Tetrahedron Letters,Vol.27,No.45,pp 5521-5524,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CARBAMATES : A METHOD OF SYNTHESIS AND SOME SYNTHETIC APPLICATIONS

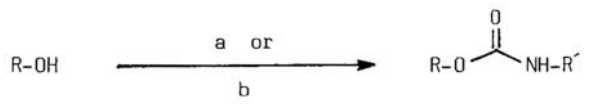
Pavel Kočovský

Institute of Organic Chemistry and Biochemistry
Czechoslovak Academy of Sciences, 16610 Prague 6, Czechoslovakia

Abstract: Alcohols are converted into unsubstituted carbamates by treatment with trichloroacetyl isocyanate followed by hydrolysis on Al_2O_3. This extremely mild procedure tolerates various labile functional groups. The synthetic utility of the carbamate moiety as a control element is demonstrated on epoxidation and epoxide opening.

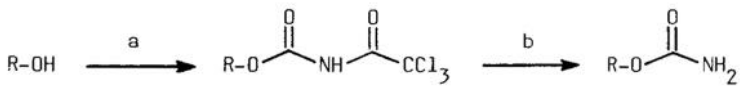
The carbamate group ($-OCONH_2$) constitutes a typical structural feature of certain classes of natural products, e.g. bleomycins and mitomycins. Furthermore, -OCONHR and related groups have frequently been used as control elements in the synthesis of natural products and their precursors[1]. Thus, for instance, $-OCONH.CH_2Ph$ can control the opening of the oxirane ring[2] and the reaction may be directed either to introduce an O- or an N-substituent[2].

Among the methods of the carbamate synthesis the most versatile are the addition of alcohols to isocyanates[3] and the reaction of alcohols with p-nitrophenyl chlorocarbonate followed by aminolysis[4] (Scheme I). However, if an unsubstituted carbamate ($-OCONH_2$) is to be prepared, the first method suffers from the fact that the R´ group (usually CH_2Ph) has to be removed, which may pose the problem of chemoselection. On the other hand, ammonolysis in the second procedure may be non-compatible with some functional groups present in the molecule.



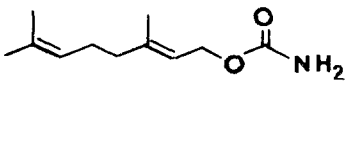
Scheme I : (a) $R´-N=C=O$; (b) 1. $p-NO_2-C_6H_4-OCOCl$, 2. $R´-NH_2$

We now report a general, two-step method of preparation of unsubstituted carbamates from alcohols. The alcohol is first treated with trichloroacetyl isocyanate (TAI) in an aprotic solvent (C_6H_6, $CHCl_3$, CH_2Cl_2, dioxane, or a mixture thereof) to produce *in situ* the corresponding trichloroacetyl carbamate (Scheme II). We have found that filtration of the reaction mixture through a pad of neutral Al_2O_3 results in a clean hydrolysis leading to an unsubstituted carbamate[5].

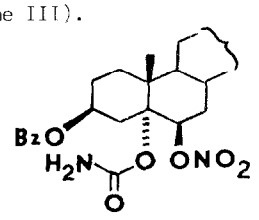


Scheme II : (a) $Cl_3CCO-N=C=O$, CH_2Cl_2, r.t., 10 min ; (b) Al_2O_3 filtration

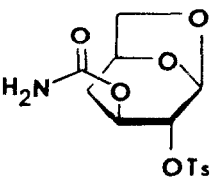
Since TAI is known to react readily even with tertiary alcohols at r.t. over several minutes[6], this procedure may be applied to a variety of substrates. Moreover, the conditions of both the reaction with TAI and the following hydrolysis are extremely mild. Hence, it was of interest to explore the compatibility of this method with the presence of other potentially labile groups. To this end, a brief study of several polyfunctional alcohols was carried out. We have found that ester, tosyloxy, silyloxy, acetal, and epoxide moieties are stable under the reaction conditions[7], and we always isolated products (1-6)[9-11] in good to excellent yields (see the numbers in parentheses in Scheme III).



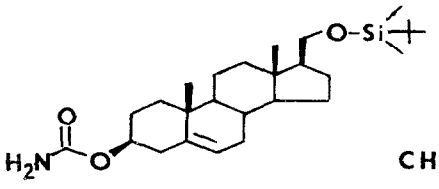
1 (97%)



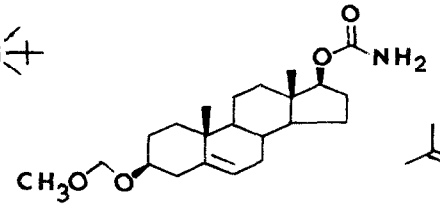
2 (85%)



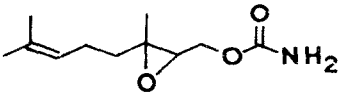
3 (81%)



