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An Improved Annelation Method with Methyl 2-(1,3-dithian-2-yl)benzoate as a Bidentate Synthon

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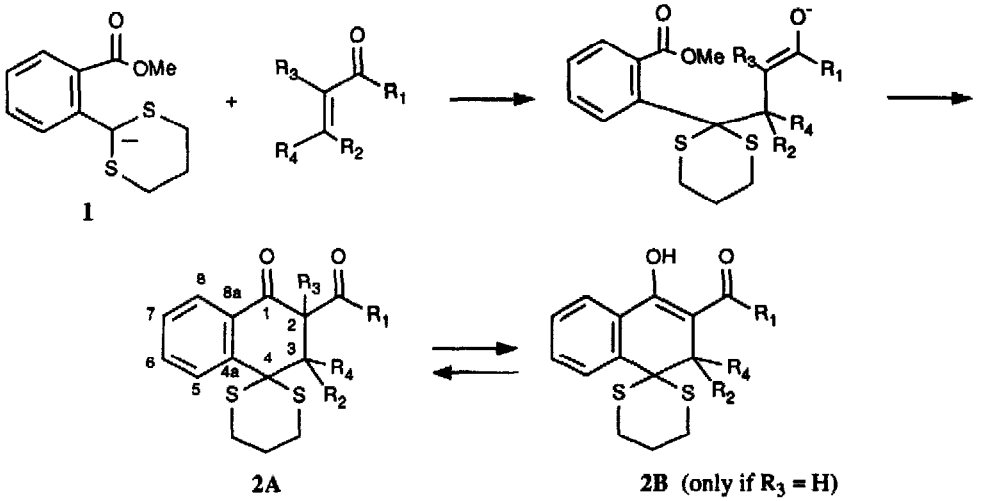
Abstract: The use of methyl 2-(1,3-dithian-2-yl)benzoate as a member of a new group of bidentate synthons in an improved annelation method, yielding polycyclic systems with three differentiated carbonyl groups, is described.

From the original Robinson method until now many annelation methods based on the Michael reaction have been described.[1] A very interesting group of processes use carbanions derived from functionalized phthalides, specially cyanophthalides, as bidentate synthons acting sequentially as Michael donor to a conjugate carbonyl system and as acceptor of the attack of the enolate resulting from the first reaction.[2] However, these processes have two major drawbacks: the preparation of the starting phthalide and the formation of polycarbonyl systems. In the literature[3] there are several ways to obtain cyanophthalides, but they are always complicated and potentially dangerous because of the use of cyanides in acidic medium. Regarding the polycarbonyl nature of these products, there is clearly a problem of chemoselectivity when they are used in subsequent synthetic steps.

To avoid these problems we have studied a new process, conceptually related, based on the use as bidentate synthon of the carbanion of methyl-2-(1,3-dithian-2-yl)benzoate **1**, a member of a family of



1 **2A** **2B** (only if $R_3 = H$)

compounds derived from the same kind of 2-alkoxycarbonylbenzaldehyde precursors as are used to prepare

cyanophthalides. In the case of **1**, the dithiane group is now the responsible for the *umpolung* of the aldehyde (scheme).

There are relatively few analogues of **1** described in the literature.[4] Several examples of conjugate additions of carbanions derived from 1,3-dithianes have been described,[5] but species such as **1** have never been used in annelation processes before. The main advantages over cyanophthalides and related compounds are: (a) the very easy preparation[6] and (b) one of the carbonyl groups in the resulting condensation product is protected as its dithiane derivative, avoiding problems of chemoselectivity in the subsequent steps.

We have applied this new method to the following substrates: cyclohexenone (**a**), chalcone (**b**), ethyl acrylate (**c**), methyl methacrylate (**d**), methyl 2-butenoate (**e**), methyl 3-methyl-2-butenoate (**f**), methyl cinnamate (**g**), methyl vinyl ketone and 1,4-naphthoquinone. Products (yields, physical and spectroscopic data presented in Tables 1, 2, and 3) were obtained in all cases except with methyl vinyl ketone and naphthoquinone where we obtained complex crude product mixtures, containing little or none of the desired product, which were not examined further.

