A Facile One-pot Synthesis of *N*-Substituted Phthalimides Using a Catalytic Amount of Crown Ether

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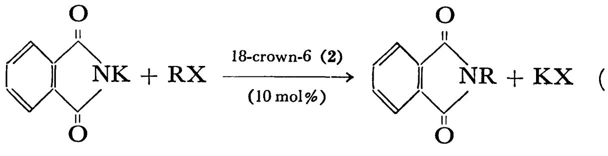
Synopsis. *N*-Substituted phthalimides, intermediates of the Gabriel synthesis, were obtained in high yields (84—100%) by the addition of a *catalytic* amount of 18-crown-6 to the reaction of potassium phthalimide and alkyl halides in toluene.

During these several years, increasing interest has been centered upon crown ethers.1) However, possibilities of their use in phase transfer catalysis (PTC) in organic synthesis have not been so fully documented as those of onium salts.2)

Though it is one of the major advantages of PTC that a *catalytic* (small) amount of the reagent can promote the reaction, no report has been appeared, to the best of our knowledge, on the alkylation of imides using a *catalytic* amount of crown ethers. Meanwhile, *N*-substituted phthalimides have been known as intermediates of the Gabriel synthesis of primary amines.3) Moreover, ethoxycarbonyl and sulfonyl derivaties are used in phthaloylation of amines and amino acids.4) Synthesis of *N*-substituted phthalimides by the alkylation of potassium phthalimide is usually run in dipolar aprotic solvents or in the presence of onium salts as PTC.5)

Concerning the synthesis of *N*-substituted phthalimides using crown ether, it is reported that halides react with *stoichiometric* amounts of the complex (**1**) of crown ether–potassium phthalimide–water.6) However, examples of halides are limited to only a few activated aromatic ones, and the synthesis has following shortcomings from the standpoint of preparative organic synthesis. (1) Use of *stoichiometric* amounts of crown ether. It is desirable to find a process in which a *catalytic* amount of crown ether promotes the reaction. (2) Prior to the reaction with halides, it is necessary to prepare **1**. (3) Since **1** contains *stoichiometric* amounts of water, competing reaction of water especially with aliphatic halides with functional groups may occur. (4) Potential suppression of anion activation by water in the medium because of anion solvation.

We wish to describe the results of our method which avoids all of these shortcomings. We have found that by the addition of a catalytic amount (10 mol%) of 18-crown-6 (**2**) an increase in the reaction rate of potassium phthalimide (**3**) and alkyl halides (**4**) was brought about in toluene and that *N*-substituted phthalimides (**5**) were obtained in high yields (Eq. 1).



(1)

3 **4** **5**

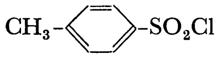
In the first place, we examined the effect of solvents on the reaction of **3** and **4** in the presence of 10 mol% of **2**. Results are summarized in Table 1. As is shown in Table 1, the overall reaction rate is

Table 1. Solvent effects on the alkylation of **3** with **4** in the presence of **2**

Entry	RX(**4**)a)	Solventb)	**5** Yield/%c)
A	$PhCH_2Br$	Toluene	98
B	$PhCH_2Br$	Toluene containing a trace amount of water	13d)
C	n-$C_8H_{17}Br$	Toluene	94
D	n-$C_8H_{17}Br$	3-Pentanol	83

a) Molar ratio of **3** : **4** : **2** was 1.2 : 1.0 : 0.1. b) Reactions were run at 100 °C for 6 h. c) Isolated yield. d) By-product was benzyl alcohol(14%).

Table 2. Preparation of *N*-substituted phthalimides(**5**) from **3** and **4** using a catalytic amount of **2**

Entry	**4**	Molar ratioa) **3** : **4** : **2**	**5** Yield/%b)		Mp θ_m/°C	Mp θ_m/°Clit.	Procedure
A	n-$C_8H_{17}Br$	1.2 : 1.0 : 0	0				A
B		1.2 : 1.0 : 0.1	94		48—49	48—49e)	A
C	$PhCH_2Cl$	0.8 : 1.0 : 0.1	89		113—114	115—116e)	A
D		1.2 : 1.0 : 0.1	100		113—114	115—116e)	A
E	$PhCH_2Br$	1.2 : 1.0 : 0.1	98		115	115—116e)	A
F	$BrCH_2CH_2Br$	1.2 : 0.5 : 0.1	84	45c)	81	82—83f)	A
				39d)	225—227	233—234g)	
G		1.2 : 1.0 : 0.1	100		231	235h)	B
H	C_2H_5OCOCl	1.2 : 1.0 : 0.1	96		79—81	80h)	B

a) Reactions were carried out at 90 °C or 100 °C for 0.5—6 h. b) Isolated yields. All compounds gave satisfactory NMR and IR spectra. c) *N*-(2-Bromoethyl)phthalimide. d) *N,N′*-Ethylenediphthalimide. e) See Ref. 7. f) *Org. Synth.*, Coll. Vol. I, 119 (1932). g) E. J. Sakellarious, *Helv. Chim. Acta*, **29**, 1675 (1946). h) See Ref. 4a.

larger in aprotic solvent than in protic solvent (Entries A, B, C, and D). Especially the presence of a trace amount of water lowered the reaction rate of alkylation considerably (Entry B), and caused the side reaction of benzyl bromide. It was concluded that absence of water was essential to accelerate the alkylation reaction and to avoid side reactions of halides.

Results of the alkylation of **3** with various kinds of **4** in the presence of 10 mol% of **3** in toluene are shown in Table 2.

Following conclusions may be drawn from the data in Table 2: (1) A *catalytic* amount of **2** was essentially necessary. This showed that crown ether behaved as a solid-liquid PTC (Entries A and B), (2) Both chloride and bromide gave high yields of **5** (Entries D and E), (3) Slight excess of **3** was required to complete the reaction (Entries C and D), (4) **4** with functional groups such as sulfone and ester gave high yields of **5** (Entries G and H).

As described above, this one-pot reaction afforded high yields of *N*-substituted phthalimides (**5**) and required only a *catalytic* amount of crown ether and avoided hydrolysis of alkyl halides.

Experimental

Procedure A. N-*Octylphthalimide*: To a mixture of **3** (0.222 g, 1.2 mmol) and 1-bromooctane (0.193 g, 1.0 mmol) in 1.3 ml of toluene was added **2** (0.1 mmol, 10 mol%). After the mixture was heated at 100 °C for 6 h with stirring under an argon atmosphere, water was added to the mixture. Organic layer was separated and aq layer was extracted with dichloromethane. Combined organic layer was dried over sodium sulfate, and then solvent was evaporated under reduced pressure. Purification on silica-gel TLC(dichloromethane–hexane 1:1 as eluent) afforded *N*-octylphthalimide (0.243 g, 94%, mp 48—49 °C[7]).

Procedure B. N-*(Ethoxycarbonyl)phthalimide*: **3** (0.222 g, 1.2 mmol) and ethyl chloroformate (0.109 g, 1.0 mmol) were allowed to react in toluene (1.3 ml) in the presence of **2** (0.1 mmol, 10 mol%) at 90 °C for 1 h. Precipitate was filtered off, and filtrate was evaporated under reduced pressure. Crystallization from hexane–chloroform afforded *N*-(ethoxycarbonyl)phthalimide (followed by two additional crops for a total of 0.210 g, 96% yield) mp 79—81 °C, (lit, mp 80 °C[4a]).

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