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PHOTOLABILE p-METHOXYPHENACYLOXYCARBONYL GROUP FOR THE PROTECTION OF AMINES

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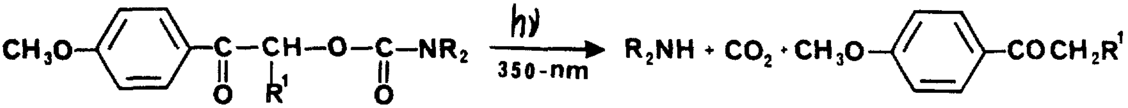
Summary: P-Methoxyphenacyloxycarbonyl (Phenoc) is a new photolabile protective group for amines. Various phenacyl urethanes, i.e. Phenoc protected amines, have been prepared. An application of the group in peptide synthesis is reported.

Various protective groups for amines are known[1]. The most commonly used are the chemical labile urethane type protected groups such as benzyloxycarbonyl(Z), t-butyloxycarbonyl (Boc), and fluorenylmethyloxycarbony (Fmoc). Photolabile benzyl urethanes have been reported [2-3] for the protection of amines. Recently, we began to study the photochemical behaviour of phenacyl urethanes.

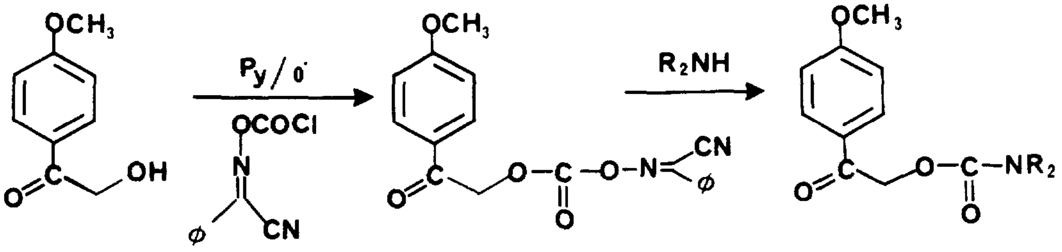
We now wish to report the preparation of phenacyl urethanes as derivatives of primary and secondary amines. The 4-methoxyphenacyloxycarbonyl (Phenoc) group incorporated in these molecules can be effectively removed by photolysis at 0° in ethanol under neutral conditions. The cleavage of the phenacyl bond leads to the formation of amines along with carbon dioxide and phenacyl ketones as byproducts.



Quenching experiments were performed wherein the photolysis reaction was examined in 1M naphthalene in ethanol. Complete quenching of the reaction was observed. It has been reported[4] that naphthalene can quench excited triplet states when their lifetime is longer than 10^{-10} sec. This evidence is indicative for a reaction proceeding through a long-lived triplet state having a lifetime longer than 10^{-10} sec.

Two approaches were used to generate phenacyl urethanes in good yields from α-hydroxy ketones derivatives. The latter were prepared following the hydroxylation method of McCormick[5].

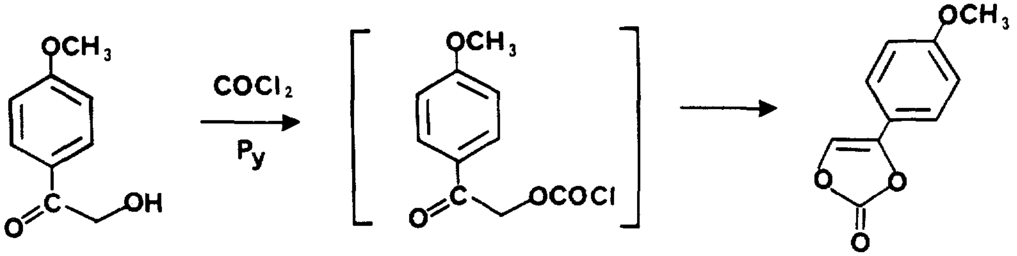
The first method involved the transformation of an α-hydroxy ketone[6] 1 to an oxime carbonate 4 in 73% yield by reaction of chloroformate 3 in toluene at 0° in the presence of pyridine. In this approach, the chloroformate 3 was generated in situ by reaction of 2-hydroxyimino-2-phenylacetonitrile[7] with phosgene in toluene at 0° in the presence of N,N-dimethylaniline.



1 3 4 5-13

The oxime carbonate 4, a white solid, m.p. 123-125°; was homogeneous by tlc. Its infrared spectrum ($CHCl_3$) showed characteristic carbonyl bands at 1704 and 1805 cm^{-1}. The nmr spectrum ($CDCl_3$) showed characteristic peaks at δ 3.90 (singlet, 3H, CH_3O), 5.49 (singlet, 2H, $O=COCH_2O$), 6.98 and 7.93 ppm (doublets, Jax= 8.6 Hz 4H, ArH). Elemental analysis: Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H,4.17;N,8.28. Found: C, 63.98; H, 4.12; N, 8.29%.

Several attempts to prepare oxime carbonate 4 via chloroformate 14 were unsuccessful. Cyclic carbonate 15 only was isolated under these conditions.

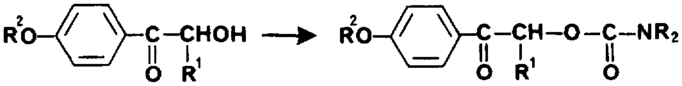


1 14 15

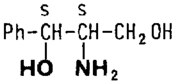
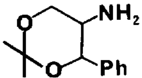
The reaction of various amines with oxime carbonate[8] 4 in dioxane afforded p-methoxyphenacyloxycarbonyl (Phenoc) derivatives 5-13 in good yield [9] (table 1). The isolation procedure of phenacyl urethanes involved column chromatography or/and crystallization.