Table 1. Yield[a], Melting Point[b], Tautomeric Form[c], and IR[d] of Compounds 2a-g.

Comp.	R_1	R_2	R_3	R_4	TF	Yield	M.P.	IR
2a	$(CH_2)_3$		H	H	B	64	155-8[e]	1600
2b	C_6H_5	C_6H_5	H	H	B	70	74-6[f]	1610
2c	OC_2H_5	H	H	H	A+B	40	g	1650, 1615
2d	OCH_3	H	CH_3	H	A	55	120-1[h]	1730, 1685
2e	OCH_3	CH_3	H	H	A+B	55	119-21[h]	1635, 1610
2f	OCH_3	CH_3	H	CH_3	A	27	g	1745, 1680
2g	OCH_3	H	H	C_6H_5	A+B	43	g	1650, 1620

a) Calculated for purified compounds; **2c** and **2e** contained a little starting material even after chromatography; (b) determined in open capillary tubes on a Büchi apparatus and are uncorrected; (c) dicarbonyl (A) or keto-enolic (B) form (see scheme); (d) recorded on a Perkin Elmer 681 Infrared spectrometer, only noteworthy absorptions in cm^{-1} are listed; (e) crystallized from acetone; (f) crystallized from methanol; (g) oily product; (h) crystallized from ether/hexane.

Because the presence of the 1,3-dithiane group protecting the carbonyl at the position 4, these compounds cannot tautomerize to the fully aromatic structure. They can however adopt two tautomeric forms (see scheme): the dicarbonyl (A) and the keto-enolic (B). Obviously, in the case of the compound **2d**, the keto-enolic structure is impossible due to the presence of a methyl group in the position C-2, and for this reason it is a good model to determine the spectroscopic characteristics of the dicarbonyl tautomers; this compound has in its IR spectrum two important peaks: 1730 cm^{-1}, due to the non conjugated ester group, and at 1685 cm^{-1}, typical of a conjugated ketone. Very similar absorptions are observed in the IR spectrum of **2f**, although at C-2 there is an apparently tautomerizable proton. NMR experiments with this molecule show a positive NOE to this proton when one of the methyl groups in C-3 position, at δ 1.60 ppm is irradiated, proving the presence of such a proton in a *cis* arrangement with respect to the methyl group. In other words, both of the IR and the NMR data indicate the absence of the keto-enolic form of **2f**. Examination of a molecular model of this compound permits the observation of a very important steric compression in the planar keto-enolic structure, due to the simultaneous presence of the two methyl groups at C-3 and the ester

group at C-2, and such steric problems are the most probable reason for the non-enolisation of **2f**. The compounds **2d** and **2f** have in the ^{13}C-NMR (Table 3) two carbons with chemical shift clearly different from the rest of the series, C-1 (≈190) and C-4(≈64). This could be a criteria to recognise the tautomeric form. On the other hand, the tautomeric equilibrium is fully displaced towards the keto-enolic form in compounds **2a** and **2b**, as is clearly shown by their IR spectra, with a strong absorptions at 1600 and 1610 cm^{-1} respectively, typical of enolized 1,3-dicarbonyl compounds, and the presence of the signal of the enolic proton at δ 12-14 ppm in their ^{1}H-NMR spectrum measured in deuterochloroform. The other compounds are intermediate cases. An important consequence of this structural characteristic is that, in fact, it is possible distinguish between the three carbonyl group in the compounds **2**, the first in the form of its dithiane derivative, the second totally or partially in enolic form and the third as a real carbonyl, with the consequent advantages in subsequent chemoselective differentiation.

Table 2. ^{1}H-NMR[a] Signals of the Common Cyclic System of Compounds 2a-g.

