A CONVENIENT APPROACH TO PENTAGONAL 2,3': 5',2"-TRIHETEROCYCLIC COMPOUNDS

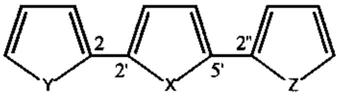
Ainhoa Rámila, Joaquín Plumet,* and Emilio Camacho

Universidad Complutense, Facultad de Química, Departamento de Química Orgánica I, E-28040 Madrid, Spain

Dedicated to Mª Victoria Martín Ramos. In Memoriam.

Abstract- A convenient synthesis of pentagonal 2,3': 5',2"-triheterocyclic compounds has been achieved using as key step the conjugate addition of 2-lithio-1,3-dithiane to 1,3-*bis* heterocyclic propenones.

Extended triheterocyclic compounds are of interest in fields such as agriculture and material science.[1] In addition, some of these compounds have been used as precursors for the preparation of more complex polyheterocyclic systems.[2] In the case of pentagonal triheterocyclic compounds, the major research concerns to the synthesis of 2,2':5',2"-**1** and 2,3':4',2"-**2**-disubstituted derivatives.[3] However, the synthesis of the related 2,3': 5',2"-systems, constituted by equal or different heterocyclic moieties (**3**), has received very little attention.[4]



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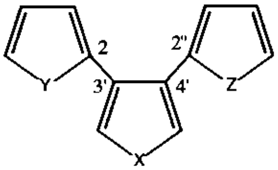

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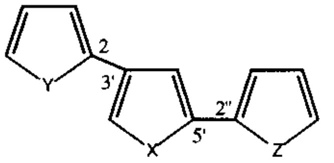

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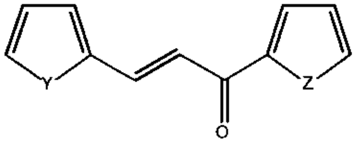

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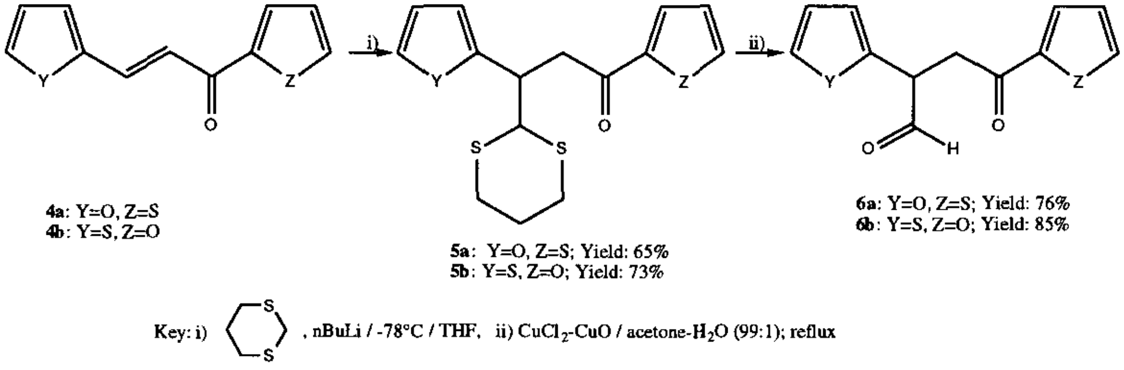
In this report we wish to account for a convenient method in order to prepare compounds such as **3** using the α,β-unsaturated ketone (**4**) as starting material. The key step in our synthetic approach is the introduction of a formyl group equivalent in conjugate fashion on **4**. Heterocyclization of the resulting βoxo aldehyde should give **3**. To the best of our knowledge, there are no known procedures for converting heterocyclic enones such as **4** in the related keto aldehydes using the conjugated addition of a formyl group anion equivalent, followed by unmasking to a formyl group. On the other hand, it is well known that the lithiated derivative of 1,3-dithiane reacts with alkenals and alkenones in the presence of HMPA[5] to give conjugate addition products in variable yields. In our hands, reaction of compounds (**4a-b**) with 2-lithio-1,3-dithiane (generated *in situ* from 1,3-dithiane and ^{n}BuLi at -78°C in THF) in the presence of HMPA afforded poor isolated yields of **5**. Nevertheless, when the reaction was achieved in absence of any additive, acceptable yields of products (**5**) were obtained (Scheme 1) and transformed in the related aldehydes **6** using the system $CuCl_2$ / CuO.[6]



