# Photosensitive Tetramethylpiperidine Urethanes: Synthesis and Characterization

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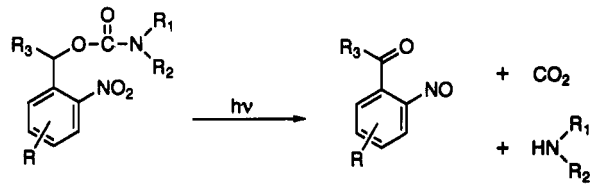
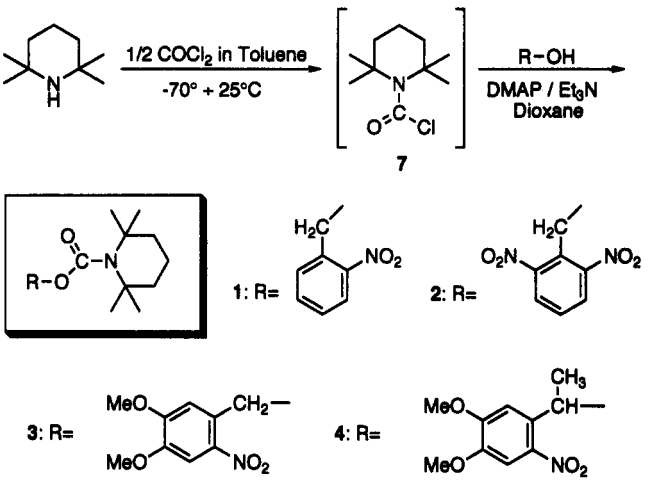
The problem of synthesizing photosensitive urethanes of the highly sterically hindered 2,2,6,6-tetramethylpiperidine is solved by first preparing the 1-chlorocarbonyl derivative which was shown to react with a series of *o*-nitrobenzylic alcohols, including 2,6-dinitrobenzyl alcohol. These products are potential photogenerators of this amine. Full characterization is reported, along with a crystal structure.

Photogeneration of base, and in particular of amines, is a relatively new field of research which is gaining attention and finding potential applications in chemically amplified photoresists.[1,2] Recently, Cameron and Fréchet described a class of amine photoprecursors based on *o*-nitrobenzyl carbamates that are effective in photoresist formulations.[3] When irradiated, these compounds decompose to the corresponding amine, $CO_2$, and *o*-nitroso carbonylic compound (Scheme 1). [(*o*-Nitrobenzyl)oxy]-carbonyl groups have also been used as photoremovable amine protecting groups.[4,5] The preparation of photoprecursors of this kind for several primary and secondary mono- and diamines has been reported.[2,3] However, none of these amines was particularly sterically hindered. We report here a facile and general method for the synthesis of (*o*-nitrobenzyl)urethanes of 2,2,6,6-tetramethylpiperidine (TMP), a very sterically hindered base. This method was applied to the synthesis of the previously unknown[6] compounds **1**–**4** (Scheme 2).

**Scheme 1**




**Scheme 2**




## Results and Discussion

While urethanes of primary amines are easily prepared by the reaction of alcohol with isocyanate, this route is not an option for secondary amines. The classic procedure to prepare urethanes of secondary amines consists of reacting the alcohol moiety with phosgene (or its less dangerous analog triphosgene[7]) and then reacting the obtained chloroformate with the desired amine. This procedure has also been used to prepare simple TMP urethanes from methanol and ethanol.[8,9] In our hands this method proved successful to prepare compound **1** (the chloroformate of *o*-nitrobenzyl alcohol was prepared according to Amit et al.[5,10] and reacted with TMP in the conditions used by Cameron and Frechét[3] for cyclohexylamine affording **1** in ≈38% yield) but was not successful for preparing compound **2**.

Several attempts to prepare **2** by routes involving first a reaction of the 2,6-dinitrobenzyl alcohol (**5**) failed. Treatment of **5** with phosgene and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) in dioxane yielded 2,6-dinitrobenzyl chloride only. A similar result had been obtained previously when triphosgene was used instead of phosgene.[11] NMR spectra of the reaction mixture always show the contemporary presence of chloroformate and chloride. Furthermore, if the reaction mixture is dried in vacuum for 1 h at rt, the chloroformate disappears almost completely. These observations suggest an intramolecular

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(1) Willson, C. G.; Cameron, J. F.; MacDonald, S. A.; Niesert, C. P.; Fréchet, J. M. J.; Leung, M. K.; Ackmann, A. *Proc. SPIE Adv. Resist Technol. Processing X* **1993**, *1925*, 354.

