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AROMATIC RETINOIDS (PART 2)[1]: A SHORT AND CONVENIENT ROUTE TO 5-(5,6,7,8-TETRAHYDRO-5,5,8,8-TETRAMETHYL-2-ANTHRACENYL)-2-FURAN AND -2-THIOPHENE CARBOXYLIC ACIDS.

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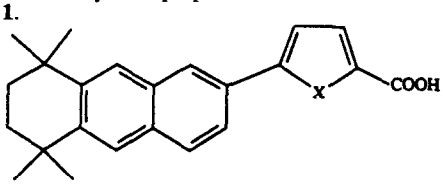
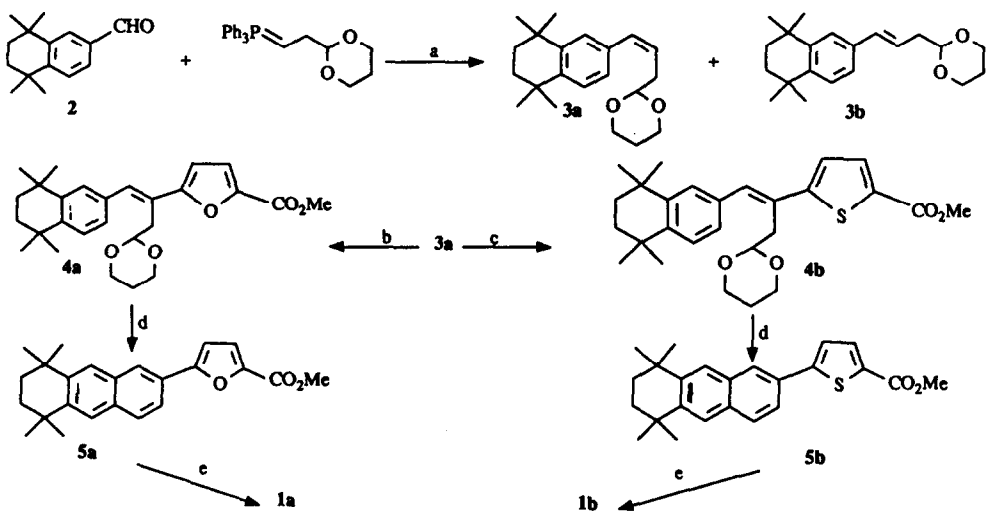
Abstract: *A convenient three step synthetic route starting from readily available materials was used for the synthesis of novel 5-(2-tetrahydroanthracenyl)-2-furan and -2-thiophenecarboxylic acid derivatives. The main features of the sequence are a Heck reaction between a substituted styrene derivative and bromo heterocycles, followed by high yield electrophilic cyclisation/aromatization of the intermediate thus obtained to afford the desired compounds.*

In the course of our research program,concerning the discovery of stable molecules with strong retinoid-like activity[2], we prepared several substituted heteroaromatic carboxylic acids of general formula **1**.



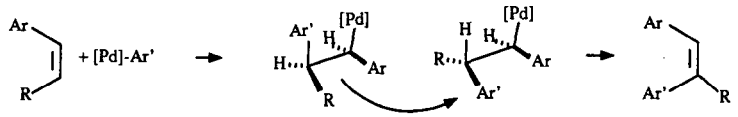
1a: X=O
1b: X=S

A simple coupling approach to the synthesis of **1** is not feasible since the preparation of a suitably substitued 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl was considered to be too cumbersome. We developed the synthetic route illustrated below, which provided a short regiospecific synthesis to the desired compounds.



a) THF, 0°C, 15mn, then 20°C, 30mn, 67%. b) 1. Methyl 5-bromo-2-furancarboxylate (1 eq), $Pd(OAc)_2$ (0.02 eq), Ph_3 (0.04 eq), K_2CO_3 (2 eq), 160°C, 2h; 2. Methyl 5-bromo-2-furancarboxylate (0.5 eq), $Pd(OAc)_2$ (0.02 eq), Ph_3 (0.04 eq), 160°C, 2h, 53%. c) 1. Methyl 5-bromo-2-thiophene carboxylate (1 eq), $Pd(OAc)_2$ (0.02 eq), Ph_3 (0.04 eq), K_2CO_3 (2 eq), 200°C, 2h; 2. Methyl 5-bromo-2-thiophenecarboxylate (0.5 eq), $Pd(OAc)_2$ (0.02 eq), Ph_3 (0.04 eq), 200°C, 2h. d) TMSOTf (cat), CH_2Cl_2, 0°C → 20°C, 30 mn, 96% (**5a**), 32% (**5b**, from **3a**). e) 2M methanolique NaOH, reflux, 4h, then HCl,93% (**1a**), 90% (**1b**).

