Access to new sulfolene derivatives via formylation of thiolan-3-one

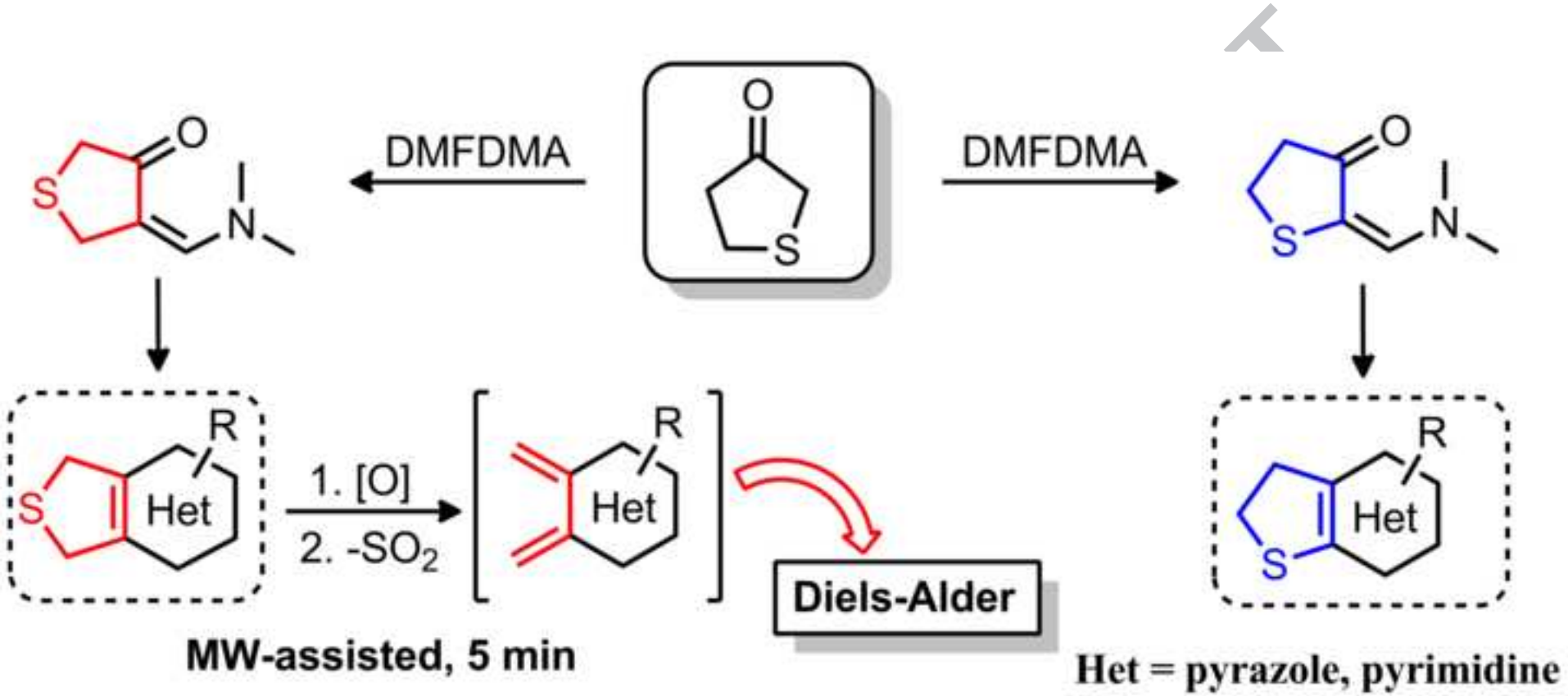
Olga Gordivska, Dmytro Listunov, Kirill Popov, Tatyana Volovnenko, Yulian Volovenko

PII: S0040-4039(13)00886-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.05.107
Reference: TETL 43007

To appear in: *Tetrahedron Letters*

Received Date: 6 December 2012
Revised Date: 11 May 2013
Accepted Date: 24 May 2013

Please cite this article as: Gordivska, O., Listunov, D., Popov, K., Volovnenko, T., Volovenko, Y., Access to new sulfolene derivatives via formylation of thiolan-3-one, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.05.107


