Cross-Dehydrogenative Coupling of Dithiolanes with Ketones and Indoles under Metal-Free Conditions

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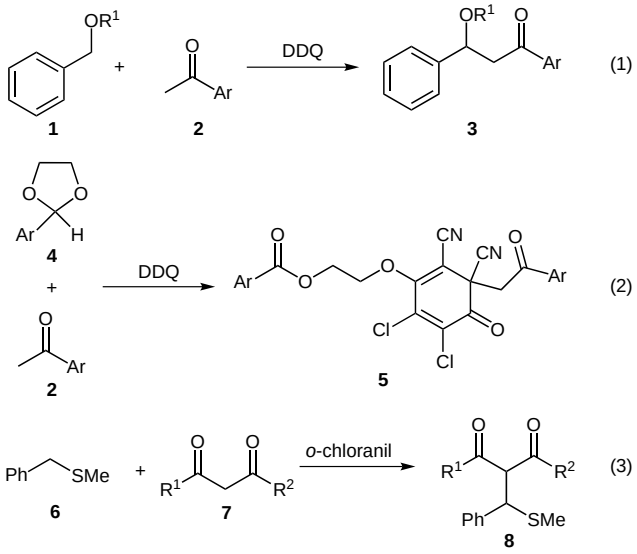
Abstract: A metal-free cross-dehydrogenative coupling of dithiolanes with ketones and indoles has been developed using DDQ as an oxidant. It provides an economical protocol for the synthesis of β-keto dithiolanes and 3-(1,3-dithiolan-2-yl) indoles.

Key words: cross-dehydrogenative coupling, dithiolane, metal-free coupling, C–C bond, DDQ

Sulfur-containing compounds are of significant interest because of their importance in pharmaceutical industry and in material science.[1] β-Keto-1,3-dithiolanes are versatile intermediates,[2a] and dithiolanes are widely used as protecting groups in natural and non-natural product synthesis.[2b–h] These compounds have been synthesized by reaction of *o*-silylated enolates with thiocarbocations,[3a,b] nucleophilic addition of thioketals to epoxides, followed by oxidation[3c] and double Michael addition of dithiol to electron-deficient acetylenic carbonyl compounds.[2a,4]

In recent years, many methods employing transition-metal-based catalysts for forming new C–C bonds have been developed and are used in synthesis.[5] Cross-dehydrogenative coupling (CDC) has evolved as an effective alternative route for the formation of C–C or C–X (X = N, O, S) bond.[6] Owing to its simplicity and nonrequirement of prefunctionalization, the CDC procedure, with or without using metal catalyst, has become a useful methodology in synthesis.[7–9] 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) has been frequently used as an oxidant in metal-free CDC reactions.[10] DDQ-promoted sp^3 C–H functionalization adjacent to nitrogen and oxygen has been reported,[10] but sulfur-containing substrates are less explored.[11] For example, Li reported that the reaction of benzyl ether **1** or cyclic ethers with ketones **2** in the presence of DDQ affords the coupled products **3** (Scheme 1, eq. 1).[12] However, in a similar reaction with acetal **4**, DDQ adduct **5** was obtained rather than the desired coupled product (Scheme 1, eq. 2).[13]

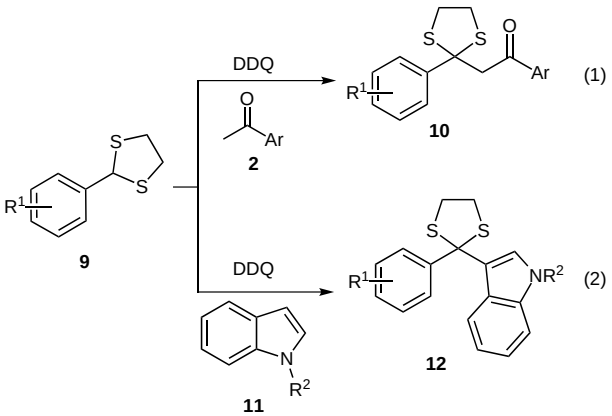
o-Chloranil-assisted coupling of thioether **6** and active methylene substrate **7** has also been investigated (Scheme 1, eq. 3).[11c]



Scheme 1 Previous work

In continuation of our interest in the development of new CDC reactions of synthetic utility,[14] we have now explored DDQ-promoted reactions of dithiolanes with ketones and indoles under metal-free conditions (Scheme 2, eq. 1 and 2), and the results are described in this communication.

