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ACYLAMINATION BY MEANS OF N-BENZYLOXYCARBONYLCARBOXAMIDES

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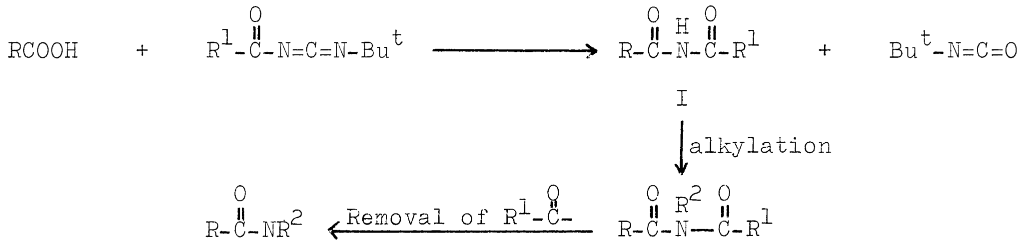
The reaction of N-benzyloxycarbonylcarboxamides with alkyl sulfonates or halides gave N-alkylated and O-alkylated products. On treatment with HBr-AcOH, the N-alkyl-N-benzyloxycarbonylcarboxamides were converted to N-alkylcarboxamides. When N-benzyloxycarbonylbenzamide was allowed to react with (S)-(-)-ethyl lactate, triphenylphosphine and diethyl azodicarboxylate, followed by treatment with HBr-AcOH, (R)-(-)-N-benzoylalanine ethyl ester was obtained with high optical purity.

The introduction of an acylamino function into organic substrates is a useful and important reaction from a synthetic standpoint, because a variety of biologically active compounds such as nucleoside antibiotics are found to have acylamino groups. The preparation of such complex compounds is generally accomplished by amination of substrates followed by acylation. Another possible approach would evolve from the structural similarity of either N-acyl- or N-alkoxycarbonylcarboxamides (I) and active methylene compounds. The key steps of this process are the preparation and alkylation of I (Scheme 1).[1]

Scheme 1.

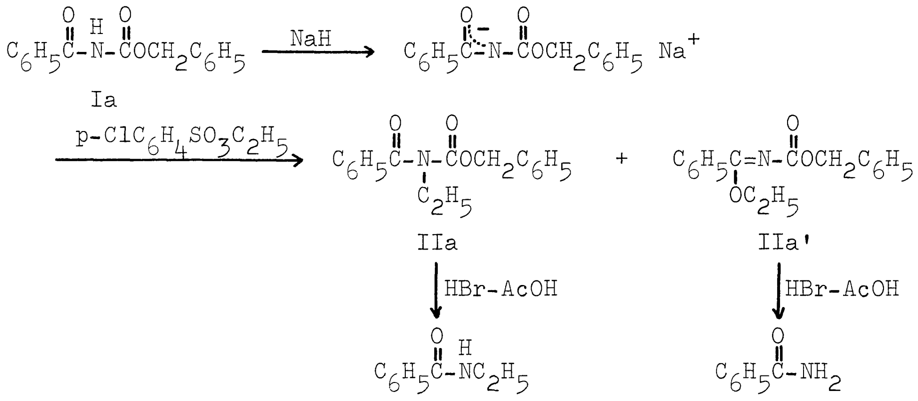


In a previous paper, we have reported a convenient method for the preparation of I (Scheme 1).[2] We now report the alkylation of I with various methods.

Alkylation by the Use of Alkyl Sulfonates and Alkyl Halides. N-Benzyloxycarbonylbenzamide (Ia; 1.02 g, 4 mmol) was treated with sodium hydride (50% assay, 144 mg, 6 mmol) in dimethylformamide (DMF; 3 ml) followed by ethyl p-chlorobenzenesulfonate (441 mg, 2 mmol) and the solution was heated at 60°C for 5 hr. After removal of sodium p-chlorobenzenesulfonate (409 mg, 95%), an oily product and recovered Ia (532 mg) were separated by silica gel tlc. The NMR spectrum of the oily product supported the structure to be N-benzyloxycarbonyl-N-ethylbenzamide (IIa; 378 mg, 67%). However, when it was rechromatographed on silica gel plates, Ia was again detected and

IIa was obtained in a 58% yield (327 mg). On treatment of IIa thus obtained with HBr-AcOH (33%) at room temperature for 2.5 hr, N-ethylbenzamide was isolated in an 89% yield (mp 96.5°C, from petroleum ether). A trace of benzamide was also obtained. These results suggested that the oily product originally obtained is a mixture of IIa and O-alkylated isomer (IIa') and the latter decomposes to Ia on silica gel plates (Scheme 2). When the reaction was carried out at room temperature for 75 hr, IIa was obtained in a 59% yield and 9% of ethyl p-chlorobenzenesulfonate was recovered. Ethyl p-toluenesulfonate was less satisfactory; IIa was isolated in a 30% yield even when the reaction was carried out at 60°C for 10 hr.

