), 1.54 (t, *J*=7.08 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 164.3, 156.2, 155.0, 132.5, 129.3, 126.8, 126.15, 126.12, 125.4, 125.4, 122.6, 122.0, 121.8, 104.9, 66.3, 14.7; MS *m/z* (%): 280 (M^++1, 72), 279 (M^+, 100). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11%; H, 4.69%; N, 5.02%. Found: C, 73.29%; H, 4.64%; N, 5.07%.

4.1.7. Synthesis of 3-(methylthio)dibenz[*b*,*f*]oxepino-[4,5-*c*]isoxazole (8). Hydroxylamine hydrochloride (0.28 g, 4 mmol) was added to a stirred suspension of $Ba(OH)_2$ (1.03 g, 6 mmol) in 95% aqueous ethanol (10 mL) at room temperature. Ketene dithioacetal **2** (0.31 g, 1.0 mmol) was added and the reaction mixture was refluxed for 4 h (monitored by TLC). Solvent was evaporated under reduced pressure and the residue was treated with ice-cold water (20 mL). Extraction was done with chloroform (2×30 mL). The combined organic extracts were washed with water (2×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (19:1) as eluant to give **8** as a white solid (0.24 g, 86%); R_f 0.4 (49:1 hexane–EtOAc); mp 100–101 °C; IR cm^{-1} (KBr): 1442, 1391, 1251, 1216, 1041, 758; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J*=7.70, 1.58 Hz, 1H, ArH), 7.63 (dd, *J*=8.18, 0.86 Hz, 1H, ArH),

7.44 (ddd, J=7.81, 7.81, 1.61 Hz, 1H, ArH), 7.34–7.29 (m, 3H, ArH), 7.27–7.20 (m, 2H, ArH), 2.72 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 159.5, 157.5, 156.0, 132.1, 129.3, 128.3, 128.1, 125.6, 125.5, 122.6, 122.3, 121.9, 112.5, 14.8; MS m/z (%): 282 (M^++1, 100), 281 (M^+, 87). Anal. Calcd for $C_{16}H_{11}NO_2S$: C, 68.31%; H, 3.94%; N, 4.98%. Found: C, 68.27%; H, 3.86%; N, 5.07%.

4.1.8. Synthesis of 3-(methylthio)dibenz[*b*,*f*]oxepino[4,5-*d*]-isoxazole (9). To a stirred solution of **2** (0.31 g, 1 mmol) in benzene (10 mL) and glacial AcOH (10 mL) at room temperature was added a solution of NaOAc (0.28 g, 3.4 mmol) and $NH_2OH\cdot HCl$ (0.28 g, 4 mmol) in water (1 mL). The mixture was made homogeneous by the addition of ethanol (5 mL) and refluxed for 68 h (monitored by TLC). Reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in chloroform (40 mL). The organic layer was washed with water (2×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (3:1) as eluant to give **9** as a white powder (0.19 g, 68%); R_f 0.5 (4:1 hexane–EtOAc); mp 114–115 °C; IR cm^{-1} (KBr): 2925, 1600, 1446, 1228, 758, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J=7.82, 1.46 Hz, 1H, ArH), 7.72 (dd, J=7.68, 1.60 Hz, 1H, ArH), 7.49 (ddd, J=7.90, 7.90, 1.34 Hz, 1H, ArH), 7.38–7.29 (m, 3H, ArH), 7.27–7.22 (m, 2H, ArH), 2.74 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 158.6, 156.7, 155.7, 132.6, 129.7, 126.70, 126.69, 125.6, 125.5, 122.8, 122.25, 122.21, 121.9, 121.5, 14.0; MS m/z (%): 282 (M^++1, 100), 281 (M^+, 75). Anal. Calcd for $C_{16}H_{11}NO_2S$: C, 68.31%; H, 3.94%; N, 4.98%. Found: C 68.22%; H, 4.06%; N, 4.96%.

