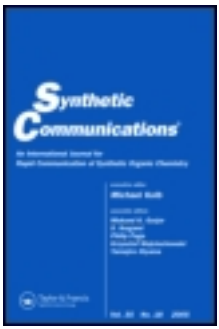

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Substituted N-Monoalkylaromatic Amines Under PTC Conditions

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Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 21(18&19), 1889-1900 (1991)

FACILE SYNTHESIS OF SUBSTITUTED N-MONOALKYLAROMATIC AMINES UNDER PTC CONDITIONS+.

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Abstract: Substituted aromatic amides were alkylated under PTC conditions. Compounds with ortho electron withdrawing substituents furnished exclusively monoalkyl amines. A plausible mechanism has been suggested.

Primary aromatic amines cannot be monoalkylated in satisfactory yields under either normal or PTC condition due to difficulty in removing the NH proton from these amines (pK_a aniline 27[1]) . This difficulty has been overcome by converting the amines to amides, thus facilitating the proton removal and hence the alkylation. We have reported a simple method for the monoalkylation of benzanilides[2] and diphenylureas[3] under PTC conditions. However, in order to get the alkyl amines these alkyl amides must be hydrolyzed in a separate step. A direct conversion of substituted amides to monoalkyl amines is reported; however, it involves

+ NCl Communication No. 5070.

either the use of costly reagents and solvents[4] or it does not have general applicability[5].

In this communication we describe a simple economical one pot synthesis of ortho substituted aromatic monoalkyl amines from corresponding amides/amines using PTC conditions where the substituent is electron withdrawing. The effects of other substituents at the meta and para positions are also discussed. A plausible mechanism is suggested to accommodate the experimental observations.

1-Acetamido or benzamidoanthraquinone (**1a,b**) and 2-nitroacetanilide or 2-nitrobenzanilide (**7n,o**) on treatment with dimethyl sulphate, powdered sodium hydroxide and potassium carbonate yielded 1-N-methylaminoanthraquinone (**3**) and o-nitro-N-methylaniline (**8n**) in quantitative yields. It is quite obvious that these amides were alkylated and deacylated in one pot reaction mainly because of the presence of the ortho substituents, since the corresponding unsubstituted compounds (**7a,b**) furnished only methylated amides (**8a,b**) under identical reaction conditions. So in order to ascertain the exact role of these substituents in the alkylation and deacylation reactions, alkylation of various substituted aromatic amides (**1a,b;5a,b;7a-w**) was studied and the results are presented in Tables 1 and 2.

Table 1

Methylation of amidoanthraquinone (**1a,b** & **5a,b**) using PTC

Substrate No	R	DMS mol.	Product No	R	Isolated % yield	M.P/B.P ^{O}C Observed (Literature)
1a	$COCH_3$	1.1	**3**	H	98	169-70 (170[7])
1b	COC_6H_5	1.1	**3**	H	95	169-70 (170[7])
1b	COC_6H_5	--	**1b**	COC_6H_5	no reaction	
2a	$COCH_3$	--	**2a**	$COCH_3$	no reaction	
5a	$COCH_3$	1.1	**6a**	$COCH_3$	95	160-61 C
5b	COC_6H_5	1.1	**6b**	COC_6H_5	93	171-2 C

Reaction temperature and time for all the reactions is 30-35^{O}C and 2 hours respectively. In all the reactions tetrabutylammonium hydrogen sulphate is used as PTC.
C: Charecterised by elemental and spectral analysis (Table 3).

