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Synthesis of Long Alkyl Chain Mono- and Di-N-substituted 4-Amino-N-methylphthalimides. Comparison of N-Alkylation Methods

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Summary. 4-Amino-N-methylphthalimide, **1**, was N-alkylated with the respective *n*-alkyl sulfonates and halides. In the former case, the di-derivative **4** was favored, while in the latter case, under phase transfer catalysis, the mono-derivative **3** was predominant.

Keywords. Mono- and di-N-substituted; 4-Amino-N-methylphthalimide; N-Alkylation.

Synthese langkettig mono- und di-N-substituierter 4-Amino-N-methylphthalimide. Ein Vergleich von N-Alkylierungsmethoden

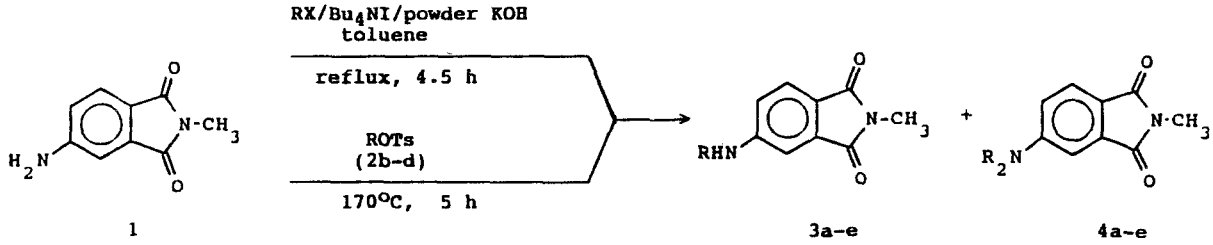
Zusammenfassung. 4-Amino-N-methylphthalimide (**1**) wurden mit den entsprechenden *n*-Alkylsulfonaten und -halogeniden N-alkyliert. Im ersten Fall wurden die Di-Derivate **4** bevorzugt gebildet, im zweiten Fall waren unter Phasentransferkatalyse die Mono-Produkte **3** vorherrschend.

Introduction

In the course of chemiluminescence studies of isoluminols N-alkylated 4-amino-N-methylphthalimides were needed as intermediates. From the preparative point of view, the reaction of alkyl halides and primary amines is not a feasible method to obtain secondary and tertiary amines, the usual practice being the use of sulfates and sulfonates instead. N-alkylations with alkyl halides under phase-transfer catalysis was recently reported [1–3] and, although N-alkylations of primary amines have been extensively studied, there is no such report on the N-alkylation on the 4-amino-N-methylphthalimide, **1**. Few N-alkylations of **1** have been reported, the alkylating agents being alkyl sulfates and sulfonates [4]. We now wish to report the synthesis of new N-alkylated derivatives of **1** using the long *n*-alkyl chain halides and/or the respective tosylates.

Results and Discussion

We synthesized the mono-, **3**, and di-N-alkylated, **4**, derivatives of **1** using the commercially available long *n*-alkyl halides and the respective tosylates, **2b–d** (Scheme 1). The reaction products formed by the N-alkylation of **1** under phase-transfer catalysis (ptc) conditions employing *n*-alkyl halides with tetrabutylam-



2,3,4	R
a	$CH_3(CH_2)_3$-
b	$CH_3(CH_2)_6$-
c	$CH_3(CH_2)_8$-
d	$CH_3(CH_2)_9$-
e	$CH_3(CH_2)_{17}$-

Scheme 1

monium iodide as the phase-transfer agent were compared with those obtained when *n*-alkyl sulfonates were used as the alkylating agents (Tables 1, 2). The ptc method required an excess of alkylating agent, potassium hydroxide and toluene, the reaction times varying with temperature. The tosylate method required heating of **1** at 170 °C for 5 h with or without potassium carbonate [4]. In both cases, a mixture of **3** and **4** was obtained, each product was isolated (Table 1), identified (Tables 1, 3) and for both alkylating methods the ratio of **3** : **4** is reported (Table 2).