4.1.9. Synthesis of 1-(methylthio)thieno[3,4-*d*]dibenz[*b*,*f*]oxepine (10). A solution of CH_2I_2 (0.2 mL, 2.5 mmol) in dry ether (5 mL) was added dropwise to a stirred suspension of Zn–Cu couple (activated by heating in oven at 100 °C for 10 h) (0.4 g, 3.0 mmol) in dry ether (20 mL) at reflux temperature under a nitrogen atmosphere. After 1 h, a solution of **2** (0.31 g, 1.0 mmol) in dry THF (10 mL) was added dropwise at reflux temperature and refluxing was continued for 6 h (monitored by TLC). The reaction mixture was cooled to room temperature and the organic layer was decanted. The residue was washed with chloroform (2×20 mL). The combined organics were washed with water (1×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (24:1%) as eluant to give **10** as a white solid (0.18 g, 61%); R_f 0.7 (19:1 hexane–EtOAc); mp 83–84 °C; IR cm^{-1} (KBr): 1438, 1235, 1196, 1100, 782, 740; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J=7.94, 1.10 Hz, 1H, ArH), 7.52 (dd, J=7.56, 0.96 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.36–7.29 (m, 4H, ArH), 7.25–7.21 (m, 1H, ArH), 7.20–7.16 (m, 1H, ArH), 2.48 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 157.3, 139.1, 136.5, 134.4, 130.9, 129.3, 129.0, 128.4, 127.5, 125.4, 124.7, 122.4, 121.4, 121.2, 21.30; MS m/z (%): 297 (M^++1, 50), 296 (M^+, 100). Anal. Calcd for $C_{17}H_{12}OS_2$: C, 68.89%; H, 4.08%. Found: C, 69.01%; H, 4.14%.

4.1.10. Synthesis of 3-(methylthio)-1,3-dihydro-1-oxofuro[3,4-*d*]dibenz[*b*,*f*]oxepine (12a). n-BuLi (1.6 M in hexane, 0.96 mL, 1.54 mmol) was added dropwise at −15 °C to a stirred suspension of trimethylsulfonium iodide (0.26 g, 1.54 mmol) in dry THF (15 mL) under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 15 min for the generation of the dimethylsulfonium methylide, and then it was cooled to −78 °C and solution of **2** (0.40 g, 1.28 mmol) in dry THF (5 mL) was added dropwise over a period of 5 min. The reaction mixture was further stirred at −78 °C for 1 h and then slowly warmed to room temperature over a period of 2 h. It was then quenched with water (0.5 mL), washed with brine (2×20 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure below 30 °C to give the unstable dihydrofuran derivative. This was dissolved in methanol (5 mL) and treated with HCl (2 M, 0.2 mL). The reaction mixture was stirred at room temperature for 5 h (monitored by TLC) and then neutralized with saturated aqueous Na_2CO_3 solution (5 mL). Extraction was done with chloroform (2×20 mL). The combined organic extracts were washed with water (1×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluant to give **12a** as a white solid (0.23 g, 61%); R_f 0.2 (49:1 hexane–EtOAc); mp 152–153 °C; IR cm^{-1} (KBr): 1752, 1487, 1442, 1217, 1102, 965, 766; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J=7.56 Hz, 1H, ArH), 7.51 (t, J=7.82 Hz, 1H, ArH), 7.42 (t, J=7.68 Hz, 1H, ArH), 7.34 (d, J=7.80 Hz, 1H, ArH), 7.30 (d, J=8.04 Hz, 1H, ArH), 7.26–7.22 (m, 3H, ArH), 7.46 (s, 1H, ArH), 2.01 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 158.4, 157.4, 154.1, 133.7, 131.8, 128.1, 127.5, 125.6, 125.4, 125.3, 124.4, 123.8, 122.4, 121.4, 82.9, 10.5; MS m/z (%): 297 (M^++1, 83), 296 (M^+, 47), 249 (100). Anal. Calcd for $C_{17}H_{12}O_3S$: C, 68.90%; H, 4.08%. Found: C, 68.93%; H, 4.04%.

