Phenanthrylalkanoic Acids, V[1]:

A Useful Access to α-Methylphenanthreneacetic Acids

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A very simple one-pot monomethylation of phenanthreneacetic acids **2** or of their methyl esters **1** yields α-methylphenanthreneacetic acids **3** in good yield. Alternatively, the process may be extended to the preparation of the corresponding α-arylisobutyric acids **4**.

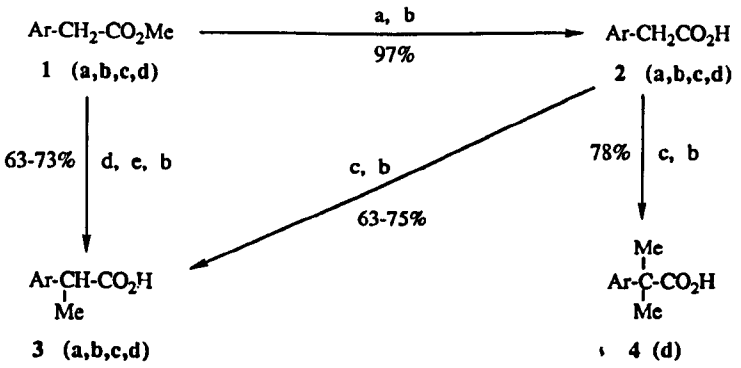
Phenanthrylalkansäuren, 5. Mitt.: Eine günstige Darstellung von α-Methylphenanthrylessigsäuren

Ein einfaches Verfahren zur Monomethylierung, in nur einem Schritt, von Phenanthrylessigsäure **2** oder ihren Methylestern **1** liefert mit guter Ausbeute α-Methylphenanthrylessigsäuren **3**; außerdem kann das Verfahren auf die Herstellung der entspr. α-Arylisobuttersäuren **4** angewendet werden.

Pharmaceutically interesting 2-arylpropanoic acids **3** can be obtained by standard methods from easily available acetylarenes *via* the intermediates 1-arylethanol, 1-arylethyl halide and 1-arylethyl cyanide. We have recently used this classical, four-step sequence to prepare the α-methylphenanthreneacetic acids **3a-d**[1], but it is time consuming and the overall yields of the final products are rather low (crude, 24-41%; purified, 11-22%).

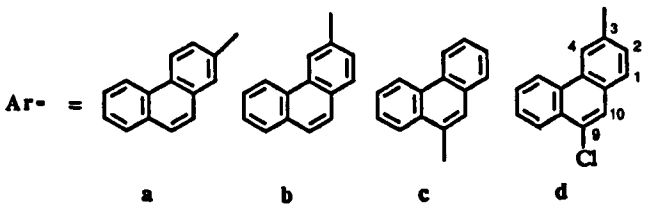
Oxidative rearrangement of acetylarenes by means of thallium trinitrate (TTN) in acidic methanol leads cleanly and almost quantitatively to the methyl arylacetates **1**[2], and we have already reported the use of this approach for the preparation of the phenanthreneacetic acids **2a-d** in excellent yields[3]. Since it had been established that some arylacetic acids can be directly α-methylated by Me_2SO_4 in the presence of KOH under Phase Transfer Catalysis conditions[4], it occurred to us that the two procedures could be combined to achieve **3** from the corresponding acetylarene in a shorter, simpler sequence with better yield than the classical route. Moreover, as methyl esters **1** are postulated as the intermediates in the above-mentioned α-methylation of free arylacetic acids[4], we thought that application of the same or similar conditions of reaction to the esters **1** would provide an even shorter route from the acetylarenes to the propanoic acids **3**.

When the conditions prescribed as standard for the monoalkylation of arylacetic acids[4] were applied to **2a-d**, a variety of results were obtained, depending on the particular



a) KOH, EtOH; b) HCl; c) KOH, Me_2SO_4, TEBACl, CH_2Cl_2;

d) KOH, TEBACl, CH_2Cl_2; e) Me_2SO_4.