In our initial study, we heated dithiolane **9a** and acetophenone (**2a**) at 100 °C for three hours in the presence of DDQ (1.2 equiv). After workup and column chromatographic separation, the product **10a** was obtained in 25%



Scheme 2 This work

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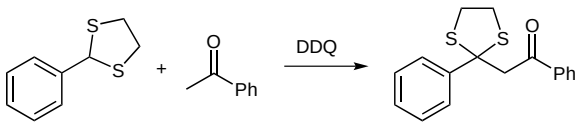
Table 1 Optimization of Reaction Conditions[a]



9a **2a** **10a**

Entry	**2a** (equiv)	Time (h)	Temp (°C)	Yield (%)[b]
1	3	3	100	25
2	5	3	100	30
3	8	3	100	55 (78)[c]
4	8	6	100	52
5	8	1	100	15
6[d]	8	3	100	23
7[e]	8	3	25	–
8	8	3	130	<5
9[f]	8	3	100	50
10[g]	8	3	100	27

[a] Reaction conditions: dithiolane (1 equiv), DDQ (1.2 equiv).
[b] Isolated yield.
[c] Yield in parenthesis is based on recovered dithiolane.
[d] Toluene (3 mL) as solvent.
[e] $CHCl_3$–CH_2Cl_2–THF–Et_2O–DMF (3 mL) as solvent.
[f] DDQ (1.5 equiv).
[g] DDQ (3 equiv).

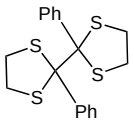


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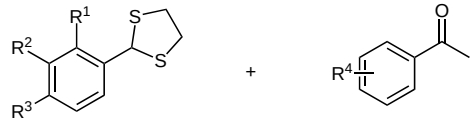
Figure 1 Homocoupled product

yield (Table 1, entry 1). To optimize the yield of the product, various changes in experimental conditions were attempted, and the results are summarized in Table 1. Increasing the amount of acetophenone to five equivalents led to a slight increase in the yield (30%) (Table 1, entry 2). Further increase in amount of acetophenone (8 equiv) improved the yield of **10a** to 55% (Table 1, entry 3). Prolonged reaction time did not affect the yield but shorter reaction time led to a decrease in the yield of **10a** (Table 1, entries 4 and 5). Using toluene as a solvent in the reaction also resulted in a decrease in the yield of **10a** (Table 1, entry 6). In reactions carried out at lower temperature (25 °C) in different solvents, no product formation was observed (Table 1, entry 7). At higher reaction temperature (130 °C) formation of **10a** was suppressed (Table 1, entry 8), instead, the homocoupled product **13** (Figure 1) was obtained in 28% yield. Moreover, an increase in amount of DDQ to 1.5 equivalents hardly affected the yield of the product (Table 1, entry 9), but use of three equivalents of DDQ drastically reduced the yield (Table 1, entry 10). This may be due to overoxidation and has

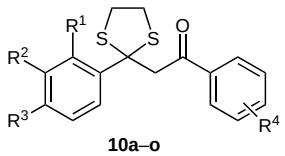
Table 2 Cross-Dehydrogenative Coupling of **9** with Acetophenones[a]



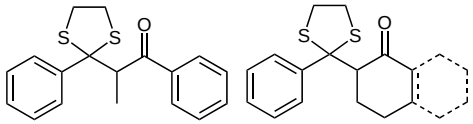
9a $R^1 = R^2 = R^3 = H$
9b $R^1 = H$, $R^2 = H$, $R^3 = OMe$
9c $R^1 = H$, $R^2 = H$, $R^3 = Cl$
9d $R^1 = H$, $R^2 = NO_2$, $R^3 = H$