4.1.11. Synthesis of 2-amino-4-(methylthio)dibenz[*b*,*f*]-oxepino[4,5-*d*]pyrimidine (13). To a stirred suspension of NaH (60%, 0.12 g, 3 mmol) in dry DMF (30 mL) at room temperature under a nitrogen atmosphere, was added guanidine nitrate (0.18 g, 1.5 mmol). After 10 min, a solution of ketene dithioacetal **2** (0.31 g, 1.0 mmol) in dry DMF (5 mL) was added dropwise and the reaction mixture was heated at 100 °C for 20 h (monitored by TLC). The reaction mixture was cooled to room temperature and poured into ice-cold water (30 mL). Extraction was done with ethyl acetate (3×30 mL). The combined organic extracts were washed with water (3×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc as eluant (7:3) to give **13** as a white solid (0.25 g, 80%); R_f 0.33 (4:1 hexane–EtOAc); mp 216–217 °C; IR cm^{-1} (KBr): 3493, 3300, 3188, 1626, 1538, 1448, 1212, 760; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, J=8.18, 1.82 Hz, 1H, ArH), 7.78 (d, J=8.08 Hz, 1H, ArH), 7.41 (ddd, J=7.74, 7.74, 1.82 Hz, 1H, ArH), 7.31–7.23 (m, 4H, ArH), 7.18–7.14 (m, 1H, ArH), 5.28 (br s, 2H, NH_2), 2.50 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 161.1, 160.0 (2C), 158.5, 131.9, 130.8, 130.5, 130.3, 129.6, 126.7,

125.3, 124.3, 121.0, 120.6, 118.9, 13.9; MS *m/z* (%): 308 (M^++1, 100), 307 (M^+, 32). Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43%; H, 4.26%; N, 13.67%. Found: C, 66.52%; H, 4.33%; N, 13.56%.

4.1.12. General procedure for the synthesis of 14a and 14b. Guanidine nitrate or 3-pyridyl amidine hydrochloride (1.2 mmol) was added to a stirred solution of sodium ethoxide (2.4 mmol, prepared in situ from 0.058 g of sodium metal and 2 mL of ethanol) in ethanol (10 mL) at room temperature. After 5 min, ketene dithioacetal **2** (0.31 g, 1.0 mmol) was added and the reaction mixture was refluxed for 5–12 h (monitored by TLC). The solvent was evaporated under reduced pressure and the residue was treated with ice-cold water (20 mL). It was then extracted with chloroform (3×20 mL). The combined organic extracts were washed with water (2×20 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (7:3) as eluant to give **14a** or **14b**.

4.1.12.1. 2-Amino-4-ethoxydibenz[*b*,*f*]oxepino[4,5-*d*]-pyrimidine (14a). White solid (0.18 g, 60%); R_f 0.3 (4:1 hexane–EtOAc); mp 183–184 °C; IR cm^{-1} (KBr): 3480, 3304, 3177, 1632, 1566, 1539, 1468, 1408, 1338, 1244; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J=7.80, 1.72 Hz, 1H, ArH), 7.70 (dd, J=7.94, 1.70 Hz, 1H, ArH), 7.40 (ddd, J=8.13, 7.25, 1.77 Hz, 1H, ArH), 7.29–7.21 (m, 4H, ArH), 7.14 (ddd, J=7.38, 7.38, 1.84 Hz, 1H, ArH), 5.21 (br s, 2H, NH_2), 4.57–4.49 (m, 1H, OCH), 4.39–4.31 (m, 1H, OCH), 1.38 (t, J=7.08 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 161.5, 161.0, 160.9, 159.2, 131.6, 131.4, 131.0, 130.0, 128.5, 126.0, 125.2, 124.2, 120.7, 120.5, 107.8, 62.6, 14.3; MS *m/z* (%): 306 (M^++1, 100), 305 (M^+, 50), 278 (30). Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81%; H, 4.95%; N, 13.76%. Found: C, 70.60%; H, 4.92%; N, 13.81%.

