

## Diazotization and Sandmeyer Reactions of Arylamines in Poly(ethylene glycol)-Methylene Dichloride: Usefulness of PEG in Synthetic Reactions<sup>1</sup>

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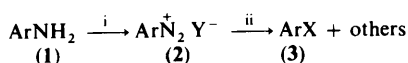
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Diazotization and Sandmeyer reactions of representative arylamines (**1a—h**) proceed smoothly in PEG-CH<sub>2</sub>Cl<sub>2</sub> and were found to be effective for the preparations of halogenoarenes (X = Cl, Br, and I) and cyanoarenes (X = CN).

The chemistry of cyclic polyethers (crown ethers) has attracted the interest of many investigators because of the rather high selectivity of the reactions of the activated anion species carried by the macrocycles. Indeed, many interesting reactions have been performed in the presence of crown ethers.

The properties of poly(ethylene glycol) (PEG) make it an excellent substitute for crown ethers in many reactions<sup>2-4</sup> and its use as a co-solvent has been reported: Santaniello *et al.* have reported oxidation of benzylic bromides to the corresponding aldehydes by K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> in PEG #400 at 110 °C (yield ~85%);<sup>3a</sup> substitution of alkyl bromides to give the corresponding RX compounds by KX (X = OAc, CN, I, and OPh) in PEG at 110 °C (yield 88–94%),<sup>3a</sup> reduction of methyl ketones to the corresponding alcohols by NaBH<sub>4</sub> in PEG at 25 °C;<sup>3a</sup> and hydrogenation of carboxylic esters to the corresponding primary alcohols by NaBH<sub>4</sub> in PEG #400 at 65 °C (10 h).<sup>3b</sup> Sukata has reported an effective ether synthesis from an alcohol and an alkyl chloride by KOH or NaOH in PEG or a dialkyl PEG and aqueous MeOH at 30–70 °C.<sup>3c</sup>

Hoping to find new preparative organic reactions using PEG as a co-solvent, we have investigated several photochemical and 'dark' reactions,<sup>2</sup> *e.g.* photochemical nucleophilic substitution reactions of anisole<sup>2a-c</sup> and *o*- and *p*-dimethoxybenzenes<sup>2c,d</sup> by <sup>-</sup>CN anion which was activated by PEG, and also assisted by electron-transfer complex formation with dicyanobenzene; catalytic hydrogenation of acetylenic compounds by H<sub>2</sub>/PdCl<sub>2</sub> in PEG-CH<sub>2</sub>Cl<sub>2</sub>;<sup>2e,f</sup> and also a novel hydrogenation of acetylenes to the corresponding *cis*-olefins by NaBH<sub>4</sub> in PEG-CH<sub>2</sub>Cl<sub>2</sub> catalysed by PdCl<sub>2</sub>.<sup>2g</sup> We have now found that effective diazotization of arylamines and Sandmeyer substitution reactions of the resulted diazonium compounds take place with NaNO<sub>2</sub>-HCl in PEG-CH<sub>2</sub>Cl<sub>2</sub><sup>5,†</sup> and with Cu<sub>2</sub>X<sub>2</sub>, Cu-MX, or K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>] in PEG-CH<sub>2</sub>Cl<sub>2</sub> systems, respectively, thus providing the first example of cyano substitution of diazonium salts using the isolated solid K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>] complex (Scheme).



- |                                                     |                                                      |
|-----------------------------------------------------|------------------------------------------------------|
| a: Ar = Ph                                          | e: Ar = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>   |
| b: Ar = <i>p</i> -PhCOC <sub>6</sub> H <sub>4</sub> | f: Ar = <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>   |
| c: Ar = 1-Naphthyl                                  | g: Ar = <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub>   |
| d: Ar = <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>   | h: Ar = <i>p</i> -PhC≡CC <sub>6</sub> H <sub>4</sub> |

X = Cl, Br, I, or <sup>-</sup>CN      Y = Cl, Br, or I

**Scheme.** Reagents and conditions: i, NaNO<sub>2</sub>-HY in PEG-CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. ii, MX in PEG-CH<sub>2</sub>Cl<sub>2</sub> at from 0 °C to room temperature. Salts MX are defined in footnote b, Table 1

### Results and Discussion

On diazotization in PEG-CH<sub>2</sub>Cl<sub>2</sub>, the starting materials (**1**) (10mm and 100mm) were consumed completely in 20 min. Three equivalents of the acid (HY) were necessary (Table 1 and 2), the same as in aqueous solutions as suggested by Kornblum<sup>5a</sup> and Wulfman.<sup>5b</sup>

Aniline (**1a**) was chlorinated quantitatively in PEG-CH<sub>2</sub>Cl<sub>2</sub>, while it did not give any chlorobenzene in an aqueous solution under similar reaction conditions (Cu<sub>2</sub>Cl<sub>2</sub> and /or Cu powder).<sup>6</sup> Chlorination of compounds (**1b—d**) was accompanied by formation of the corresponding reduction products, ArH (**4**), under similar conditions.†

Bromination proceeded in good yield when HBr was used as HY, while the major product was aryl chloride instead of bromide when HCl was employed as HY. Iodination proceeded in excellent yield when HI§ was used as HY.