TABLE 2

Methylation of amides(**7a-w**) in presence of PTC

Substrate			Product			Isolated	M.P/B.P ^0C	
	Substituent			Substituent				
No	R	R´	No	R	R´	% yield	Observed	Literature
7a	$COCH_3$	H	**8a**	$COCH_3$	H	98	102	102[8]
7b	COC_6H_5	H	**8b**	COC_6H_5	H	95	60	60[8]
7c	$COCH_3$	2-Cl	**8c**	$COCH_3$	2-Cl	96	125-30/12mm	130/12mm[9]
7d	COC_6H_5	2-Cl	**8d**	COC_6H_5	2-Cl	96	64	64[2]
7e	COC_6H_5	3-Cl	**8e**	COC_6H_5	3-Cl	98	46	46[2]
7f	COC_6H_5	4-Cl	**8f**	COC_6H_5	4-Cl	98	68	69[10]
7g	$COCH_3$	2,6-Cl_2	**8g**	$COCH_3$	2,6-Cl_2	98	66	C
7h	COC_6H_5	2,6-Cl_2	**8h**	COC_6H_5	2,6-Cl_2	92	116	C
7i	$COCH_3$	2,6-$(CH_3)_2$	**8i**	$COCH_3$	2,6-$(CH_3)_2$	98	92	C
7j	$COCH_3$	2,6-$(C_2H_5)_2$	**8j**	$COCH_3$	2,6-$(C_2H_5)_2$	96	135-40/3mm	C
7k	COC_6H_5	2-OCH_3	**8k**	$COCH_3$	2-OCH_3	90	80	80[2]
7l	COC_6H_5	3-OCH_3	**8l**	$COCH_3$	3-OCH_3	95	55	56[11]
7m	COC_6H_5	4-OCH_3	**8m**	$COCH_3$	4-OCH_3	92	73	76[10]

Substrate			Product			Isolated	M.P/B.P ^{0}C	
	Substituent			Substituent		% yield	Observed	Literature
No	R	R´	No	R	R´			
7n	$COCH_3$	2-NO2	**8n**	H	2-NO2	98	37	37[8]
7o	COC_6H_5	2-NO2	**8n**	H	2-NO2	98	37	37[8]
7p	$COCH_3$	4-NO2	**8p**	$COCH_3$	4-NO2	90	153	153[12]
7q	COC_6H_5	4-NO2	**8q**	COC_6H_5	4-NO2	95	111	112[8]
7r	$COCH_3$	2-COC_6H_5	**8r**	H	2-COC_6H_5	98	68	69[13]
7s	COC_6H_5	2-COC_6H_5	**8r**	H	2-COC_6H_5	96	69	69[13]
7t	$COCH_3$	4-COC_6H_5	**8t**	$COCH_3$	4-COC_6H_5	96	106	C
7u	COC_6H_5	4-COC_6H_5	**8u**	COC_6H_5	4-COC_6H_5	95	101	C
7v	$COCH_3$	2-COC_6H_5-5-Cl	**8v**	H	2-COC_6H_5-5-Cl	98	95	96[8]
7w	COC_6H_5	2-COC_6H_5-5-Cl	**8v**	H	2-COC_6H_5-5-Cl	97	96	96[8]

Reaction temperature and time for all the reactions is 30-35^{0}C and 2 hours respectively. In all the reactions, dimethyl sulphate (DMS) 1.05 mole/1.0 mol of amide is used as methylating agent and tetrabutylammonium hydrogen sulphate is used as PTC.
C: Charecterised by elemental and spectral analysis (Table 3).

The major conclusions that can be drawn from the observations presented in Tables 1 and 2 may be summarized as follows.

1. Compounds having no substitutents (**7a,b**) yielded only alkyl amides (**8a,b**).

2. Compounds having ortho electron donating substituents (**7c,d,k**) also furnished alkyl amides (**8c,d,k**).

3. Compounds having ortho substitution with electron withdrawing groups (**1a,b;7n,o,r,s,v,w**) gave exclusively monoalkyl amines (**3,8n,r,v**).

4. para-substituents do not have any marked effect on the product pattern. However, compounds having para electron withdrawing substituents (**7p,q,t,u**) furnished mainly alkyl amides (**8p,q,t,u**).

5. meta substituents (**7e,l**) do not alter the course of the reaction and thus furnish alkyl amides (**8e,l**).

