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NOVEL SYNTHESIS OF SOME TRICYCLIC KETONES VIA LITHIUM DI-ISOPROPYLAMIDEMEDIATED CYCLIZATION OF 2-o-CARBOXYPHENYL ETHENYLFURANS, THIOPHENS, AND SELENOPHENS

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Abstract—The syntheses of 10H-benzo[4, 5]cyclohepta[2, 1-*b*]-thiophen-10-one 10H-benzo[4, 5]cyclohepta[2, 1-*b*]selenophen-10-one, and 10H-benzo[4, 5]cyclohepta[2, 1-*b*]furan-10-one(**1a–c**) by lithiumdiisopropylamide-induced cyclization of (*Z*)-2-[2-(3-thienyl)-vinyl]benzoic acid, (*Z*)-2-[2-(3(selenienyl)vinyl]benzoic acid and (*Z*)-2-[2-(3-furano)vinyl]benzoic acid (**2a–c**), respectively, are reported.

In connection with studies of heterocyclic-fused tropylium ions,[1] we planned to use the ketones **1a–c**, as synthetic intermediates. Cyclization of the corresponding *Z*-acids **2a–c** was considered as a possible means to obtain these ketones. However, in contrast to 2-[2-(3-thienyl)ethyl]benzoic acid, **3**, which undergoes cyclization smoothly under commonly used acid-catalyzed conditions,[2] the unsaturated analogue, (*Z*)-2-[2-(3-thienyl)vinyl]benzoic acid, **2a**, gave only a low yield of **1a**. Also, several by-products and a considerable amount of tar were formed. We found, however, that it was possible to achieve cyclization to all three ketones **1**, via lithiation of the lithium salts of **2**. Here we report a study of this modification of the Parham cyclo-acylation reaction.[3-5]

Mixtures of the *Z*- and *E*-isomers, **5** and **6** respectively, were prepared by Wittig reaction of o-carboxybenzyltriphenylphosphonium bromide methyl ester, **7**, with the appropriate 3-formyl heterocycle, **8**, using sodium methoxide as base. The *Z*/*E* ratio of the isomers was 50/50 starting from 3-formylfuran **8c**, and 70/30 starting from 3-formylthiophene **8a** or 3-formylselenophene **8b**. Reaction of 3-thenylphosphonium bromide with methyl o-formylbenzoate resulted in a lower yield of the *Z*-isomer **5a** (*Z*/*E*; 58/42). The thiophen and furan *Z*-isomers, **5a** and **5c** respectively, were easily obtained pure after distillation, whereas the selenophene analogue **5b**, could be separated from the *E*-isomer due to its higher solubility in hexane. The esters **5a–c** were hydrolyzed with aqueous sodium hydroxide to give the *Z*-carboxylic acids **2a–c**.

The carboxylic acids (*Z*)-2-[2-(3-thienyl)-vinyl]benzoic acid, **2a**, (*Z*)-2-[2-3-(selenienyl)vinyl]benzoic acid, **2b**, and (*Z*)-2-[2-(3-furano)vinyl]benzoic acid, **2c**, respectively, were treated with 2 eqv of lithium diisopropylamide in ether/hexane at room temperature, and after 2 hrs the tropones **1** were isolated in yields of 59% (**1a**), 65% (**1b**) and 42% (**1c**). According to NMR and GC analysis, the only products formed were the ketones, and the uncyclized carboxylic acids **2** could be recovered in good yields. Work-up 5 min after completed addition of the metalation reagent gave slightly lower yields, whereas prolonged reaction times (over-night) increased the yields with approx. 5% on average. An attempt to increase the yields of ketones **1**, by using 3 eqv of lithium diisopropylamide gave the same amounts of **1**, but led also to formation of by-products, particularly when starting from the furan derivative **2c**. It is of interest, from a preparative point of view, to note that only slightly lower yields of **1**, based on the amount of *Z*-isomer **2**, were obtained when mixtures of acids **2** and **9** were treated with 3 eqv of the lithiation reagent. Thus, in the preparation of the tricyclic systems **1**, a mixture of *Z*- and *E*-acids can be used, thereby making initial separation of isomers **5** and **6** superfluous.