DMFDMA
DMFDMA
1. [O]
2. -SO2
Het
R
Diels-Alder
MW-assisted, 5 min
Het = pyrazole, pyrimidine

Access to new sulfolene derivatives via formylation of thiolan-3-one

Olga Gordivska[a,b], Dmytro Listunov[a], Kirill Popov[a,b]*, Tatyana Volovnenko[a], Yulian Volovenko[a]

[a] *Department of Ogranic Chemistry, Kiev National University, 64 Volodymirska str., Kiev 01033, Ukraine*
[b] *Centre for Analysis and Synthesis, Department of Chemistry, Lund University, Getingevägen 60, 221 00 Lund, Sweden*

*Corresponding Author:
Dr. Kirill Popov
Kiev National University, Ukraine
Department of Ogranic Chemistry
Hospitalny st. 1A apt. 54
01133 Kiev
Ukraine
Phone: +380679436067
Fax: not available
E-mail: kirillpopov@bk.ru, Kirill.Popov@chem.lu.se

Access to new sulfolene derivatives via formylation of thiolan-3-one

Olga Gordivska, Dmytro Listunov, Kirill Popov*, Tatyana Volovnenko, Yulian Volovenko

*Corresponding Author: Tel. +380679436067. E-mail address: kirillpopov@bk.ru (Popov K.)

Abstract: New tetrahydrothiophene derivatives, which are demonstrated to be reactive towards various nucleophiles and provide access to [*b*]- and [*c*]-fused sulfolenes are described. Application of heterocyclic sulfides as *o*-quinodimethane precursors is documented.

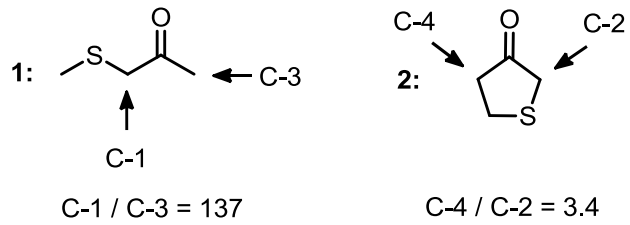
Keywords: *o*-Quinodimethanes; Cheletropic extrusion of sulfur dioxide; Thiolanes; Formylation; Regioselectivity

In our previous work[1-3] we utilized the formylation of α-methyleneketones as a robust transformation providing access to a variety of heterocyclic derivatives. Our current study was influenced by a question: would the formylation of thiolan-3-one (**2)** be consistent with a known anomaly in its keto-enol tautomerism?

More specifically: while measurement of the kinetic acidity in 1-(methylthio)propan-2-one (**1**) predictably demonstrates 137-fold faster C-1 proton-deuterium exchange compared to C-3, thiolan-3-one (**2**) has the reverse kinetic acidity: the C-4 protons exchange 3.375-times faster than the C-2 hydrogen atoms (Scheme 1).[4]

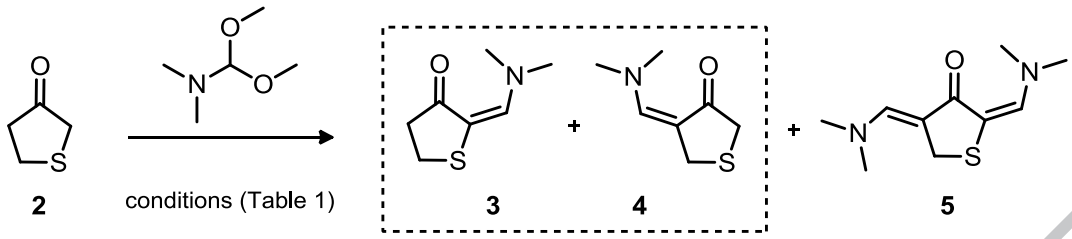
The reason for such an anomaly is the remarkable steric hindrance between the hydrogen atoms at C-4 and C-5 in thiolanone **2**. This strain is released upon enolisation at C-4, rendering this process highly preferable.

