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A four-step domino Knoevenagel–hetero-Diels–Alder reaction

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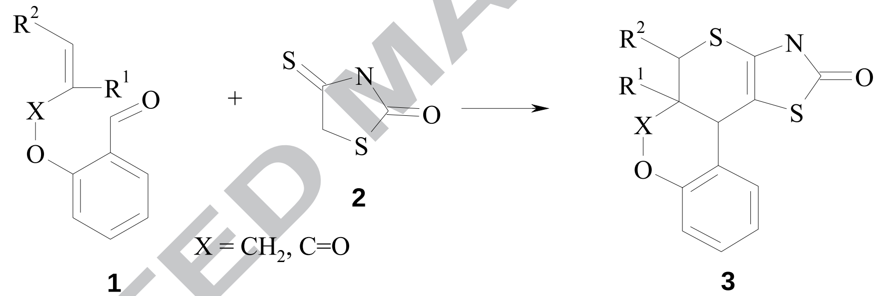
Abstract

A new, catalyst-free, domino Knoevenagel–hetero-Diels–Alder elimination oxidation reaction is reported. 5-Aryl-2*H,6H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-ones are formed in moderate to good yields via reaction of 2-(3-aryl-3-chloro-2-propenyloxy)benzaldehydes with 4-thioxo-1,3-thiazolidin-2-one.

Keywords:
Domino reactions
Domino Knoevenagel–hetero-Diels–Alder reaction
4-Thioxo-1,3-thiazolidin-2-one
Thiazolidinone derivatives
2-Allyloxybenzaldehyde

Due to the importance of ecological considerations in modern chemistry, domino reactions have become more and more popular. This type of reaction allows complex structures to be obtained with high efficiency and stereoselectivity. At the same time, the amount of waste produced is decreased significantly. Domino reactions have been studied in detail by Tietze. The domino Knoevenagel–hetero-Diels–Alder reactions of aromatic and aliphatic aldehydes which contain an alkene moiety with different 1,3-dicarbonyl compounds have been reported previously.[1–3]

Earlier we reported[4] the domino Knoevenagel–hetero-Diels–Alder reactions of unsaturated aldehydes **1** with 4-thioxo-1,3-thiazolidin-2-one (**2**) (Scheme 1). The reaction is controlled by the interaction of the HOMO of the diene and the LUMO of the dienophile (normal electron demand), so the presence of electron-donating groups for activating the alkene moiety is not necessary, as is the case in reactions with Meldrum's acid or isoxazolones.[5,6]

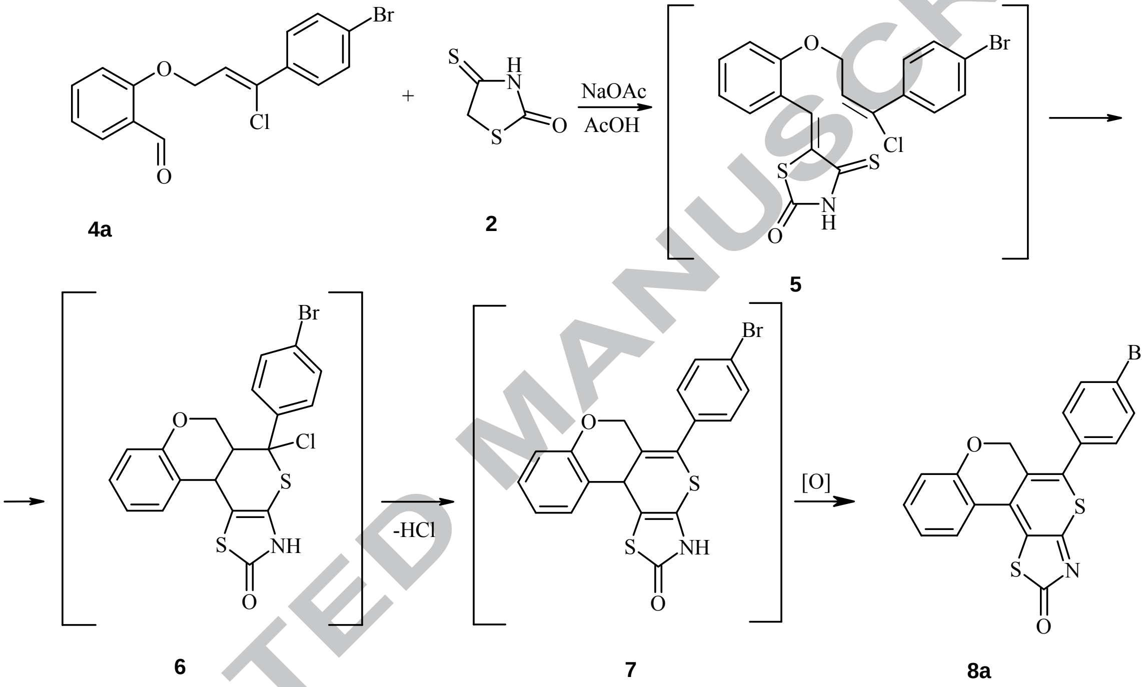


1 **2** **3**

Scheme 1.

