CHEMISTRY LETTERS, pp. 1225-1228, 1973. Published by the Chemical Society of Japan

A CONVENIENT METHOD FOR THE SYNTHESES OF BENZYL N-ALKYLCYANOCARBAMATES AND N-MONOALKYLISOTHIOUREAS

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A convenient method for the syntheses of benzyl N-alkylcyanocarbamates [III] and N-monoalkylisothioureas [V] have been established. Benzyl N-alkylcyanocarbamates [III] were obtained in high yields by the reactions of the potassium salt of benzyl cyanocarbamate with various alkyl halides. Further, it was found that N-alkyl-S-ethylisothioureas or N-alkyl-S-phenylisothioureas [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 isothioureas, 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 Nmonoalkylcarbamates through the reaction of the potassium salt of benzyl N-(pchlorophenylthio)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-alkylcyanocarbamates 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.

$$(N \cdot NCO_2CH_2C_6H_5 + RX \longrightarrow (N \cdot N(R)CO_2CH_2C_6H_5 + KX)$$

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-ethylisothiourea or N-alkyl-S-phenylisothiourea 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-phenylisothiourea 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.

$$(IIII) \qquad (IV) \qquad (V) \qquad$$

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

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RX [II]	Solvent	Conditions Temp.	Time(hr)	[III] Yield (%)
p-NO ₂ C ₆ H ₄ CH ₂ Br	CH3CN	refl.	3	quant.
^{n-C} 8 ^H 17 ^{Br}	CH ₃ CN	refl.	8	94
C6H5CH2CH2Br	CH ₃ CN	refl.	6	91
HOCH2CH2CH2Br	CH ₃ CN	refl.	5	90
BrCH2CH2CH2Br	D.M.F. ^{a)}	r.t.	48	69 ^b)
BrCH2CO2C2H5	CH ₃ CN	r.t.	16	87
BrCH (CH ₃) CO ₂ C ₂ H ₅	CH ₃ CN	r.t.	16	93
$\operatorname{BrCH}(\operatorname{CO}_2\operatorname{C}_2\operatorname{H}_5)_2$	CH ₃ CN	refl.	4	92
clch ₂ cch ₃	сн ₃ си	refl.	7	80
BrCH2 ^{CC} 6 ^H 5	CH3CN	r.t.	4	quant.
$ \begin{array}{c} AcO \\ OAC \\ AcO \\ OAC \end{array} \begin{array}{c} c \\ Br \\ OAc \end{array} $	снзси	r.t.	16	93 e)
BzO OBz	CH3CN	r.t.	16	97 ^{e)}

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

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.

R	R'SH[IV]	Solvent	Conditions Temp.(°C)	Time(hr)	[V] Yield (%)
p-NO2C6H4CH2-	с ₂ н ₅ sн	CH3CN	35	24	75
p-NO2C6H4CH2-	с ₆ н ₅ ѕн	CH3CN	r.t.	16	80
ACO ACO OAC	с ₆ н ₅ ѕн	сн ₃ си	r.t.	6	86
BZO OBZ	с _{6^н5} ен	сн ₃ си	r.t.	5	79

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

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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(Received September 21, 1973)