6. Bulk of the substituents (i.e. chlorine) (**7g**) does not seem to accelerate the deacylation as anticipated. However, this non-acceleratain could be ascribed partly to the electron donating capacity of the chlorine atom.

It was essential to determine the chronology of the reactions, alkylation and deacylation: (a) The deacylation takes place only after alkylation. (b) In the absence of PTC N-alkylacetamido anthraquinone (**2a**)

did not deacylate to give the corresponding alkyl amine (3) thus establishing the essentiality of PTC even for the deacylation step.

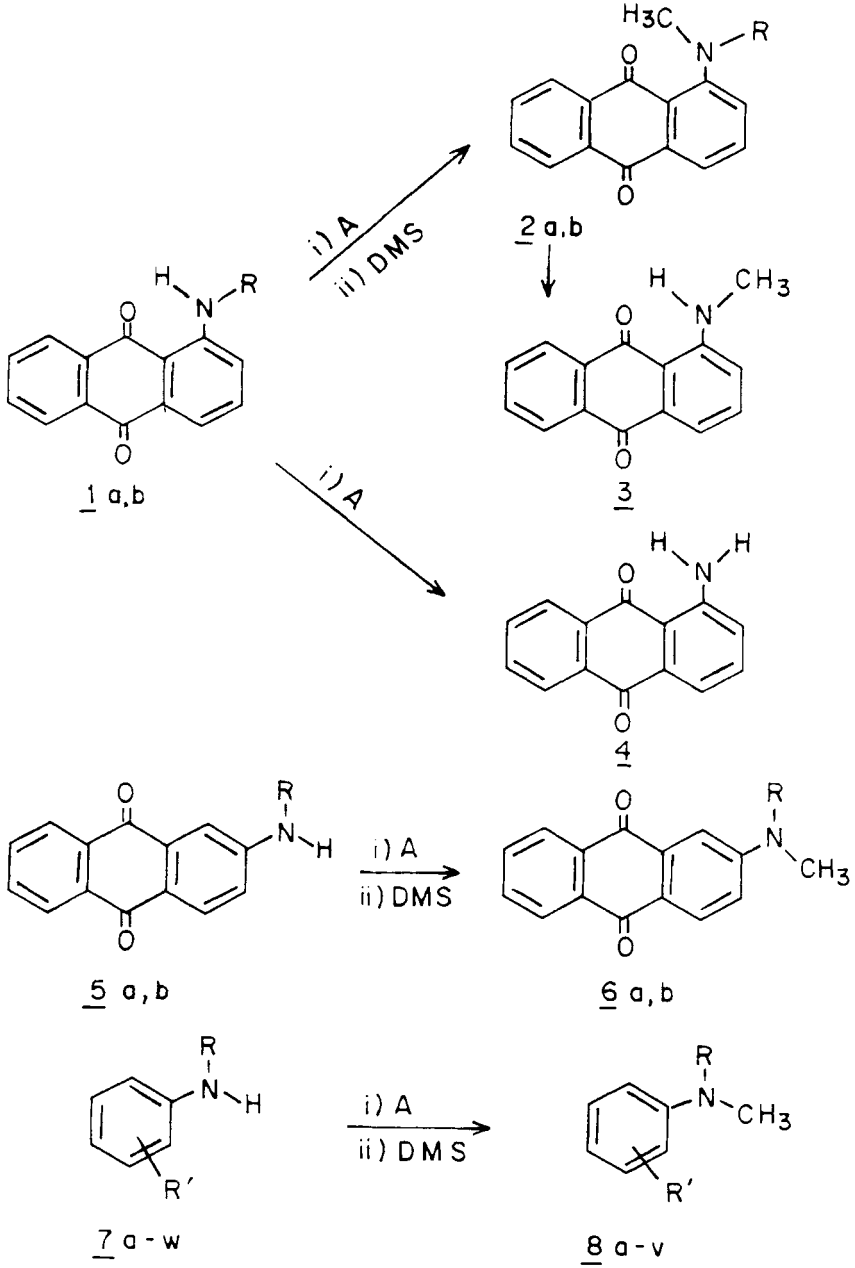
c) Under the reaction conditions the N-alkylated amide could not be isolated or its presence detected by TLC.