Thus, the goal of current study was to establish the regioselectivity of the formylation of thiolan-3-one and to test the reactivity of the resulting derivatives.



Scheme 1. Kinetic C-H acidity in **1** and **2** estimated by proton-deuterium exchange.

We chose *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) as the formylating agent. The reaction of thiolan-3-one (**2)** with DMFDMA was found to afford mixtures of isomeric dimethylaminovinyl ketones **3** and **4** (Scheme 2).[5] Correlations between the product ratios of **3:4** with the reaction conditions were observed (Table 1). Treatment of **2** with phosphorus oxychloride under Vilsmeier conditions resulted in no reaction.



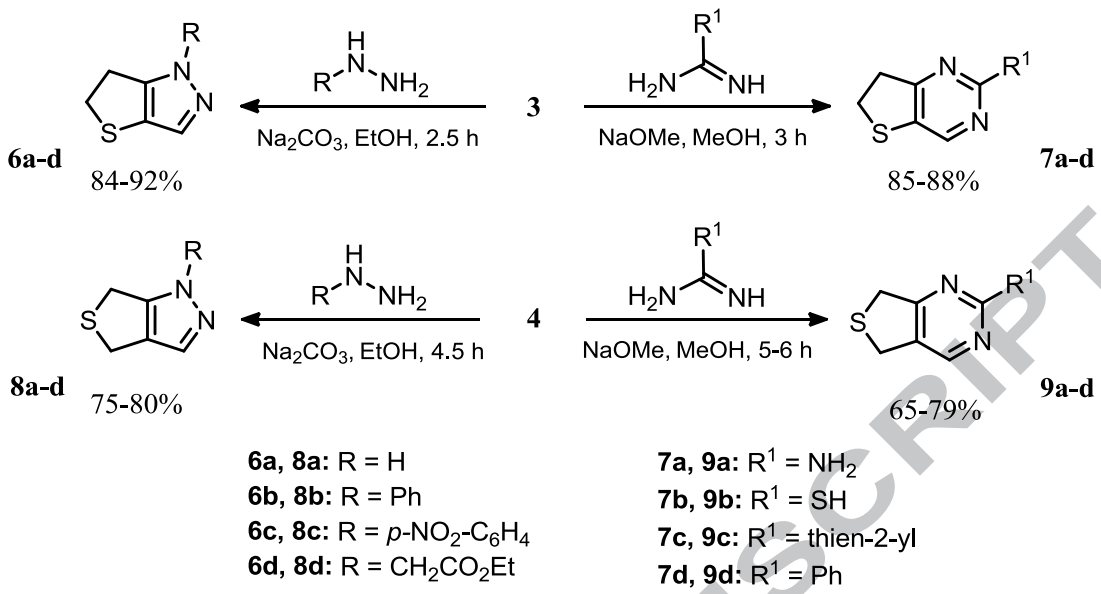
Scheme 2. Reaction of **2** with DMFDMA.

Reaction conditions	Product distribution **3 : 4 : 5**	Overall yield
DMFDMA (1.2 eq.), PhH, 80 ˚C, 4 h	~35:65:0	92%
DMFDMA (1.2 eq.), $PhCH_3$, 110 ˚C, 4 h	~25:75:0	98%
DMFDMA (1.2 eq.), $PhCH_3$, 110 ˚C, 5-6 h	~20:65:15	~99%

Table 1. The results of the reaction of **2** with DMFDMA, depending on the conditions.

Formylation was found to occur in full compliance with the enolisation studies. Isomeric dimethylaminovinyl ketones **3** and **4** were formed in 1:2 to 1:3 ratios with respect to the temperature. Upon extended heating (over 5 h) with excess DMFDMA, a new mixture of components was formed. This was established to be 2,4-bis[(dimethylamino)methylene]dihydrothiophen-3(2*H*)-one (**5)**, which was previously synthesized by a different route.[6]

Flash-chromatographic separation allowed the isolation of pure novel compounds **3** and **4**. We found that dimethylaminovinyl ketones **3** and **4** were highly reactive towards 1,2- and 1,3-bis-nucleophiles. Treatment of **3** and **4** with hydrazines, amidines, guanidine and thiourea furnished isomeric fused pyrazoles and pyrimidines **6-9** (Scheme 3).[7-8]