4a: Y=O, Z=S
4b: Y=S, Z=O

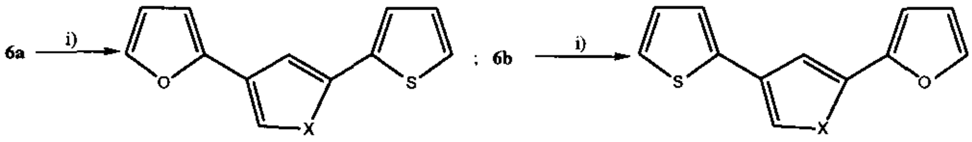
5a: Y=O, Z=S; Yield: 65%
5b: Y=S, Z=O; Yield: 73%

6a: Y=O, Z=S; Yield: 76%
6b: Y=S, Z=O; Yield: 85%

Key: i) , nBuLi / -78°C / THF, ii) $CuCl_2$-CuO / acetone-H_2O (99:1); reflux

Scheme 1

Heterocyclizations of **6** were achieved on the crude aldehyde without further purification. In this way, triheterocycles (**8**) and (**10**) were isolated in almost quantitative yields in the reaction crude. Further purification afforded these compounds in 70% and 76% isolated yield respectively, whereas compounds (**9**) and (**11**) have been obtained in 60% and 50% yields respectively (Scheme 2). *N*-Methylpyrrole derivatives were prepared by reaction of compounds (**6**) with methylamine hydrochlroride[7] whereas thienyl derivatives were synthesized using the Lawesson's reagent.[7]



8: X=N-Me; **9**: X=S

10: X=N-Me; **11**: X=S

i) $MeNH_2$. HCl for **8** and **10**; Lawesson's reagent for **9** and **11**

Scheme 2

In summary, in this report a convenient and versatile approach for pentagonal 2,3': 5',2"-triheterocyclic compounds is described.

EXPERIMENTAL

Compounds (**4a**) and (**4b**) were synthesized by aldolic reaction of 2-furfural or 2-thiophenecarboxaldehyde and 2-acetylfuran or 2-acetylthiophene respectively in ethanol with NaOH 10%. Cold water was added to the reaction mixture and the precipitate was filtered and crystallizated (EtOH/water) yielding **4a** (90%, mp: 54-55°C) and **4b** (86%, mp: 93-84°C).

1-(2-Thienyl)-3-(2-furyl)-3-(2,4-dithianyl)propanone (5a). Under Ar, ^{n}BuLi (4.99 mmol, 1.6 M in hexane) was added at -78°C to a solution of 1,3-dithiane (500 mg, 4.16 mmol) in THF (2 mL). The mixture was stirred at -20°C for 1 h and cooled to -78°C. Then 1-(2-thienyl)-3-(2-furyl)propenone (850 mg, 4.16 mmol) was added. After stirring for 5 h, the solution was quenched with sat. NH_4Cl and extracted with ether. The organic layer was washed with water and sat. NaCl, dried over $MgSO_4$ and concentrated in vacuo. The crude reaction mixture was chromatographed on silica gel using hexane-ethyl acetate (10:1) to produce 875 mg (65%) of pure **5a** as an oil. ^{1}H-NMR ($CDCl_3$,): δ 7.69 (dd, 1H, J= 4.0 and 1.0 Hz, H-C5'), 7.56 (dd, 1H, J= 5.1 and 1.0 Hz, H-C3'), 7.27 (d, 1H, J= 1.8 Hz, H-C5"), 7.05 (dd, 1H, J= 5.1 and 4.0 Hz, H-C4'), 6.21 (dd, 1H, J=3.2 and 1.8 Hz, H-C4"), 6.13 (d, 1H, J= 3.2 Hz, H-C3"), 4.35 (d, 1H, J=6.5 Hz, dithiane CH), 3.98-3.90 (m, 1H, H-C3), 3.47 (ABX system, δ_A=3.60, δ_B=3.33, 2H, J=17.0 Hz and 5.0 Hz, H-C2), 2.79-2.74 and 2.05-1.96 (m, dithiane CH_2) ppm, ^{13}C-NMR ($CDCl_3$) δ 190.40 (C=O), 153.32 (C2"), 144.08 (C2'), 141.77 (C5"), 134.99 (C3'), 132.24 (C4'), 128.26 (C5'), 110.37 (C3"), 107.88 (C4"), 51.14 (dithiane CH), 40.30 (C2), 39.35 (C3), 30.23 and 25.79 (dithiane $\underline{C}H_2$) ppm. Anal. Calcd for $C_{15}H_{16}O_2S_3$: C, 64.71; H, 3.92. Found: C, 64.85; H, 4.01.