(2) McKean, D. R.; Wallraff, G. M.; Volksen, W.; Hacker, N. P.; Sanchez, M. I.; Labadie, J. W. In *Polymers for Microelectronics*; Thompson, L. F., Willson, C. G., Tagawa, S., Eds.; American Chemical Society: Washington, D.C., 1994; p 417.

(3) Cameron, J. F.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4303.

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(6) CAS-on-line search.

(7) Eckert, H.; Foster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.

(8) Werchan, H. G.; Russew, R. I.; Held, P.; Schubert, H. *J. Prakt. Chem.* **1977**, *319*, 516.

(9) Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025.

(10) Attempts to use in this reaction an easy to handle 20% solution of phosgene in toluene instead of the pure gas failed to give the desired product.

(11) Cameron, J. F. Personal communication.

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transformation of the chloroformate to the benzyl chloride with loss of $CO_2$. An attempt to react the chloroformate in situ with TMP after rapid elimination of the residual phosgene with vacuum was also unsuccessful. When 5 is reacted with commercial 4-nitrophenyl chloroformate, a mixed carbonate is obtained where the nitrophenyl should be almost as good a leaving group as chlorine, but possibly eliminate the problem of rearrangement. However, after 18 h reflux of this carbonate in anhydrous THF with 2 equiv of TMP, less than 15% reacted. In order to verify that the carbonate reacts with unhindered amines, an excess of cyclohexylamine was added and the carbonate disappeared completely within 5 min (TLC). Clearly, the steric hindrance of TMP prevents the reaction. An attempted transesterification of ethoxycarbonyl-TMP with 5 in toluene/DMAP left the reagents unchanged.

Also in the case of 1-(2-nitro-4,5-dimethoxyphenyl)-ethanol (6), attempts to react the alcohol first failed. Reaction of 6 with phosgene and then with TMP did not yield 4 but a mixture of symmetric carbonate, 2-nitro-4,5-dimethoxystyrene, and other unidentified products.

The strategy that eventually proved successful for the synthesis of these compounds was to first form the C–N bond of the urethane instead of the C–O bond, following the reaction sequence depicted in Scheme 2. The use of compound 7 in the synthesis of sterically hindered ureas has been reported by Hassel and Seebach;[12] however, these workers did not provide experimental details. Gold-Aubert and Gysin have described the synthesis of diisopropylchloroformamide from diisopropylamine and phosgene.[13] This synthesis has been successfully repeated by us. However, when the same procedure is applied to TMP, a mixture of at least two liquid products is obtained whose IR spectrum shows no significative carbonyl absorption and a very strong peak at 2258 $cm^{-1}$, i.e., in the region of cumulated double bonds. From the NMR it can be said only that the desired product is not present. One possible interpretation is that the chloroformamide forms but then decomposes to isocyanate with opening of the ring, and the product rearranges further with heating.

It turned out that 7 can be obtained if it is synthesized at low temperature (see Experimental Section). The fact that a solution of phosgene can be used instead of the dangerous pure gas is a point in favor of this method; a 5% excess of the base is used to assure complete consumption of the phosgene. 7 is stable for at least 1 h in solution if kept at $T < 25$ °C. This allows at least a rapid IR check: if a drop of solution is pressed between two NaCl disks a spectrum can be measured showing the correct carbonyl peak at 1735 $cm^{-1}$. However, if the solution is evaporated (at low $T$, i.e., by blowing $N_2$ on it) the residue decomposes rapidly with development of heavy white vapor and the IR shows no carbonyl absorption but rather the strong peak at 2258 $cm^{-1}$. The same transformation happens if the solution is kept at rt longer than a few hours. However, the solution can be stored safely for several days in a Dewar filled with dry ice. The final proof for the structure of 7 was obtained by reacting it with *o*-nitrobenzyl alcohol: the resulting product was identical to the one obtained by the reaction of *o*-nitrobenzyl chloroformate and TMP, e.g., 1. Compound 7 proved to be reactive enough to condense with all four alcohols tested (Scheme 2), including the dinitrobenzylic

(12) Hassel, T.; Seebach, D. *Helv. Chim. Acta* **1978**, *61*, 2237.
(13) Gold-Aubert, P.; Gysin, E. *Helv. Chim. Acta* **1961**, *44*, 105.