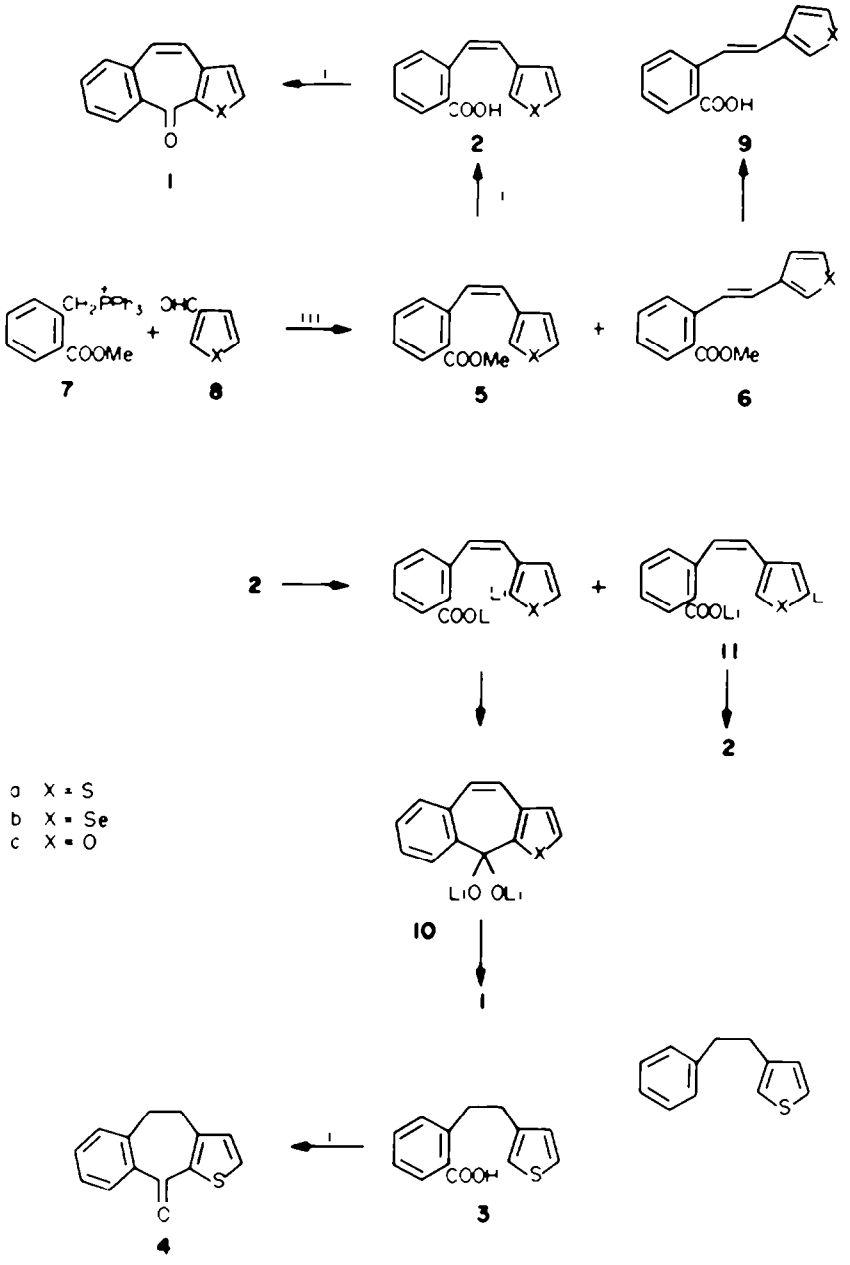
Formation of ketones from arylithium and lithium carboxylates has been extensively studied.[6-9] The work-up procedure in these reactions has been reported to be of great importance for the yields of ketones. The use of aniline or formaldehyde, instead of water, as hydrolyzing agent has been reported to give higher yields of ketones.[6] However, in the preparation of **1**, no improvement of yields was noticed using this method of work-up.