As non-activated alkynes display lower reactivity in Diels-Alder reactions than the corresponding alkenes, there are quite a few examples in the literature of reactions with triple bonds, but which are mainly restricted to the reaction of 2-(2-propynyloxy)benzaldehydes with 2-(1,3-benzothiazol-2-yl)acetonitrile, barbituric acids, 4-hydroxycoumarin and indolin-2-thiones.[7–9] For this reason, we previously investigated[10] the reactions between 4-thioxo-1,3-thiazolidin-2-one (**2**) and 2-(2-propynyloxy)benzaldehydes. It was discovered that the classical cyclodiene product of the domino Knoevenagel–hetero-Diels–Alder reaction underwent oxidation under the reaction conditions.

To expand our investigation we decided to test salicylaldehyde with a β-chloroallyl substituent under the same reaction conditions. As the carbonyl compound for the first step we chose 2-[3-(4-bromophenyl)-3-chloro-2-propenyloxy]benzaldehyde (**4a**), the chlorine atom of which would undergo elimination to afford the same cyclodiene compound as mentioned before. As in the case of aldehydes containing an alkyne moiety, the reaction proceeded smoothly in refluxing acetic acid in the presence of sodium acetate (Scheme 2).[11] No catalyst was used for activation of the alkene moiety.

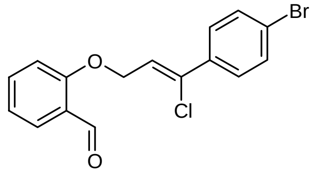
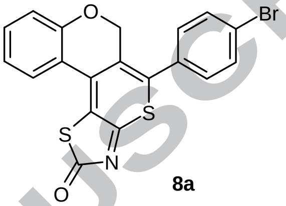
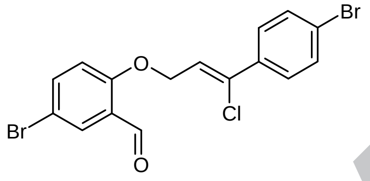
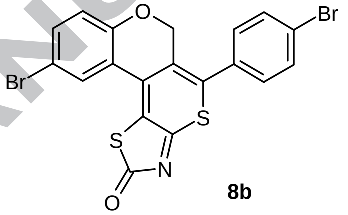
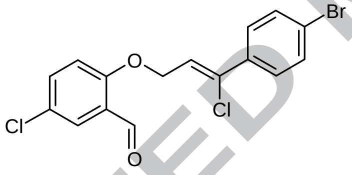
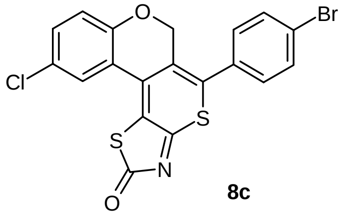
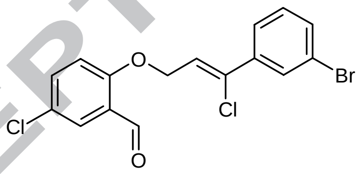
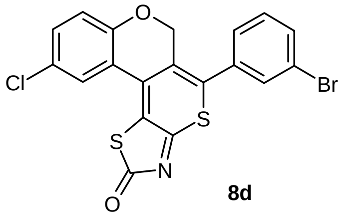
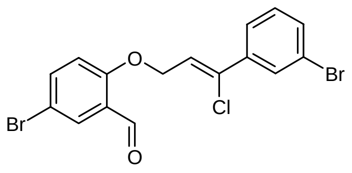
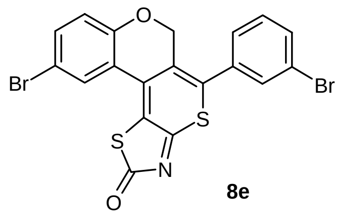


Scheme 2.