2a $R^4 = H$
2b $R^4 = 4\text{-OMe}$
2c $R^4 = 4\text{-Br}$
2d $R^4 = 4\text{-Cl}$
2e $R^4 = 4\text{-Me}$

DDQ, 100 °C
3 h



10a–o

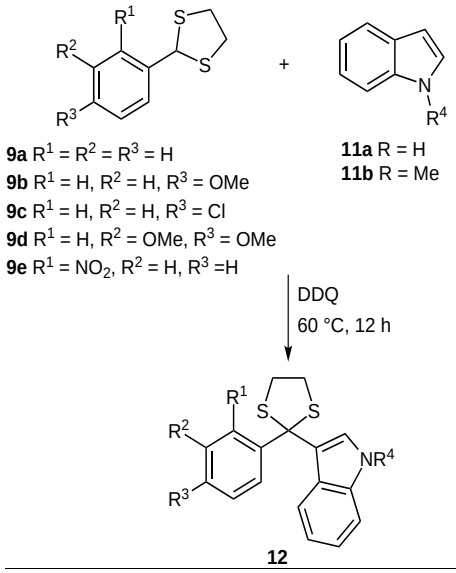


10p **10q,r**

Entry	**9**	**2**	**10**	Yield (%)[b]
1	**9a**	**2a**	**10a**	55 (78)[c]
2	**9a**	**2b**	**10b**	45 (64)
3	**9a**	**2c**	**10c**	58 (82)
4	**9a**	**2d**	**10d**	55 (80)
5	**9a**	**2e**	**10e**	65 (88)
6	**9b**	**2a**	**10f**	45 (65)
7	**9b**	**2c**	**10g**	60 (85)
8	**9b**	**2d**	**10h**	55 (82)
9	**9b**	**2e**	**10i**	62 (88)
10	**9c**	**2a**	**10j**	56 (80)
11	**9c**	**2c**	**10k**	50 (83)
12	**9c**	**2d**	**10l**	50 (85)
13	**9c**	**2e**	**10m**	60 (80)
14	**9c**	**2b**	**10n**	65 (78)
15	**9d**	**2a**	**10o**	50 (82)
16	**9a**	**2f**[d]	**10p**	41 (73)
17	**9a**	**2g**[e]	**10q**	45 (66)
18	**9a**	**2h**[f]	**10r**	40 (68)

[a] Reaction conditions: dithiolane **9** (1 equiv), acetophenone **2** (8 equiv), DDQ (1.2 equiv), 100 °C, 3 h.
[b] Isolated yields.
[c] Yields in parentheses are based on recovered dithiolane.
[d] Propiophenone.
[e] Cyclohexanone.
[f] α-Tetralone.

Table 3 Cross-Dehydrogenative Coupling of **9** with Indoles[a]



Entry	9	11	12	Yield (%)[b,c]
1	**9a**	**11a**	**12a**	35 (52)
2	**9a**	**11b**	**12b**	44 (63)
3	**9b**	**11a**	**12c**	45 (57)
4	**9b**	**11b**	**12d**	40 (68)
5	**9c**	**11a**	**12e**	35 (61)
6	**9e**	**11a**	**12f**	35 (54)
7	**9f**	**11a**	**12g**	38 (66)

[a] Reaction conditions: dithiolane **9** (1 equiv), indole **11** (2 equiv), DDQ (1.2 equiv), 60 °C, 12 h.
[b] Isolated yields.
[c] Yields in parentheses are based on recovered dithiolane.