1-(2-Furyl)-3-(2-thienyl)-3-(2,4-dithianyl)propanone (5b). The same procedure was applied to 850 mg (4.16 mmol) of 1-(2-furyl)-3-(2-thienyl)propenone. After 5 h of stirring the reaction mixture was worked up and purified as before, to yield 984 (73%) mg of pure **5b** as an oil. ^{1}H-NMR ($CDCl_3$,): δ 7.42 (d, 1H, J= 1.8 Hz, H-C5'), 7.11-7.06 (m, 2H, H-5" and H-C3"), 6.88 (d, 1H, J= 3.7 Hz, H-C3'), 6.80 (dd, 1H, J= 2.7 and 1.8 Hz, H-C4"), 6.40 (dd, 1H, J=3.7 and 1.8 Hz, H-C4'), 4.25 (d, 1H, J=6.3 Hz, dithiane CH), 4.11-4.07 (m, 1H, H-C3), 3.44 (ABX system, δ_A=3.48, δ_B=3.28, 2H, J=17.1 Hz and 6.0 Hz, H-C2), 2.75-2.70 and 1.94-1.90 (m, dithiane CH_2) ppm, ^{13}C-NMR ($CDCl_3$) δ 186.41 (C=O), 152.61 (C2'), 146.62 (C5'), 143.46 (C2"), 126.59 (C3"), 126.27 (C4"), 124.40 (C5"), 117.52 (C3'), 112.41 (C4'), 53.49 (dithiane CH), 42.66 (C2), 40.69 (C3), 30.49 and 25.74 (dithiane CH_2) ppm. Anal. Calcd for $C_{15}H_{16}O_2S_3$: C, 64.71; H, 3.92. Found: C, 64.92; H, 3.88.

2-(2-Thienyl)4-(2-furyl)-4-oxabutanal (6a). Under Ar, CuO (324 mg, 4.08 mmol) and $CuCl_2$ (274 mg, 2.02 mmol) were added to a solution of **5a** (330 mg, 1.01 mmol) in acetone-water (99:1, 10 mL). After reflux for 6 h, the reaction mixture was washed with hexane-CH_2Cl_2 (1:1) and extracted with 5M $AcONH_4$. The organic layer was washed with water and sat. NaCl, dried over $MgSO_4$ and the solvent was evaporated in vacuo. Yield: 180 mg of oil (76%, from crude's ^{1}H-NMR spectrum). ^{1}H-NMR ($CDCl_3$,): δ 9.67 (s, 1H, H-CO), 7.69 (dd, 1H, J= 3.8 and 1.1 Hz, H-C5'), 7.56 (dd, 1H, J= 4.9 and 1.1 Hz, H-C3'), 7.31 (d, 1H, J= 1.8 Hz, H-C5"), 7.04 (dd, 1H, J= 4.9 and 3.8 Hz, H-C4'), 6.28 (dd, 1H, J=3.3 and 1.8 Hz, H-C4"), 6.21 (d, 1H, J= 3.3 Hz, H-C3"), 4.41 (q, 1H, J= 7.5 Hz, H-C3), 3.46 (ABX system, δ_A=3.47, δ_B=3.45, 2H, J=17.6 Hz and 7.5 Hz, H-C2), ppm, ^{13}C-NMR (CDCl$_3$) δ 196.70 (CH=O), 189.75 (C=O), 148.94 (C2"), 143.39 (C2'), 143.22 (C5"), 134.18 (C3'), 132.45 (C4'), 128.31 (C5'), 110.95 (C3"), 108.79 (C4"), 47,33 (C3), 37.36 (C2) ppm.

