

A CONVENIENT METHOD FOR THE SYNTHESSES OF
BENZYL N-ALKYLCYANOCARBAMATES AND N-MONOALKYLISOTHIUREAS

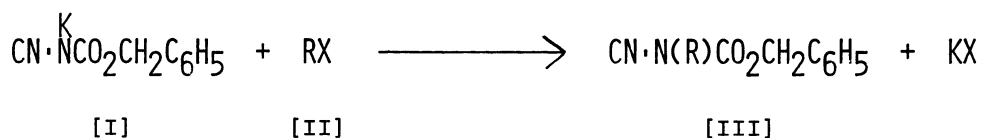
Takeo TAGUCHI, Yoshinari SATO, and Teruaki MUKAIYAMA
Laboratory of Organic Chemistry, Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo 152

A convenient method for the syntheses of benzyl N-alkylcyano-
carbamates [III] and N-monoalkylisothiureas [V] have been es-
tablished. Benzyl N-alkylcyanocarbamates [III] were obtained in
high yields by the reactions of the potassium salt of benzyl cyano-
carbamate with various alkyl halides. Further, it was found that
N-alkyl-S-ethylisothiureas or N-alkyl-S-phenylisothiureas [V]
were obtained in good yields by the treatment of the benzyl N-alkyl
cyanocarbamates [III] thus obtained with ethanethiol or benzenethiol.

It is known that cyanamide derivatives are important intermediates for the
preparations of isothiureas, isourea or guanidine derivatives.¹⁾ However, it is
difficult to prepare monoalkylcyanamide exclusively from cyanamide and alkyl
halides, because dialkyl cyanamide and dicyandiamide, dimer of cyanamide, are
produced at the same time.²⁾

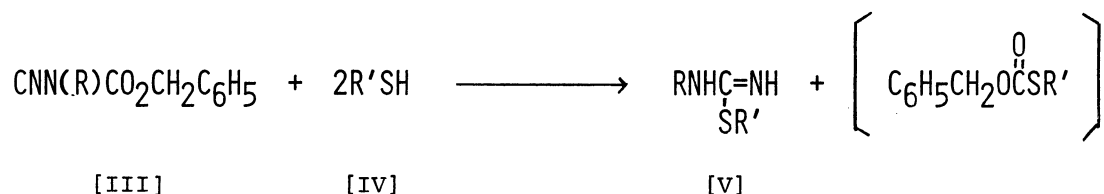
In the previous paper, a convenient method for the preparations of benzyl N-
monoalkylcarbamates through the reaction of the potassium salt of benzyl N-(p-
chlorophenylthio)carbamate with alkyl halides has been reported.³⁾ Based on the
finding that a replacement of one hydrogen atom of benzyl carbamate by an electron
withdrawing group such as p-chlorophenylthio group decreases the basicity of the
nitrogen atom, which resulted in the formation of an N-monoalkylcarbamate by the
nucleophilic substitution with alkyl halide, it was expected that benzyl N-alkyl-
cyanocarbamates are prepared by the reactions of the potassium salt of benzyl
cyanocarbamate having a strong electron withdrawing group with alkyl halides.

Expectedly, it was established that benzyl N-alkylcyanocarbamate is obtained in high yield by the reaction of the potassium salt of benzyl cyanocarbamate with alkyl halide in acetonitrile.⁴⁾ For example, benzyl N-p-nitrobenzylcyanocarbamate was obtained in quantitative yield by the reaction of the potassium salt of benzyl cyanocarbamate with p-nitrobenzyl bromide refluxing in acetonitrile for 3 hr.



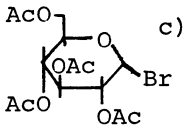
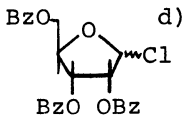
Similarly, various benzyl N-alkylcyanocarbamates were successfully prepared by the reactions of the potassium salt of benzyl cyanocarbamate with various alkyl halides such as primary alkyl halides, α -halo esters, α -halo ketones and glycosyl halides. These results are summarized in Table I.