6a, 8a: R = H
6b, 8b: R = Ph
6c, 8c: R = *p*-NO_2-C_6H_4
6d, 8d: R = CH_2CO_2Et

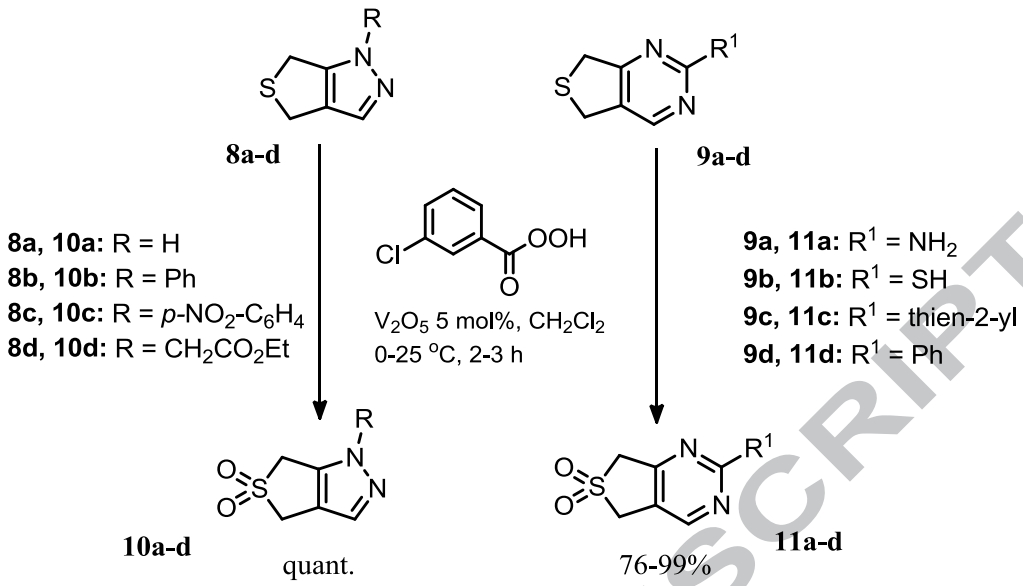
7a, 9a: R^1 = NH_2
7b, 9b: R^1 = SH
7c, 9c: R^1 = thien-2-yl
7d, 9d: R^1 = Ph

Scheme 3. Nucleophilic reactions of **3** and **4**.

Dimethylaminovinyl ketone **3** was found to be slightly more reactive than **4**. The reactions of **3** with nucleophiles proceeded faster and gave higher yields (Scheme 3). Presumably, this was the result of sulfur atom influence on the electronic properties of the masked carbonyl group.

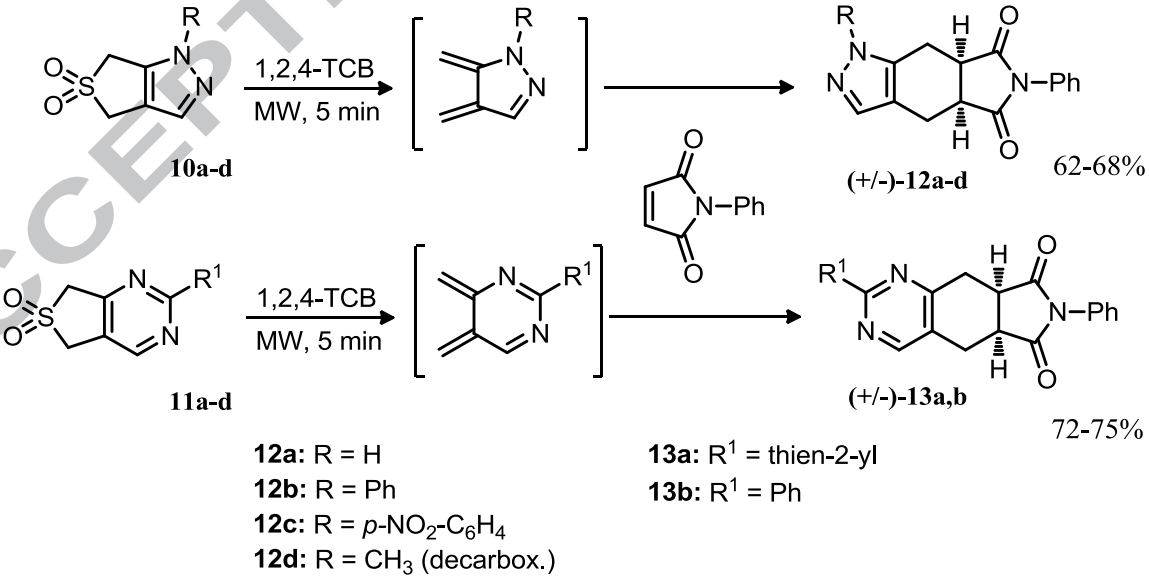
It is noteworthy that the reactions with arylhydrazines were higher yielding compared to those with alkylhydrazines. Among the 1,3-bis-nucleophiles, guanidine and benzamidine were found to react more efficiently, while thiourea afforded the corresponding pyrimidine in only moderate yield, and urea gave no reaction.

