Conjugate Addition of Grignard Reagents to Nitroarenes: A New Synthesis of 9-Alkylanthracenes, 9-Nitro-10-alkylanthracenes, and 10,10-Dialkylanthrones

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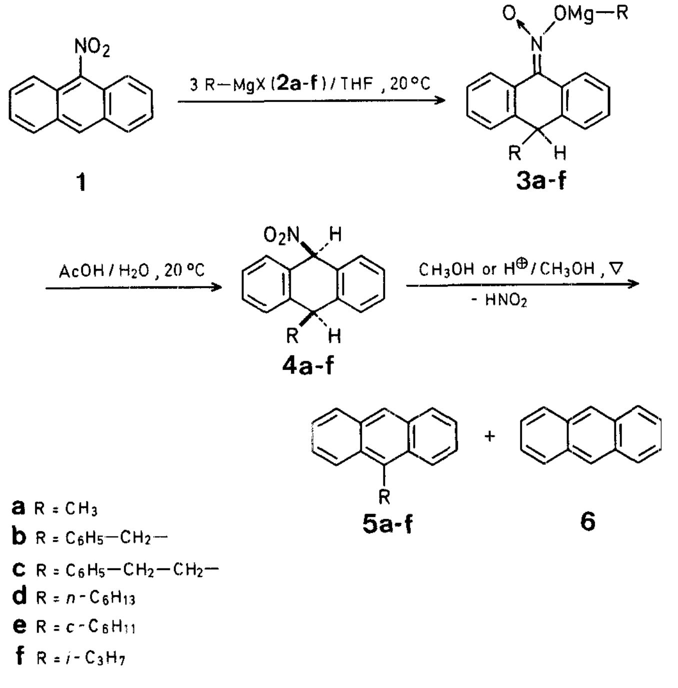
9-Alkylanthracenes are usually prepared by Grignard reactions of 9-anthrone, followed by dehydration of the resultant 9-alkyl-9-hydroxy-9,10-dihydroanthracenes[1-5]. This method affords fair to satisfactory results with Grignard reagents derived from primary short-chain alkyl halides[1-6] whereas the yields of reductive alkylation product are distinctly lower when Grignard reagents derived from secondary[7] or primary long-chain[1,8] alkyl halides are used. The synthesis of 9-*sec*-alkylanthracenes by cyclization methods[7] affords only poor yields and is generally accompanied by the formation of undesired side products[9]. As regards the synthesis of 10,10-dialkylanthrones, good yields may be achieved for anthrones having identical alkyl groups by reaction of the lithium salt of 9-anthrone with an alkyl iodide[10]; the only reported synthesis of a 10,10-dialkyl-9-anthrone having different alkyl groups is a multistage route starting with 9,10-dicyanoanthracene[11].

We have recently shown[12,13,14] that the conjugate addition of an alkylmagnesium halide to a nitroarene represents a useful method for the alkylation of aromatic rings including those in benzo-fused heterocyclic systems. We report here a further application of this reaction type: the synthesis of 9-alkylanthracenes (**5**) and 10-alkyl-9-nitroanthracenes (**7**), as well as the conversion of the 10-alkyl-9-nitroanthracenes (**7**) into 10,10-dialkyl-9-anthrones (**9**).