4.1.12.2. 4-Ethoxy-2-(3-pyridyl)dibenz[*b*,*f*]oxepino-[4,5-*d*]pyrimidine (14b). White solid (0.21 g, 58%); R_f 0.2 (4:1 hexane–EtOAc); mp 143–144 °C; IR cm^{-1} (KBr): 2987, 1583, 1531, 1403, 1371, 1249, 1026, 760; ^1H NMR (400 MHz, $CDCl_3$): 9.76 (s, 1H, ArH), 8.82 (d, J=8.04 Hz, 1H, ArH), 8.72 (br d, J=3.92 Hz, 1H, ArH), 8.20 (dd, J=7.80, 1.48 Hz, 1H, ArH), 7.82 (d, J=7.32 Hz, 1H, ArH), 7.48 (ddd, J=7.69, 7.69, 1.54 Hz, 1H, ArH), 7.43 (dd, J=7.96, 4.76 Hz, 1H, ArH), 7.38–7.29 (m, 4H, ArH), 7.21 (ddd, J=8.04, 6.2, 2.42 Hz, 1H, ArH), 4.78–4.74 (m, 1H, OCH), 4.64–4.60 (m, 1H, OCH), 1.50 (t, J=6.96 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 161.3, 160.6, 160.1, 159.7, 151.1, 149.8, 135.5, 133.0, 132.1, 131.6, 130.8, 130.6, 129.9, 125.3, 125.1, 124.4, 123.3, 121.0, 120.6, 115.6, 63.3, 14.3; MS *m/z* (%): 368 (M^++1, 100), 105 (58). Anal. Calcd for $C_{23}H_{17}N_3O_2$: C, 75.19%; H, 4.66%; N, 11.44%. Found: C, 75.31%; H, 4.58%; N, 11.56%.

4.1.13. Synthesis of bis(4-ethoxydibenz[*b*,*f*]oxepino-[4,5-*d*] pyrimidin-2-yl)disulfide (15). Thiourea (0.11 g, 1.5 mmol) was added to a stirred solution of sodium ethoxide (3.0 mmol, prepared in situ from 0.069 g of sodium metal and 1 mL of ethanol) in ethanol (10 mL) at room temperature. After 5 min, ketene dithioacetal **2** (0.31 g, 1.0 mmol) was added and the reaction mixture was refluxed for 7 h (monitored by TLC). The solvent was evaporated under reduced pressure and the residue was treated with ice-cold water (20 mL). It was then extracted with chloroform (3×20 mL). The combined organic extracts were washed with water (3×20 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (7:3) as eluant to yield **15** as a yellow solid (0.61 g, 63%); R_f 0.70 (1:1 hexane–EtOAc); mp 184–185 °C; IR cm^{-1} (KBr): 1532, 1377, 1334, 1217, 1022, 767; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (br d, J=6.84 Hz, 2H, ArH), 7.60 (d, J=7.56 Hz, 2H, ArH), 7.36–7.32 (m, 2H, ArH), 7.25–7.05 (m, 10H, ArH), 4.46–4.42 (m, 2H, OCH), 4.45–4.42 (m, 2H, OCH), 1.17 (t, J=6.94 Hz, 6H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 166.5, 161.2, 161.0, 159.9, 132.2, 131.4, 130.6, 130.3, 129.8, 125.4, 124.8, 124.4, 121.0, 120.5, 113.7, 63.7, 14.1; MS *m/z* (%): 643 (M^++1, 78), 206 (100). Anal. Calcd for $C_{36}H_{26}N_4O_4S_2$: C, 67.27%; H, 4.08%; N, 8.72%. Found: C, 67.25%; H, 4.22%; N, 8.70%.