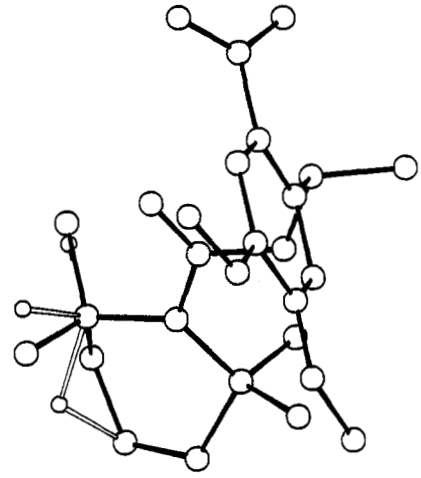

**Figure 1.** Crystal structure of 4 (see text). A table of the torsional angles of the piperidine ring as well as a stereoscopic view of the unit cell are available as supplementary material.

one. The presence of at least 50% dioxane as cosolvent in this reaction is indispensable; in one experiment 6 was dissolved in anhydrous THF for the addition to the solution of 7, but almost no reaction was observed even after 1.5 h (TLC), but when dioxane was added the reaction started and proceeded normally.[14]

The precipitate formed in the reaction of TMP and phosgene was confirmed to be TMP·HCl; in particular, its IR spectrum showed no carbonyl absorption and it was completely soluble in water, thus ruling out the presence of urea. Its weight after drying was consistent with a quantitative reaction every time it was checked. Given this, the relatively low yields of the urethanes (20–50%, based on starting alcohol) are somewhat surprising and may be due to the poor long-term stability of 7. The yield can probably be improved by using less alcohol. If desired the unreacted alcohol can be recovered during the chromatographic purification of the products.

While the $^1$H-NMR signal of the methyl groups on the piperidine ring in 3 appears as a singlet, in 4 it is split into two singlets of equal intensity (within the experimental error) 0.09 ppm apart.[15] The structure of 4 was proved beyond doubt by X-ray structure determination on a single crystal (see below). Therefore, the inequivalence of the methyls must be due either to the presence of the stereocenter or to a hindered rotation/ring-flip. The last possibility has been ruled out by measuring a spectrum at 90 °C (in DMSO-$d_6$) which was essentially identical with the one obtained at rt. Therefore, the stereocenter must be responsible for the splitting although it is at a certain distance from the groups in question.

Single crystals of all four urethanes have been obtained by slow evaporation of solutions in the respective recrystallization solvents. The crystal structure of 4 is shown in Figure 1. In the crystal the piperidine ring is present in two different conformations of almost equal volume; one conformation is shown with white bonds in the figure. The site occupancy factor for the disordered atoms has been refined and found to be 50% for each. Of interest for the photochemistry, the distance between the benzylic proton and the closest oxygen of the nitro group is 2.19 Å.

(14) Dioxane is not used initially because the commercially available phosgene solution is in toluene.
(15) The same behavior is observed in the $^{13}$C-NMR spectrum, where the splitting is 1.35 ppm.

Work to test the performance of these compounds in actual photoresist formulations is in progress.

## Experimental Section

**5** was obtained by reduction of the corresponding, commercially available, aldehyde;[16] **6** was a gift from Dr. Nigel P. Hacker, IBM Almaden Research Center; 3,4-dimethoxy-6-nitrobenzyl alcohol (6-nitroveratryl alcohol) was purchased from Lancaster; and all other reagents were purchased from Aldrich or Fluka Co. and used as received. NMR spectra were measured in $CDCl_3$ with a Bruker AC 250 instrument (250 MHz), IR spectra were recorded on a IBM Instruments IR/32 spectrometer, and UV spectra were recorded on a HP 8450A spectrometer using acetonitrile as solvent. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Elemental analysis was performed by Galbraith Laboratories, Inc. Column chromatography was carried out on silica gel 60, 230–400 mesh. All reactions were carried out under Ar to avoid water condensation from the atmosphere at low temperatures. All operations involving phosgene should be carried out in a well-ventilated hood due to the high toxicity of phosgene.[17]