2-(2-Furyl)4-(2-thienyl)-4-oxabutanal (6b). The same procedure was used with **5b** (480 mg, 1.48 mmol) and after 6 h reflux the reaction mixture was worked up as above to yield **6b** as an oil (236 mg, 85%, from crude's ^{1}H-NMR spectrum).^{1}H-NMR (CDCl$_3$,): δ 9.66 (s, 1H, H-CO) 7.51 (d, 1H, J= 1.7 Hz, H-C5'), 7.20 (dd, 1H, J= 5.1 and 1.0 Hz, H-C3'), 7.15 (dd, 1H, J= 3.5 and 1.0 Hz, H-C5"), 6.94 (dd, 1H, J= 5.1 and 3.7 Hz, H-C4"), 6.88 (d, 1H, J= 3.6 Hz, H-C3'), 6.46 (dd, 1H, J=3.6 and 1.7 Hz, H-C4'), 4.57 (q, 1H, J= 8.0 Hz, H-C3), 3.41 (ABX system, δ_A=3.99, δ_B=32.88, 2H, J=17.7 Hz and 8.0 Hz, H-C2) ppm, ^{13}C-NMR (CDCl$_3$) δ 197.06 (CHO), 185.95 (C=O), 152.24 (C2'), 146.78 (C5'), 137.15 (C2"), 127.73 (C3"), 126.94 (C4"), 126.05 (C5"), 117.90 (C3'), 112.54 (C4'), 48.00 (C3), 39.50 (C2) ppm.

2-(2-Thienyl)-4-(2-furyl)-*N*-methylpyrrole (8). Compound (**6a**) (123 mg, 0.52 mmol), methylamine hydrochloride (35 mg, 0.52 mmol) and sodium acetate (1424 mg, 10.47 mmol) were refluxed in 7 mL of ethanol for 2 h under Ar. The reaction mixture was cooled and 20 mL of water was added. The solid formed was chromatographed on silica gel using hexane-ethyl acetate (10:1) to produce 83 mg (70%) of pure **8** as a yellow solid. ^{1}H-NMR (CDCl$_3$,): δ 7.26 (d, 1H, J= 1.8 Hz, H-C5"), 7.21 (dd, 1H, J= 4.8 and 1.5 Hz, H-C3'), 7.06-6.96 (m, 2H, H-C4' and H-C5'), 6.89 (d, 1H, J= 1.9 Hz, H-C5), 6.44 (d, 1H, J= 1.9 Hz, H-C3), 6.32 (dd, 1H, J= 3.2 and 1.8 Hz, H-C4"), 6.20 (d, 1H, J= 3.2 Hz, H-C3"), 3.63 (s, 3H, H-N-C$\underline{H}_3$) ppm, ^{13}C-NMR (CDCl$_3$) δ 151.07 (C2"), 140.09 (C5"), 134.37 (C2'), 127.99 (C2), 127.49 (C3'), 125.48 (C4'), 125.03 (C5'), 120.41 (C5), 115.66 (C4), 111.17 (C3"), 107.00 (C4"), 102.18 (C3), 35.41 (CH$_3$) ppm.