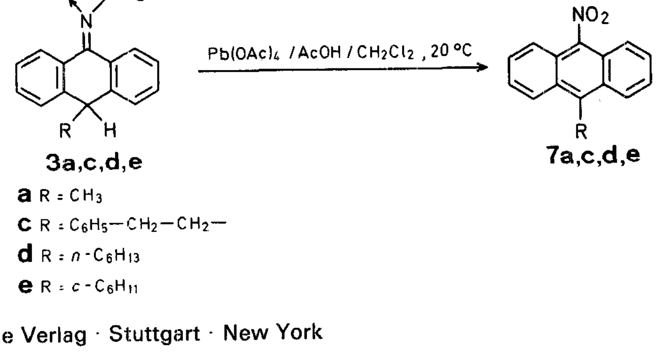
We recently reported[15] that the reaction of 9-nitroanthracene (**1**) with methyl- (**2a**) and benzylmagnesium halides (**2b**) in tetrahydrofuran at room temperature results in 1,6-addition to give the nitronate compounds **3a**, **b**. Treatment of **3a**, **b** *in situ* with dilute acetic acid leads to highly stereoselective *C*-protonation at the nitronate function with formation of *cis*-10-alkyl-9-nitro-9,10-dihydroanthracenes (**4a**, **b**) in high yields together with small amounts of unidentified polymeric products. We now report that compounds **4a**, **b** can be almost quantitatively converted into 9-methyl- (**5a**) and 9-benzylanthracene (**5b**), respectively, by heating in methanol for 1 day (Method A). Using the same procedure, 9-(2-phenylethyl)- (**5c**) and 9-hexylanthracene (**5d**) can be obtained in good yields via intermediates **4c**, **d**. In all cases, the decomposition reaction **4a-d**→**5a-d** gives only traces of anthracene (**6**) as byproduct. More significant amounts of anthracene (**6**) are formed from the decomposition in methanol of compounds **4**, R=*sec*-alkyl, such as **4e**, **f** which are obtained in 65% yields from **1** and cyclohexyl- (**2e**) or isopropylmagnesium halides (**2f**), respectively. In these cases, the formation of anthracene (**6**) can be drastically reduced by performing the elimination of HNO_2 from **4e**, **f** in the presence of a mineral acid as catalyst (Method B). It should be noted that Method B, which requires shorter reaction times than Method A, gives less satisfactory results for the 9-(*prim*-alkyl)-anthracenes **5a**, **b**, **c**.



a R = CH_3
b R = $C_6H_5-CH_2-$
c R = $C_6H_5-CH_2-CH_2-$
d R = n-C_6H_{13}
e R = c-C_6H_{11}
f R = i-C_3H_7

In conclusion, the synthesis of 9-alkylanthracenes (**5**) via conjugate addition of alkylmagnesium halides (**2**) to 9-nitroanthracene (**1**) appears to be an advantageous alternative to the 1,2-addition of alkylmagnesium halides to anthrone.

The conversion of nitroarenes into alkylnitroarenes via the addition of alkylmagnesium halides to the nitroarenes and treatment of the resultant nitronate adducts with oxidizing agents[12,16] has proved to be a useful synthetic method. Nevertheless, in the synthesis of 10-alkyl-9-nitroanthracenes (**7**) complications arise from the use of the previously employed oxidizing agents[18]. We have therefore devised a further modification of this method which utilizes lead(IV) acetate in a weakly acidic medium. The addition of an equimolecular amount of lead(IV) acetate in dichloromethane (containing 1% of acetic acid) to a solution of adducts **3a**, **c**, **d**, **e** in tetrahydrofuran leads to the formation of the 10-alkyl-9-nitroanthracenes **7a**, **c**, **d**, **e** in satisfactory yields and minor amounts (5-9%) of starting material **1**.



a R = CH_3
c R = $C_6H_5-CH_2-CH_2-$
d R = n-C_6H_{13}
e R = c-C_6H_{11}

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Table 1. 10-Alkyl-9-nitro-9,10-dihydroanthracenes (4) via Conjugate Addition of Alkylmagnesium Halides (2) to 9-Nitroanthracene (1)