Reaction of the known aldehyde **2**[3] with the phosphorane derived from commercially available [(1,3-dioxan-2-yl) ethyl]triphenyl phosphonium bromide afforded the mixture of styrene derivative **3** (yield:67%). Chromatography (silica gel,CH_2Cl_2/hexane, 4:1) afforded the pure Z and E isomers respectively **3a** and **3b** (ratio 9:1). Palladium catalyzed coupling of **3a** with methyl 5-bromo-2-furancarboxylate (excess ester, $(P\phi_3)_2/Pd(OAc)_2$ (cat),K_2CO_3, 160°C, neat), afforded after chromatography (silica gel,CH_2Cl_2/hexane, 4:1), the ester **4a** in 53% yield. Compound **4a** was tentatively assigned the E configuration on the basis of the nature of the product obtained in the subsequent step. Following treatment of **4a** with a catalytic amount of trimethylsilyl trifluoromethanesulfonate, cyclisation/aromatization occured to immediately afford the desired aromatic ester **5a** in 96% yield[4]. Thus the obtention of a E-stilbene derivative starting from a Z-styrene precursor deserves some comments. As we anticipated the product should in our case have the Z configuration (the Heck reaction involves cis addition of the aryl-[Pd] species followed by [Pd]-H β-elimination in a syn fashion, the overall result being inversion of the double bond configuration as shown below)[5].



Our result can be explained by the occurence of an additional inversion step. Indeed, careful TLC monitoring of the reaction mixture showed the transient appearance of a new product corresponding to **3b** suggesting that cis-trans isomerisation had occured under the reaction conditions. When **3b** pure was treated as above, formation of 70 % of **4a** was observed, thus confirming our hypothesis. Condensation of **3a** with methyl 5-bromo-2-thiophene carboxylate proved to be more difficult. Under forced conditions (excess ester, $(P\phi_3)_2/Pd(OAc)_2$, K_2CO_3, 200°C, neat) a mixture containing ester **4b** (60%) and **3b** (40%) was obtained[6]. **4b** and **3b** could not be separated and the mixture was used as such for the subsequent step. Treatment as described above (TMSOTf(cat), CH_2Cl_2) gave, after chromatographic separation and recrystallisation from cyclohexane, pure **5b** (overall yield: 32% from **3a**). After treatment with 2M methanolic sodium hydroxide, **5a** and **5b** were converted in 93% and 90% yield respectively into the corresponding carboxylic acids **1a** and **1b**.

The two acids were evaluated in biological assays for retinoid activity namely: induction of differentiation of F9 teratocarcinoma cells in culture[7] and inhibition of induced ornithine decarboxylase activity in tape stripped rat skin[8,9]. Compound **1a** was found to be weakly active in both tests whereas **1b** showed strong retinoid-like activity. Structure-activity relationships and further biological results for this series of compounds will be reported elsewhere.

References and notes:

1.Part 1: Eustache,J.; Bernardon,J.M.;Shroot,B. Tetrahedron; Lett. 1987, 4681.
2.For related work, see: Dawson,M.I.; R.L.S.Derdzinski,K.; Hobbs,P.D.; Chao,W-R.; Schiff,L.J. J.Med.Chem., 1983,**26**, 1653.
3.Wood,T.F.; Evans,W.F. (Givaudan corp.) US pat. 3499751, 1970; Chem. Abstr. 1970, **72**, 132389e. (In our laboratorie the aldehyde was prepared in 83% yield from 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-bromonaphthalene by conversion to the corresponding Grignard, and treatment with DMF).
4.**5a**: mp 126-127°C; **5b**: mp 147-148°C; **1a**: mp 229-230°C; **1b**:mp 254-255°C. These compounds produced satisfactory elemental analyses and spectral data (NMR, mass).
5.For a review on the Heck reaction, see: Davies,S.G. "Organotransition metal chemistry: Application to organic synthesis", Pergamon Press, 1982.
6.As determined by comparison of the 1H NMR signals attributed to **3b** and **4b**.
7.Strickland,S.; Sawey,M.J. Develop. Biol., 1980, **78**, 76.
8.Lowe,N.J.; Connor,M.J.; Ashton,R.; Wortzman,M. British J. of Dermatology, 1984,**III**,(27),98
9.Bouclier,M.; Shroot,B.; Eustache,J.; Hensby,C.N. J.of Pharmacological Methods, 1986, **16**, 151.

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