The first step of the reaction sequence involved the Knoevenagel condensation to form the heterodiene C=C–C=S system. Then, without changing the conditions, intermediate **5** underwent the hetero-Diels–Alder cyclization to give intermediate **6**. An investigation of the NMR and mass spectra showed that the product of the domino Knoevenagel–hetero-Diels-Alder reaction **6** eliminated HCl as expected. The cyclodiene ring formed after elimination of HCl underwent oxidation to give 5-(4-bromophenyl)-2*H,*6*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one (**8a**).[12] However, analysis of the bond lengths taken from X-ray data led us to conclude that product **8a** does not exist as an alternative betaine structure.[10] A conjugated π-electron system was formed as shown in Scheme 2.

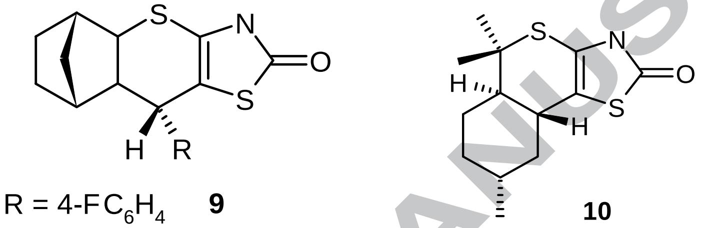
In further studies, we used different 2-[(3-chloro-3-phenylprop-2-en-1-yl)oxy]benzaldehydes in reactions with 4-thioxo-1,3-thiazolidin-2-one (**2**) under the same conditions. The reactions were similarly effective giving the products **8b**–**e** (Table 1).[12,13]

Table 1

Entry	Alkene	Product	Yield (%)
1	 **4a**	 **8a**	56
2	 **4b**	 **8b**	65
3	 **4c**	 **8c**	60
4	 **4d**	 **8d**	45
5	 **4e**	 **8e**	39

Single crystal X-ray structure determination was carried out on compound **8a** (Figure 1).[14] The crystal structure consists of three independent molecules with very similar geometry. The O2-C13-C5-C4-C19-C14 ring adopts an intermediate conformation between that of a half-chair and a screw-boat with the following

Cremer and Pople puckering parameters: Q = 0.422(3), 0.487(3) and 0.471(3) Å, = 68.5(4), 71.6(4) and 70.3(4)°, = 37.9(4), 25.6(4) and 34.5(4)° for the three independent molecules, respectively. Consequently, the molecules were not planar, the dihedral angles between the planes of the phenyl (C14-C19) ring and condensed thiopyrano-thiazolone ring were 18.0, 27.6 and 26.5° for the three independent molecules, respectively. The geometrical parameters of the condensed thiopyrano-thiazolone ring were different to those of previously studied related compounds **9**[15] and **10**[4] (Figure 2) due to the presence of additional double bonds in the studied compound.



R = 4-FC_6H_4 **9**

10

Figure 2.

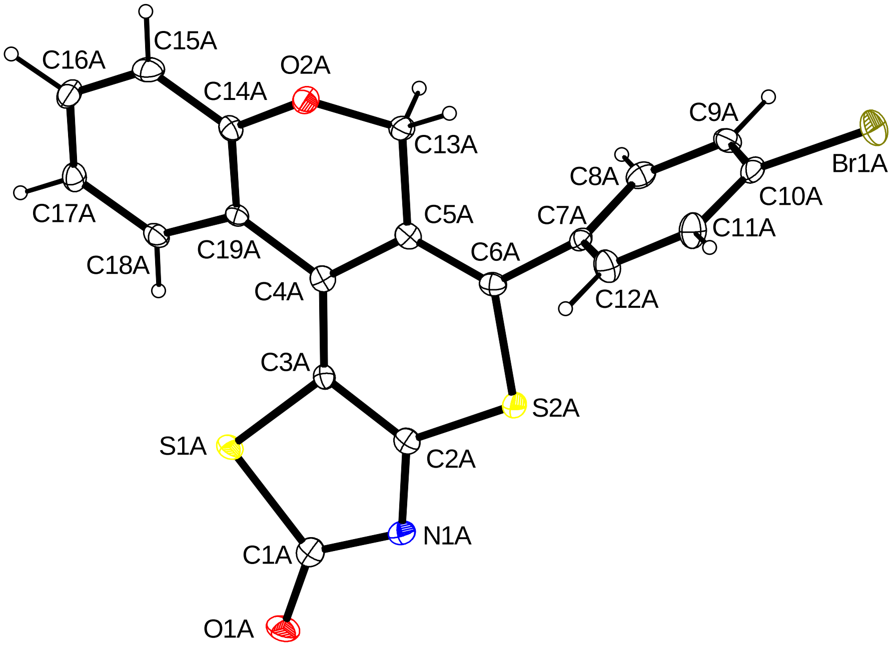


Figure 1. The view of one of the three independent molecules of **8a** along with the numbering scheme. Thermal ellipsoids are shown at the 50% probability level.[16]