4[a]	X in 2	Yield[b] [%]	m.p.[c] [°C]	Molecular formula[d] or m.p. [°C] reported	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	Cl	72	154-156°	154-156°[15]	1.65 (d, CH_3, J_{10,CH_3} = 7.5 Hz); 4.24 (br q, 10-H, $J_{9,10}$ < 0.6 Hz); 6.7 (br d, 9-H); 7.2-7.7 (m, 8 H_{arom})[e]
b	Cl	78	158-160°	148 – 160°[15]	3.09 (d, CH_2, J_{10,CH_2} = 8.0 Hz); 4.16 (br t, 10-H, $J_{9,10}$ < 0.6 Hz); 6.60 (br s, 9-H); 6.83-7.67 (m, 13 H_{arom})[e]
c	Br	90	oil	$C_{22}H_{19}NO_2$ (329.4)	1.8-2.9 (m, CH_2—CH_2); 3.90 (br t, 10-H, J_{10,CH_2} = 6.0 Hz, $J_{9,10}$ < 1.0 Hz); 6.45 (br s, 9-H); 6.90-7.60 (m, 13 H_{arom})
d	Br	65	53-54°	$C_{20}H_{23}NO_2$ (309.4)	0.7-2.0 (m, 13 $H_{aliphatic}$); 3.90 (br t, 10-H, J_{10,CH_2} = 6.5 Hz, $J_{9,10}$ < 1.0 Hz); 6.50 (br s, 9-H); 7.1-7.6 (m, 8 H_{arom})
e	Br	65	148-150°	$C_{20}H_{21}NO_2$ (307.4)	0.96-1.72 (m, 11 $H_{aliphatic}$); 3.60 (br d, 10-H, $J_{10,CH}$ = 8.0 Hz, $J_{9,10}$ < 1.0 Hz); 6.40 (br s, 9-H); 7.24-7.7 (m, 8 H_{arom})
f	Br	66	124-126°	$C_{17}H_{17}NO_2$ (267.3)	0.94 [d, CH($C\underline{H}_3$)$_2$, $J_{CH_3,CH}$ = 6.0 Hz]; 1.64 [m, $C\underline{H}(CH_3)_2$]; 3.58 (br d, 10-H, $J_{10,CH}$ = 9.0 Hz, $J_{9,10}$ < 1.0 Hz]; 6.44 (br s, 9-H); 7.32-7.74 (m, 8 H_{arom})

[a] I.R. (KBr or neat) of all compounds **4**: Two strong absorption bands at ν = 1540-1550 and 1340-1360 cm^{-1} (aliphatic NO_2).

[b] Yield of isolated pure product.

[c] From dichloromethane/hexane.

[d] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.08; N, ±0.08.

[e] Data from Ref. [15].

Table 2. 9-Alkylanthracenes (5) from 10-Alkyl-9-nitro-9,10-dihydroanthracenes (4)

5	Method	Yield[a] [%]	(Anthracene, 6, isolated [%])	Overall yield 1→5 [%]	m.p.[b] [°C]	Molecular formula[c] or m.p. [°C] reported	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	A	>98	(trace)	71	80-81°	79-80°[5]	3.00 (s, 3H, CH_3); 7.30-8.32 (m, 9 H_{arom})
	B	75	(trace)	54			
b	A	>98	(trace)	76	132-133°	133°[5]	4.96 (s, 2H, CH_2); 7.10-8.36 (m, 14 H_{arom})
	B	83	(trace)	65			
c	A	>98	(trace)	88	86-87°	$C_{21}H_{18}$ (270.4)	3.0-3.24 (m, 4H, CH_2—CH_2); 7.28-8.46 (m, 14 H_{arom})
d	A	78	(2-4)	51	64-66°	$C_{20}H_{22}$ (262.4)	0.8-2.0 (m, 11 $H_{aliphatic}$); 3.58 (br d, 2H, CH_2, $J_{CH_2-CH_2}$ = 8.0 Hz); 7.34-8.4 (m, 9 H_{arom})
e	A	35	(32)	22	134-135°	133-136°[7]	1.5-2.7 (m, 10 $H_{aliphatic}$); 4.0-4.3 (m, 1H, CH); 7.36-8.68 (m, 9 H_{arom})
	B	72	(2-3)	47			
f	A	37	(28)	24	76-78°	75-76°[2]	1.78 (d, 6H, 2CH_3, $J_{CH_3,CH}$ = 7.0 Hz); 4.62 (hept, 1H, CH); 7.4-8.6 (m, 9 H_{arom})
	B	55	(2-5)	36			