The results concerning the cyclization can be interpreted by the assumption that the lithium salts of the carboxylic acids **2** are formed and that, then, the second equivalent of the lithium diisopropyl-amide metalates the 2-position of the heterocyclic ring. Spontaneous intramolecular trapping then produces a dilithio-alkoholate **10**, inert to further attack by the lithiation reagent. The fact that 26–35% of the starting material is recovered, can be explained by the assumption that lithiation of **2** occurs not only in the 2-position, but also in the 5-position, giving the lithium intermediate **11**, which is hydrolyzed during work-up to give **2**.

It has recently been reported[10] that lithium di-isopropylamide lithiates phenyl-2-(3-thienyl)ethane, **12**, in the 2- and 5-positions of the thiophen ring, in a 17/83 ratio. Because of the comparatively low degree of 2-lithiation, due to the absence of an electron withdrawing 3-substituent, we considered it interesting to study the metalation of the corresponding carboxylic acid **3**. A high yield of ketone would indicate involvement of directed metalation by the carboxylate group. However, only a low yield, 4% (12% GC), of 10H-4, 5-dihydro-benzo[4, 5]cyclohepta[2, 1-b]thiophen-10-one **4**, was obtained after treatment of **3** with two eq lithium diisopropyl amide, indicating that no heteratom-facilitated metalation is involved in this system.

EXPERIMENTAL

All temperature readings are uncorrected. ^{1}H NMR spectra were recorded on Jeol MH-100 and PMX-60 instruments, using tetramethylsilane as internal standard and solvents as specified.



Infrared spectra were recorded on a Perkin–Elmer 298 spectrophotometer. Mass spectra were recorded on a Finnigan 4021 mass spectrometer equipped with GLC inlet. Elemental analyses were made by the Analytical Department, Chemical Center, and by Ilse Beetz Microanalytical Laboratories, Kronach, West Germany. All experiments using butyl-lithium were carried out under an inert atmosphere of dry nitrogen. Gas chromatograms were recorded with a Varian 1400 Gas Chromatograph equipped with a SE 30, 1.6 m column and FID.

(Z)-Methyl-2-[2-(3-thienyl)vinyl]benzoate (5a)

o-Carboxybenzyl triphenylphosphonium bromide methyl ester[11] (53.0 g, 0.11 mol) was stirred with 200 ml DMF. At 0°, freshly prepared sodium methoxide (10.2 g, 0.16 mol) was added. The deep red solution was stirred for 30 min, and then 3-formylthiophen[12] (12.0 g, 0.11 mol) in 50 ml of dimethylformamide was added dropwise (15 min). Stirring was continued for one hr at room temperature. Dilute hydrochloric acid and ice were added followed by extraction with ether. Evaporation gave a mixture of the *Z*- and *E*-isomers (70/30), together with triphenylphosphine oxide. This crude product was extracted with hexane. Evaporation and distillation gave pure *Z*-isomer, 15.1 g (58%), b.p. 156–8°/0.3 mmHg. IR: $\nu_{C=O}$ 1720 cm^{-1}, *m/e* 244 (M^+), 185 (100%). NMR ($CDCl_3$): δ 8.00–6.56 (m, 9H), $J_{CH=CH}$ = 11.7 Hz, 3.90 (s, 3H) (Found: C, 68.71; H, 4.82; S, 13.12. Calc for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12%).

This compound was also prepared as above, but from 3-thenyl-triphenylphosphonium bromide[13] and methyl o-formylbenzoate[14] giving a *Z*/*E* ratio of 58/42 instead and an isolated yield of cis isomer of 42%.