Further, it was found that N-alkyl-S-ethylisothioureia or N-alkyl-S-phenylisothioureia was obtained in good yield by the treatment of the benzyl N-alkylcyanocarbamate [III], prepared from the potassium salt [I] and alkyl halide [II], with ethanethiol or benzenethiol in the presence of a catalytic amount of the corresponding sodium thiolate. For example, N-p-nitrobenzyl-S-phenylisothioureia hydrochloride was obtained in 80% yield by the reaction of benzyl N-p-nitrobenzylcyanocarbamate with 4 equivalents of benzenethiol and catalytic amount of sodium benzenethiolate in acetonitrile at room temperature for 16 hr, followed by the treatment of the reaction mixture with hydrogen chloride in ether.



In a similar way, several N-alkyl-S-phenylisothioureas and N-alkyl-S-ethylisothioureia were successfully prepared as shown in Table II.

Table I. Yields of Benzyl N-alkylcyanocarbamates [III]

RX [II]	Solvent	Conditions Temp.	Time(hr)	[III] Yield (%)
p-NO ₂ C ₆ H ₄ CH ₂ Br	CH ₃ CN	refl.	3	quant.
n-C ₈ H ₁₇ Br	CH ₃ CN	refl.	8	94
C ₆ H ₅ CH ₂ CH ₂ Br	CH ₃ CN	refl.	6	91
HOCH ₂ CH ₂ CH ₂ Br	CH ₃ CN	refl.	5	90
BrCH ₂ CH ₂ CH ₂ Br	D.M.F. ^{a)}	r.t.	48	69 ^{b)}
BrCH ₂ CO ₂ C ₂ H ₅	CH ₃ CN	r.t.	16	87
BrCH(CH ₃)CO ₂ C ₂ H ₅	CH ₃ CN	r.t.	16	93
BrCH(CO ₂ C ₂ H ₅) ₂	CH ₃ CN	refl.	4	92
ClCH ₂ C(=O)CH ₃	CH ₃ CN	refl.	7	80
BrCH ₂ C(=O)C ₆ H ₅	CH ₃ CN	r.t.	4	quant.
 c)	CH ₃ CN	r.t.	16	93 ^{e)}
 d)	CH ₃ CN	r.t.	16	97 ^{e)}

a) D.M.F.; Dimethylformamide

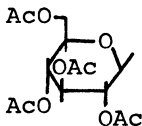
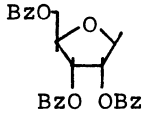
b) In this case, 4 equivalents of trimethylene bromide was used. Disubstituted product, benzyl N,N'-trimethylene-N,N'-dicyanocarbamate, was also obtained in 10% yield.

c) 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide was prepared by C. E. Redemann's method.⁵⁾

d) 2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl chloride was prepared in situ from 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-ribose by H. K. Kissman's method.⁶⁾

e) In these cases, benzyl N-glycosylcyanocarbamates were prepared by the reaction of the silver salt of benzyl cyanocarbamate, prepared from the potassium salt and silver nitrate in water, with glycosyl halides. These reactions proceeded in darkness.

Table II. Yields of N-alkyl-S-phenylisothioureas and N-alkyl-S-ethylisothioureas

R	R'SH[IV]	Conditions		Time(hr)	[V] Yield (%)
		Solvent	Temp.(°C)		
p-NO ₂ C ₆ H ₄ CH ₂ -	C ₂ H ₅ SH	CH ₃ CN	35	24	75
p-NO ₂ C ₆ H ₄ CH ₂ -	C ₆ H ₅ SH	CH ₃ CN	r.t.	16	80
	C ₆ H ₅ SH	CH ₃ CN	r.t.	6	86
	C ₆ H ₅ SH	CH ₃ CN	r.t.	5	79

In summary, it is noted that benzyl N-alkylcyanocarbamates are obtained in high yields by the reactions of the potassium or the silver salt of benzyl cyanocarbamate with alkyl halides.

Further, it was established that N-alkyl isothiourea derivative is prepared in good yield by the treatment of benzyl N-alkylcyanocarbamate with thiol.

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