With the use of *n*-butyl tosylate, **2a**, the syntheses of the mono-, **3a**, and di-*n*-butylamino, **4a**, derivatives of **1** have been reported earlier [4], the ratio of the products **3a** : **4a** being 1 : 0.4, and the total yield 42% (Table 2). In the same report, the *n*-heptyl tosylate and **1** with added potassium carbonate, produced the di-*n*-heptylamino **4b** derivative in a 30% yield, but without any reference to the mono-alkylated **3b**. From the respective tosylates **2b–d**, using the latter method, we synthesized the mono- **3b** and di-*n*-heptylamino **4b**, also the mono- **3c** and di-*n*-nonylamino **4c** derivatives with an average total yield of 62% (chromatographically pure), the average ratio of **3** : **4** being 1 : 3.0. In the absence of potassium carbonate, as in the reported *n*-butyl alkylation [4], the derivatives **3d** and **4d** were obtained and compared with the total yields and the product ratios under conditions of added weak base. The total yield was 35% instead of 62% while the ratio of mono- to di-*n*-alkylated products **3d** : **4d** was 1 : 1.5, a much lower ratio than the 1 : 3.0 reported above. Under the same conditions the said ratio 1 : 1.5 for **3d** : **4d** when compared with the reported one for the *n*-butylamino **3a** : **4a** was much higher in favor of the di-*n*-alkyalted derivative **4d** (Tables 1, 2).

In a separate set of experiments we prepared the N-alkylated products **3b–e** and **4b–e** under ptc conditions employing solid/liquid reaction mixtures, namely **1** and *n*-alkyl bromide in toluene with tetrabutylammonium iodide as the phase-

Table 1. Experimental data for the N-alkylation of 4-amino-N-methylphthalimide, **1**

Compound no.	Alkylating agent	Added base	Yield %[a]	M.p. °C	Formula (M.W.)
3a	*ROTs*		(30)[b]		
3b				111–112	$C_{16}H_{22}N_2O_2$
	ROTs	K_2CO_3	16		(274.4)
	*R*Br	KOH	42[c]		
	*R*Br	KOH	45[d]		
3c				101–102	$C_{18}H_{26}N_2O_2$
	ROTs	K_2CO_3	15		(302.4)
	*R*Br	KOH	39[c]		
	*R*Br	KOH	49[d]		
3d				107–108	$C_{19}H_{28}N_2O_2$
	ROTs		14		(316.4)
	*R*Br	KOH	41[d]		
3e				108–110	$C_{27}H_{44}N_2O_2$
	*R*Br	KOH	38[c]		(428.7)
	*R*Br	KOH	40[d]		
4a	*ROTs*		(12)[b]		
4b				oil[b]	$C_{23}H_{36}N_2O_2$
	ROTs	K_2CO_3	(30)[b]		(372.6)
	ROTs	K_2CO_3	50		
	*R*Br	KOH	14[c]		
	*R*Br	KOH	8[d]		
4c				oil	$C_{27}H_{44}N_2O_2$
	ROTs	K_2CO_3	42		(428.7)
	*R*Br	KOH	16[c]		
	*R*Br	KOH	6[d]		
4d				oil	$C_{29}H_{48}N_2O_2$
	ROTs		21		(456.7)
	*R*Br	KOH	8[d]		
4e				59–61	$C_{45}H_{80}N_2O_2$
	*R*Br	KOH	18[c]		(681.1)
	*R*Br	KOH	7[d]		

[a] Pure chromatographed yield based on **1**

[b] (), from Ref. [3]

[c] Ptc, reaction conditions: 40 °C for 5 days

[d] Ptc, reaction conditions: refluxed for 4.5 hours

transfer agent in the presence of powdered potassium hydroxide. Our results were consistent with the recently reported ones where indole was N-alkylated with the application of ultrasound under ptc conditions [5]. In our studies the above combination was successful enough to provide us with a mixture of mono- **3** and di-*n*-alkylated **4** products while other attempts failed (e.g. benzyltriethylammonium

Table 2. Yield ratio in the N-alkylation of 4-amino-N-methylphthalimide, **1**

R	Alkylating agent	Added base	Yield %[a] of **3**+**4**	Yield ratio[a] of **3**:**4**
$CH_3(CH_2)_3-$	*ROTs*		(42)[b]	(1:0.4)[b]
$CH_3(CH_2)_6-$	*ROTs*	K_2CO_3	(30)[b]	(−)[b]
	ROTs	K_2CO_3	66	1:3.1
	*R*Br	KOH	56[c]	1:0.3
	*R*Br	KOH	53[d]	1:0.2
$CH_3(CH_2)_8-$	*ROTs*	K_2CO_3	57	1:2.8
	*R*Br	KOH	55[c]	1:0.4
	*R*Br	KOH	55[d]	1:0.1
$CH_3(CH_2)_9-$	*ROTs*		35	1:1.5
	*R*Br	KOH	49[d]	1:0.2
$CH_3(CH_2)_{17}-$	*R*Br	KOH	56[c]	1:0.5
	*R*Br	KOH	47[d]	1:0.2