Taking into consideration the above phenomena i.e. chronology of reactions, essentiality of PTC and effect of various substituents, a plausible mechanism accommodating all these factor may be depicted as shown in Scheme 2.

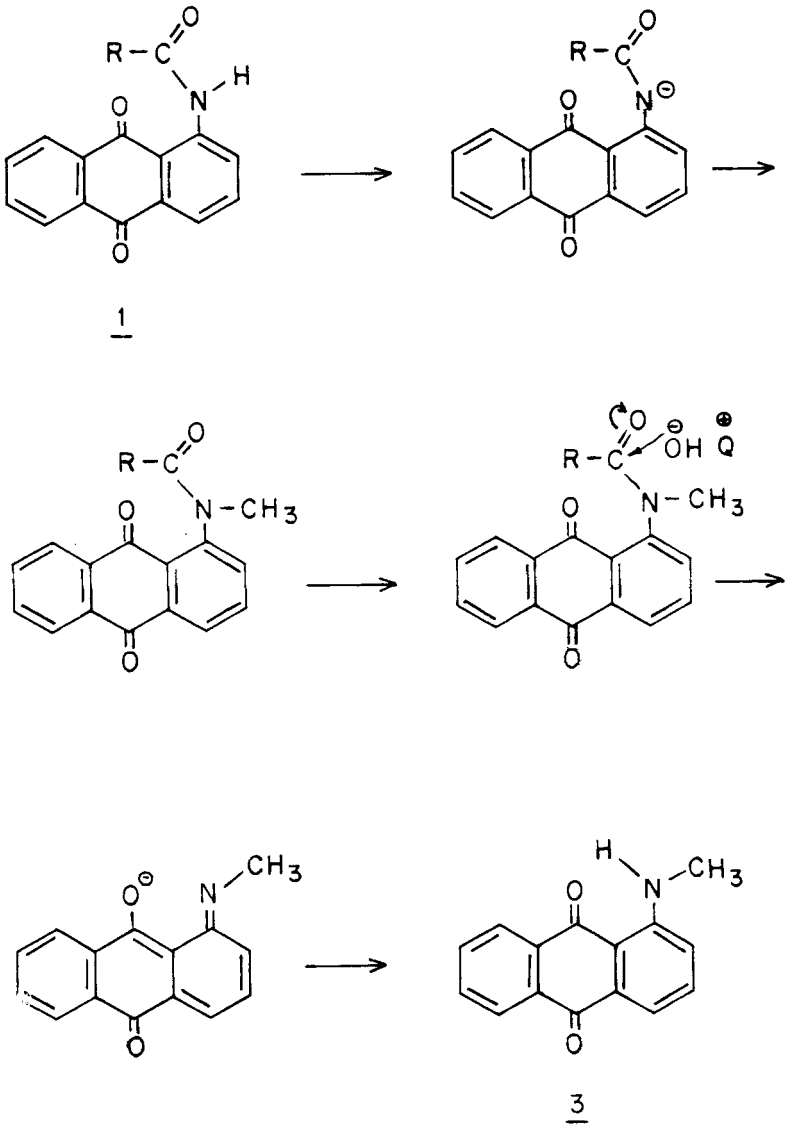
The proposed mechanism was verified[6] experimentally by alkylation of 1-amino anthraquinone and 1,4-diamino anthraquinone to monoalkyl aminoanthraquinones using various alkylating agents in excellent yields.

EXPERIMENTAL

All the melting points/boiling points are uncorrected. Infra red spectra were recorded on Perkin Elmer 137 B in nujol mull in cm^{-1}. ^{1}HNMR were recorded on Brucker W.H.-90 FT spectrometer using TMS as internal standard. Mass spectra were scanned on CEC-21-110 B machine. Purity of the compounds were checked by TLC. All the new compounds gave satisfactory elemental analysis. All the substrates were either procured from market or prepared following established procedures.