Cyanation in PEG-CH<sub>2</sub>Cl<sub>2</sub> did not proceed under ordinary reaction conditions.<sup>7,8</sup> Only chlorination or bromination products were obtained, depending on the acid employed. Significantly, high yields of cyanation products were obtained only when excess of dried K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>] complex<sup>9,¶</sup> was employed as cyanating reagent. This provides the first example of the cyanation of diazonium salts using the solid K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>] complex. The present reaction is useful for the preparation, in fairly dilute solution (10–100mm), of the amines (**1**).

Several preparative Sandmeyer reactions of arenediazonium compounds in various organic solvents,† *e.g.* xylene, dimethyl sulphoxide (DMSO), 18-crown-6-CHCl<sub>3</sub>, and tetrahydrofuran, have been shown to give good-to-excellent yields only when the substrate concentrations employed are comparatively high (≥73mm). The ordinary aqueous Sandmeyer reactions which were reported in *Organic Synthesis*<sup>7b,10</sup> gave only very poor

† See the following references for examples of the preparation of diazonium compounds in organic solvents; (a) in xylene (starting material 500mm; yield, 70%): T. L. Fletcher and M. J. Namkung, *Chem. Ind. (London)*, 1961, 179; (b) in DMSO (yield 50–70% in chlorination; 59–97% in cyanation): M. Kobayashi, E. Yamada, M. Matsui, and N. Kobori, *Org. Prep. Proced. Int.*, 1969, 1, 221; M. Kobayashi, H. Minato, E. Yamada, and N. Kobori, *Bull. Chem. Soc. Jpn.*, 1970, 43, 215; (c) in CH<sub>2</sub>Cl<sub>2</sub> (73mm; 75%): C. G. Swain and R. J. Rogers, *J. Am. Chem. Soc.*, 1975, 97, 799; (d) in 18-crown-6-CHCl<sub>3</sub> (100mm; 82%): S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 1977, 3519; J. R. Beadle and G. W. Gokel, *ibid.*, 1984, 25, 1681.

‡ This reduction is performed in EtOH either by the classical procedure or with H<sub>3</sub>PO<sub>2</sub>; see ref. 5b, p. 286; S. Yasui, K. Nakamura, and A. Ohno, *J. Org. Chem.*, 1984, 49, 878.

§ Organic product was used, which showed colour due to iodine.

¶ This complex has been used only as an aqueous solution in the literature. The structure of the complex used has not been well documented in the literature (ref. 9); it could have a different structure.

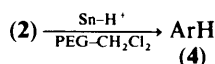
**Table 1.** Diazotization and Sandmeyer reactions of compounds (1) (10mM) in PEG-CH<sub>2</sub>Cl<sub>2</sub><sup>i</sup>

Amine (1) (10mM; 10 ml)	HY <sup>a</sup>	Consumption <sup>j</sup> of (1) (%)	MX <sup>b</sup>	Yield of products (%) <sup>c</sup>		
				ArX (3)	ArH (4)	ArCl
<b>Chlorination</b>						
(1a)	3M A	96	D	100 [93] <sup>h</sup>		
(1a) <sup>d</sup>	3M A	96	D (or E)	1 (17)		
(1a) <sup>d,e</sup>	conc. A <sup>f</sup>	100	D (or E)	70 (74)		
(1b)	3M A	100	D	19	78	
(1b)	5M A	100	D	20	66	
(1c)	3M A	100	D	7	25	
(1d)	3M A	99	D	35	56	
<b>Bromination</b>						
(1a)	3M A	96	F	11		43
(1a)	4M B	97	F	92 [86] <sup>h</sup>		
(1e)	4M B	100	F	32	14	
<b>Iodination</b>						
(1a)	3M A	99	G	57		2
(1a)	3M C <sup>g</sup>	99	G	100 [85] <sup>h</sup>		
<b>Cyanation</b>						
(1a)	3M A	88	H	15		75
(1a)	3M A	100	J/D; J/K; or J/E	0		40
(1a)	3M A	95	L	11		19
(1a)	3M A	100	M	67 [62] <sup>h</sup>		16
(1b)	3M A	100	M	28	44	
(1c)	3M A	100	M	50 [69] <sup>h</sup>	17	
(1d)	3M A	100	M	51	25	20
(1f)	3M A	97	M	93	7	
(1g)	3M A	100	M	39	12	
(1h)	3M A	99	M	38	53	