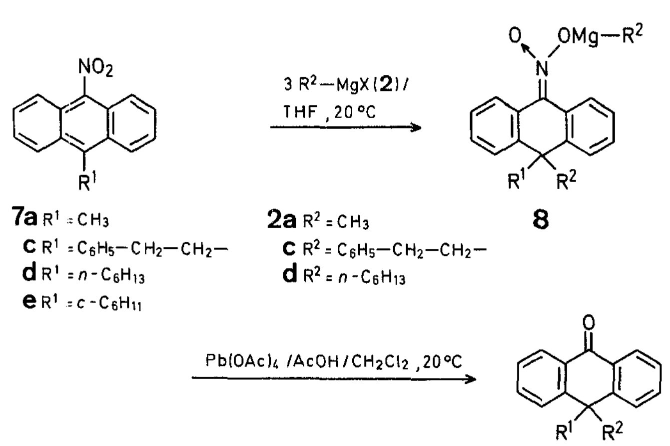
[a] Yield of isolated pure product.

[b] From hexane.

[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.25; H, ±0.10.

Since the formation of **1** is not observed even in traces in the conversion **3**→**4**, it may be assumed that the preceding conversion **1**→**3** is accompanied by the reduction of **1** by the alkylmagnesium halide (**2**) to give a by-product which is converted to a polymeric material on treatment with water and acid and which may be oxidized to **1** by lead(IV) acetate. The formation of **1** in the synthesis of **7** and that of a polymeric material in the synthesis of **5** cannot be abated by performing the conversion **1**→**3** with a larger excess of alkylmagnesium halide (**2**) or by prolonging the reaction time.

The reaction of 10-alkyl-9-nitroanthracenes (**7a**, **c**, **d**, **e**) with excess alkylmagnesium halide (**2**) results in 1,6-addition to give the nitronate derivatives **8** which on treatment with an equimolecular amount of lead(IV) acetate in dichloromethane are converted into 10,10-dialkylanthrones (**9**) in good yields. Satisfactory results are even obtained when one of the alkyl groups is a sterically hindered secondary alkyl group (R^1 = *c*-C_6H_{11}); however, the reaction fails under the same conditions when both alkyl groups are cyclohexyl groups (R^1 = R^2 = *c*-C_6H_{11}).



9

8,9	R^1	R^2
aa	CH_3	CH_3
cc	C_6H_5—CH_2—CH_2—	C_6H_5—CH_2—CH_2—
dd	*n*-C_6H_{13}	*n*-C_6H_{13}
ca	C_6H_5—CH_2—CH_2—	CH_3
da	*n*-C_6H_{13}	CH_3
ea	*c*-C_6H_{11}	CH_3
cd	C_6H_5—CH_2—CH_2—	*n*-C_6H_{13}

Table 3. 10-Alkyl-9-nitroanthracenes (**7**) from 9-Nitroanthracene (**1**) via Nitronate Derivatives **3**

7	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
a	67[c]	201–202°	$C_{15}H_{11}NO_2$ (237.25)	3.10 (s, 3H); 7.52–7.74 (m, 4H); 7.9–8.0 (m, 2H); 8.24–8.4 (m, 2H)
c	75	133–134°	$C_{22}H_{17}NO_2$ (327.4)	2.94–3.2 (m, 2H); 3.76–4.06 (m, 2H); 7.3–7.4 (m, 6H); 7.48–7.7 (m, 4H); 7.8–8.6 (m, 2H); 8.13–8.45 (m, 2H)
d	80	101–102°	$C_{20}H_{21}NO_2$ (307.4)	0.74–1.96 (m, 11H); 3.37–3.72 (m, 2H); 7.4–7.7 (m, 4H); 7.8–8.0 (m, 2H); 8.12–8.44 (m, 2H)
c	53	80–82°	$C_{20}H_{19}NO_2$ (305.4)	1.33–2.76 (m, 10H); 4.16 (m, 1H); 7.4–7.65 (m, 4H); 7.7–8.03 (m, 2H); 8.33–8.73 (m, 2H)

[a] From acetic acid.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.20; H, ±0.11; N, ±0.05.

[c] The product contains 5% of 9-nitroanthracene (**1**). Repeated recrystallization from acetic acid gives pure **7a** in 35% yield.

