Conjugate Addition of 2-Heteroaryl-1,3-dithianes to Furan-2(5*H*)-one

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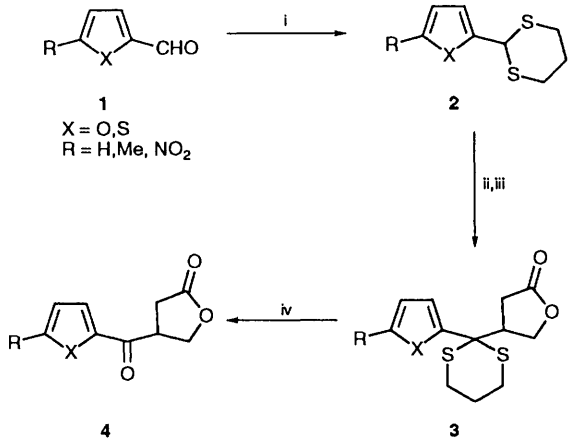
Conjugate addition of lithiated 2-heteroaryl-1,3-dithianes to furan-2(5*H*)-one has been successfully achieved. This reaction proceeds with higher yields than the addition of the 2-aryl derivatives, although it fails if the heteroaryl ring has strong deactivating substituents.

Since the introduction by Seebach and Corey [1] of 1,3-dithianes and other dithioacetals as versatile reagents, they have proven to constitute a useful approach to the formation of C–C bonds. Conjugate addition of lithiated 1,3-dithianes and dithioacetals to α,β-unsaturated ketones and aldehydes is now a common process in organic synthesis [2] and has also been employed in the conjugate addition to α,β-unsaturated esters and lactones. An example of this is the addition of 2-aryl-1,3-dithiane anions (with an activated aryl group) to furan-2(5*H*)-one (γ-crotonolactone).[3] For *p*-methoxyphenyl derivatives, the yield is acceptable but it decreases significantly when the aryl is unsubstituted.

In view of the potential usefulness of this reaction for the preparation of 3-monosubstituted and 2,3-disubstituted γ-butyrolactones, which are common features in many natural products (sesquiterpenoids,[4] steroids,[5] pilocarpine related alkaloids[6] and in particular lignans[7]), we planned to study its applicability for the synthesis of some hetero analogues. The extension of this methodology will allow the synthesis of new heterocyclic lignanolides (heterolignanolides).[8] Furthermore, the products from this reaction, possessing either a carboxylic ester or a lactone, a heteroaromatic moiety and a potential ketone group (protected as dithioketal), could be used in the synthesis of more complex molecules.

Since five-membered, unsaturated heterocyclic compounds with one heteroatom have a π-excessive character and are thus comparable to polyoxygenated phenyl groups, we first studied the reaction of 1,3-dithianes carrying these type of substituents at position 2. We started with the reaction of the 1,3-dithiane **2a** (X = O, R = H) obtained from furfuraldehyde **1** (X = O, R = H) (Scheme 1). Compound **2a** was quantitatively produced by the trimethylsilyl chloride (TMSCl) promoted reaction of the aldehyde with propane-1,3-dithiol[9] and purified



Scheme 1 *Reagents and conditions:* i, $HS[CH_2]_3SH$, TMSCl; ii, BuLi, −78 °C, THF; iii, furan-2(5*H*)-one, −78 °C, THF; iv, $HgO–BF_3·Et_2O$, $THF–H_2O$

Table 1 Results of conjugate addition of 2-heteroaryl-1,3-dithianes to furan-2(5*H*)-one

2	R	X	Addition method	3 Yield (%)[a]
a	H	O	A	87
b	H	S	A	97
c	Me	O	A	80
d	Me	S	A	82
e	NO_2	O	B	0
f	NO_2	S	B	0
g	H	NTs	B	0

[a] After chromatography, yields > 55% after crystallization.

by crystallization. The conjugate addition reaction was carried out in tetrahydrofuran (THF) at −78 °C by treatment of **2a** with BuLi, followed by slow addition of furan-2(5*H*)-one in THF. The reaction was complete after 2 h at −78 °C and compound **3a** (X = O, R = H) was obtained, despite the absence of activating substituents on the furan ring. A similar result is produced with a weak electron-releasing substituent on the heteroaromatic ring as, for example, when commercially available 5-methylfurfuraldehyde **1** (X = O, R = Me) was used as the starting material.

In the same way, the thiophene derivatives **2** (**b**: X = S, R = H; **d**: X = S, R = Me), prepared from thiophene-2-carbaldehyde **1** (X = S, R = H) and 5-methylthiophene-2-carbaldehyde **1** (X = S, R = Me), reacted to produce the addition compounds **3b** and **3d**. All of these reactions proceeded with good yields (> 80%) on both a small and a multigram scale (Table 1).