4.1.14. Synthesis of 3-cyano-4-(methylthio)-1*H*-dibenz[*b*,*f*]oxepino[4,5-*b*]pyridin-2-one (16). To a stirred suspension of NaO^{t}Bu (0.23 g, 2.4 mmol) in Bu^{t}OH (10 mL) at room temperature, cyanoacetamide (0.067 g, 0.8 mmol) was added. After 10 min, ketene dithioacetal **2** (0.25 g, 0.8 mmol) was added and the reaction mixture was refluxed for 7 h (monitored by TLC). The solvent was evaporated under reduced pressure to give the salt of pyridone **16**, which was dissolved in water (10 mL) followed by acidification with dilute HCl (5 mL, 5%). Extraction was done with chloroform (3×30 mL). The combined organic extracts were washed with water (2×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (1:1) as eluant to afford **16** as a yellow solid (0.13 g, 50%); R_f 0.5 (3:7 hexane–EtOAc); mp >280 °C decomposes; IR cm^{-1} (KBr): 2220, 1638, 1484, 1443, 1219, 747; ^1H NMR (400 MHz, DMSO-d_6): δ 7.76 (d, J=7.80 Hz, 1H, ArH), 7.62–7.56 (m, 2H, ArH), 7.45–7.40 (m, 3H, ArH), 7.33 (t, J=7.58 Hz, 1H, ArH), 7.24–7.20 (m, 1H, ArH), 2.32 (s, 3H, SMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 159.4, 133.7, 131.9, 130.7, 130.4, 126.1, 125.7, 125.1, 121.0, 120.7, 115.7, 18.7; MS *m/z* (%): 333 (M^++1, 100). Anal. Calcd for $C_{19}H_{12}N_2O_2S$: C, 68.66%; H, 3.64%; N, 8.43%. Found: C, 68.71%; H, 3.59%; N, 8.36%.

4.1.15. Synthesis of 4-(methylthio)-2-phenyldibenz[*b*,*f*]-oxepino[4,5-*b*]pyridine-3-carbonitrile (18). To a stirred solution of freshly distilled acetonitrile (0.1 mL, 1.9 mmol) in dry THF (5 mL), *n*-BuLi (1.3 mL, 1.9 mmol) was added dropwise at −78 °C under a nitrogen atmosphere. After 10 min, a solution of benzonitrile (0.19 mL, 1.9 mmol) in dry THF (5 mL) was added dropwise at the same temperature. The reagent was stirred for 30 min followed by the dropwise addition of the solution of ketene dithioacetal **2** (0.40 g, 1.28 mmol) in dry THF (10 mL) at the same temperature. Reaction mixture was warmed to room temperature

over a period of 2 h followed by refluxing for 10 h (monitored by TLC). Reaction mixture was cooled to room temperature and poured into saturated ammonium chloride solution (20 mL). Extraction was done with chloroform (3×30 mL). The combined organic extracts were washed with water (2×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluant to give **18** as white solid (0.30 g, 60%); R_f 0.5 (9:1 hexane–EtOAc); mp 214–215 °C; IR cm^{-1} (KBr): 2218, 1512; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, J=7.70, 1.58 Hz, 1H, ArH), 8.06–8.03 (m, 2H, ArH), 7.78 (dd, J=7.82, 1.46 Hz, 1H, ArH), 7.56–7.48 (m, 3H, ArH), 7.48–7.23 (m, 6H, ArH), 2.23 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 160.5, 159.7, 155.1, 153.8, 137.0, 132.3, 131.7, 131.6, 131.5, 130.8, 130.3, 129.3, 128.5, 127.7, 125.5, 125.2, 121.1, 120.5, 116.9, 108.9, 18.8; MS m/z (%): 393 (M^++1, 100), 392 (M^+, 50). Anal. Calcd for $C_{25}H_{16}N_2OS$: C, 76.51%; H, 4.11%; N, 7.14%. Found: C, 76.44%; H, 4.12%, N, 7.28%.

4.1.16. Synthesis of 4-(methylthio)-2-phenyldibenz[*b*,*f*]-oxepino[4,5-*b*]pyridine (20). A solution of acetophenone (0.15 mL, 1.28 mmol) in dry DMF (5 mL) was added dropwise to a stirred suspension of NaH (60%, 0.07 g, 1.8 mmol) in dry DMF (5 mL) at 0 °C under a nitrogen atmosphere. The anion was further stirred at the same temperature for 45 min. A solution of **2** (0.4 g, 1.28 mmol) in dry DMF (5 mL) was added dropwise at 0 °C and the reaction mixture was further stirred at room temperature for 8 h (monitored by TLC). The reaction mixture was poured into saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with water (3×20 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure to yield the adduct **19** (0.40 g, 80%), which was used directly for the cyclization step.