In summary, we have developed an efficient method for the construction of 5-aryl-2*H*,6*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-ones using a four-step, domino Knoevenagel–hetero-Diels-Alder elimination oxidation approach using 2-[(3-chloro-3-phenylprop-2-en-1-yl)oxy]benzaldehydes and 4-thioxo-1,3-thiazolidine-2-one (**2**). The starting unsaturated aldehydes **4a**–**e** were prepared via alkylation of commercially available salicylaldehydes with the corresponding β-chloroallyl chlorides.

Acknowledgement

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10. Bryhas, A. O.; Horak, Y. I.; Ostapiuk, Y. V.; Obushak, M. D.; Matiychuk V. S. *Tetrahedron Lett.* **2011**, *52*, 2324–2326.
11. *Typical procedure for the domino-Knoevenagel-hetero-Diels-Alder elimination oxidation reaction*: ice-cold AcOH (20 ml) was added to a mixture of 4-thioxo-1,3-thiazolidin-2-one (**2**) (0.3 g, 2.2 mmol), 2-{[3-(4-bromophenyl)-3-chloroprop-2-en-1-yl]oxy}benzaldehyde (**4a**) (0.8 g, 2.2 mmol) and NaOAc (0.04 g, 0.5 mmol). The mixture was heated at reflux for 5 h. The precipitate formed after cooling was filtered, washed with H_2O and purified by recrystallization from EtOH/DMF to give light-brown crystals of 5-(4-bromophenyl)-2*H,*6*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one (**8a**).
12. *5-(4-Bromophenyl)-2H,6H-chromeno[4',3':4,5]thiopyrano[2,3-d][1,3]thiazol-2-one* (**8a**): Yield 56%, mp 297–298 °C; ^{1}H NMR (400 MHz, CF_3COOH): δ = 4.98 (s, 2H, CH_2), 7.17 (d, J = 8.3 Hz, 1H, C_6H_4), 7.35 (t, J = 7.3 Hz, 1H, C_6H_4), 7.57–7.60 (m, 3H, C_6H_4), 7.83 (d, J = 8.3 Hz, 2H, C_6H_4), 8.13 (d, J = 7.8 Hz, 1H, C_6H_4); ^{13}C NMR (100 MHz, CF_3COOH): δ = 66.2, 119.3, 120.4, 124.8, 125.4, 128.5, 128.9, 129.4, 130.7 (2C), 132.7, 133.8 (2C), 139.3, 147.5, 150.9, 159.7, 160.8, 174.7; MS (*m/z*): 428 (M^++1, ^{79}Br), 430 (M^++1, ^{81}Br). Anal. Calcd for $C_{19}H_{10}BrNO_2S_2$: C, 53.28; H, 2.35; N, 3.27. Found: C, 53.45; H, 2.41; N, 3.16.
13. *10-Bromo-5-(4-bromophenyl)-2H,6H-chromeno[4',3':4,5]thiopyrano[2,3-d][1,3]thiazol-2-one* (**8b**): Yield 65%, mp 288–289 °C; ^{1}H NMR (400 MHz, CF_3COOH): δ = 5.01 (s, 2H, CH_2), 7.16 (d, J = 8.8 Hz, 1H, C_6H_3), 7.57 (d, J =

7.8 Hz, 2H, C_6H_4), 7.74 (d, *J* = 8.8 Hz, 1H, C_6H_3), 7.84 (d, *J* = 8.3 Hz, 2H, C_6H_4), 8.21 (s, 1H, C_6H_3); ^{13}C NMR (100 MHz, CF_3COOH): δ = 66.2, 120.9, 121.7, 125.1, 125.8, 129.2, 129.3, 130.5, 130.6 (2C), 132.4, 133.9 (2C), 141.6, 145.8, 151.3, 157.7, 159.6, 170.0; MS (*m/z*): 506 (M^++1, ^{79}Br, ^{79}Br), 508 (M^++1, ^{79}Br, ^{81}Br), 510 (M^++1, ^{81}Br, ^{81}Br). Anal. Calcd for $C_{19}H_9Br_2NO_2S_2$: C, 44.99; H, 1.79; N, 2.76. Found: C, 44.71; H, 1.90; N, 2.62.