To check the effect of deactivating substituents upon the reactivity, 5-nitro-2-furyl **2e** (X = O, R = NO_2) and 5-nitro-2-thienyl **2f** (X = S, R = NO_2) derivatives (from commercially available aldehydes) were assayed. Under similar conditions, unchanged starting materials were recovered. Even after 4 h at −78 °C, or even if the mixture was allowed to reach room temp., no reaction was observed. These results indicated that the deactivating effect of one nitro group outweighed the activating effect of the heteroaromatic ring. In nitro derivatives of compound **2** the stabilization by charge delocalization of the anion by the nitro group would be responsible for their observed lack of reactivity.

Since pyrrole would be more electron releasing than thiophene, it is expected that the conjugate addition of 2-pyrrol-2-yl-1,3-dithianes **2** (X = NH, NMe; R = H), to furan-2(5*H*)-one would be more efficient. Unfortunately, it was not possible to check this reaction because trials directed to the synthesis of the dithianes from pyrrolecarbaldehydes **1** (X = NH, NMe; R = H) were unsuccessful, complex polymers being produced after the addition of the acidic reagent to the mixture of the pyrrolecarbaldehyde and propane-1,3-dithiol. When the tosyl derivative was used **1** (X = NTs, R = H) the dithiane **2g** (X = NTs, R = H) was readily obtained, but failed to produce the

conjugate addition to furan-2(5*H*)-one. In this case, the deactivating effect of the tosyl group was also stronger than the activating effect of the heteroaromatic ring.

Reaction products **3** were deprotected with HgO–BF_3·Et_2O[10] to produce the expected keto lactones **4**. The heteroaryldithiane lactones **3** and heteroaryl keto lactones **4** obtained by this procedure were fully characterized and their structures confirmed spectroscopic techniques.

In conclusion, this methodology is very useful for the synthesis of 4-heteroaryl substituted butanolides and other carboxylic ester derivatives, which are obtained in higher yield than the products of the already known addition of 2-phenyl-1,3-dithianes.[11] The synthesis of several heterocyclic analogues of various biological active compounds and natural products is now under progress.

Experimental

M.p.s were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were measured using a Beckmann (Acculab VIII) in 4% $CHCl_3$ solution. NMR spectra were recorded on a Bruker WP200SY (200 MHz for ^1H and 50.3 MHz for ^{13}C) in $CDCl_3$ solution. Chemical shifts are reported in ppm from internal TMS and *J* values in Hz. Mass spectra were measured on a VG-TS-250 spectrometer (electron impact 70 eV). Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyser.

Preparation of 2-Heteroaryl-1,3-dithianes.—To a 1.2 mol dm^{-3} solution of the commercially available (Aldrich) aldehydes **1** in $CHCl_3$, propane-1,3-dithiol (1 equiv.) and an excess of TMSCl were added at 0 °C. The reaction mixture was stirred for 24 h at room temp. and then quenched with aqueous NaOH (4%). Extraction (EtOAc) and crystallization (hexane–EtOAc 5:1) of the crude product led to the dithianes **2**. *N*-Tosylpyrrole-2-carbaldehyde **1g** was prepared from pyrrole-2-carbaldehyde.[12]

Addition Reactions.—Method A: To a 1 mol dm^{-3} solution of dithiane **2a–d** in THF at −78 °C under argon, BuLi (1.6 mol dm^{-3} in hexanes; 1.1 equiv.) was added. After 30 min furan-2(5*H*)-one (1 mol dm^{-3} in THF) was added to the mixture which was then stirred for 2–3 h at −78 °C. The reaction was quenched with NH_4Cl (aq. sat. sol.) and the mixture extracted with EtOAc. The products **3a–d** were isolated by flash chromatography (hexane–EtOAc, 3:1).

4-[2-(2-*Furyl*)-1,3-*dithian*-2-*yl*]*dihydrofuran*-2(3H)-*one* **3a**. (Found: C, 53.3; H, 5.05. $C_{12}H_{14}O_3S_2$ requires C, 53.54; H, 4.83%); ν_{max}/cm^{-1} 1790 (γ-lactone), 1500 and 1480 (heterocycle); δ_H 7.46 (1 H, d, *J* 1.8), 6.64 (1 H, d, *J* 3.3), 6.41 (1 H, dd, *J* 3.3 and 1.8), 4.47 (1 H, dd, *J* 9.6 and 6.9), 4.30 (1 H, dd, *J* 9.6 and 8.1), 3.24 (1 H, m), 2.86 (1 H, dd, *J* 18.0 and 7.6), 2.86 (2 H, m), 2.73 (2 H, dt, *J* 14.2 and 4.2), 2.55 (1 H, dd, *J* 18.0 and 9.6), 2.05 (1 H, dq, *J* 14.4 and 4.2) and 1.91 (1 H, dtt, *J* 14.4, 12.0 and 4.2); δ_C 175.6 (s), 151.6 (s), 143.5 (d), 112.5 (d), 110.8 (d), 68.4 (t), 54.2 (s), 43.4 (d), 30.0 (t), 27.4 (2 × t) and 24.7 (t); *m/z* 270 (M^+, 18%), 185 (100).