Anhydrous NH_4OAc (0.24 g, 3.12 mmol) was added to a solution of adduct **19** (0.39 g, 1.04 mmol) in glacial acetic acid (10 mL) and the reaction mixture was refluxed for 5 h (monitored by TLC). It was then cooled, poured into ice-cold water (40 mL), and extracted with chloroform (3×30 mL). The combined organic extracts were washed with water (3×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (9:1) as eluant to yield **20** as a white solid (0.24 g, 63%); R_f 0.13 (19:1 hexane–EtOAc); mp 189–190 °C. IR cm^{-1} (KBr): 3045, 1552, 1198, 761; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, J=7.56, 1.72 Hz, 1H, ArH), 8.14 (d, J=7.08 Hz, 2H, ArH), 7.78 (d, J=7.80 Hz, 1H, ArH), 7.59 (s, 1H, ArH), 7.51 (t, J=7.20 Hz, 2H, ArH), 7.45 (t, J=7.20 Hz, 1H, ArH), 7.42–7.37 (m, 3H, ArH), 7.32–7.24 (m, 2H, ArH), 7.21–7.17 (m, 1H, ArH), 2.54 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 160.6, 155.1, 152.3, 151.0, 138.5, 131.9, 131.6, 131.3, 130.9, 130.3, 129.4, 129.1, 128.7, 127.5, 127.2, 125.3, 124.1, 121.2, 120.2, 114.8, 16.0; MS m/z (%): 368 (M^++1, 100), 367 (M^+, 75), 352 (25), 341 (44). Anal. Calcd for $C_{24}H_{17}NOS$: C, 78.45%; H, 4.66%; N, 3.81%. Found: C, 78.54%; H, 4.64%; N, 3.77%.

4.2. General procedure for the cycloaromatization of 10,11-dihydro-11-[bis(methylthio)methylene]dibenz[*b*,*f*]-oxepin-10-one (2) with allyl, methallyl, and benzyl Grignard reagents: synthesis of benzo-(21a,c) and naphtho-(22a) fused dibenz[*b*,*f*]oxepines

A solution of ketene dithioacetal **2** (0.6 g, 2 mmol) in dry THF (20 mL) was added dropwise at 0 °C to a stirred solution of allyl/methallyl/benzyl magnesium chloride [halide (10 mmol) and magnesium turnings (0.2 g, 8 mmol)] in dry ether (30 mL) under a nitrogen atmosphere and the reaction mixture was further stirred at room temperature for 2 h (monitored by TLC). It was then poured into saturated aqueous NH_4Cl solution (30 mL) and extracted with chloroform (2×40 mL). The combined organic extracts were washed with water (2×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure to afford the crude carbinols as viscous liquids. The crude carbinols were dissolved in dry benzene (30 mL) followed by addition of $BF_3\cdot OEt_2$ (0.5 mL, 4.0 mmol) dropwise at 0 °C. The reaction mixture was then refluxed for 3–4 h (monitored by TLC). It was then cooled to room temperature, poured into saturated aqueous $NaHCO_3$ solution (20 mL), and extracted with chloroform (2×30 mL). The combined organic extracts were washed with water (2×30 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc as eluant (49:1).

4.2.1. 1-(Methylthio)tribenz[*b*,*d*,*f*]oxepine (21a). Colorless liquid (0.37 g, 63%); R_f 0.47 (49:1 hexane–EtOAc); IR cm^{-1} (neat): 2920, 1204, 746; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J=7.32, 0.96 Hz, 1H, ArH), 7.59 (dd, J=7.58, 1.46 Hz, 1H, ArH), 7.43–7.36 (m, 3H, ArH), 7.34–7.31 (m, 3H, ArH), 7.28 (dd, J=5.98, 1.58 Hz, 1H, ArH), 7.26–7.15 (m, 2H, ArH), 2.40 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 160.7, 138.2, 137.6, 135.0, 132.6, 132.3, 129.7, 129.5, 129.4, 129.3, 128.0, 126.5, 126.1, 125.3, 123.8, 120.7, 120.4, 17.4; MS m/z (%): 291 (M^++1, 86), 290 (M^+, 100), 275 (50), 244 (83). Anal. Calcd for $C_{19}H_{14}OS$: C, 78.59%; H, 4.86%. Found: C, 78.48%; H, 4.90%.