Scheme 2.



Next, the alkylation of sodium salt of Ia (1 mmol) with alkyl halide (2 mmol) was attempted. The scope of the procedure is illustrated in Table 1. Using primary alkyl bromide and iodide, corresponding N-alkylated products were obtained in good yields. Secondary alkyl halides as well as secondary alkyl sulfonate were less satisfactory. Contrary to the case of a mixture of IIa and IIa', the NMR spectra of the isolated products having a secondary alkyl group exhibited overlapping absorptions which are compatible with a mixture of N-alkylated and O-alkylated compounds.

Table 1. Alkylation of N-Benzyloxycarbonylbenzamide by Means of Alkyl Halides.

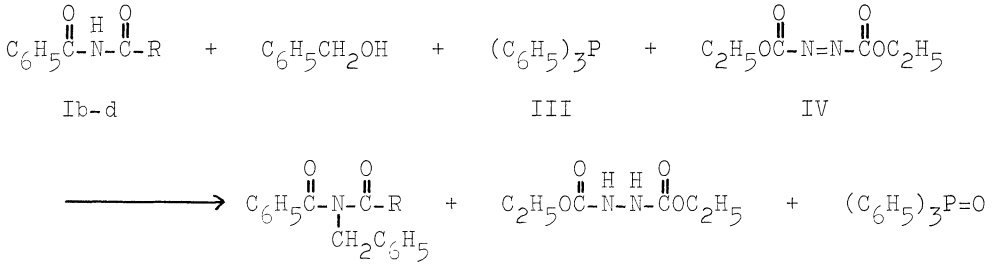
RX	Yield (%)* N-Alkylation	O-Alkylation	RX	Yield (%)* N-Alkylation	O-Alkylation
C_2H_5I	77	0	$(CH_3)_2CHI$	7	6
$C_6H_5CH_2Cl$	38	0	$CH_3\underset{Br}{C}HCOOC_2H_5$	22 (30)	6 (10)
$C_6H_5CH_2Br$	92	0	$CH_3\underset{OSO_2C_6H_4Cl}{C}HCOOC_2H_5$	(10)	(5)

* The reaction was carried out in DMF at 60°C for 4 hr and the products were isolated by preparative tlc. The ratios of N-alkylated and O-alkylated products were determined by NMR spectroscopy. When tlc of the alkylated product indicated the absence of Ia, only N-alkylation was assumed to take place.

( ): The reaction was carried out in DMF at 60°C for 12 hr.

Alkylation by the Use of Alcohols in the Presence of Triphenylphosphine (III) and Diethyl Azodicarboxylate (IV). When 1 mmol of Ib (R = C_6H_5-), Ic (R = CH_3-) or Id (R = C_2H_5O-) was treated with equimolar amounts of III, IV and benzyl alcohol in a similar manner described previously,[3] the corresponding N-benzylated imide (IIb, IIc or IId) was obtained as shown in Scheme 3.

Scheme 3.



$C_6H_5C(=O)NHC(=O)R + C_6H_5CH_2OH + (C_6H_5)_3P + C_2H_5OC(=O)N{=}NC(=O)OC_2H_5 \longrightarrow C_6H_5C(=O)N(CH_2C_6H_5)C(=O)R + C_2H_5OC(=O)NHNHC(=O)OC_2H_5 + (C_6H_5)_3P{=}O$