14. Crystallographic data for **8a**: Empirical formula: $C_{19}H_{10}BrNO_2S_2$, formula weight: 428.31 g/mol, orange blocks, crystal system: triclinic, space group: *P*-1 (#2), a = 13.312(4), b = 13.461(4), c = 14.363(4) Å, α = 73.91(3), β = 79.29(3), γ = 84.26(3)° , V = 2426.6(12) Å^3, T = 100(2) K, Z = 6, D_{calc} = 1.76 g/cm^3, F(000) = 1284, diffractometer: Oxford Diffraction Xcalibur CCD, residuals: $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$: 0.0348, 0.0770.

   Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 863094. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1233 336033 or e-mail deposit@ccdc.cam.ac.uk).

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16. Diamond – Crystal and Molecular Structure Visualization Crystal Impact – Dr. H. Putz & Dr. K. Brandenburg GbR, Kreuzherrenstr. 102, 53227 Bonn, Germany http://www.crystalimpact.com/diamond

Graphical abstract

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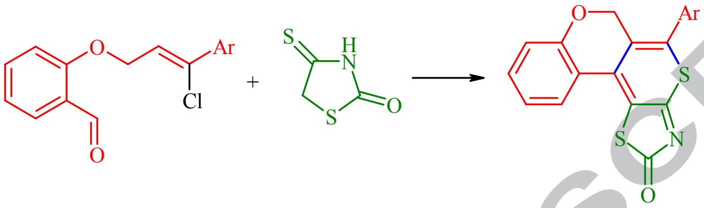
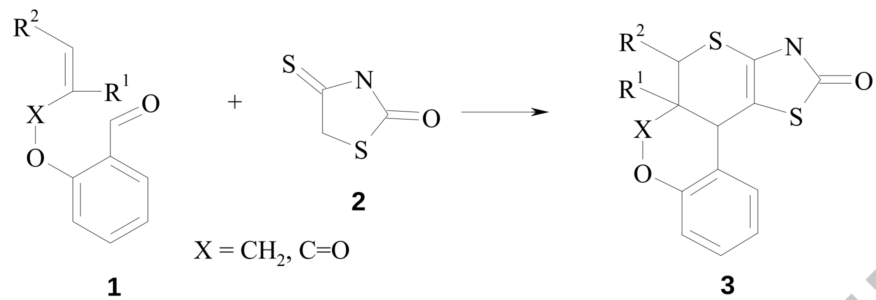
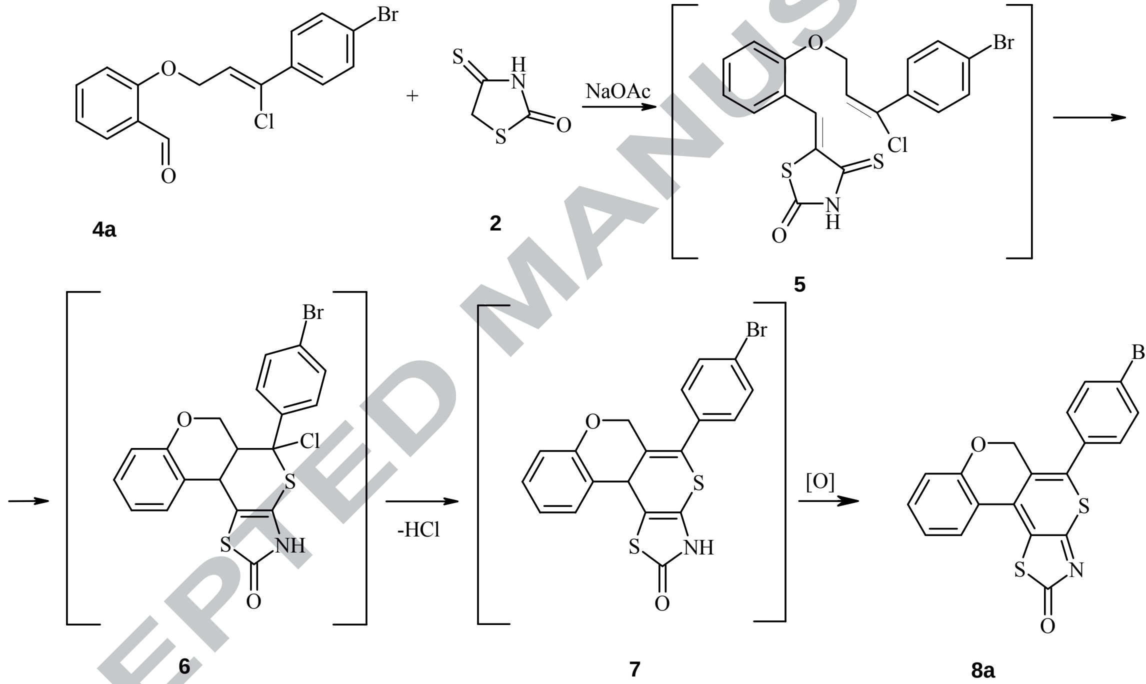