Table 4. 10,10-Dialkyl-9-anthrones (**9**) via Conjugate Addition of Alkylmagnesium Halides (**2**) to 10-Alkyl-9-nitroanthracenes (**7**)

9[a]	Yield [%]	m.p.[b] [°C]	Molecular formula[c] or m.p. [°C] reported	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
aa	64	97–98°	97–98°[17]	1.76 (s, 6H, $2CH_3$); 7.4–7.9 (m, $6H_{arom}$); 8.3–8.5 (m, $2H_{arom}$)
cc	78	99–101°	$C_{30}H_{26}O$ (402.5)	1.72–1.99, 2.42–2.68 (2m, 8H, $2CH_2$—CH_2); 6.76–7.22 (m, 10H, $2C_6H_5$); 7.4–7.86 (m, $6H_{arom}$); 8.4–8.56 (m, $2H_{arom}$)
dd	68	83–84°	$C_{26}H_{34}O$ (362.5)	0.3–1.15, 2.08–2.34 (2m, 26H, $2C_6H_{13}$); 7.34–7.74 (m, $6H_{arom}$); 8.34–8.5 (m, $2H_{arom}$)
ca	84	93–96°	$C_{23}H_{20}O$ (312.4)	1.74 (s, 3H, CH_3); 1.72–1.94, 2.42–2.64 (2m, 4H, CH_2—CH_2); 6.79–7.2 (m, 5H, C_6H_5); 7.36–7.76 (m, $6H_{arom}$); 8.36–8.5 (m, $2H_{arom}$)
da	68	51–52°	$C_{21}H_{24}O$ (292.4)	0.32–1.28, 2.08–2.32 (2m, 13H, C_6H_{13}); 1.72 (s, 3H, CH_3); 7.32–7.78 (m, $6H_{arom}$); 8.32–8.46 (m, $2H_{arom}$)
ea	74	80–83°	$C_{21}H_{22}O$ (290.4)	0.31–1.76 (m, 11H, C_6H_{11}); 1.90 (s, 3H, CH_3); 7.36–7.83 (m, $6H_{arom}$); 8.34–8.54 (m, $2H_{arom}$)
cd	71	oil	$C_{28}H_{30}O$ (382.5)	0.32–1.20, 2.10–2.34 (2m, 13H, C_6H_{13}); 1.74–1.96, 2.46–2.68 (2m, 4H, CH_2—CH_2); 6.76–7.25 (m, 5H, C_6H_5); 7.4–7.84 (m, $6H_{arom}$); 8.38–8.56 (m, $2H_{arom}$)

[a] I.R. (KBr or neat) of all compounds **9**: Strong absorption band at $\nu = 1670–1680\ cm^{-1}$ (C=O).

[b] From hexane.

[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.28; H, ±0.14.

This synthesis of 10,10-dialkylanthrones (**9**) may represent an improvement as compared with the known methods since the reaction of the lithium salt of anthrone with alkyl iodides[10] (which is a one-step procedure, however) is carried out under less mild conditions and is only applicable to the synthesis of compounds **9** having identical alkyl groups.

cis-10-Alkyl-9-nitro-9,10-dihydroanthracenes (4a-f); General Procedure:

The procedure previously described[15] for compounds **4a, b** is generalized as follows: a solution of the alkylmagnesium halide (**2**; 30 mmol) is prepared from the corresponding alkyl halide (30 mmol) and magnesium (0.73 g, 0.03 mol) in tetrahydrofuran (20 ml). To this is added a solution of 9-nitroanthracene (**1**; 2.233 g, 10 mmol) in tetrahydrofuran (30 ml), the mixture is stirred under nitrogen for 2 h at room temperature, and then added dropwise to stirred aqueous 3% acetic acid (20 ml). Stirring is continued for 10 min and the mixture then extracted with ethyl acetate (3 × 30 ml). The organic layer is filtered from some insoluble polymeric material, washed with a saturated sodium hydrogen carbonate solution (30 ml), dried with sodium sulfate, and concentrated to a volume of 10–20 ml. This solution is submitted to chromatographic filtration through a short silica gel column. Elution with cyclohexane/ethyl acetate (19/1) gives the pure compounds **4a–f**.