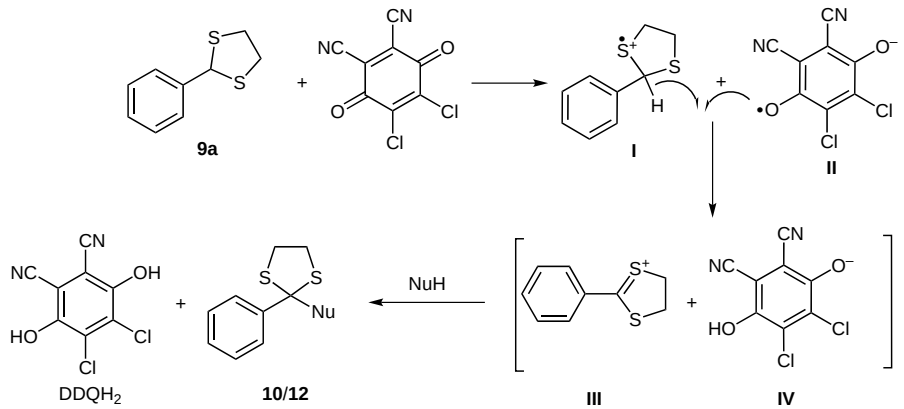
been observed in other cases also.[10d,11c] No reaction occurred in the absence of DDQ. Thus, the best result was obtained by using eight equivalents of acetophenone and 1.2 equivalents of DDQ at 100 °C (Table 1, entry 3). Some unreacted dithiolane was always observed (as indicated by TLC analysis) in these reactions.

After establishing the optimized reaction conditions, the substrate scope for both reactants was examined, and the results are summarized in Table 2.[15] It was found that the reaction is tolerant to electron-donating and electron-withdrawing groups in both substrates. An increase in the yield of **10** was observed when *p*-methyl acetophenone (**2e**) was used (Table 2, entries 5, 9, and 13). Also, *p*-halo-substituted ketones **2c** and **2d** gave comparable yields (Table 2, entries 3, 4, 7, 8, 11, and 12). Use of substituted dithiolanes did not show any marked difference in the yield of the product (Table 2, entries 6–15). Other ketones like propiophenone, cyclohexanone, and α-tetralone also coupled well under these conditions (Table 2, entries 16–18).

Encouraged by these results, we extended this methodology to indole (**11a**) as the nucleophile, using slightly modified reaction conditions. Indoles are considered as good coupling partners[6] and C3-functionalized indoles show many important biological and pharmaceutical activities.[16] Dithiolane-bearing indoles are also of synthetic interest.[17] The reaction of **9a** (1 equiv) and **11a** (2 equiv) was carried out at 60 °C for 12 hours using DDQ (1.2 equiv). Workup and separation by column chromatography gave the coupled product **12a** in 35% isolated yield (Table 3, entry 1). Different dithiolanes **9a**–**c** and **9e**–**f** coupled smoothly with indole (**11a**) and *N*-methyl indole (**11b**) to afford the products **12a**–**g** in moderate yields (Table 3).

In accordance with an earlier proposed mechanism involving DDQ,[10] a plausible mechanism of reaction of **9a** with (pro)nucleophile is depicted in Scheme 3. Single-electron transfer (SET) from dithiolane **9a** to DDQ generates the radical cation species **I** and a DDQ radical anion **II**. Abstraction of the H atom by **II** from **I** gives the thionium cation **III** and DDQ anion **IV**. Further reaction with Nu–H furnishes the coupled product **10**/**12** and $DDQH_2$.

In conclusion, we have demonstrated that a facile metal-free coupling at sp^3 α-C–H center of dithiolane with ketones and indoles can occur. Proper reaction conditions are critical for obtaining the cross-coupled product as major product because slight variations can result in the formation of homocoupled product. DDQ worked effectively



Scheme 3 Tentative mechanism

as an oxidant, and the reactions provide clean and economical pathways for the synthesis of β-keto-1,3-dithiolanes and 3-(1,3-dithiolan-2-yl) indoles. The scope, mechanism, and application of these reactions are under investigation.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) (a) **Typical Procedure for Coupling of 9 and 2**
To a 10 mL two-necked round-bottom flask charged with acetophenone **2** (8 equiv) and DDQ (1.2 equiv) was added dithiolane **9** (1 equiv) under nitrogen atmosphere. The reaction mixture was heated at 100 °C immediately and stirred at this temperature for 3 h. The resultant crude material was directly purified by flash chromatography on silica gel (EtOAc–hexane, 3:97) to afford the pure product **10**.

