Anormalous Halogen to Dimethylamino Replacement with *N,N*-Dimethylformamide Catalyzed by Ethylenediamine or 2-Aminoethanol

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Synopsis. 1- And 2-chloroanthraquinone and 2-amino-4-chloro-6-hydroxypyrimidine exclusively gave the dimethylamino derivatives upon heating in DMF at 90 °C in the presence of ethylenediamine or ethanolamine. A possible reaction pathway for this unusual exchange reaction was discussed.

The active chlorine atoms that are attached to an acyl group[1] or certain aromatic and heteroaromatic nuclei[2-7] (*e.g.*, nitrobenzene[2] and pyridine[6]) are replaced by dimethylamino groups upon boiling with *N,N*-dimethylformamide (DMF) for a prolonged period according to Scheme 1. We will describe here a similar type of exchange reaction which is, however, characteristically catalyzed by ethylenediamine (EDA) or 2-aminoethanol at *ca.* 90 °C.

$$RCl + Me_2NCHO \longrightarrow RNMe_2 + HCl\ (or RN^+HMe_2Cl^-) + CO$$

Scheme 1.

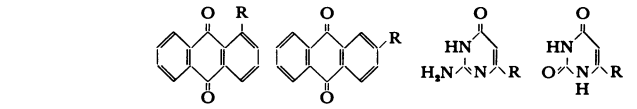
The treatment of 1- and 2-chloroanthraquinone (**1** and **2**) and the chloropyrimidines (**3** and **4**) with 1.0—2.0 mol equiv. of EDA or 2-aminoethanol in DMF at 90 °C afforded exclusively the dimethylamino compounds (**5**—**8**) instead of the normally expected substitution products (*e.g.*, **9**—**11**), as is recorded in Entry 1 of Table 1. Since all these chloro compounds were stable in DMF alone at this temperature, EDA and 2-aminoethanol are thought to act as catalysts for the dimethylamination. The catalytic efficiency was shown best by EDA or 2-aminoethanol, moderately by 1,3-propanediamine, and only slightly by 1,4-butanediamine, *N,N*- and *N,N'*-dimethylethylenediamine, 2-(methylamino)ethanol, or butylamine (Entry 2). No catalytic effect was found with triethylamine or ethylene glycol.

N-Methylformamide and *N*-formylmorpholine afforded a moderate yield of the corresponding exchange products (**12**—**15**), along with an appreciable amount of the substitution products (**9**, **10**), whereas, with *N,N*-diethylformamide and *N,N*-dimethylacetamide, the chloro compounds (**1**—**3**) either remained unreactive or preferably produced **9** and **10**. Thus, the reactivities of the aminating reagents depended upon the combination of the amines and the *N*-acyl groups (Entry 3).

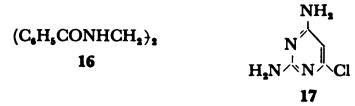
The use of ethanol as a solvent in the reaction of **1** with DMF–2-aminoethanol (2 mol equiv. each) suppressed the formation of both **5** and **9** (Entry 4). It should also be noticed that the reaction temperature plays an important role, as was observed in the predominant formation of **9** when **1** was heated with DMF or *N*-formylmorpholine in the presence of 2-aminoethanol at a lower temperature, such as 60 °C (Entry 4).

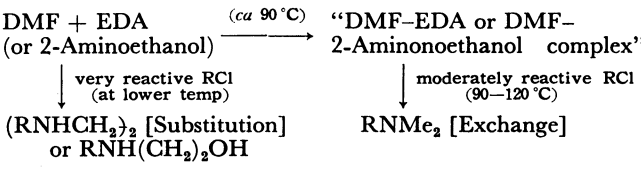
Benzoyl chloride, bearing a chlorine atom highly reactive towards nucleophiles, reacted with EDA in DMF, even at 0 °C, to give solely the *bis*-compound (**16**); without EDA, *N,N*-dimethylbenzamide is slowly produced upon heating in DMF only above 150 °C.[1] On the other hand, 2,4-diamino-6-chloropyrimidine (**17**), with a less reactive chlorine atom than **3** or **4**, remained almost unchanged, even on heating with DMF–EDA at 120 °C (Entry 4).