(Z)-Methyl-2-[2-(3-selenienyl)vinyl]benzoate (5b)

From 9.0 g (56 mmol) of 3-formylselenophen,[14] 10.1 g (62%) of the title compound was obtained, following the same procedure as above, with the exception that *Z*- and *E*-isomers were separated by means of their different solubilities in hexane. The *Z*-isomer was obtained by hexane extraction of the crude product. An analytical sample was obtained by chromatography

(silica–toluene). IR: $\nu_{C=O}$ 1715 cm^{-1}. *m/e* 292 (M$^+$), 152 (100%). NMR (CS_2): δ 6.30–7.90 (m, 9H), $J_{CH=CH}$ = 11.8 Hz, 3.68 (s, 3H). (Found: C, 58.14; H, 4.45; Se, 27.03. Calc. for $C_{14}H_{12}O_2Se$: C, 57.74; H, 4.15; Se, 27.11%).

(Z)-Methyl-2-[2-(3-furyl)vinyl]benzoate (**5c**)

From 8.0 g (83 mmol) of 3-formylfuran[16] 8.1 g (42%) of the title compound was obtained, following the same procedure as for the thiophen analogue, b.p. 128–130°/2 mmHg. IR: $\nu_{C=O}$ 1718 cm^{-1}. *m/e* 228 (M$^+$), 141 (100%). NMR (CS_2): 7.85–5.6 (m, 9H), $J_{CH=CH}$ = 11.7 Hz, 3.71 (s, 3H). (Found: C, 72.74; H, 5.42. Calc. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%).

(Z)-2-[2-(3-Thienyl)vinyl]benzoic acid (**2a**)

8.0 g (32 mmol) of the methyl ester **5a** was stirred with 150 ml of 0.5N aqueous sodium hydroxide at 80–100° overnight. Acidification and extraction with ether gave, after evaporation and recrystallisation from toluene, 6.1 g (83%) of the title acid, m.p. 127–129.5°. IR: $\nu_{C=O}$ 1680 cm^{-1}. *m/e* 130 (M$^+$), 185 (100%). NMR (acetone-d_6): δ 8.1–6.5 (m, 9H), $J_{CH=CH}$ = 11.8 Hz, 3.69 (s, 1H). (Found: C, 67.36; H, 4.30; S, 13.72. Calc. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.92%).

(Z)-2-[2-(3-Selenienyl)vinyl]benzoic acid (**2b**)

From 9.0 g (31 mmol) of methyl ester, 6.7 g (78%) of the title acid was obtained as above, m.p. (toluene) 139–140°. IR: $\nu_{C=O}$ 1680 cm^{-1}. *m/e* 278 (M$^+$), 152 (100%). NMR (acetone-d_6): δ 8.2–6.4 (m, 9H), $J_{CH=CH}$ = 11.7 Hz, 4.4 (s, 1H). (Found: C, 56.42; H, 3.62; Se, 28.41. Calc. for $C_{13}H_{10}O_2Se$: C, 56.33; H, 3.64; Se, 28.49%).

(E)-2-[2-(3-Selenienyl)vinyl]benzoic acid (**9b**)

The hexane-insoluble part of the crude product obtained from the Witting reaction of 3-formylselenophen with (7) was hydrolyzed by heating overnight with 250 ml of 0.5 N aqueous sodium hydroxide at 80–100°. After extraction with ether, the aqueous phase was acidified and the precipitated acid was extracted with ether. Drying and evaporation gave *E*-acid **9b**, which was recrystallized from toluene. Yield 2.1 g (13.5%), m.p. 157–9°. *m/e* 278 (M$^+$), 152 (100%). NMR (acetone-d_6); δ 8.17–7.06 (m, 9H), $J_{CH=CH}$ = 16.2 Hz, 5.04 (s, 1H). (Found: C, 56.91; H, 3.77; Se, 28.50. Calc. for $C_{13}H_{10}O_2Se$: C, 56.33; H, 3.64; Se, 28.49%).