Data for Representative Examples

1-Phenyl-2-(2-phenyl-1,3-dithiolan-2-yl)ethanone (10a)[2a,4a]

Yield 0.11 g (55%); white solid; mp 129–131 °C (EtOAc–hexane, 5:95). IR: ν = 3064, 2962, 2921, 2855, 1681, 1659, 1603, 1595, 1529, 1446, 1340, 1242, 1207 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.81 (d, *J* = 1.5 Hz, 2 H), 7.67 (d, *J* = 1.5 Hz, 2 H), 7.43–7.41 (m, 1 H), 7.35–7.30 (m, 2 H), 7.19–7.14 (m, 2 H), 7.08–7.06 (m, 1 H), 4.17 (s, 2 H), 3.29–3.20 (m, 4 H). ^{13}C NMR [75 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 195.0, 144.6, 136.7, 133.1, 128.5, 128.1, 127.9, 127.1, 126.9, 69.0, 54.2, 39.4. MS (ES^+): *m/z* = 323.4 $[M + Na]^+$.

2-[2-(4-Methoxyphenyl)-1,3-dithiolan-2-yl]-1-*p*-tolyl-ethanone (10i)

Yield 0.100g (62%); white solid, mp 110–113 °C (EtOAc–hexane = 5:95). IR: ν = 3016, 2835, 1682, 1605, 1576, 1505, 1507, 1463, 1414, 1338, 1291, 1249, 1215 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.71 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.8 Hz, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 4.10 (s, 2 H), 3.67 (s, 3 H), 3.24–3.21 (m, 4 H), 2.32 (s, 3 H). ^{13}C NMR [75 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 194.7, 158.4, 143.6, 136.7, 134.4, 129.2, 128.4, 128.3, 113.1, 68.9, 55.0, 53.9, 39.3, 21.7. HRMS (ES^+): *m/z* calcd for $C_{19}H_{20}S_2O_2Na$ $[M + Na]^+$: 367.0796; found: 367.0780.

2-[2-(4-Chlorophenyl)-1,3-dithiolan-2-yl]-1-phenyl-ethanone (10j)

Yield 0.086 g (56%); viscous oil. IR: ν = 3018, 2924, 2855, 1687, 1596, 1488, 1448, 1397, 1342, 1260, 1213 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.81 (t, *J* = 7.0 Hz, 2 H), 7.64–7.59 (m, 2 H), 7.48 (t, *J* = 7.0 Hz, 1 H), 7.36–7.31 (m, 2 H), 7.18–7.12 (m, 2 H), 4.16 (s, 2 H), 3.31–3.16 (m, 4 H). ^{13}C NMR [75 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 195.0, 143.3, 136.4, 133.3, 132.9, 128.6, 128.0, 127.9, 68.4, 54.1, 39.4. HRMS (ES^+): *m/z* calcd for $C_{17}H_{15}S_2ClONa$ $[M + Na]^+$: 357.0145; found: 357.0146.

2-[2-(4-Chlorophenyl)-1,3-dithiolan-2-yl]-1-*p*-tolyl-ethanone (10m)

Yield 0.096 g (60%); viscous oil. IR: ν = 3016, 2922, 2859, 2055, 1682, 1606, 1571, 1488, 1404, 1337, 1216 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 8.7 Hz, 2 H), 7.18–7.12 (m, 4 H), 4.17 (s, 2 H), 3.32–3.18 (m, 4 H), 2.31 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.2, 144.3, 143.4, 133.8, 132.7, 129.2, 128.4, 128.1, 127.9, 68.2, 53.8, 39.3, 21.6. HRMS (ES^+): *m/z* calcd for $C_{18}H_{17}S_2ClONa$ $[M + Na]^+$: 371.0301; found: 371.0378.

(b) **Typical Procedure for Coupling of 9 and 11**

To a 10 mL two-necked round-bottom flask charged with indole **11** (2 equiv) and DDQ (1.2 equiv) was added dithiolane **9** (1 equiv) under nitrogen atmosphere. The reaction mixture was heated at 60 °C immediately and stirred at this temperature for 12 h. The resultant crude material was directly purified by flash chromatography on silica gel (EtOAc–hexane, 10:90) to afford the pure product **12**.