Chlorine atoms in hydroxy- or amino-chloropyrimidines are known to be replaced by alcoholic solution of amines, usually at relatively elevated temperatures in a sealed tube;[8] *e.g.*, 6-methylaminouracil is obtained from **4** at 130 °C, and 2,4,6-triaminopyrimidine, from **17** at 200 °C. However, such nucleophilic substitution with liberated dimethylamine is not conceivable in the present, unusual exchange reaction, since no dimethylamine was produced upon the heating of a 1 : 1 mixture of DMF and EDA (or 2-aminoethanol) at 90—100 °C for 2—20 h (by ^{1}H-NMR and GLC). Instead, DMF is likely to form a certain complex with EDA or 2-aminoethanol at *ca.* 90 °C; this complex subsequently reacts with chloro compounds (**1**—**4**) to give the dimethylamino derivatives at much faster rates than those of the exchange reaction (without using such catalysts) as are illustrated in Scheme 2. The predominant formation of the substitution products (**9**, **16**) with the catalysts at 0—60 °C can be explained in terms of the sluggish formation of such an intermediate complex at low temperatures.



R	1	2	3	4
Cl	1	2	3	4
NMe_2	5	6	7	8
$NH(CH_2)_2OH$	9	10		
$NMe(CH_2)_2OH$	11			
NHMe	12	13		
Morpholino	14	15		





Scheme 2.

Although the exact nature of the complex and the reaction mechanism remain to be clarified further, the present procedure is apparently a convenient method for the dimethylamination of some aromatic and heteroaromatic compounds bearing a reactive chlorine atom. The results also demonstrate the necessity of

Table 1. Active chlorides to amines

Entry	Starting matl.	Reagent[a]	Catalyst[b]	Reaction temp/°C (Time/h)	Exchange product; Yield[c]/%	Substitution product; Yield[c]/%	Yield[c] of the recovered starting matl./%
1	**1—4**	DMF	None	90 (22)			100
	1	DMF	EDA	90 (9)	**5**[d] ; 60		18
	1	DMF	AE	90 (22)	**5** ; 75	**9**[e] ; 15	
	2	DMF	EDA	90 (30)	**6**[d] ; 63		20
	2	DMF	AE	90 (22)	**6** ; 84		
	3[f]	DMF	EDA	90 (3)	**7**[e] ; 90		
	4[g]	DMF	EDA	90 (5)	**8**[h] ; 45		28
2	**1, 3**	DMF	TEA	90 (10)			100
	1, 2	DMF	EG	90 (22)			95
	1	DMF	MAE	90 (20)	**5** ; 5	**11**[i] ; 70	17
	2	DMF	DME	90 (22)	**6** ; 14		65
	2	DMF	DMED	90 (24)	**6** ; 8		80
	3	DMF	PDA	90 (7)	**7** ; 31		28
	3	DMF	BDA	90 (6)	**7** ; 3		67
	3	DMF	BA	90 (9)	**7** ; †		55
3	**1**	MeNHCHO	AE	90 (19)	**12**[d] ; 41	**9** ; 28	20
	2	MeNHCHO	AE	100 (60)	**13**[d] ; 36		25
	1	FM	AE	90 (22)	**14**[k] ; 45	**9** ; 33	
	2	FM	AE	90 (22)	**15**[l] ; 37	**10**[l] ; 4	45
	1	Et_2NCHO	AE	90 (22)		**9** ; 63	25
	2	Et_2NCHO	AE	90 (22)		**10** ; 5	90
	1	Me_2NAc	AE	90 (22)	**5** ; 2	**9** ; 73	12
	2	Me_2NAc	AE	100 (40)	**6** ; 21	**10** ; 60	7
	3	Me_2NAc	EDA	90 (5)			100
4	**1**	DMF+EtOH	AE	90 (22)	**5** ; 18	**9** ; 12	65
	1	DMF	AE	60 (10)	**5** ; Trace	**9** ; 38	40
	1	FM	AE	60 (10)	**14** ; Trace	**9** ; 27	56
	PhCOCl	DMF	EDA	0 (0.5)		**16**[m] ; 71	
	PhCOCl	DMF	None	150 (6)	$PhCONMe_2$[n] ; 85		
	17[o]	DMF	EDA	120 (10)			90