4.2.2. 3-Methyl-1-(methylthio)tribenz[*b*,*d*,*f*]oxepine (21c). Colorless liquid (0.46 g, 75%); R_f 0.57 (49:1 hexane–EtOAc); IR cm^{-1} (neat): 1438, 1203, 748; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (dd, J=7.80, 1.96 Hz, 1H, ArH), 7.57 (dd, J=7.80, 1.48 Hz, 1H, ArH), 7.33–7.27 (m, 3H, ArH), 7.26 (dd, J=6.24, 1.60 Hz, 1H, ArH), 7.20–7.12 (m, 4H, ArH), 2.44 (s, 3H, SMe), 2.38 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.66, 160.64, 137.9, 137.8, 137.4, 132.6, 132.3, 129.56, 129.49, 129.44, 129.3, 127.9, 127.3, 127.0, 125.3, 123.8, 120.6, 120.4, 21.4, 17.4; MS m/z (%): 304 (M^+, 100), 258 (70). Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91%; H, 5.30%. Found: C, 78.98%; H, 5.27%.

4.2.3. 5-(Methylthio)naphtho[2,3-*d*]dibenz[*b*,*f*]oxepine (22a). Colorless solid (0.35 g, 52%); R_f 0.3 (49:1 hexane–EtOAc); mp 167–168 °C; IR cm^{-1} (KBr): 1481, 1444, 1181, 751; ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J=8.32 Hz, 1H, ArH), 8.0 (s, 1H, ArH), 7.92 (d, J=7.80 Hz, 1H, ArH), 7.75 (d, J=7.70 Hz, 2H, ArH), 7.63

(ddd, J=7.69, 7.69, 1.53 Hz, 1H, ArH), 7.55 (ddd, J=7.45, 7.45, 0.97 Hz, 1H, ArH), 7.37–7.28 (m, 4H, ArH), 7.26–7.17 (m, 2H, ArH), 2.09 (s, 3H, SMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 161.2, 135.3, 134.6, 134.3, 134.1, 133.2, 132.7, 131.2, 129.6, 129.5, 129.4, 129.3, 128.7, 127.2, 127.2, 126.6, 125.5, 123.9, 120.4, 120.3, 19.8; MS m/z (%): 341 (M^++1, 80), 340 (M^+, 100), 294 (63). Anal. Calcd for $C_{23}H_{16}OS$: C, 81.14%; H, 4.74%. Found: C, 81.08%; H, 4.69%.

4.3. General procedure for Raney-Ni dethiomethylation of 5a, 6a, 12a, 21a, and 22a

Raney-Ni (W_2, five times by weight) was added to an ethanolic solution (10 mL) of appropriate substrates **5a**, **6a**, **12a**, **21a**, and **22a** (1.0 mmol), and the suspension was heated under reflux for 2–9 h (monitored by TLC). Reaction mixture was filtered through a sintered glass funnel and the residue was washed with hot ethanol (3×5 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel using hexane–EtOAc (49:1) as eluant.

4.3.1. 2-Phenyldibenz[*b*,*f*]oxepino[4,5-*c*]pyrazole (5b). White solid (0.232 g, 75%); R_f 0.4 (98:2 hexane–EtOAc); mp 133–134 °C; IR cm^{-1} (KBr): 3060, 2923, 1501, 1449, 1204, 760; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H, ArH), 7.89 (dd, J=7.58 Hz, 1.46, 1H, ArH), 7.74 (dd, J=8.08, 0.96 Hz, 2H, ArH), 7.43–7.37 (m, 3H, ArH), 7.31–7.14 (m, 6H, ArH), 7.10 (ddd, J=7.39, 7.39, 1.38 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 156.3, 148.4, 139.8, 130.1, 129.5, 128.7, 127.6, 127.3, 126.8, 126.1, 125.3, 123.9, 122.0, 121.7, 120.4, 119.2; MS m/z (%): 310 (M^++1, 100). Anal. Calcd for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03%. Found: C, 81.29; H, 4.50; N, 9.11%.