(Z)-2-[2-(3-Furyl)vinyl]benzoic acid (**2c**)

From 5.5 g (24 mmol) of the methyl ester **5c**, 4.3 g (83%) of the title acid (**2c**) was obtained as above, m.p. (toluene) 97–100°. IR: $\nu_{C=O}$ 1680 cm^{-1}. *m/e* 214 (M$^+$), 141 (100%). NMR (acetone-d_6): δ 8.1–5.8 (m, 9H), $J_{CH=CH}$ = 11.7 Hz, 4.95 (s, 1H). (Found: C, 72.91; H, 4.78. Calc. for $C_{13}H_{10}O_3$: C, 72.81; H, 4.70%).

(E)-2-[2-(3-Furyl)vinyl]benzoic acid (**9c**)

The distillation residue, obtained after distilling ester **5c**, was heated overnight with 200 ml of 0.5 N aqueous sodium hydroxide. After washing the aqueous phase with ether, dilute hydrochloric acid was added, and the acid was taken up in ether. Evaporation and recrystallisation from toluene gave 1.1 g (6%) of acid **9c**, m.p. 158–159°, *m/e* 214 (M$^+$), 141 (100%). NMR (acetone-d_6): δ 7.96–6.75 (m, 9H), $J_{CH=CH}$ = 16.2 Hz, 5.0 (s, 1H). (Found: C, 73.15; H, 4.96. Calc. for $C_{13}H_{10}O_3$: C, 72.81; H, 4.70%).

General procedure for the preparation of ketones **1a–c**

To 200 ml of dry ether, 14.2 ml (21.2 mmol) of butyllithium (1.55 N in hexane) was added under an atmosphere of dry nitrogen, followed by 3.2 ml (22 mmol) of diisopropylamine in 25 ml of ether. After 15 min at room temperature, the acid (10 mmol) in ether was added rapidly. After two hr, water was added and the organic phase was washed with dilute aqueous sodium hydroxide and water. Drying and evaporation gave the cyclic ketones **1a–c**. These were purified by recrystallisation from ethanol, if not otherwise stated.

10H-*Benzo*[4, 5]*cyclohepta*[2, 1-*b*]*thiophen*-10-*one*(**1a**)

From 2.30 g (10 mmol) of *cis* acid **2a**, 1.25 g (59%) of the title ketone was obtained, m.p. 108–109°. IR: 1560 cm^{-1} (C=O), *m/e* 212 (M$^+$), 184 (100%). NMR ($CDCl_3$): δ 8.78 (m, 1H, benzene), 7.69 (d, 1 H, thiophen), 7.26 (d, 1H thiophen), $J_{2,3}$ = 5.2 Hz, 7.66 (m, 3H, benzene), 7.17 (s, 2H, CH=CH) (Found: C, 73.50; H, 3.96; S, 14.82%. Calc. for $C_{13}H_8OS$: C, 73.56; H, 3.80; S, 15.10%).

10H-*Benzo*[4, 5]*cyclohepta*[2, 1-*b*]*selenophen*-10-*one*(**1b**)

From 2.8 g (10 mmol) of *cis* acid **2b**. 1.7 g (65%) of the title ketone was obtained, m.p. 97–99°. IR: 1540 cm^{-1} (C=O). *m/e* 260 (M$^+$), 152 (100%). NMR ($CDCl_3$): δ 8.78 (m, 1H, benzene), 8.40 (d, 1H, selenophen), 7.66 (d, 1H, selenophen), $J_{2,3}$ = 5.6 Hz, 7.72 (m, 3H, benzene), 7.35 (d, 1H, CH=CH), 7.20 (d, 1H, CH=CH), $J_{CH=CH}$ = 11.6 Hz. (Found: C, 59.79; H, 3.32; Se, 30.36. Calc. for $C_{13}H_8OSe$: C, 60.25; H, 3.11; Se 30.47%).