Ib-d III IV

II; b) R = C_6H_5-, 13%

c) R = CH_3-, 13%

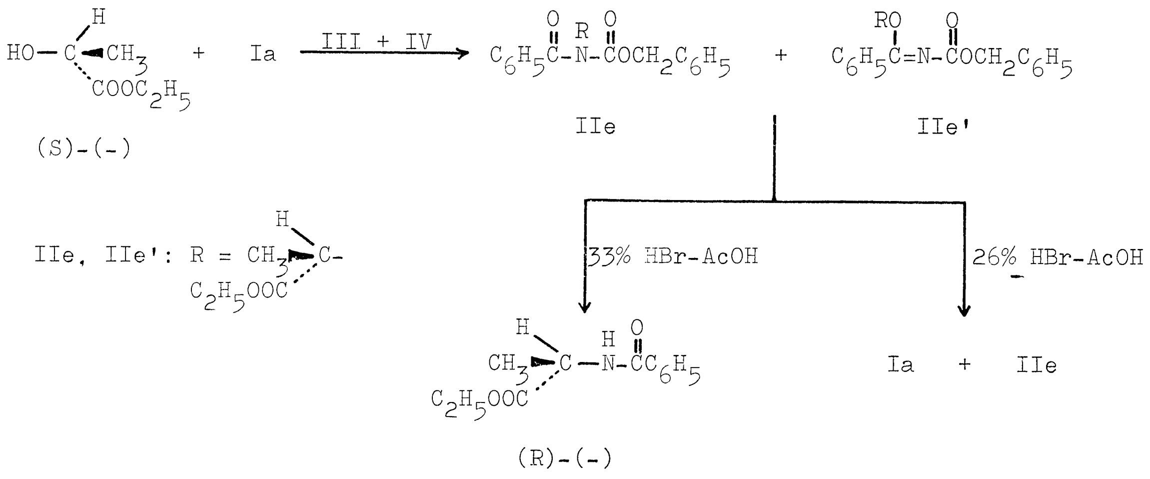
d) R = C_2H_5O-, 35%

By this procedure, benzoylamination of ethyl lactate was examined. (S)-(-)-Ethyl lactate (2 mmol; $[\alpha]_D^{21}$ = -11.3° (neat)[4]) and Ia (2 mmol) were allowed to react with 4 mmol each of III and IV in THF at room temperature for 8 hr. The alkylated product was isolated by preparative tlc (67%). The complexity of its NMR spectrum suggested that it would be a mixture of N-alkylated and O-alkylated compounds (IIe and IIe'). This product was treated with 26% HBr-AcOH (5 ml) at room temperature for 2hr to give Ia and a material; its stability and NMR spectrum indicated that it was pure IIe. By substructing the signals pertaining to the latter from the total spectrum of the mixture, the proton resonance of IIe' could be obtained (Table 2). Based on this result, the ratio of IIe and IIe' was estimated to be 1 : 2.5. On treatment with 33% HBr-AcOH (5 ml) at room temperature for 3 hr, the mixture gave (R)-(-)-N-benzoylalanine ethyl ester in a 92% yield (based on IIe; mp 99.5-100°C, $[\alpha]_D^{18}$ = -40°±5° (c 0.012, $CHCl_2CHCl_2$)[4]). Since (S)-(+)-N-benzoylalanine ethyl ester has been reported to have specific rotation of $[\alpha]_D^{13}$ = +39.3°, the present reaction can be concluded to proceed stereospecifically with inversion of the configuration at asymmetric carbon (Scheme 4).[5]

Table 2. NMR Spectra of IIe and IIe' in CCl_4 (δ values).

	$-OCH_2\underline{CH_3}$	$>N-CH\underline{CH_3}$	$-OCH\underline{CH_3}$	$-O\underline{CH_2}CH_3$	$-\underline{CH_2}C_6H_5$	$>N-\underline{CH}CH_3$	$-O\underline{CH}CH_3$
IIe	1.15 t	1.60 d		4.15 q	4.95 s	5.10 q	
IIe'	1.20 t		1.55 d	4.20 q	5.05 s		5.10 q

Scheme 4.



References and Notes

* To whom correspondence should be addressed.

1. Hauser et al., and Wolfe et al. have extensively studied the alkylation of carboxamide anions. With limitted amount of base, N-alkylation ordinarily takes place. However, for compounds where additional structural features enhance the acidity of the α-C hydrogen, alkylation occurs at this site via carbanion intermediate. B. C. Challis and J. A. Challis, "The Chemistry of Amides," edited by J. Zabicky, Interscience Publishers, (1970), p. 731.
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3. O. Mitsunobu, M. Wada and T. Sano, J. Amer. Chem. Soc., 94, 679 (1972); M. Wada and O. Mitsunobu, Tetrahedron Lett., 1279 (1972).
4. Optical rotation was measured with JASCO ORD/UV-5.
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