Scheme

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substrate. Besides the monoalkylated acid **3** (which was not always the main product), the presence of substantial amounts of the α,α-dialkylated acid **4** and, in some cases, of the starting acid **2** was detected. In general, concentration of the reactants, the Me_2SO_4/**2** mole ratio and reaction time were the parameters that most influenced the result. Decreasing one or more of them reduced the formation of dimethylated acids **4** to reasonable proportions. In fact, no more than three test-runs for each substrate were sufficient to determine conditions affording a crude reaction product that was ≥ 90% **3**. These conditions are given in the Table, together with the yields of purified products.

Contrarywise, higher Me_2SO/**2** mole ratios, smaller amounts of solvent and/or longer reaction times increase the formation of the dimethylated acids **4**, which if desired may be obtained in good yields. Suitable conditions for preparation of **4d** are shown in the Table.

Table: One-pot α-Methylation of Phenantreneacetic Acids **2a-d**

Substrate /(mmol)	Solvent (mL)	Me_2SO_4 (mmol)	Time (h)	Components of the crude product (%)[a] 2	3	4	Isolated acid/Yield (%)[b]	M.p. (°C)
2a/(20)	125	45	8	8	91	1	**3a**/63	176-177[c,d]
2b/(20)	40	60	5	-	93	7	**3b**/65	144-145[c,e]
2c/(20)	50	40	3	-	90	10	**3c**/64	182-184[c,f]
2d/(20)	150	50	7	5	92	3	**3d**/75	164-165[c,g]
2d/(20)	40	100	8	-	3	97	**4d**/78	169-170[c]

[a] By GC analysis of an aliquot esterified with CH_2N_2; the relative retention times of the respective methyl esters of each phenanthrene substrate were, **2a**:**3a**:**4a**: 0.93:1.00:1.15; **3b**:**4b**: 1.00:1.11; **3c**:**4c**: 1.00:1.08; **2d**:**3d**:**4d**: 0.90:1.00:1.10. Concurrently, ^{1}H-NMR spectra were used to identify and quantify the components of the crude mixture. Percentages of components found by both methods agreed within ± 1%.

[b] Once recrystallized from toluene.

[c] Satisfactory microanalyses were obtained for compounds **3a-d** and **4d**: C ± 0.26, H ± 0.14, Cl ± 0.19.

[d] Lit.[1] m.p. 176.5-177°C

[e] Lit.[1] m.p. 145.5-146°C

[f] Lit.[1] m.p. 183-184°C

[g] Lit.[1] m.p. 164.5-165°C

When the conditions established as optimal for the monomethylation of the acids **2** were applied to the esters **1**, the percentages of dialkylated products obtained were again higher than expected. Instead of seeking specific conditions for the monomethylation of the esters, a simpler strategy was followed. We used basically the same one-pot conditions needed for the methylation of the acids **2**, but delayed the addition of Me_2SO_4, thus allowing the previous *in situ* saponification of the starting material. This way, product distribution and yields of the isolated acids **3a-d** were within ± 1% of those obtained methylating the acids **2**. In all cases, a single recrystallization from toluene was enough to get > 98% pure (GC, ^{1}H-NMR) α-methylphenanthreneacetic acids **3** with satisfactory microanalyses. Yields of these purified products ranged from 63 to 73%, thus notably higher than those obtained by the alternative route from acetylarenes[1].

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Experimental Part

Starting materials **1** were prepared from acetylarenes[5] by procedures reported[3] and used crude[6]. Saponification of **1a-d** by hot ethanolic KOH[3] afforded acids **2a-d** in virtually quantitative yields. Other reagents and solvents: commercial quality (Aldrich Chemical Co).- Melting points: Kofler Thermopan Reichert apparatus, uncorrected.- Microanalyses: Perkin-Elmer 240B element analyser, Microanalysis Service, University of Santiago.- IR spectra: Perkin-Elmer 681 spectrometer.- ^{1}H-NMR spectra: Varian FT-80A spectrometer.- GC: Hewlett Packard 5710A instrument, FID, HP-3380S integrator: Column: 10% OV-101 on Chromosorb W-HP (2 m x 1/8"); carrier gas: N_2, 20 mL/min, 230°C.