**1-[[(2-Nitrobenzyl)oxy]carbonyl]-2,2,6,6-tetramethylpiperidine (1).** A 983-mg (6.96 mmol) portion of TMP dissolved in 2 mL of anhydrous THF was dropped into a solution of [(2-nitrobenzyl)oxy]carbonyl chloride[5] (750 mg, 3.48 mmol) in 3.5 mL of anhydrous THF at rt. At the end of the addition the mixture was refluxed for 2.5 h and then stirred at rt overnight. The solvent was eliminated and the residue dissolved in $Et_2O$/$H_2O$. After conventional separation and drying ($Na_2SO_4$) the product was purified by flash column chromatography, eluent hexanes/AcOEt (4:1), and recrystallized from MeOH. Yield: 424 mg (38%), colorless crystals. Mp: 87 °C. IR (KBr): 1692 (C=O), 1522 ($NO_2$), 1324, 1066 $cm^{-1}$. UV: $\lambda_{max}$ = 259 nm, $\epsilon_0$ = 5780. $^1$H-NMR $\delta$: 8.10 (d(d), 1H, $J_1$ = 7 Hz, $J_2$ = 1.2 Hz), 7.62 (m, 2H), 7.46 (m, 1H), 5.53 (s, 2H), 1.67 (m, 6H), 1.43 (s, 12H). $^{13}$C-NMR $\delta$: 156.4, 147.3, 133.8, 133.6, 128.9, 128.2, 124.8, 62.7, 56.3, 39.1, 29.7, 15.3. Anal. Calcd for $C_{17}H_{24}N_2O_4$ ($M$ = 320.39): C, 63.73; H, 7.55; N, 8.74. Found: C, 63.39; H, 7.50; N, 8.77.

**General Procedure for the Synthesis of 2,2,6,6-Tetramethylpiperidine Urethanes. 1-[[(2,6-Dinitrobenzyl)oxy]carbonyl]-2,2,6,6-tetramethylpiperidine (2).** A 4.85-mL (9.37 mmol) portion of a 20% (1.93 M) solution of phosgene in toluene was placed in a three-necked round-bottomed flash equipped with thermometer, Ar inlet, and magnetical stirring, and the mixture was cooled to −70 °C. A dropping funnel containing 2.78 g (19.68 mmol) of TMP in 5 mL of toluene under Ar was placed on the flask,[18] and the solution was dropped at such a rate that the temperature never increased over −55 °C. The mixture was stirred for 1 h at −70 °C, and then the cooling bath was removed. The temperature increased relatively rapidly (exothermic reaction). As soon as the temperature reached 25 °C the bath was restored, the mixture was cooled to −25 °C, and then the bath was removed again. The temperature increased slowly; when it had reached 20 °C the mixture was rapidly filtered through a Buchner funnel. The almost clear solution was put back into the cleaned flask and cooled to 0 °C.[19] A previously prepared solution of 1.3 g (6.56 mmol) of **5**, 1.3 mL (9.37 mmol) of $Et_3N$, and 158 mg (1.4 mmol, 15%) of DMAP in ≈20 mL of dioxane[20] was dropped in the solution. The ice bath was removed, and the reaction was stirred at rt overnight. The solvents were eliminated at the rotavap, and the residue was dissolved in $Et_2O$/$H_2O$. After conventional separation and drying ($Na_2SO_4$) the product was purified by flash chromatography, eluent $CH_2Cl_2$, giving 1.1 g of a solid (first fraction) which was recrystallized from methylcyclohexane. Final yield: 650 mg (27%), colorless crystals. Mp: 123 °C. IR (KBr): 1691 (C=O), 1532 ($NO_2$), 1066 $cm^{-1}$. UV: $\lambda_{max}$ = 231 nm, $\epsilon_0$ = 11 580. $^1$H-NMR $\delta$: 8.03 (d, 2H, $J$ = 8 Hz), 7.63 (t, 1H, $J$ = 8 Hz), 5.50 (s, 2H), 1.63 (m, 6H), 1.30 (s, 12H). $^{13}$C-NMR $\delta$: 155.8, 159.9, 129.4, 127.6, 127.5, 57.2, 56.2, 38.3, 29.3, 15.0. Anal. Calcd for $C_{17}H_{23}N_3O_6$ ($M$ = 365.39): C, 55.88; H, 6.34; N, 11.50. Found: C, 55.91; H, 6.20; N, 11.50.

**1-[[(2-Nitro-4,5-dimethoxybenzyl)oxy]carbonyl]-2,2,6,6-tetramethylpiperidine (3).** $COCl_2$ in toluene (13 mL, 25 mmol), TMP (7.41 g, 52.5 mmol) in 13 mL of toluene, 6-nitroveratryl alcohol (5.35 g, 25 mmol), $Et_3N$ (3.48 mL, 25 mmol), DMAP (420 mg, 3.75 mmol), dioxane (≈15 mL), eluent for chromatography hexanes/AcOEt 2:1; recrystallization solvent EtOH. Yield: 1.67 g (18%), colorless needles. Mp: 80 °C IR (KBr): 1695 (C=O), 1525 ($NO_2$), 1277, 1080 $cm^{-1}$. UV: λ = 243 nm, $\epsilon_0$ = 10 920, λ = 302 nm, $\epsilon_0$ = 4690, λ = 346 nm, $\epsilon_0$ = 6350. $^1$H-NMR $\delta$: 7.72 (s, 1H), 7.06 (s, 1H), 5.55 (s, 2H), 3.96 (s, 6H), 1.7 (m, 6H), 1.46 (s, 12H). $^{13}$C-NMR $\delta$: 156.4, 153.4, 147.7, 139.5, 129.1, 109.9, 108.0, 62.9, 56.3, 56.2, 39.3, 29.7, 15.3. Anal. Calcd for $C_{19}H_{28}N_2O_6$ ($M$ = 380.44): C, 59.99; H, 7.42; N, 7.36. Found: C, 59.67; H, 7.38; N, 7.33.