Data for Representative Examples

3-(2-Phenyl-1,3-dithiolan-2-yl)-1*H*-indole (12a)[17a]

Yield 0.070 g (35%); yellow reddish solid, mp 91–93 °C (EtOAc–hexane, 5:95). IR: ν = 3406, 3052, 2921, 1593, 1567, 1517, 1492, 1455, 1443, 1413, 1337, 1241, 1210 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.84 (br s, 1 H), 7.64 (d, *J* = 7.0 Hz, 2 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.21–7.12 (m, 5 H), 7.06 (t, *J* = 7.0 Hz, 1 H), 6.91 (t, *J* = 7.2 Hz, 1 H) 3.45–3.30 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4 = 1:1): δ = 143.4, 137.6, 128.2, 127.9, 127.3, 125.6, 124.8, 122.4, 121.9, 120.7, 119.6, 111.1, 71.1, 40.0. MS (ES^+): *m/z* = 298.1 $[M + H]^+$.

3-[2-(4-Methoxyphenyl)-1,3-dithiolan-2-yl]-1*H*-indole (12c)

Yield 0.069 g (45%); orange solid, mp 125–130 °C (EtOAc–hexane, 5:95). IR: ν = 3334, 2962, 2923, 1708, 1599, 1504, 1419, 1303, 1244, 1213 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.78 (br s, 1 H), 7.52 (d, *J* = 9.0 Hz, 2 H), 7.35 (d, *J* = 7.4 Hz, 1 H), 7.19–7.14 (m, 2 H), 7.05–7.00 (m, 1 H), 6.91–6.85 (m, 1 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 3.70 (s, 3 H), 3.41–3.30 (m, 4 H). ^{13}C NMR [75 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 137.7, 129.6, 124.8, 122.4, 122.3, 119.6, 113.2, 111.0, 71.1, 55.0, 39.9. HRMS (ES^+): *m/z* calcd for $C_{18}H_{18}S_2NO$ $[M + H]^+$: 328.0824; found: 328.0873.

3-[2-(4-Chlorophenyl)-1,3-dithiolan-2-yl]-1*H*-indole (12e)

Yield 0.053g (35%); yellow oil. IR: ν = 3407, 2923, 1630, 1589, 1540, 1485, 1445, 1413, 1393, 1331, 1241, 788 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.80 (br s, 1 H), 7.56 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 7.19–7.11 (m, 4 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 6.92 (t, *J* = 7.2 Hz, 1 H), 3.43–3.29 (m, 4 H). ^{13}C NMR [75 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 142.0, 137.6, 133.3, 129.8, 128.0, 125.5, 124.7, 122.6, 122.0, 120.4, 119.8, 111.1, 70.5, 40.1. HRMS (ES^+): *m/z* calcd for $C_{17}H_{15}S_2NCl$ $[M + H]^+$: 332.0328; found: 332.0341.

3-[2-(3,4-Dimethoxyphenyl)-1,3-dithiolan-2-yl]-1*H*-indole (12f)

Yield 0.051 g (35%); brown solid, mp 100–103 °C (EtOAc–hexane, 5:95). IR: ν = 3158, 2917, 2848, 1594, 1565, 1510, 1439, 1379, 1334, 1268, 1201 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 7.83 (br s, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.30 (d, *J* = 2.2 Hz, 1 H), 7.18 (t, *J* = 3.6 Hz, 1 H), 7.11 (d, *J* = 2.2 Hz, 1 H), 7.06 (t, *J* = 7.2 Hz, 2 H), 6.92 (t, *J* = 7.2 Hz, 1 H), 6.60 (d, *J* = 8.1 Hz, 1 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.41–3.30 (m, 4 H). ^{13}C NMR [75 MHz, $CDCl_3$–CCl_4 (1:1)]: δ = 148.4, 137.6, 135.5, 125.6, 125.0, 122.4, 122.2, 120.9, 119.6, 112.1, 111.0, 110.2, 71.2, 55.8, 55.7, 39.9. HRMS (ES^+): *m/z* calcd for $C_{19}H_{19}S_2NO_2Na$ $[M + Na]^+$: 380.0749; found: 380.0750.

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