We next investigated the possibility of employing tetrahydrothiophenes **8** and **9** as precursors for the synthesis of *o*-quinodimethanes (*o*-QDMs).[9-12] Oxidation of **8** and **9** using a modified literature procedure[13] afforded the corresponding sulfolenes **10** and **11** in quantitative yields (Scheme 4).[14] We observed a dramatic decrease in the conversion time (10 h to 2-3 h) upon the addition of vanadium dioxide as the catalyst (5 mol%).



Scheme 4. The synthesis of pyrazolo- and pyrimido-sulfolenes **10a-d** and **11a-d.**

When heated to 215 ˚C in 1,2,4-trichlorobenzene (1,2,4-TCB) under microwave irradiation for 5 minutes, compounds **10** and **11** underwent cheletropic extrusion of sulfur dioxide[15] yielding *o*-quinodimethanes. To the best of our knowledge, such a route to *o*-QDMs has not been reported. If a dienophile is present in the reaction mixture a very rapid Diels-Alder reaction occurs. Compounds **12** and **13** were isolated after flash-chromatographic purification (Scheme 5).[16] When ethyl ester **10d** was subjected to these reaction conditions, decarboxylation occurred yielding *N*-methyl adduct **12d**.



Scheme 5. *o*-QDM generation and subsequent Diels-Alder reactions.

In conclusion, we have described new dimethylaminovinyl ketones **3** and **4,** which are demonstrated to be reactive towards various nucleophiles and provide access to [*b*]- and [*c*]-fused sulfolenes. Heterocyclic sulfides **8** and **9** are useful as *o*-quinodimethane precursors.

References

1. Popov, K. S.; Volovnenko, T.A.; Volovenko, Yu. M. *Tetrahedron Lett.* **2009**, *60*, 1171.

2. Popov, K. S.; Volovnenko, T.A.; Volovenko, Yu. M. *Beilstein J. Org. Chem.* **2009**, *5*, 42.

3. Popov, K. S.; Volovnenko, T.A.; Volovenko, Yu. M. *J. Heterocycl. Chem.* **2013**, in press.

4. Guth, Ja. J.; Gross, R. L.; Carson, F. W. *J. Org. Chem*. **1982**, *47*, 2666.

5. **Formylation of thiolan-3-one.** To a solution of **2** (0.1 mol, 10.2 g) in benzene (100 ml) was added DMFDMA (0.12 mol, 14.28 g). The mixture was refluxed for 4 h. After evaporation of the solvent, hexane was added to the crude material. The resulting precipitate was filtered off, washed with hexane and air-dried. The crude product was purified by column chromatography (EtOAc/hexanes 1:9) to give **3** and **4** as individual pure compounds, in 90% combined yield.