**1-[[1-(2-Nitro-4,5-dimethoxyphenyl)ethoxy]carbonyl]-2,2,6,6-tetramethylpiperidine (4).** $COCl_2$ in toluene (17.5 mL, 33.8 mmol), TMP (12 mL, 70.98 mmol) in 18 mL of toluene, **6** (5 g, 22.01 mmol), $Et_3N$ (3.3 mL, 23.66 mmol), DMAP (569 mg, 3.75 mmol), and dioxane ≈25 mL; eluent for chromatography hexanes/AcOEt (2:1); recrystallization solvent MeOH. Yield: 3.76 g (43%), pale yellow crystals. Mp: 123 °C. IR (KBr): 1683 (C=O), 1524 ($NO_2$), 1335, 1277 $cm^{-1}$. UV: λ = 244 nm, $\epsilon_0$ = 10 180, λ = 303 nm, $\epsilon_0$ = 4210, λ = 347, $\epsilon_0$ = 5100. $^1$H-NMR $\delta$: 7.64 (s, 1H), 7.07 (s, 1H), 6.43 (q, 1H, $J$ = 6.5 Hz), 3.94 (s, 6H), 1.78–1.62 (m, 6 + 3H), 1.50 (s, 6H), 1.41 (s, 6H). $^{13}$C-NMR $\delta$: 155.6, 153.4, 147.4, 139.2, 135.2, 108.0, 107.8, 69.1, 56.22, 56.16, 56.07, 39.7, 30.5, 29.1, 22.0, 15.3. Anal. Calcd for $C_{20}H_{30}N_2O_6$ ($M$ = 394.47): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.54; H, 7.62; N, 7.05.

**Alternative Preparation of 1 To Prove the Structure of 7.** Solution of **7** in toluene containing *approximately* 24.7 mmol of **7**, 2-nitrobenzyl alcohol (3.8 g, 24.8 mmol), $Et_3N$ (3.45 mL, 24.71 mmol), DMAP (278 mg, 2.48 mmol), dioxane (≈15 mL); eluent for chromatography hexanes/AcOEt (2:1); recrystallization solvent MeOH. Yield: 1.65 g (43%). Analytical data identical with previous preparation.

**X-ray Analysis of 4.** Space group $P2_1/c$, monoclinic, $a$ = 10.6850(6) Å, $b$ = 15.2669(8) Å, $c$ = 13.2692(9) Å, $\beta$ = 104.193(4)°, $V$ = 2098.5 Å$^3$, $Z$ = 4, $D_x$ = 1.249 g $cm^{-3}$, $\mu$(CuK$_\alpha$) = 7.23 $cm^{-1}$. Enraf-Nonius CAD-4 diffractometer, $\theta$–$2\theta$ scan, rt. A total of 3250 reflections were measured, of which 2701 were observed ($I > 3\delta I$). The structure was solved by direct methods using SIR.[21] Refinement with a full-matrix least-squares method with anisotropic temperature factors for C, N, O; H's isotropic in the riding mode. $R$ = 0.057 ($R_w$ = 0.058). Empirical absorption correction.[22]

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**Supplementary Material Available:** Table of torsional angles in the piperidine ring of **4**, ORTEP plot, and stereoscopic view of the unit cell of **4** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) Houlihan, F. M.; Shugard, A.; Gooden, R.; Reichmanis, E. *Macromolecules* **1988**, *21*, 2001.

(17) The Merck Index, 10th edition; Merck & Co., Inc.; Rahway, NJ, USA; p 1058.

(18) If the dropping funnel is put on the flask from the beginning, the gaseous phosgene present reacts with the amine in the funnel generating a messy precipitate and a temperature increase.

(19) At this point the presence of **7** can be rapidly checked by IR (see main text).

(20) If the alcohol is not completely soluble in dioxane, a suspension will work as well.

(21) SIR: M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spargna, D. Viterbo, J. Appl. Cryst. (1989).

(22) The authors have deposited atomic coordinates for compound **4** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.