4.3.2. 1-Phenyldibenz[*b*,*f*]oxepino[4,5-*d*]pyrazole (6b).[1a] White solid (0.257 g, 83%); mp 174–175 °C (lit. mp 171–173; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H, ArH), 7.57 (d, J=7.08 Hz, 1H, ArH), 7.52–7.21 (m, 10H, ArH), 6.95–6.92 (m, 1H, ArH), 6.81 (d, J=7.80 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 155.9, 139.9, 137.9, 136.3, 130.2, 129.2, 128.7, 128.6, 127.9, 127.1, 125.5, 125.6, 125.1, 122.9, 122.7, 122.3, 121.5, 120.3.

4.3.3. 1,3-Dihydro-1-oxo-furo[3,4-*d*]dibenz[*b*,*f*]oxepine (12b). White solid (0.228 g, 91%); R_f 0.20 (19:1 hexane–EtOAc); mp 181–182 °C.; IR cm^{-1} (KBr): 1753, 1443, 1221; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, J=8.04, 1.48 Hz, 1H, ArH), 7.55–7.7.51 (m, 1H, ArH), 7.43 (ddd, J=7.70, 7.70, 1.38 Hz, 1H, ArH), 7.34 (d, J=8.04 Hz, 1H, ArH), 7.28–7.22 (m, 4H, ArH), 5.25 (s, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 158.1, 157.0, 154.9, 133.7, 131.4, 127.9, 126.0, 125.63, 125.60, 125.2, 124.1, 123.9, 122.5, 121.4, 68.8; MS m/z (%): 251 (M^++1, 100), 250 (M^+, 63). Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.79%; H, 4.03%. Found: C, 76.71%; H, 4.05%.

4.3.4. Tribenz[*b*,*d*,*f*]oxepine (21b).[21] White solid (0.18 g, 75%); R_f 0.5 (49:1 hexane–EtOAc); mp 113–114 °C (lit. mp 115–116 °C); IR cm^{-1} (KBr): 3060, 1482, 1427, 1207, 733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, J=5.86, 3.42 Hz, 2H, ArH), 7.56 (dd, J=7.22, 1.24 Hz, 2H, ArH), 7.48 (dd, J=5.86, 3.42 Hz, 2H, ArH), 7.36–7.29 (m, 4H, ArH), 7.24 (ddd, J=8.72, 6.60, 2.20 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 136.5, 132.8, 129.6, 129.3, 128.0, 125.5, 120.8; MS m/z (%): 245 (M^++1, 94), 244 (M^+, 100). Anal. Calcd for $C_{18}H_{12}O$: C, 88.50%; H, 4.95%. Found: C, 88.62%; H, 5.02%.

4.3.5. Naphtho[2,3-*d*]dibenz[*b*,*f*]oxepine (22b). White solid (0.23 g, 78%); R_f 0.4 (99:1 hexane–EtOAc); mp 139–140 °C; IR cm^{-1} (KBr): 3052, 1231, 759; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 2H, ArH), 7.94 (dd, J=6.22, 3.30 Hz, 2H, ArH), 7.72 (dd, J=7.56, 0.96 Hz, 2H, ArH), 7.53 (dd, J=6.36, 3.16 Hz, 2H, ArH), 7.38–7.33 (m, 4H, ArH), 7.30–7.26 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 134.7, 132.9, 132.8, 130.0, 129.3, 128.4, 127.8, 126.5, 125.6, 120.8; MS m/z (%): 295 (M^++1, 92), 294 (M^+, 100). Anal. Calcd for $C_{22}H_{14}O$: C, 89.77%; H, 4.79%. Found: C, 89.80%; H, 4.81%.

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