Comp.	H-2	H-3	H-5	H-6	H-7	H-8
2a	--	2.93-3.22 (m)	8.00 (dd) 7.4;1.7	7.41 (ddd) 7.5;7.4;1.3	7.52 (ddd) 7.5;7.7;1.7	8.07 (dd) 7.7;1.3
2b	--	4.50 (s)	--- 6.85-7.60 (m) ----			8.20 (dd)
2c	--	3.43 (s)	7.80-8.05 (m)	-- 7.20-7.60 -- (m)		7.80-8.05 (m)
2d	--	2.66, 3.78 (2d) 14.7	8.11 (dd) 7.5; 1.5	7.46 (ddd) 7.7;7.5;1.1	7.64 (ddd) 8.0;7.3;1.5	8.15 (dd)[b] 8.0;1.1
2e	--	3.73 (c)	7.80-8.00 (m)	-- 7.40-7.60 -- (m)		7.80-8.00[c] (m)
2f	4.45 (s)	--	8.04 (dd) 7.7;1.2	7.39 (dd) 7.7;7.7	7.60 (ddd) 8.0;7.7;1.2	8.20(d)[d] 8.0
2g	--	4.69 (s)	7.82 (dd) 6.2;2.3	-- 7.30-7.65 -- (m)		7.99 (dd) 6.1;2.3

(a) NMR data of predominant tautomer, recorded on a Varian Gemini-200 Spectrometer in $CDCl_3$ solution with TMS as internal standard; s= singlet, d= doublet, dd= double doublet, ddd= double double doublet, c= quadruplet, m= multiplet, J values in Hz; (b) C_2-CH_3 at 1.57 ppm as a singlet; (c) C_3-CH_3 at 1.09 ppm as a doublet, J= 6.8 Hz; (d) $C_3(CH_3)_2$ as two singlets at 1.20 and 1.60 ppm.

Table 3. ^{13}C-NMR[a] Signals of the Common Cyclic System in Compounds 2a-g.

Comp.[b]	C-1	C-2	C-3	C-4	C-4a	C-5[c]	C-6[c]	C-7	C-8	C-8a	C^2-CO
2a (B)	183.15	57.69	45.76	105.34	130.11	127.50	127.80	125.92	131.85	133.90	188.83
2b (B)	182.12	56.05	50.75	110.10	137.08	d	d	d	133.02	139.50	188.50
2c (A)	192.08	50.00	36.25	95.60	---	129.05	128.90	127.81	134.83	---	172.29
2c (B)	164.46	50.94	32.98		---	128.61	126.28	125.38	131.64	---	
2d (A)	194.02	51.67	44.36	64.30	131.18	128.62	128.78	127.95	134.17	143.12	172.80
2e (B)	163.20	54.00	34.52	102.20	131.14	127.11	128.58	125.52	131.88	139.54	172.80
2f (A)	192.76	61.61	47.62	64.02	130.29	128.18	128.36	127.89	133.65	146.15	169.82
2g (B)	164.05	56.00	48.01	101.46	131.10	127.41	127.73	125.75	132.05	139.95	172.78

(a) Recorded on a Varian Gemini-200 Spectrometer in $CDCl_3$ solution; (b) Predominant tautomeric form; (c) Interchangeable signals; (d) Indistinguishable from the other aromatic signals.

General Procedure. Methyl 2-(1,3-dithian-2-yl)benzoate **1** (200 mg, 0.79 mmol) was dissolved in anh. THF (3 mL). The solution was cooled to -78 °C and LDA in anh. THF (0.4 mL of 2 M solution) was added, the mixture was stirred for 15 min and one equivalent of conjugated carbonyl compound dissolved in anh. THF (2 mL) was slowly added. After 3 hours at -78 °C, the mixture was heated at room temperature and stirred for 12 h, acidified with aqueous solution of NH_4Cl (10 mL, 5 %),and extracted with diethyl ether (3 x 5 mL). The ethereal layer was dried over anh. Na_2SO_4, the solvent removed and the residue purified by chromatography over silica gel with methylene chloride as eluent.

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