10H-*Benzo*[4, 5]*cyclohepta*[2, 1-*b*]*furan*-10-*one* (**1c**)

From 2.1 g (10 mmol) of *cis* acid **2c**, 0.82 g (42%) of the title ketone was obtained, m.p. 149–150°. IR: 1580 cm^{-1} (C=O). *m/e* 196 (M$^+$), 168 (100%). NMR ($CDCl_3$): δ 8.95 (m, 1H, benzene), 7.55 (d, 1H, furan), 6.78 (d, 1H, furan), $J_{2,3}$ = 1.8 Hz, 7.73 (m, 3H, benzene), 7.32 (d, 1H, CH=CH) 7.09 (d, 1H, CH=CH), $J_{CH=CH}$ = 11.3 Hz. Found: C, 78.68; H, 4.27. Calc. $C_{13}H_8O_2$: C, 79.58; H, 4.11%).

4,5-*Dihydro*-10H-*benzo*[4, 5]*cyclohepta*[2, 1-*b*]*thiophen*-10-*on* (**4**)

To 2.8 ml (4.2 mmol) of 1.5 *N* butyllithium (hexane) in 40 ml of ether, 0.6 ml (4.3 mmol) of diisopropylamine was added under nitrogen. After stirring at room temperature for 15 min, 0.5 g (2.1 mmol) of acid (**3**)[2] was added in 10 ml of ether. The reaction mixture was stirred at room temperature for 90 min, whereupon water was added. The organic phase was washed with dilute, aqueous sodium hydroxide and 5 *N* hydrochloric acid. Evaporation gave an oil, which after TLC gave 18 mg (4%) of the title ketone, m.p. 53–55° (hexane). *m/e* 214 (M$^+$, 100%). Lit[2]: m.p. 57–59°. Most of the starting acid (**3**) was recovered. According to GLC of the crude product, the yield was 12% (internal standard).

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REFERENCES

[1]S. Gronowitz and P. Pedaja, *Tetrahedron* **34**, 587 (1978).
[2]J. M. Bastian, A. Ebnöther, E. Jucker, E. Rissi and A. P. Stoll, *Helv. Chim. Acta* **54**, 277 (1971).
[3]W. E. Parham, L. D. Jones and Y. Sayed, *J. Org. Chem.* **40**, 2394 (1975).
[4]R. J. Boatman, B. J. Whitlock and H. W. Whitlock, Jr., *J. Am. Chem. Soc.* **99**, 4822 (1977).
[5]D. C. Reames, D. A. Hunt and C. K. Bradsher, *Synthesis* 454 (1980).
[6]M. J. Jorgenson, *Org. React.* **18**, 1 (1970).
[7]R. Levine, M. J. Karten and W. M. Kadunce, *J. Org. Chem.* **40**, 1770 (1975).
[8]R. Levine and M. J. Karten, *J. Org. Chem.* **41**, 1176 (1976).
[9]D. E. Nicodem and M. L. P. F. C. Marchiori, *J. Org. Chem.* **46**, 3928 (1981).
[10]S. Gronowitz, K. Stenhammar and L. Svensson, *Heterocycles* **15**, 947 (1981).
[11]I. Hirao, T. Fujimoto, T. Morita, F. Tone and S. Kono, *Mem. Kyushu Inst. Technol.* **6**, 89 (1976).
[12]S. Gronowitz, *Arkiv Kemi* **8**, 441 (1956).
[13]D. W. Allen and B. G. Hutley, *J. Chem. Soc. Perkin* **2**, 67 (1972).
[14]C. Brown and M. V. Sargent, *J. Chem. Soc.* (*C*), 1818 (1969).
[15]S. Gronowitz, I. Johnson and A.-B. Hörnfeldt, *Chemica Scripta* **7**, 111 (1975).
[16]S. Gronowitz and U. Michael, *Arkiv Kemi* **32**, 283 (1971).