[a] Pure chromatographed yield based on **1**
[b] (), from Ref. [3]
[c] Ptc, reaction conditions: 40 °C for 5 days
[d] Ptc, reaction conditions: refluxed for 4.5 hours

chloride and tetrabutylammonium bromide or solvents with increased polarity, or a weaker base). The results obtained with tetrabutylammonium bromide differ from those reported for the N-alkylation of aniline [3]; the reason for this discrepancy is not clear. The choice of temperatures varied from 40 °C to reflux, the latter resulting in shorter reaction times. Both at 40 °C for 5 days and at reflux for an average of 4.5 hours **3** and **4** were obtained in ratios ranging from 1:0.1 to 1:0.5. As shown, the ptc alkylating method favored the formation of the mono-derivative **3**, whereas with sulfonate as the alkylating agent the di-derivative **4** was predominant; also, in the ptc method, at reflux, the total yield was 56% (Table 1). It was found that prolonged reaction times after the disappearance of the starting material should be avoided since an increase of side products was observed.

In conclusion, for the N-alkylation of **1** under ptc conditions, the mono-derivative was favoured, while the yield of the di-derivative **4** was inversely proportional to the reaction temperature. When alkyl sulfonates were used **4** was favoured, though the ratio of **3** to **4** increased with the length of the alkyl chain (Tables 1, 2).

Experimental Part

Melting points were determined on an electrothermal apparatus and are uncorrected. Infrared spectra were measured on a Perkin Elmer 397 spectrophotometer. The NMR spectra were recorded on a Varian FT-80 A spectrometer and the chemical shifts are expressed in ppm (δ), downfield from the internal *TMS* standard. The UV spectra were recorded using a Hitachi 220 double beam spectrophotometer. The mass spectra were obtained using a Hitachi-Perkin Elmer RMU-6 L mass spectrograph. The elemental analyses were made using a Perkin Elmer 240 B automatic analyzer; they were in accord with the calculated C, H, N values within experimental error.

Table 3. Spectral data of **3b–e** and **4b–e**

Compound	UV ($CHCl_3$) λ (nm)	IR ν (cm^{-1})	^1H NMR δ (ppm)	MS (70 ev) m/e
3b	265, 310 320, 384	(KBr) 3390, 2940, 2880, 1765, 1700	($CDCl_3$) 7.54 (d, 1H, J=8.2 Hz), 6.93 (d, 1H, J=2.0 Hz), 6.73–6.60 (dd, 1H, J=8.2 Hz, 2.0 Hz), 4.58 (s, 1H), 3.20 (t, 2H), 3.08 (s, 3H), 1.72–0.86 (m, 13H)	274 (M^+)
3c	265, 310 320, 384	(KBr) 3390, 2980, 2875, 1770, 1720	($CDCl_3$) 7.53 (d, 1H, J=8.2 Hz), 6.93 (d, 1H, J=2.0 Hz), 6.73–6.60 (dd, 1H, J=8.2 Hz, 2.0 Hz), 4.59 (s, 1H), 3.18 (t, 2H), 3.08 (s, 3H), 1.75–0.88 (m, 17H)	302 (M^+)
3d	265, 310 320, 384	(KBr) 3370, 2910, 2840, 1745, 1685	($CDCl_3$) 7.52 (d, 1H, J=8.2 Hz), 6.94 (d, 1H, J=2.0 Hz), 6.72–6.60 (dd, 1H, J=8.2 Hz, 2.0 Hz), 4.60 (s, 1H), 3.14 (t, 2H), 3.10 (s, 3H), 1.80–0.91 (m, 19H)	316 (M^+)
3e	265, 310 320, 384	(KBr) 3370, 2980, 2930, 1765, 1700	($CDCl_3$) 7.54 (d, 1H, J=8.2 Hz), 6.93 (d, 1H, J=2.0 Hz), 6.73–6.60 (dd, 1H, J=8.2 Hz, 2.0 Hz), 4.58 (s, 1H), 3.20 (t, 2H), 3.08 (s, 3H), 1.72–0.86 (m, 35H)	428 (M^+)
4b	272, 330 406	(neat) 2940, 2875, 1760, 1700	(CCl_4) 7.58 (d, 1H, J=8.4 Hz), 6.97 (d, 1H, J=2.4 Hz), 6.75–6.61 (dd, 1H, J=8.4 Hz, 2.4 Hz), 3.35 (t, 4H, J=8.1 Hz), 3.09 (s, 3H), 1.83–0.87 (m, 26H)	373 (M^+)[a]
4c	272, 330 406	(neat) 2940, 2875, 1760, 1700	(CCl_4) 7.53 (d, 1H, J=8.4 Hz), 6.93 (d, 1H, J=2.4 Hz), 6.72–6.60 (dd, 1H, J=8.4 Hz, 2.4 Hz), 3.34 (t, 4H, J=8.1 Hz), 3.10 (s, 3H), 1.70–0.84 (m, 34H)	429 (M^+)[a]
4d	272, 330 406	(neat) 2940, 2870, 1765, 1700	(CCl_4) 7.52 (d, 1H, J=8.4 Hz), 6.94 (d, 1H, J=2.4 Hz), 6.72–6.60 (dd, 1H, J=8.4 Hz, 2.4 Hz), 3.34 (t, 4H, J=8.1 Hz), 3.09 (s, 3H), 1.80–0.82 (m, 38H)	457 (M^+)[a]
4e	272, 330 406	(neat) 2940, 2875, 1770, 1700	(CCl_4) 7.52 (d, 1H, J=8.4 Hz), 6.94 (d, 1H, J=2.4 Hz), 6.72–6.60 (dd, 1H, J=8.4 Hz, 2.4 Hz), 3.34 (t, 4H, J=8.1 Hz), 3.09 (s, 3H), 1.80–0.80 (m, 70H)	682 (M^+)[a]