4-[2-(2-*Thienyl*)-1,3-*dithian*-2-*yl*]*dihydrofuran*-2(3H)-*one* **3b**. (Found: C, 50.8; H, 4.6. $C_{12}H_{14}O_2S_3$ requires C, 50.53; H, 4.56%); ν_{max}/cm^{-1} 1780 (γ-lactone) and 1480 (heterocycle); δ_H 7.36 (1 H, dd, *J* 5.2 and 1.2), 7.26 (1 H, dd, *J* 3.7 and 1.2), 7.02 (1 H, dd, *J* 5.2 and 3.7), 4.52 (1 H, dd, *J* 9.7 and 7.8), 4.28 (1 H, dd, *J* 9.7 and 8.1), 3.15 (1 H, m), 2.93 (1 H, dd, *J* 17.9 and 8.4), 2.88 (2 H, ddd, *J* 14.4, 12.1 and 3.5), 2.75 (2 H, dt, *J* 14.4 and 3.5), 2.53 (1 H, dd, *J* 17.9 and 9.3), 2.05 (1 H, dq, *J* 14.0 and 3.5) and 1.91 (1 H, dtt, *J* 14.0, 12.1 and 3.5); δ_C 175.8 (s), 146.8 (s), 129.1 (d), 127.9 (d), 127.7 (d), 66.4 (t), 56.5 (s), 48.3 (d), 30.2 (t), 27.5 (2 × t) and 24.5 (t); *m/z* 286 (M^+, 15%) and 201 (100).

4-[2-(5-*Methyl*-2-*furyl*)-1,3-*dithian*-2-*yl*]*dihydrofuran*-2(3-H)-*one* **3c**. (Found: C, 55.0; H, 5.6. $C_{13}H_{16}O_3S_2$ requires C, 54.91; H, 5.67%); ν_{max}/cm^{-1} 1780 (γ-lactone), 1610, 1545 and 1485 (heterocycle); δ_H 6.50 (1 H, d, *J* 3.2), 5.97 (1 H, d, *J* 3.2), 4.47 (1 H, dd, *J* 9.7 and 6.7), 4.31 (1 H, dd, *J* 9.7 and 8.2), 3.21 (1 H, m), 2.89 (2 H, m), 2.87 (1 H, dd, *J* 18.0 and 8.2), 2.72 (2 H, dt, *J* 14.2 and 3.9), 2.56 (1 H, dd, *J* 18.0 and 9.5), 2.29 (3 H, s), 2.00 (1 H, m) and 1.92 (1 H, m); δ_C 175.8 (s), 153.3 (s), 149.2 (s), 113.5 (d), 106.8 (d), 68.6 (t), 54.2 (s), 45.3 (d), 30.1 (t), 27.4 (2 × t), 24.8 (t), 13.8 (q); *m/z* 284 (M^+, 12%) and 199 (100).

4-[2-(5-*Methyl*-2-*thienyl*)-1,3-*dithian*-2-*yl*]*dihydrofuran*-2-(3-H)-*one* **3d**. (Found: C, 51.8; H, 5.4. $C_{13}H_{16}O_2S_3$ requires C, 51.94; H, 5.37%); ν_{max}/cm^{-1} 1780 (γ-lactone) and 1485 (heterocycle); δ_H 7.02 (1 H, d, *J* 3.5), 6.65 (1 H, d, *J* 3.5), 4.50 (1 H, dd, *J* 9.6 and 7.1), 4.29 (1 H, dd, *J* 9.6 and 8.1), 3.10 (1 H, m), 3.02–2.64 (2 H, m), 2.67 (1 H, dd, *J* 7.4 and 3.6), 2.60–2.41 (3 H, m), 2.43 (3 H, s) and 2.06–1.89 (2 H, m); δ_C 175.5 (s), 143.5 (s), 142.3 (s), 129.1 (d), 125.6 (d), 68.4 (t), 56.7 (s), 48.1 (d), 30.1 (t), 27.5 (2 × t), 24.6 (t) and 15.4 (q); *m/z* 300 (M^+, 11%) and 215 (100).

Method B: The reaction was carried out as in Method A but stirred for 4 h at −78 °C. The mixture was allowed to reach room temp., and then was stirred overnight and worked up as previously described. Starting material **2e–g** was completely recovered.