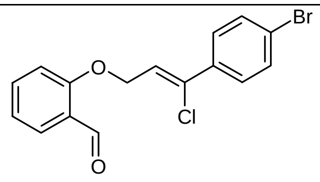
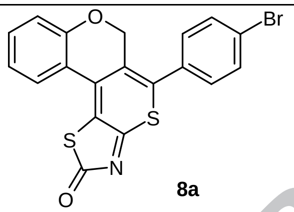
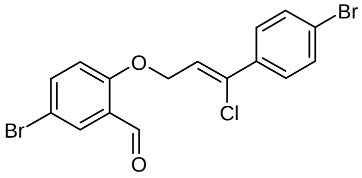
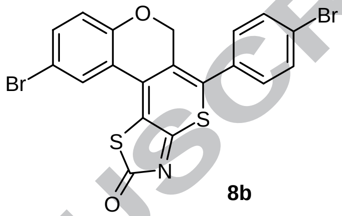
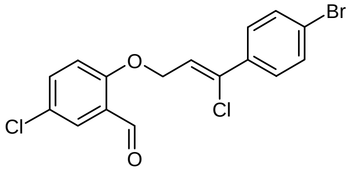
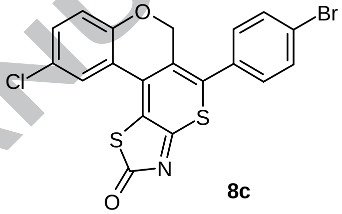
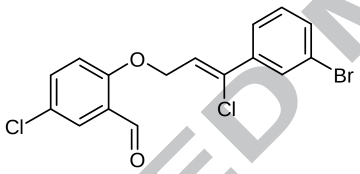
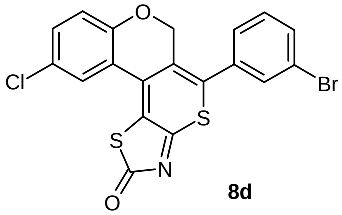
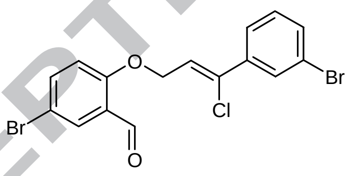
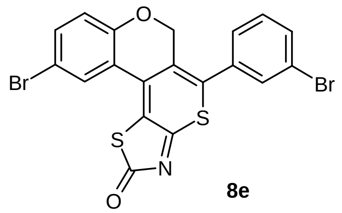
Scheme 1. Domino Knoevenagel–hetero-Diels–Alder reaction

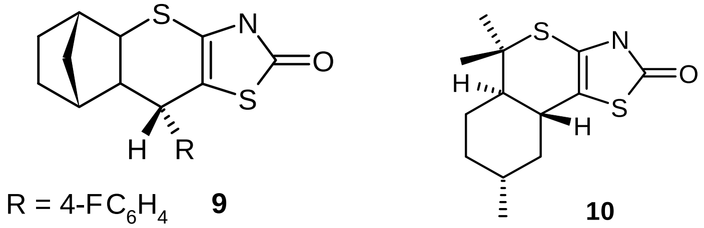


Scheme 2. Reaction of 2-[3-(4-bromophenyl)-3-chloro-2-propenyloxy]benzaldehyde **4a** with 4-thioxo-1,3-thiazolidin-2-one **2**

Table 1

5-Aryl-2*H*,6*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-ones **8a–e**

Entry	Alkene	Product	Yield (%)
1	 **4a**	 **8a**	56
2	 **4b**	 **8b**	65
3	 **4c**	 **8c**	60
4	 **4d**	 **8d**	45
5	 **4e**	 **8e**	39


R = 4-FC$_6$H$_4$ **9**

10

Scheme 3. Condensed thiopyrano-thiazolones