Scheme 1



R = $COCH_3$, COC_6H_5

Scheme 2

Table 3

Spectral and elemental analysis of N-monoalkylanilides(**6a,b** and **8g-j,t,u**)

Comp No.	M^+ ion	IR C=O cm^{-1}	^{1}HNMR ($CDCl_3$) Chemical shift in (δ) PPM	Molecular formula	Elemental analysis% Found (calculated) C	H	N
6a	279	1640	1.94(s, 3H), 3.31(s, 3H) 7.50-7.87(m, 3H), 8.0-8.37 (m, 4H)	$C_{17}H_{13}NO_3$	73.25 (73.11)	4.96 (4.65)	5.15 (5.01)
6b	341	1635	3.59(s, 3H), 7.0-746(m, 5H) 7.62-7.82(m, 3H), 8.13-8.34 (m, 4H)	$C_{22}H_{15}NO_3$	77.34 (77.71)	4.67 (4.31)	4.55 (4.10)
8g	218	1680	1.7(s, 3H), 3.1(s, 3H) 7.17-7.53(m, 3H)	$C_9H_9Cl_2NO$	50.26 (49.54)	4.16 (4.13)	6.20 (6.42)
8h	280	1650	3.17(s, 3H), 6.63-7.26 (m, 8H)	$C_{14}H_{11}Cl_2NO$	60.05 (60.00)	3.85 (3.93)	5.10 (5.00)
8i	177	1660	1.46(s, 3H), 2.23(s, 6H) 3.06s, 3H), 7.1(s, 3H)	$C_{11}H_{15}NO$	74.32 (74.57)	8.52 (8.47)	7.86 (7.91)
8j	205	1660	1.50(m, 6H), 1.83(s, 3H) 2.70(q, 4H), 3.23(s, 3H) 7.06-7.3(m, 3H)	$C_{13}H_{19}NO$	75.82 (76.09)	9.30 (9.26)	6.50 (6.83)
8t	253	1640	2.04(s, 3H), 3.37(s, 3H) 7.22-8.11(m, 9H)	$C_{16}H_{15}NO_2$	75.41 (75.88)	5.95 (5.92)	5.36 (5.53)
8u	315	1630	3.56(s, 3H), 7.0-7.81 (m, 14H)	$C_{21}H_{17}NO_2$	80.10 (80.00)	5.57 (5.93)	4.50 (4.44)

General procedure for N-alkylation of aromatic amides.

N-Methylation of 1-benzamido anthraquinone (1b)

In a three necked round bottom flask, mixture of 1b (0.02 mol) powdered sodium hydroxide (0.08 mol), powdered anhydrous potassium carbonate (0.2 mol) and tetrabutylammonium hydrogen sulphate (0.0004 mol) was stirred in toluene (100 ml) for 30 minutes at 30-35^{0}C. Reaction mixture was deep yellow initially became deep violet and slimy mass was seen sticking to the walls of the flask. Freshly distilled dimethyl sulphate (0.021 mol) diluted with toluene 10 ml was slowly added to the reaction mixture over a period of 30 minutes. As addition proceeded, deep violet color turned in to deep red (reaction was monitored by TIC). The reaction mixture was stirred at 30-35 ^{o}C for 1 h, filtered and washed with toluene (3 x 25 ml). Toluene main filtrate and washings were combined, washed with water (2 x 50 ml), dried over anhydrous sodium sulphate and concentrated to yield colored solid product, which was characterized as 1-N-methylamino anthraquinone **3** (4.5 g., 0.019 mol, 95%) m.p. 169-70^{o}C (Lit. 170[13]).

Similarly **1a**, **5ab** and **7a-w** were methylated under identical conditions and results are tabulated in Table 1 and 2. Elemental analysis and spectral data for new compounds are given in Table 3

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(Received in UK 16 May, 1991)