Tetrahedron Letters,Vol.24,No.42,pp 4569-4572,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

Convenient Methods for Syntheses of Active Carbamates, Ureas and Nitrosoureas Using N,N'-disuccinimido Carbonate (DSC)[1)]

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The reaction of DSC and amino compounds afforded the corresponding carbamates which were able to be converted into ureas and nitrosoureas.

Recently, we have reported that DSC was used as a reagent for active ester formation,[2)] β-elimination,[3)] and carbonyl insertion[4)] in peptide chemistry or heterocyclic chemistry.

We now report a new method using DSC which make some carbamates, ureas and nitrosoureas more conveniently accesible. Several derivatives of carbamates, ureas and nitrosoureas having 2-chloroethylamino group are known to have antitumor activity as the alkylating agent *in vivo*. In general, the carbamates or ureas are synthesized by using isocyanate derivatives with alcohols or amino compounds and alcohols with phosgene. Conventional methods on nitrosation of ureas give N-substituted isomer of nitroso groups.[5)] However, in our method, single products are obtained, because nitrosoureas are formed via nitrosocarbamates.

DSC reacted with primary or secondary amines in large volume of acetonitrile at room temperature to give carbamates (1a-1i), and trace of ureas (2) (Table I). These carbamates (1a-1i) would be produced by nucleophilic attack of the amino groups on carbonyl group of DSC.

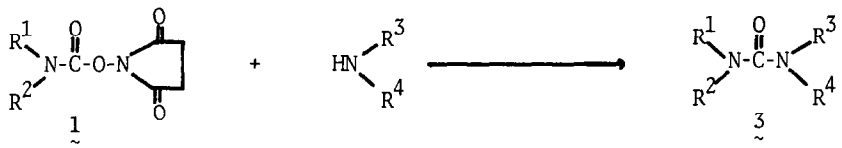
Ureas (3) would be produced by the nucleophilic attack of amino compounds on carbonyl group of carbamates (1), because the carbonyl group of carbamates (1) was activated by electron attractivity of succinimidyl group (Table II).

Table I

1	R^1	R^2	m.p.(°C)	Yield(%)	nmr($CDCl_3$,δ) (Succinimide protons) (4H,Singlet)
a)	$PhCH_2$	H	129-131	72.6	2.79
b)	n-propyl	n-propyl	oil	90.0	2.79
c)	iso-propyl	H	136-139	50.5	2.80
d)	cyclohexyl	H	149-151	56.6	2.80
e)	n-hexyl	H	75-77	64.0	2.84
f)	Ph	H	150-151	70.0	2.85
g)	CH_3	H	113-114	63.1	2.86
h)	$ClCH_2CH_2$	$ClCH_2CH_2$	69-70	60.0	2.90
i)	$ClCH_2CH_2$	H	85-87	61.5	2.84

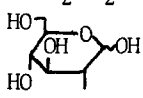
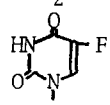
The typical procedure is described. (1) A mixture of amino compound or amino compound hydrochloride (0.01 mol) and triethylamine (0.01 mol) in acetonitrile (100 ml) or dichloromethane was added dropwise to DSC 5.02 g (0.02 mol) in acetonitrile (200 ml) during 5-10 hr at room temperature under stirring. After 24 hr, reaction mixture was evaporated, the residue was dissolved in chloroform, and insoluble unreacted DSC was filtered off. The chloroform solution was washed consecutively with water, 1N-hydrochloric acid, water, 4% sodium hydrogencarbonate, and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After removal of the solvent, crystals or oil was obtained. The crude compounds were chromatographed on silica gel, when necessary. The reaction of 2-chloroethylamine hydrochloride and triethylamine with DSC gave 2-chloroethylamino N-succinimidyl carbamate (1i) and trace of bis(2-chloroethyl)urea (2i) after silica gel chromatography. The nmr spectra of compound (1i) showed an imide at 2.84 ppm (s); $-CH_2-CH_2-$ at 3.60 ppm (m); and NH at 6.10 (b) in deutro chloroform.

(2) A mixture of a molar equivalent of carbamates (1) and amino compound in acetonitrile or water was stirred at room temperature. After 2-10 hr, there were obtained ureas (3) in reasonable yields as shown in Table (II).



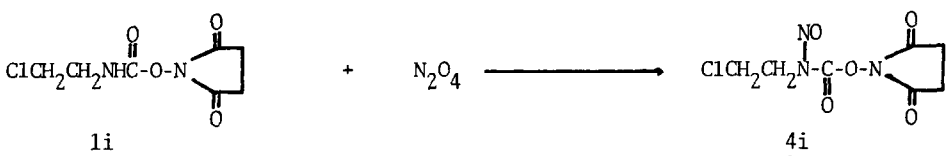
1 + HNR³R⁴ → 3

Table II

3	R^1	R^2	R^3	R^4	m.p.(°C)(Ref.)	Yield(%)
a)	cyclohexyl	H	n-propyl	n-propyl	92	48.7
b)	"	"	$ClCH_2CH_2$	H	129(130)[5]	68.6
C)	"	"		H	192-194	41.3
d)	"	"	$PhCH_2$	H	158-159	51.7
e)	"	"		H	156-158(156-157)[6]	41.6*

*solvent; dimethylacetamide, base; DBU

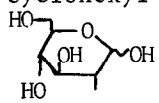
On the other hand, 2-chloroethylamino N-succinimidyl carbamate (1i) was nitrosated by dinitrogen tetraoxide in the presence of sodium acetate in carbon tetrachloride to give nitrosocarbamate (4i) in good yield. The nmr spectra of this compound showed an imide at 2.97 ppm (s); $-CH_2Cl$ at 3.52 ppm (t); and $-CH_2N$ at 4.13 ppm (t), in deutero chloroform. 2-Chloroethylamino N-succinimidyl nitrosocarbamate (4i) was stable in refrigerator.



1i + N_2O_4 → 4i

2-Chloroethylamino N-succinimidyl nitrosocarbamate (4i) reacted with amino compounds at room temperature in high yields. In this method, we have synthesized 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and chlorozotocin which are used clinically as an antitumor agent (Table III). Structure of these products were confirmed by nmr, ir, and mass spectral data and by comparing their physical properties with those of authentic samples.

Table III

R^1	R^2		m.p.(°C)(Ref.)	Yield(%)
cyclohexyl	H	(CCNU)	87-89(90)[5]	81.0
	H	(Chlorozotocin)	139-142(140-141)[7]	85.0

The above method is very convenient for synthesizing not only carbamates but also ureas and nitrosoureas. The authors belive that these synthetic methods will be widely used in future.

References

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(Received in Japan 27 June 1983)