a) Used as the solvent; DMF, *N,N*-dimethylformamide; FM, *N*-formylmorpholine. b) 1.0—2.0 mol equiv. to the substrate; EDA, ethylenediamine; AE, 2-aminoethanol; TEA, triethylamine; EG, ethylene glycol; MAE, 2-(methylamino)ethanol; DME, *N,N*-dimethylethylenediamine; DMED, *N,N'*-dimethylethylenediamine; PDA, 1,3-propanediamine; BDA, 1,4-butanediamine; BA, butylamine. c) Yield referred to isolated, pure (TLC) products. d) Ref. 3. e) H. W. Coover, J. B. Bickey, and E. B. Towne, U. S. Patent 2459149, *Chem. Abstr.*, **43**, 3205 (1949). f) Ref. 8, p. 575. g) R. Huegi and W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **759**, 76 (1972). h) Ref. 8, p. 602. i) Ref. 8, p. 559. j) V. V. Russkikh and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, **1966**, 91. k) K. Bredereck, M. Diamantoglou, and F. Sommermann, *Chem. Ber.*, **103**, 1748 (1970). l) New compound. m) P. Ruggli, R. Patti, and E. Henzi, *Helv. Chim. Acta*, **12**, 347 (1929). n) Ref. 1. o) Ref. 8, p. 544.

taking precaution in employing DMF as a solvent in combination with certain amines, such as EDA and 2-aminoethanol.

Expermiental

The ^{1}H-NMR Spectra were measured with a Hitachi High-resolution NMR Spectrometer, R 20A (60 MHz), at 27 °C, using TMS as the internal standard, and the IR spectra, with a JASCO IRA-1 Spectrophotometer. Column chromatograhpy was carried out with alumina (Merck, Activity I, basic) or silica gel (Wako C-200), with ether–benzene or methanol–chloroform as the eluant. All the reactions were monitored by means of TLC.

Materials. The starting materials and products cited in this study are all known compounds except for **10** and **15**; thus, they are either commercially availabel or are prepared according to the literature methods (*cf.* Table 1) and purified before use.

General Procedures. A mixture of 50 mg of the active chloro compounds (**1**—**4**, PhCOCl, and **17**), 1.0 mol equiv. of the ethylenediamines (or 2.0 mol equiv. of 2-amonoethanol or other amines), and 1 ml of freshly distilled DMF (or the aminating reagent) was heated under nitrogen (or, in some cases, in a sealed tube); the reaction time and temperature are shown in Table 1. In many cases, the pure product was precipitated and subsequently isolated simply by filtration. The dilution of the filtrate with water gave the second crop. When the reaction products were a mixture, they were extracted with benzene after being diluted with water. The combined organic extracts were concentrated, and the residue was chromatographed. The products were characterized by a mixed-melting-point determination and by means of comparative TLC with authentic specimens prepared by alternative routes (Table 1) as well as by means of their ^{1}H-NMR and IR spectra.

*2-(2-Hydroxyethylamino)anthraquinone (**10**)*: Brown prisms; mp 206—207 °C (from EtOH); IR (Nujol) 3390, 3280 (OH, NH), 1660 (C=O), 1595 and 1560 cm^{-1} (C=C); ^{1}H-NMR δ ($CDCl_3$–DMSO-d_6, 1 : 1) 3.29† (1H, s, HO-2′), 3.40 (2H, brt, J=5.0 Hz, H_2-1′), 3.80 (2H, brt, J=5.0 Hz, H_2-2′), 4.91† (1H, m, NH), 6.90 (1H, dd, J=9.0, 2.5 Hz, H-3), 7.40 (1H, d, J=2.5 Hz, H-1), 7.80 (2H, m, H-6,7), 8.15 (1H, d, J=9.0 Hz, H-4), and 8.25 (2H, m, H-5,8), Found: C, 72.08; H, 4.82; N, 4.93%. Calcd for $C_{16}H_{13}NO_3$: C, 71.89; H, 4.91; N, 5.25%.

*2-Morpholinoanthraquinone (**15**)*: Reddish orange needles; mp 223—224 °C (from benzene); IR ($CHCl_3$) 1670 (C=O), 1595 (C=C), 1325, 1290 and 915 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$–DMSO-d_6) 3.3—3.8 (8H, m, morpholino) and 7.0—8.3 (7H, m, aromatic). Found: C, 73.65; H, 5.28; N, 4.43%. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.77%.

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† Signals being D_2O exchangeable.