9-Alkylanthracenes (5a–f); General Procedure:

Method A: A solution of a compound **4** (10 mmol) in methanol (50 ml) is kept at reflux for 36 h, then diluted with cold water (100 ml), and extracted with dichloromethane (3 × 30 ml). The organic layer is washed with water (3 × 30 ml), dried with sodium sulfate, and evaporated at reduced pressure. Recrystallization from hexane gives the pure products **5a, b, c**. For purification of **5d**, the crude material is submitted to chromatographic separation on a silica gel column. Elution with hexane gives pure **5d**. Further elution gives pure anthracene (**6**). Purification of products **5e, f** (presence of large amounts of **6** in the crude material) is performed by high-pressure chromatography, using an Ivon Jobin PREP 10 apparatus. Elution with hexane gives the pure products **5e, f**; further elution gives anthracene (**6**).

Method B: A solution of a compound **4** (10 mmol) in methanol (50 ml) containing sulfuric acid ($d = 1.83$; 2 ml) is kept at reflux for 20 min, then poured into cold water (100 ml), and extracted with dichloromethane (3 × 30 ml). The organic layer is washed with water, dried with sodium sulfate, and evaporated at reduced pressure. Chromatography of crude material on a silica gel column using hexane as eluent gives the pure products **5**.

9-Alkyl-10-nitroanthracenes (7a, c, d, e); General Procedure:

A solution of the alkylmagnesium halide (**2**; 30 mmol) is prepared from the corresponding alkyl halide (30 mmol) and magnesium (0.73 g, 0.03 mol) in tetrahydrofuran (20 ml). To this is added a solution of 9-nitroanthracene (**1**; 2.233 g, 10 mmol) in tetrahydrofuran (30 ml), the mixture is stirred under nitrogen for 2 h at room temperature, and then glacial acetic acid (1.802 g, 30 mmol) is added dropwise with stirring. To this mixture, a solution of lead(IV) acetate (4.523 g, 10.2 mmol) in dichloromethane (50 ml) containing acetic acid (0.5 ml) is added dropwise at room temperature. Stirring is continued for 10 min and the solid inorganic material then filtered off. A few drops of ethylene glycol are added and stirring is continued for 15 min. The resultant mixture is washed with water (3 x 30 ml) and with saturated aqueous sodium hydrogen carbonate, dried with sodium sulfate, and evaporated at reduced pressure. The residual yellow material is submitted to chromatographic purification on a short silica gel column. Elution with petroleum ether/ethyl acetate (20/1) gives the pure products **7c, d, e.** Further elution gives small amounts of 9-nitroanthracene **(1).** This procedure partially fails for **7a** which is only obtained in impure form (contaminated by 5% of **1**). Further purification of **7a** (>98%) requires several recrystallizations from acetic acid.

10,10-Dialkylanthrones (9); General Procedure:
A solution of the alkylmagnesium halide (**2**; 30 mmol) in tetrahydrofuran (20 ml) is added dropwise to a stirred solution of the 10-alkyl-9-nitroanthracene (**7**; 10 mmol) in tetrahydrofuran (20 ml) at room temperature under nitrogen. The mixture is stirred for 5 h and then added dropwise to a stirred cold solution of lead(IV) acetate (4.434 g, 10 mmol) in dichloromethane (50 ml) + glacial acetic acid (1.802 g, 30 mmol). Stirring is continued for 10 min and the solid inorganic material then filtered off. A few drops of ethylene glycol are added and the mixture is stirred for a further 15 min. The organic layer is separated, washed with water (3 x 30 ml) and saturated sodium hydrogen carbonate solution (30 ml), dried with sodium sulfate, and evaporated at reduced pressure. The residual product is purified by chromatography on a short silica gel column using petroleum ether/ethyl acetate (10/1) as eluent.

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[18] The use of DDQ or of bromine in triethylamine is not possible (see Ref. [16]) because a large excess of alkylmagnesium halide is required in the formation of the intermediate nitronate **3**. On the other hand, unsatisfactory results are obtained with potassium permanganate (see Ref. [12]); when this reagent is used, some starting material **1**, anthraquinone, and other unidentified by-products are obtained in addition to compounds **7**.