The second method for preparation of phenacyl urethanes was the direct addition of α-hydroxy ketones to aryl isocyanates. Reaction of α-hydroxy ketone[10] 2 with phenylisocyanate in toluene for 4 hr at 50° gave urethane 16 in 86% yield (table 1).

Table 1



1 $\cdot R^1 = H$; 2 $R^1 = CH_3$

Compound	R^1	R^2	R_2NH	Yield[a,b] (%)	M.p. (°C)	$[\alpha]_D^{25}$ (c=1,CH_3OH)
5	H	CH_3	Pro OCH_3	75	97-100	-58.6[c]
6	H	CH_3	Pro	90	134-138	-55.5
7	H	CH_3	Pro NH_2	50	139-140	-47.6
8	H	CH_3	Ala	68	146-148	-37.1[d]
9	H	C_2H_5	Ala OCH_3	60	89-90	-41.2
10	H	CH_3	Gln	85	195-197	-23.6[d]
11	H	CH_3	Thr	78	128-130	-6.0
12	H	CH_3	 $Ph\text{-}\overset{S}{\underset{HO}{CH}}\text{-}\overset{S}{\underset{NH_2}{CH}}\text{-}CH_2OH$	55	133-135	+16.3
13	H	CH_3		70	Foam*	+26.5
16	CH_3	CH_3	Ph—NH_2	86	182-184	

a) Yields of homogeneous isolated material (3 mmole scale). b) Compounds characterized by elemental analysis, nmr* and MS*. c) c=1.66, CH_3OH. d) c=1, DMF.

The p-methoxyphenacyloxycarbonyl (Phenoc) group of phenacyl urethanes was effectively removed by photolysis under mild conditions.[11] Other well known protecting groups of amines, carboxylic acids and alcohols (Fmoc, Boc, Z, Bu^t, Bn) were stable under these conditions. The stability of the Phenoc group towards acids and bases also was evaluated. Phenoc Pro OCH_3 5 was converted to Phenoc Pro 6 in 90% yield by saponification. Phenoc $ProNH_2$ 7 was recovered unchanged after standing for 24 hr in 50% trifluoroacetic acid in methylene chloride or 20% piperidine in DMF. The Phenoc group can thus be very useful in orthogonal protection schemes in peptide synthesis.

The utility of this group can further be demonstrated by the preparation of dipeptide 19. The removal of the Phenoc group of ester 17 in the presence of the Boc group of succinyl ester 18 was studied to show the chemoselectivity of the photolytic method.

When this photochemical deprotection was carried under coupling conditions in DMF-ethanol at 0° for 15hr, the dipeptide 19 was isolated in 74% yield.

$$\underset{\mathbf{18}}{\text{Boc-Val-OSu}} + \underset{\mathbf{17}}{\text{Phenoc-Ala-OCH}_3} \xrightarrow{h\nu} \underset{\mathbf{19}}{\text{Boc-Val-Ala-OCH}_3}$$

Work is now in progress to evaluate further the synthetic potential of this new protective group.

References and Notes

1. T.W. Greene, "Protective Group in Organic Chemistry" John Wiley & Sons, 218 (1981).
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4. J.C. Sheehan, R.M. Wilson, and A.W. Oxford, J. Am. Chem. Soc., 93, 7222 (1971).
5. J.P. McCormick, W. Tomasik, and M.W. Johnson, Tetrahedron Lett., 22 607 (1981).
6. I. Elphinoff-Felkin and M. Verrier, Bull. Soc. Chim. Fr. 1047 (1967).
7. M. Itoh, D. Hagiwara, and T. Kamiya, Bull. Chem. Soc. Jpn., 50, 718 (1978).
8. The 4-ethoxyphenacyl *analogue of oxime carbonate* 4 *was also prepared in a similar manner:* m.p. 124.5-126° (76%).
9. Typical procedure for the preparation of phenacyl urethanes: A mixture of L-threonine (2.00g, 16.8 mmole) and oxime carbonate 4 (6.25g, 18 mmole) was stirred in 30% aqueous dioxane (50 ml) at room temperature in the presence of triethylamine (3.50 ml, 25 mmole). After 4 hr, the solvent was removed under reduced pressure. The residue was diluted with water (60 ml) and the mixture was extracted with ethyl acetate (2X20 ml). The aqueous layer was acidified with 5% citric acid solution and extracted twice with ethyl acetate. The combined extracts were worked up in the usual manner to afford a crude solid. Recrystallization from ethyl acetate-hexane afforded Phenoc L-Thr 11 (4.08g, 78%) as white crystals m.p. 128-130°.
10. H. Schubert, G. Giesemann, P. Steffen and J. Bleichert, J. Prakt. Chem., 18, 192 (1962).
11. Representative removal of the Phenoc group: a solution of Phenoc Thr 11 (3 mmoles) in ethanol (100 ml) was irradiated under argon at 0° using a Rayonet RPR 208 photochemical reactor fitted with 350 nm lamps. Tlc analysis of the reaction mixture after 4 hr showed a small amount of starting material. After 14 hr, the solution was concentrated and solid residue triturated in diethyl ether to afford L-threonine mp 255-258° (75%). The filtrate was worked up to give p-methoxyacetophenone m.p. 36-38° (94%).

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