2-[(Dimethylamino)methylene]dihydrothiophen-3(2H)-one (3): R_f 0.54; m.p. 231-233 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 2.62 (t, J = 14Hz, 2H), 3.02 (t, J = 14Hz, 2H), 3.12 (s, 6H), 7.34 (s, 1H); MS: *m/z* 158 $(M+H)^+$; Analysis calculated for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91; S, 20.39. Found: C, 53.52; H, 7.07; N, 8.96; S, 20.43.

4-[(Dimethylamino)methylene]dihydrothiophen-3(2H)-one (4): R_f 0.32; m.p. 122-124 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 3.14 (s, 6H), 3.17 (s, 2H), 3.97 (s, 2H), 7.09 (s, 1H); MS: *m/z* 158 $(M+H)^+$; Analysis calculated for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91; S, 20,39. Found: C, 53.42; H, 7.07; N, 8.92; S, 20.34.

6. Zhang, W.; Henry, Y. *Synlett* **2001**, *7*, 1129.

7. **General procedure for the synthesis of thieno[3,2-*c*]pyrazoles 6a-d and thieno[3,4-*c*]pyrazoles 8a-d.**
The mixture of **3** or **4** (0.01 mol, 1.57 g), substituted hydrazine (0.015 mol) and 30 ml *i*-PrOH was refluxed for 2.5 h. After cooling down to r.t. the resulting precipitate was filtered off, washed with ethanol and air-dried to afford pure product.

5,6-dihydro-1H-thieno[3,2-*c*]pyrazole (**6a):** Yield 84%; m.p. >250 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 3.58 (t, J = 14Hz, 2H), 4.02 (t, J = 14Hz, 2H), 7.92 (s, 1H), 11.54 (br. s, 1H); MS: *m/z* 127 $(M+H)^+$; Analysis calculated for $C_5H_6N_2S$: C, 47.59; H, 4.79; N, 22.20; S, 25.41. Found: C, 47.66; H, 4.84; N, 22.27; S, 25.45.

4,6-dihydro-1H-thieno[3,4-c]pyrazole (8a): Yield 80%; m.p. >250 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 3.67 (s, 2H), 3.82 (s, 2H), 7.37 (s, 1H), 12.11 (br. s, 1H); MS: *m/z* 127 $(M+H)^+$; Analysis calculated for $C_5H_6N_2S$: C, 47.59; H, 4.79; N, 22.20; S, 25.41. Found: C, 48.05; H, 4.84; N, 22.27; S, 25.45.

8. **General procedure for the synthesis of thieno[3,2-*d*]pyrimidines 7a-d and thieno[3,4-*d*]pyrimidine 9a-d.**
The mixture of **3** or **4** (0.01 mol, 1.57 g), amidine or thiourea (0.15 mol), sodium bicarbonate (0.15 mol) in 20 ml of DMF was heated to 100 ˚C and stirred for 3 h. The mixture was cooled down to r.t., resulting precipitate was filtered, washed with alcohol and air-dried.

6,7-dihydrothieno[3,2-*d*]pyrimidin-2-amine (7a) : Yield 86%; m.p. 122-123 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 3.14 (t, *J* = 7.2Hz, 2H), 3.36 (t, *J* = 7.2Hz, 2H), 7.03 (br. s, 2H), 8.11 (s, 1H); MS: *m/z* 154 $(M+H)^+$; Analysis calculated for $C_6H_7N_3S$: C, 47.04; H, 4.61; N, 27.43; S, 20.93. Found: C, 47.11; H, 4.64; N, 27.48; S, 20.97.

5,7-dihydrothieno[3,4-*d*]pyrimidin-2-amine (9a): Yield 65%; m.p. 115-117 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 3.54 (s, 2H), 3.58 (s, 2H), 6.51 (br. s, 1H), 8.11 (s, 1H); MS: *m/z* 154 $(M+H)^+$; Analysis calculated for $C_6H_7N_3S$: C, 47.04; H, 4.61; N, 27.43; S, 20.93. Found: C, 47.11; H, 4.64; N, 27.48; S, 20.97.