Deprotection.—To a solution of red HgO (2 equiv.) and BF_3·Et_2O (2 equiv.) in THF (H_2O 15%), the dithiane **3a–d** (1 mol dm^{-3} in THF) was slowly added and allowed to react for 20 h. The mixture was diluted with CH_2Cl_2, filtered and washed with saturated aq. $NaHCO_3$. The keto lactones **4a–d** were obtained in quantitative yield.

4-(2-*Furoyl*)*dihydrofuran*-2(3H)-*one* **4a**. (Found: C, 60.1; H, 4.3. $C_9H_8O_4$ requires C, 60.00; H, 4.48%); ν_{max}/cm^{-1} 1785 (γ-lactone), 1670 (aryl ketone), 1570 and 1465 (heterocycle); δ_H 7.66 (1 H, d, *J* 1.5), 7.32 (1 H, d, *J* 3.7), 6.62 (1 H, dd, *J* 3.7 and 1.5), 4.64 (1 H, dd, *J* 9.0 and 8.9), 4.46 (1 H, dd, *J* 9.0 and 6.7), 4.22 (1 H, m), 3.00 (1 H, dd, *J* 17.8 and 7.7) and 2.77 (1 H, dd, *J* 17.8 and 9.5); δ_C 185.3 (s), 175.2 (s), 151.6 (s), 147.4 (d), 118.7 (d), 113.0 (d), 68.7 (t), 42.7 (d) and 30.2 (t); *m/z* 180 (M^+, 5%), 152 (5) and 95 (100).

4-(2-*Thenoyl*)*dihydrofuran*-2(3H)-*one* **4b**. (Found: C, 55.2; H, 4.1. $C_9H_8O_3S$ requires C, 55.09; H, 4.11%); ν_{max}/cm^{-1} 1790 (γ-lactone), 1675 (arylketone), 1515 and 1420 (heterocycle); δ_H 7.76 (2 H, m), 7.21 (1 H, dd, *J* 4.4 and 4.3), 4.62 (1 H, dd, *J* 9.0 and 8.8), 4.49 (1 H, dd, *J* 9.0 and 6.8), 4.27 (1 H, m), 3.02 (1 H, dd, *J* 17.5 and 7.7) and 2.79 (1 H, dd, *J* 17.5 and 9.3); δ_C 189.3 (s), 176.5 (s), 142.4 (s), 135.5 (d), 132.9 (d), 128.8 (d), 69.2 (t), 43.5 (d) and 31.2 (t); *m/z* 196 (M^+, 4%), 168 (5) and 111 (100).

4-(5-*Methyl*-2-*furoyl*)*dihydrofuran*-2(3H)-*one* **4c** (Found: C, 62.0; 5.2. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19%); ν_{max}/cm^{-1} 1785 (γ-lactone), 1675 (aryl ketone), 1515 and 1385 (heterocycle); δ_H 7.22 (1 H, d, *J* 3.5), 6.24 (1 H, d, *J* 3.5), 4.61 (1 H, dd, *J* 9.0 and 8.9), 4.45 (1 H, dd, *J* 9.0 and 7.2), 4.16 (1 H, m), 2.98 (1 H, dd, *J* 17.7 and 8.2), 2.74 (1 H, dd, *J* 17.7 and 9.4) and 2.43 (3 H, s); δ_C 184.7 (s), 175.4 (s), 159.1 (s), 125.6 (s), 120.7 (d), 109.9 (d), 69.1 (t), 42.5 (d), 30.6 (t) and 14.1 (q); *m/z* 194 (M^+, 16%), 166 (3) and 109 (100).

4-(5-*Methyl*-2-*thenoyl*)*dihydrofuran*-2(3H)-*one* **4d**. (Found: C, 57.1; H, 4.75. $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79%); ν_{max}/cm^{-1} 1780 (γ-lactone), 1660 (aryl ketone) and 1450 (heterocycle); δ_H 7.56 (1 H, d, *J* 3.8), 6.86 (1 H, d, *J* 3.8), 4.59 (1 H, dd, *J* 9.0 and 7.0), 4.45 (1 H, dd, *J* 9.0 and 7.0), 4.20 (1 H, m), 3.00 (1 H, dd, *J* 17.7 and 7.8), 2.75 (1 H, dd, *J* 17.7 and 9.6) and 2.57 (3 H, s); δ_C 187.7 (s), 175.3 (s), 151.2 (s), 134.2 (s), 133.5 (d), 127.4 (d), 69.4 (t), 42.9 (d), 31.2 (t) and 16.1 (q); *m/z* 210 (M^+, 10%), 182 (3), 168 (4) and 125 (100).

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