4 (76%)



5 (89%)

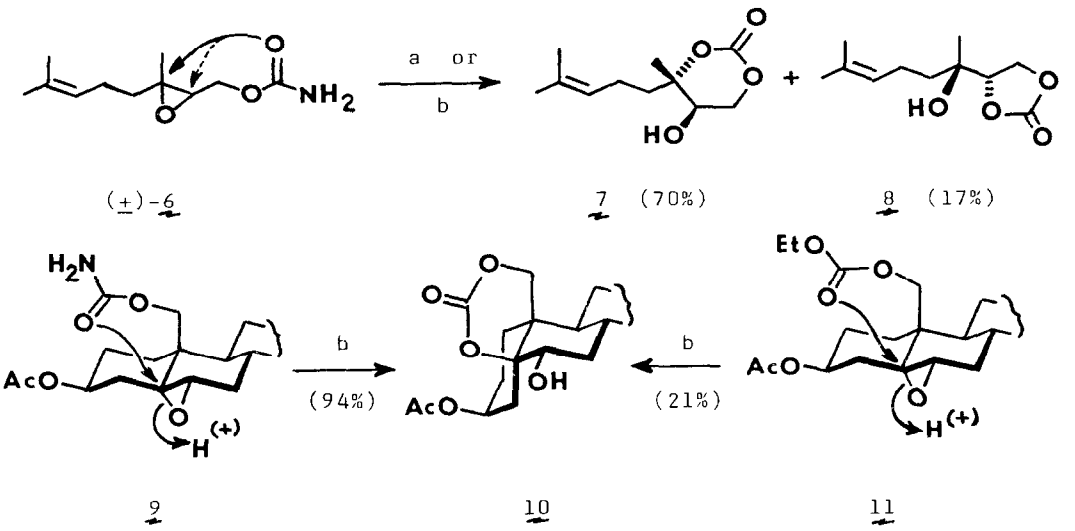


6 (92%)

Scheme III

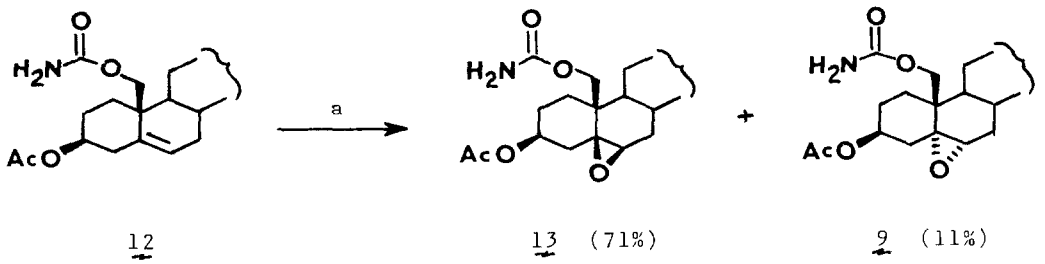
The preparation of epoxycarbamates is worth further interest. As follows from Scheme III, the epoxide derived from geraniol gives the corresponding carbamate 6 in high isolated yield. Since the starting epoxy alcohol is available in high optical purity in either enantiomeric form through the Katsuki-Sharpless epoxidation[12] of geraniol[12,13], the carbamate 6 might become a suitable starting material in the synthesis of various natural products. Thus, for instance, acid treatment of 6 leads to the corresponding carbonates 7 and 8 in a 4:1 ratio[9] (Scheme IV). The steroidal epoxide 9 is cleaved to afford the hydroxycarbonate 10 as the only product[9,14]. In this respect the carbamates behave similarly to carbonates[16,17] (e.g., 11)[16]. However, carbamates seem to be superior for they react faster and formation of by-products is suppressed.

There is another noteworthy feature of carbamates containing a double bond. The carbamate group itself offers a potential for coordination to transition metals and other electrophilic reagents. This might, possibly, influence the reactivity, e.g. the course of epoxidation[18,19]. In order to verify this hypothesis epoxidation of the carbamates 1 and 12 was attempted. Both 1 and 12, however, turned out to be inert to standard[18b] t-BuOOH/$(acac)_2VO$ treatment. On the other hand, the steroidal compound 12 (Scheme V) reacted smoothly with m-chloroperoxybenzoic acid (MCPBA) to afford the 5β,6β-epoxide 13 as the major product (6:1)[9] while the corresponding 19-



Scheme IV : (a) $BF_3.Et_2O$, Et_2O, 0°C, 15 min ; (b) $HClO_4$, H_2O, dioxane, r.t. 15 min.

-carbonate is known to produce mainly 5α,6α-diastereoisomer[16] resulting from the ordinary α-side attack by MCPBA.



Scheme V : (a) MCPBA, $CHCl_3$, r.t. 30 min.