[a] Analysis of the hydrazide derivative

Compounds **3b–e** and **4b–e** were purified by column chromatography; the yields and ratios in the product mixture were determined on the basis of the pure isolated products.

1 was synthesized from 4-nitrophthalic acid [6, 7].

N-Alkylation of 4-Amino-N-methylphthalimide, **1**, *by Phase-Transfer Catalysis* (**3b–e**), (**4b–e**). *General Procedure* (Exemplified by **3c**, **4c**)

To a mixture of **1** (0.3 g, 1.7 mmol) and *n*-nonyl bromide (1.0 g, 4.8 mmol) in toluene (40 ml), KOH powder (0.3 g, 5.4 mmol) and Bu_4NI (0.1 g, 0.3 mmol) were added and the mixture was stirred under

reflux for 4.5 h. The reaction was monitored by tlc, the R_f's (ethyl acetate : petroleum ether = 1 : 5) being 0.32 and 0.64 for **3c** and **4c**. After filtration of the reaction mixture the solvent was removed in vacuo and the residual crude mass was purified by column chromatography over silica gel (Merck, 70–230 mesh, ASTM). The mono- **3c** and di-*n*-alkylated **4c** derivatives were separated when the column was eluted with diethyl ether : petroleum ether : toluene = 1 : 3 : 1, **4c** being eluted first, followed by **3c**. Furthermore, **3c** and **4c** were against subjected to column chromatography over silica gel with $CHCl_3$ and toluene as eluents. Yields: total 295.6 mg (55%), **3c** 251.9 mg (49%) and **4c** 43.7 mg (6%). For data see Tables 1, 2.

Heptyl, Nonyl and Decyl Tosylates (**2b–d**). *General Procedure*

2b–d were synthesized from the respective alcohols by the use of the Timpson method [8] at 0 °C for 24 h, the molar ratio of alc : py : tosyl chloride being 1.0 : 7.6 : 1.2. Upon adding crushed ice to the reaction mixture and after 10 min standing followed cold diethyl ether addition and successive extractions of the organic layer with cold 2*N* H_2SO_4, H_2O, 5% Na_2CO_3, sat. NaCl solution and drying with $MgSO_4$. The purities were checked by tlc (ethyl acetate : petroleum ether = 1 : 5) followed by spraying with 50% H_2SO_4 in ethanol and subsequently burning the plate over a flame. All tosylates were oils [9–11] and were purified at −5 °C by an oiling out technique from *n*-hexane. Average yield of tosylates: 65–70%. Similar IR and NMR spectral data were obtained for all **2b–d**. IR ν (cm^{-1}) (neat): 2900, 2870 (CH_2), 1590 (*Ar*), 1350, 1185 (SO_2). ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7.0 Hz, CH_3), 1.23 [br s, (x−4) H $(CH_2)_{x-2}$, where x is the total of methylenes], 1.60 (br s, 2H, CH_2CH_2O), 2.44 (s, 3H, $ArCH_3$), 4.02 (t, 2H, J=7.0 Hz, CH_2O), 7.58 (m, 4H, *Ar*H).

N-Alkylation of 4-Amino-N-methylphthalimide, **1**, *Using n-Alkyl Tosylates* (**3b–d**), (**4b–d**). *General Procedure*

3b–d and **4b–d** were synthesized from **1** and the tosylates **2–d**, heating at 170 °C for 5 h in the presence or absence of potassium carbonate [4] (Tables 1, 2). The products were isolated and purified as described above, the total yields and product ratios are given in Tables 1, 2.

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