<sup>a</sup> A, HCl; B, HBr; C, HI (0.1 ml). <sup>b</sup> D, Cu<sub>2</sub>Cl<sub>2</sub>; E, copper powder; F, Cu<sub>2</sub>Br<sub>2</sub>; G, KI; H, Cu<sub>2</sub>(CN)<sub>2</sub>; J, KCN; K, Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O; L, 0.39M-K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>]; M, solid K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>]. <sup>c</sup> Based on the consumption of (1). <sup>d</sup> In aq. soln. <sup>e</sup> 333mM. <sup>f</sup> 2.5 ml. <sup>g</sup> 0.2 ml. <sup>h</sup> Isolated yield based on amount of starting material (1). <sup>i</sup> For the other reaction conditions, see text. <sup>j</sup> Determined g.l.c.

yields at highly dilute substrate concentration (10mM). The present method therefore offers some improvements for the reaction of dilute substrates (10mM) as well as for reaction on the preparative scale (100mM). This may be explained by the activation of the reaction anion species by complex-formation of the counter cation with PEG.<sup>4</sup>

Some extent of the reduction products was obtained in the chlorination, bromination, and cyanation reactions when electron-deficient amines were employed. This can be explained in terms of reduction of the diazonium salts by an alcoholic moiety -CHOH- of PEG, since such reduction occurs in ethanol as well with H<sub>3</sub>PO<sub>2</sub>.<sup>5a</sup> However, with tetraglyme, use of the dimethyl ether of PEG instead of PEG did not suppress the side reaction giving (4) (Table 3).



Aromatic diazonium salts are fairly stable thermally and have long enough life-times to react with reactants, while aliphatic ones are much less stable. If PEGs were able to stabilize the aliphatic ones as Bartsch *et al.* described,<sup>4</sup> it would be expected that the present reaction could be applied to aliphatic diazonium salts. Thus, we examined the stabilization using the aromatic diazonium compound (2a) as follows; the diazotized

**Table 2.** Diazotization and Sandmeyer reactions of compounds (1) (100mM) in PEG-CH<sub>2</sub>Cl<sub>2</sub>

Amine (1) (100mM; 10 ml)	HY <sup>a</sup> (1 ml)	Consumption <sup>j</sup> of (1) (%)	MX <sup>b</sup>	Yield of products (%) <sup>c</sup>		
				ArX (3)	ArH	ArCl
<b>Chlorination</b>						
(1a)	3M A	100	D	75 (22) <sup>h</sup>		
<b>Bromination</b>						
(1a)	3M B	100	F	60 (34) <sup>h</sup>		
<b>Iodination</b>						
(1a)	3M C	100	G	100 (100) <sup>h</sup>		
<b>Cyanation</b>						
(1a)	3M A	100	M	85 (32) <sup>h</sup>		
(1b)	3M A	96	M	28 (26) <sup>h</sup>	44 (41) <sup>h</sup>	13 (12) <sup>h</sup>
(1c)	3M A	100	M	69 (56) <sup>h</sup>	11	
(1d)	3M A	100	M	67 (54) <sup>h</sup>	30	3
(1e)	3M A	100	M	85 (80) <sup>h</sup>	16	
(1f)	3M A	100	M	88 (85) <sup>h</sup>	12	
(1g)	3M A	100	M	80 (62) <sup>h</sup>	11	

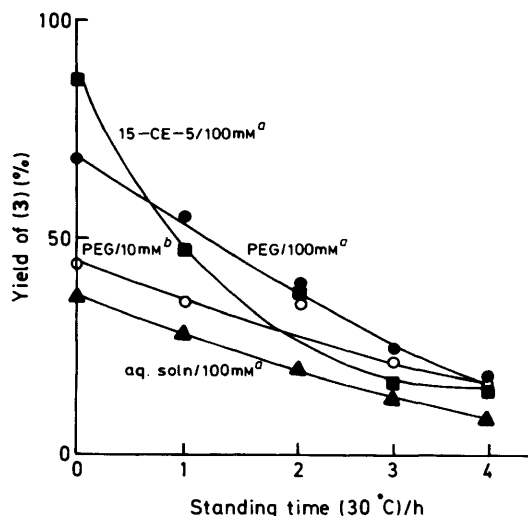
<sup>a-c</sup>, <sup>h</sup>, and <sup>j</sup> See footnotes in Table 1.