2-(2-Thienyl)-4-(2-furyl)thiophene (9). A mixture of compound (**6a**) (170 mg, 0.73 mmol) and Lawesson´s reagent (178 mg, 0.44 mmol) was refluxed for 3 h in 5 mL of toluene. The toluene was evaporated and the residue was chromatographed in hexane-ethyl acetate (10:1) to yield 101 mg (60%) of **9** as a yellow solid. ^{1}H-NMR (CDCl$_3$,): δ 7.33 (d, 1H, J= 1.8 Hz, H-C5"), 7.29 (d, 1H, J= 1.3 Hz, H-C5), 7.24 (d, 1H, J= 1.3 Hz, H-C3), 7.15 (dd, 1H, J= 5.1 and 1.0 Hz, H-C3'), 7.12 (dd, 1H, J= 3.6 and 1.0 Hz, H-C5'), 6.94 (dd, 1H, J= 5.1 and 3.6 Hz, H-C4'), 6.41 (d, 1H, J= 3.3 Hz, H-C3"), 6.36 (dd, 1H,J= 3.3 and 1.8 Hz, H-C4') ppm, ^{13}C-NMR (CDCl$_3$) δ 150.68 (C2"), 141.63 (C5"), 138.19 (C4), 137.06 and 133.16 (C2 and C2'), 127.96, 124.84, 124.21, 121.11 and 117.75 (C3, C3', C4', C5 and C5'), 111.48 (C3"), 105.11 (C4") ppm.

2-(2-Furyl)-4-(2-thienyl)-*N*-methylpyrrole (10). The same procedure used for the synthesis of **8** was applied to **6b** (147 mg, 0.63 mmol) to yield 109 mg (76%) of **10** as a yellow solid. ^{1}H-NMR (CDCl$_3$,): δ 7.36 (d, 1H, J= 1.7 Hz, H-C5'), 7.00 (dd, 1H, J= 4.9 and 1.2 Hz, H-C3"), 6.95 (dd, 1H, J= 3.5 and 1.2 Hz, H-C5"), 6.90 (dd, 1H, J= 4.9 and 3.5 Hz, H-C4"), 6.79 (d, 1H, J= 1.9 Hz, H-C5), 6.53 (d, 1H, J= 1.9 Hz, H-C3), 6.37 (dd, 1H, J= 3.3 and 1.7 Hz, H-C4'), 6.30 (d, 1H, J= 3.3 Hz, H-C3'), 3.66 (s, 3H, H-N-C$\underline{H}_3$) ppm, ^{13}C-NMR (CDCl$_3$) δ 147.48 (C2'), 141.51 (C5'), 139.03 (C2"), 127.60 (C3"), 125.89 (C2), 121.91 (C4"), 121.16 (C5"), 120.90 (C5), 118.42 (C4), 111.25 (C3'), 106.99 (C4'), 106.02 (C3), 35.98 (CH$_3$) ppm.

2-(2-Furyl)-4-(2-thienyl)thiophene (11). The same procedure used for the synthesis of **9** was applied to **6b** (63 mg, 0.27 mmol) to yield 31 mg (50%) of **11** as a yellow solid. ^{1}H-NMR (CDCl$_3$,): δ 7.45 (d, 1H, J= 1.5 Hz, H-C5"), 7.43 (d, 1H, J= 1.4 Hz, H-C5), 7.26 (d, 1H, J= 1.4 Hz, H-C3), 7.23 (d, 2H, J= 4.5 Hz, H-C3" and 5"), 7.05 (t, 1H, J= 4.5 Hz, H-C4"), 6.56 (d, 1H, J= 3.3 Hz, H-C3'), 6.47 (dd, 1H, J= 3.3 and 1.5 Hz, H-C4') ppm, ^{13}C-NMR (CDCl$_3$) δ 149.01 (C2'), 141.90 (C5'), 138.84 (C4), 136.03 and 134.45 (C2 and 2"), 127.73, 124.07, 123.36, 121.29 and 118.13 (C3, C3", C4", C5" and C5), 111.76 (C3'), 105.52 (C4') ppm.

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