2-(9-Chloro-3-phenanthryl)-2-methylpropanoic acid (**4d**)

In a dried, 2-neck round bottomed flask with a magnetic stirrer, reflux condenser and septum joint, a mixture of acid **2d** (5.41 g, 20 mmol), KOH[7] (11.22 g, 200 mmol), triethylbenzylammonium chloride (TEBACl) (1.41 g, 6.2 mmol), Me_2SO_4 (12.61 g, 100 mmol) and dry CH_2Cl_2 (40 mL) under Ar is stirred and heated under reflux for 8 h. The mixture is poured onto H_2O (300 mL) and stirred for 3 min, then the aqueous phase is separated, washed with more CH_2Cl_2 (100 mL), acidified to pH 3 with 2M HCl and reextracted with 1:1 C_6H_6-Et_2O (2 x 200 mL). These extracts are combined, washed with brine (2 x 100 mL) and dried (Na_2SO_4)[8], and the solvents are removed *in vacuo*. The residue, crude **4d**, is recrystallized once from hot toluene. Yield 4.66 g (78%).- White crystalline powder, m.p. 169-170°C.- IR (KBr): 625; 640; 700; 750; 775; 878; 945; 1025; 1050; 1165; 1210; 1285; 1380; 1415; 1500; 1598; 1615; 1690; 2975; 3095 cm^{-1}.- ^{1}H-NMR (DMSO-d_6/TMS): δ (ppm) = 1.67 (s, 6H, >C(CH_3)$_2$), 7.67 (dd,

$J_{2,1}$ = 8.4 Hz, $J_{2,4}$ = 1.7 Hz, 1H, 2-H), 7.76-7.88 (m, 2H, 6,7-H), 7.96 (d; $J_{1,2}$ = 8.4 Hz, 1H, 1-H), 8.10 (s, 1H, 10-H), 8.25-8.37 (m, 1H, 8-H), 8.71 (virtual s, 1H, 4-H), 8.88-9.00 (m, 1H, 5-H).- $C_{18}H_{15}ClO_2$ (298.8) Calcd. C 72.4 H 5.06 Cl 11.9 Found C 72.2 H 4.97 Cl 12.0.

One-pot preparation of **3a-d** *from* **2**

The acids **3a-d** are obtained from the respective phenanthreneacetic acids **2a-d** in the same way as **4d**, but with the process parameters listed in the Table.

One pot preparation of **3(a-d)** *from* **1**

In a dried, argon filled 2-neck round-bottomed flask fitted with reflux condenser, magnetic stirrer and septum joint, a mixture of the methyl phenanthreneacetate **1a-d** (20 mmol), KOH[7] (200 mmol), TEBACl (6.2 mmol), and dry CH_2Cl_2 (as in the Table) is flushed with Ar and stirred at room temp. for 3 h. Then Me_2SO_4 (as in the Table) is added through the septum and the mixture is refluxed with vigorous stirring for the time listed in the Table. Work up as before leads to the acids **3a-d**.

References and Notes

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6 Crude products obtained by oxythallation of the corresponding acetylarenes are ≥ 97% **1**, provided a 30% excess of TTN is employed. These crude esters are suitable for direct use in the α-methylation processes.

7 Solid KOH is finely ground in a mortar under dry CH_2Cl_2.

8 An aliquot (ca. 1/100) is withdrawn at this moment for CH_2N_2 esterification and GLC analysis and/or NMR quantitation of the components of the crude product. [Ph864]