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SYNTHESIS AND USE OF DIBENZYLPYROCARBONATE : PREPARATION OF DIPEPTIDE FREE N-BENZYLOXYCARBONYL GLYCINE

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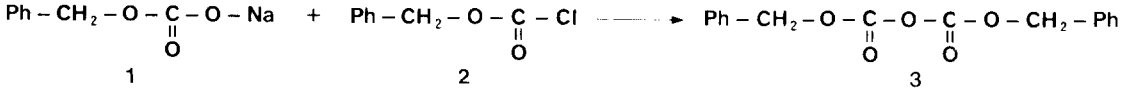
Dibenzylpyrocarbonate was prepared and reacted with amino acids. The quantity of dipeptides formed was evaluated.

For years, benzyl chloroformate has been used to prepare N-benzyloxycarbonyl amino acids both in laboratory and industrial scale. However, apart its low stability on storage, serious side reactions, e.g. formation of dipeptides, restrict the use of this widely know reagent[1]. Alternative acylating agents like mixed carbonates with phenols or N-hydroxysuccinimide are not suitable because of their laborious and costly preparation.

The recent announcement[2] of an imminent publication by Wuensch and coworkers[3] of the synthesis of dibenzyl pyrocarbonate (Z_2O) prompted us to report our own results on the synthesis and use of this attractive reagent.



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Numerous methods exists to prepare pyrocarbonates[4], but although the product has been claimed in a patent[5], attempts to synthesize dibenzyl pyrocarbonate analogously to the popular di-tert-butyl-dicarbonate failed[1]. Since the corresponding chloroformate is commercially available, we decided to run a more conventional synthesis.

Thus benzyl alcohol (21.6 g, 0.2 mole) is treated with sodium hydride (0.2 mole) in refluxing THF (200 ml) for 2 hours. The solution is cooled to room temperature and CO_2 is bubbled in while maintaining efficient stirring and external cooling. After one hour, benzyl chloroformate (28.5 ml, 0.2 mole) is slowly added and the mixture is stirred for three hours at room temperature. The precipitate is centrifuged and the supernatant is evaporated to dryness under vacuum. The resulting oil slowly crystallizes in the refrigerator. Crystals are then triturated with cold hexane, filtered and dried under vacuum. Yield : 45.8 g (79 %) ; mp=28° C ; NMR ($CDCl_3$, TMS) 5.2 (s, 4H) 7.4 (s, 10H) ppm ; IR(neat) ν =1820, 1760, 1500, 1455, 1380, 1290, 1220, 1190, 1150 cm^{-1}. Combustion analysis : calculated for $C_{16}H_{14}O_5$: C 67.12 H 4.93 O 27.95 ; found C 66.93 H 4.83 O 28 .02.
The reagent was found to be reasonably stable at room temperature which ensures normal laboratory use.

The reaction with amino acids was performed under standard pH stat conditions and N- benzyloxycarbonyl amino acids were obtained in high yield (Table 1).

Table 1-Preparation of N-benzyloxycarbonyl amino acids.

Product	Yield	m.p. (°C) ; $[\alpha]_D$	Lit. Data[6] : m.p. (°C) ; $[\alpha]_D$
Z-Gly	91 %	118-119° C	120°C
Z-Ala	80 %	80-81°C ; -14.5 c=2 AcOH	85-86°C ; -14.3 c=2 AcOH
Z-Val	92 %	60°C ; +0.3 c=10 EtOH	66-67°C ; +0.1 c=10 EtOH
Z-Leu, DCHA	72 %	157-158°C ; -7.5 c=3 AcOH	151-152°C ; -7.8 c=3 AcOH

We have concentrated on the examination of dipeptide formation. In this view, glycine was chosen because of the relative ease of formation of by-products during the protection step. We have compared the amount of dipeptide (Z-Gly-Gly) formed in an optimized reaction with benzyl chloroformate with that formed when dibenzyl pyrocarbonate was used under various conditions (Table 2). We found that, although the dipeptide amount was lowered, use of an organic base and of solutions enriched in organic solvents were not suitable for the preparation of dipeptide free protected amino acids. In this case, the dipeptide amount was even higher than that obtained with benzyl chloroformate. However, if the pH is carefully regulated, high purity N-benzyloxycarbonyl glycine can be obtained and formation of contaminating by-products avoided.

Table 2-Comparative preparations of N-benzyloxycarbonyl-glycine

Reagent	Reaction Conditions	pH	Yield	Z-Gly[a]	Z-Gly-gly
Ph-CH_2OC (O) -Cl	NaOH/H_2O	8.5	93 %	96.5%	0.7 %
3	Dioxane/H_2O (1/1) Et_3N	-	88 %	93.5 %	1.8 %
3	Dioxane/H_2O (4/1) NaOH	9.0	91 %	100 %	$\ll$ 0.1 %

a) Determined by HPLC (Whatman Partisil ODS 5 ; MeCN/H_2O/20 % Et_4NOH. 600/400/20, H_3PO_4 to pH 3 ; 1 ml/mn).

Notes and References

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