9. Toméa, A. C.; Cavaleiroa, J. A. S.; Storr, R. C. *Tetrahedron* **1996**, *52*, 1735.

10. Ko, C.-W.; Chou, T.-s. *J. Org. Chem.* **1998**, *63*, 4645.

11. Exon C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739.

12. Connolly, T. J.; Durst, T. *Tetrahedron* **1997**, *53*, 15969.

13. Altenbacha, R. J.; Kalvodab, L.; Carrolla, W. A. *Synth. Commun*. **2004**, *34*, 567.

14. **General procedure for the oxidation of 8a-d and 9a-d to 10a-d and 11a-d respectively.**
To the solution of **8a-d** or **9a-d** (0.01 mol) in CH_2Cl_2 (50 mL) were added V_2O_5 (5 mol%) and *m*-CPBA (1.5 mol) at 0 ˚C, and the mixture was stirred for 2 h with gradient temperature increase to 25 ˚C. *m*-CBA was collected by filtration. The organic layer was washed with water, sodium bicarbonate and brine. After drying over magnesium sulfate the solvent was evaporated, residue was air-dried.

4,6-dihydro-1H-thieno[3,4-*c*]pyrazol-5,5-dioxide (10a): Yield 98%; m.p. >250 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 4.56 (s, 2H), 4.71 (s, 2H), 8.08 (s, 1H), 13.02 (br. s, 1H); MS: *m/z* 159 $(M+H)^+$; Analysis calculated for $C_5H_6N_2O_2S$: C, 37.97; H, 3.82; N, 17.71; S, 20.27. Found: C, 38.04; H, 3.83; N, 17.74; S, 20.31.

5,7-dihydrothieno[3,4-*d*]pyrimidin-2-amine-6,6-dioxide (11a): Yield 91%; m.p. 138-139 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 4.61 (s, 2H), 4.67 (s, 2H), 7.19 (br. s, 1H), 8.52 (s, 1H); MS: *m/z* 186 $(M+H)^+$; Analysis calculated for $C_6H_7N_3O_2S$: C, 38.91; H, 3.81; N, 22.69; S, 17.31. Found: C, 38.96; H, 3.83; N, 22.72; S, 17.34.

15. Fernandez , T.; Sordo, J. A.; Monnat, F.; Deguin, B; Vogel, P. *J. Am. Chem. Soc.* **1998**, *120*, 13276.

16. **General procedure for the *o*-QDMs formation and subsequent Diels-Alder trapping to form 12a-d and 13a,b.**

The mixture of **10a-d** or **11a-d** (1 mmol) and N-phenylmaleimide (1.1 mmol) in 1,2,4-trichlorobenzene (5mL) in a sealed vial was subjected to MW irradiation, such that the solvent boiled vigorously (220 ˚C) for 5 min. Reaction mixture was cooled down to r.t. and diluted with ethanol. Resulting precipitate was filtered off and subjected to flash purification (EtOAc : Hexanes, 2:1) to afford pure Diels-Alder adducts.

6-Phenyl-4,4a,7a,8-tetrahydropyrrolo[3,4-*f*]indazole-5,7(1*H*,6*H*)-dione (12a): Yield 62%; m.p. 189-190 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 2.68-2.71 (m, 2H), 3.04-3.14 (m, 4H), 7.19 (m, 1H), 7.28 (s, 1H), 7.44-7.48 (m, 4H), 10.31 (br. s, 1H); MS: *m/z* 268 $(M+H)^+$; Analysis calculated for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.45; H, 4.91; N, 15.74.

7-Phenyl-2-(thiophen-2-yl)-5,5a,8a,9-tetrahydro-7*H*-pyrrolo[3,4-*g*]quinazoline-6,8-dione (13a): Yield 72%; m.p. 231-232 ˚C; ^{1}H-NMR (DMSO-d_6), δ: 2.76-2.79 (m, 2H), 3.01-3.11 (m, 4H), 7.16-7.22 (m, 2H), 7.45-7.51 (m, 4H), 7.69 (d, J = 6.8Hz, 1H), 7.82 (d, J = 6.8Hz, 1H), 8.79 (s, 1H); MS: *m/z* 362 $(M+H)^+$; Analysis calculated for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.63; S, 8.87. Found: C, 66.49; H, 4.19; N, 11.65; S, 8.88.