

A NEW METHOD OF ALKYLATION WITH CHLOROFORMATE ESTERS

I. APPLICATION TO IMIDES

Julius A. Vida

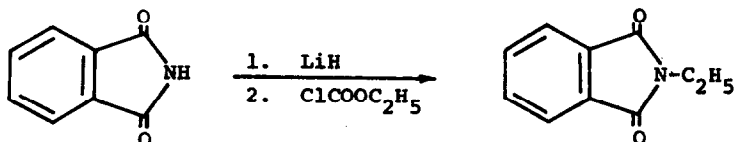
KENDALL Company, Theodore Clark Laboratory

Cambridge, Massachusetts 02142  
(Received in USA 5 July 1972; received in UK for publication 14 August 1972)

Chloroformate esters have been widely used to introduce carbalkoxy groups into a variety of chemical compounds. Chloroformate esters react with acids to produce mixed anhydrides<sup>1</sup> and with alcohols to produce esters<sup>2</sup> (e.g. cathylates). Chloroformate esters have also been used to synthesize  $\beta$ -cyanoesters<sup>3</sup> and to demethylate tertiary amines<sup>4</sup>.

It has been reported that at low temperatures, (5-10°) the reaction of ethyl chloroformate in N,N-dimethylformamide with potassium phthalimide or with phthalimide and triethylamine yields N-carboethoxyphthalimide<sup>5</sup>.

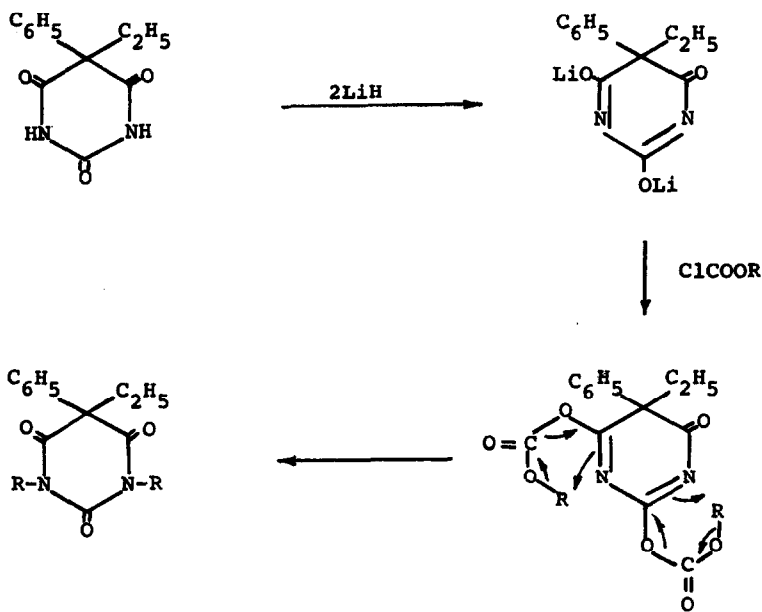
It has now been found that the reaction of ethyl chloroformate in N,N-dimethylformamide with lithium phthalimide at elevated temperatures (60-100°) produces N-ethylphthalimide, shown:



N-Alkylation was also carried out in other examples (barbiturate, hydantoin and succinimide) which are summarized in the accompanying Table 1. In a typical alkylation reaction the imide was dissolved in N,N-dimethylformamide, an equivalent amount (1 or 2 equivalents) of lithium hydride was added to the solution, and the reaction mixture was heated to 60-100°. At that temperature chloroformate ester was added to the reaction mixture over a period of

30 minutes. Vigorous  $\text{CO}_2$  evolution accompanied the reaction. After an additional hour of stirring the reaction mixture was poured into cold water and the product was purified by crystallization. All products were characterized by microanalyses and physical measurements (TLC, IR, UV, NMR and mass spectra). All products gave appropriate spectra and TLC values which were identical to those of the corresponding authentic samples.

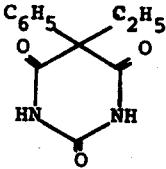
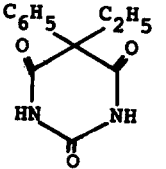
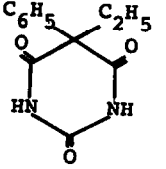
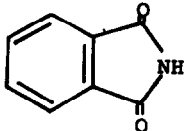
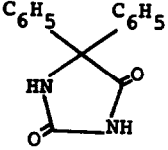
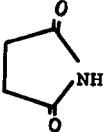
We propose the following mechanism for the alkylation reaction:



The dilithium salt of phenobarbital<sup>6</sup> obtained from phenobarbital and two moles of  $\text{LiH}$  in DMF is converted into an enol ester (lactim ester), which rearranges to the  $N,N'$ -dialkyl derivative with concomitant loss of  $\text{CO}_2$ .

The application of this new alkylation reaction to compounds of other classes is under investigation.

TABLE 1

<u>Compound</u>	<u>Reagent</u>	<u>Product</u>	<u>% Yield</u>
	$\text{ClCOOC}_2\text{H}_5$	1,3-diethyl phenobarbital	80
	$\text{ClCOOCH}_3$	1,3-dimethyl phenobarbital	85
	$\text{ClCOOCH}_2\text{C}_6\text{H}_5$	1,3-dibenzyl phenobarbital	92
	$\text{ClCOOC}_2\text{H}_5$	N-ethyl phthalimide	80
	$\text{ClCOOCH}_3$	3-methyl 5,5-diphenyl hydantoin <sup>a</sup>	91
	$\text{ClCOOCH}_2\text{C}_6\text{H}_5$	N-benzyl succinimide <sup>b</sup>	75

<sup>a</sup>One equivalent of lithium hydride was used.

<sup>b</sup>Product was purified by column chromatography followed by crystallization.

REFERENCES

1. L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. 1, 1967, Wiley, N. Y., p. 364.
2. ibid., p. 366
3. ibid., p. 367
4. M. M. Abdel-Monem and P. S. Portoghese, J. Med. Chem., 15, 208 (1972)
5. L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. 1, 1967, Wiley, N. Y., p. 112
6. C. M. Samour, J. F. Reinhard and J. A. Vida, J. Med. Chem., 14, 187 (1971).