**Table 3.** Reactions in tetraglyme-CH<sub>2</sub>Cl<sub>2</sub>

Amine (1) (10mM)	HY <sup>a</sup> (0.1 ml)	Consumption <sup>j</sup> of (1) (%)	MX <sup>b</sup>	Yields of products (%) <sup>c</sup>	
				ArX	ArH
(1b)	3M A	100	M	46 (28) <sup>d</sup>	38 (44) <sup>d</sup>
(1c)	3M A	100	M	14 (50) <sup>d</sup>	26 (17) <sup>d</sup>
(1c)	3M B	100	F	8 (2.5) <sup>d</sup>	8 (6) <sup>d</sup>

<sup>a-c</sup>, and <sup>j</sup> See footnotes in Table 1. <sup>d</sup> Results in PEG #200.

mixtures, prepared from aniline (1a) at 0 °C, were warmed up to 30 °C and kept at that temperature for 1–4 h and then treated by the reagent K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>]. The Sandmeyer product (3a) was processed and estimated as described above (see Figure). In comparison with the results in tetraglyme, 15-crown-



**Figure.** Yields of cyanation products (3a) vs. standing time of (2a) at 30 °C. [K<sub>2</sub>Cu(CN)<sub>4</sub>·NH<sub>3</sub>] 780mM. <sup>a</sup> [(1)] 100mM. <sup>b</sup> [(1)] 10mM

5, and water, the diazonium ions are stabilized only to a small extent in PEG #200. This conclusion agrees with the observation of Bartsch *et al.*<sup>4</sup> They observed the stabilization in PEGs or their mono- and di-methyl ethers having molecular weights above 300; the diazonium-PEG complexes are stabilized by only ca. 30% (in PEG #300) (as measured by life-times) compared with the naked salts, and by slightly more as the molecular weights are higher.

### Experimental

PEG #200 (average molecular wt. 200; Nakarai Chem. Co.) was dried azeotropically with benzene. Tetraglyme (Aldrich) was distilled under reduced pressure. Methylene dichloride was distilled from CaH<sub>2</sub>. The arylamines (1) used were purchased (Wako), except for (1h) which was prepared according to the methods described in the literature.<sup>11</sup> The authentic hydrocarbons, halides, and cyanides (Wako) were purchased, except for (3h) which was prepared according to the literature methods.<sup>12</sup> Copper powder was prepared from CuSO<sub>4</sub> and Zn dust according to the literature procedure.<sup>6</sup> The complex K<sub>2</sub>[Cu(CN)<sub>4</sub>·NH<sub>3</sub>] was prepared from CuSO<sub>4</sub>, KCN, and NH<sub>3</sub> according to the literature method.<sup>9</sup>\* The resultant solution was dried, and used without isolation (contains K<sub>2</sub>SO<sub>4</sub>).

Each arylamine (1; 0.1 mmol; 10mM)† mixed with acid (aqueous HY; 0.3 mmol; 0.1 ml of 3M solution) was placed in a 100 ml-flask fitted with a rubber stopper with a balloon connected by an injection needle, and was diazotized at 0 °C by addition of NaNO<sub>2</sub> (0.1 mmol) dissolved in PEG #200 (2 g; 1M)\*-CH<sub>2</sub>Cl<sub>2</sub>. Onto a solid reagent (MX; 0.1 mmol—excess) was added the above diazotized solution (at 0 °C), and the mixture kept at room temperature. Samples were withdrawn at intervals and washed with 1M-NaOH in order to remove PEG. The products were identified by comparison of g.l.c. retention time and i.r. spectra with those of authentic samples. For isolation, 100 ml of the solutions (the same concentration) and also 10-ml solutions with 10-times higher concentration [100mM for (1)] were employed and gave results similar to those in the original experiments. However, a series of blank tests in the absence of aniline confirmed that no halogenation product was produced under otherwise identical conditions. As a comparison, some experiments in aqueous solution were performed without using the PEG-CH<sub>2</sub>Cl<sub>2</sub> system. For reactions in

tetraglyme, tetraglyme (2 g) was used instead of PEG #200 (2 g). The other conditions were identical with those of the reactions in PEG. For reactions using crown ether, 15-crown-5 (200 mg) was used instead of PEG #200 (2 g). The other conditions were identical with those of the reactions in PEG. Tables 1—3 show the results.

### Acknowledgements

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\* As footnote ¶ on p. 645.

† Final concentration in a 10 ml solution of PEG (2 g)-CH<sub>2</sub>Cl<sub>2</sub>-water (0.1 ml).

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