In light of the above results, we believe that the simple and mild procedure we have devised represents a useful method of carbamate synthesis. Since it tolerates a large variety of functional groups it may find application in synthetic chemistry. Furthermore, the carbamate functionality thus created can control subsequent chemical transformations, as we have demonstrated in several instances[20].

References and Notes :

1. Kočovský P., Tureček F., Hájíček J.: "Synthesis of Natural Products: Problem of Stereoselectivity", Vol. I and II, CRC Press, Boca Raton, FL, 1986.

2. (a) Roush W.R., Brown R.J., DiMare M.: J.Org.Chem. 48, 5083 (1983); (b) Roush W.R., Brown R.J.: J.Org.Chem. 48, 5093 (1983); (c) Roush W.R., Adam M.A.: J.Org.Chem. 50, 3752 (1985); (d) Hirama M., Iwashita M., Yamazaki Y., Itô S.: Tetrahed. Lett. 25, 4963 (1984); (e) Minami M., Ko S.S., Kishi Y.: J.Am.Chem.Soc. 104, 1109 (1982); (f) Hirama M., Uei M.: Tetrahed. Lett. 23, 5307 (1982); (g) Overman L.E., Campbell C.B., Knoll F.M.: J.Am.Chem.Soc. 100, 4822 (1978).

3. Satchell D.P.N., Satchell R.S.: Chem.Soc.Rev. 4, 231 (1975).

4. (a) Vaterlaus B.P., Kiss J., Spielberg H.: Helv.Chim.Acta 47, 381 (1964); (b) Kuzuhara H., Emoto S.: Tetrahed.Lett. 1973, 5051; (c) Omoto S., Takita T., Maeda K., Umezawa S.: Carbohyd.Res. 30, 239 (1973); (d) Millar A., Kim K.H., Minster D.K., Ohgi T., Hecht S.M.: J.Org.Chem. 51, 189 (1986).

5. Partial hydrolysis of N-acetyl carbamates during preparative chromatography on alumina was noticed by Hecht et al.[4d] when our work was in progress.

6. (a) Goodlett V.W.: Austral.J.Chem. 37, 431 (1965); (b) Samek Z., Buděšínský M.: Collect. Czech.Chem.Commun. 44, 558 (1979).

7. Trifluoroacetates would be hydrolyzed on Al_2O_3 (for analogy see ref.[8a]) while formates should be stable during the short period[8b] requested for splitting off the Cl_3CCO group.

8. (a) Kočovský P.: Collect.Czech.Chem.Commun. 48, 3660 (1983); (b) Kočovský P., Procházka Ž.: ibid. 39, 1905 (1974).

9. All new products gave satisfactory elemental analyses and spectral data (^{1}H-NMR, IR, mass).

10. For the preparation of some of the starting alcohols see: (a) Kočovský P., Černý V.: Collect.Czech.Chem.Commun. 41, 2620 (1976); (b) Černý I., Trnka T., Černý M.: ibid 48, 2386 (1983); (c) Vašíčková S., Pouzar V., Černý I., Drašar P., Havel M.: ibid 51, 90 (1986); (d) Pouzar V., Černý I., Drašar P., Havel M.: ibid 51 (1986), in press.

11. Representative procedure: To a solution of 1,6-anhydro-4-deoxy-2-O-p-toluenesulfonyl-β-D-xylo-hexopyranose (312 mg, 2 mmol) in dry $CHCl_3$ (4 ml) was added IAl (2.1 mmol) in benzene (2 ml) under argon atmosphere and the mixture was set aside for 15 min at r.t. The solution was then soaked into a pad of aluminum oxide (neutral, activity II, Brockmann) and after 5 min the product was washed out using a mixture of C_6H_6 - CH_2Cl_2 (2:1). The filtrate was evaporated in vacuo to yield pure carbamate 3 (322 mg, 81%); ^{1}H-NMR ($CDCl_3$, TMS, 200 MHz): 1.73 (dm, J = 15.5, 3.0, 1.2, and 1.2 Hz, 4-eq-H), 2.35 (dddd, J = 15.5, 5.7, 4.2, and 1.4 Hz, 4-ax-H), 2.45 (s, CH_3), 3.70 (ddd, J = 7.0, 5.2, and 1.2 Hz, 6-exo-H), 4.05 (dd, J = 7.0 and 0.7 Hz, 6-endo-H), 4.34 (q, J = 1.8, 1.6, and 1.2 Hz, 2-H), 4.53 (bt, J = 5.7, 5.2, 3.0, 1.2, and 0.7, 5-H), 4.75 (dp, J = 5.7, 1.6, 1.6, 1.6, 1.2, and 1.2 Hz, 3-H), 5.12 (bs, NH_2), 5.36 (bt, J = 1.8 and 1.6, 1-H), 7.35 and 7.82 (aromatic-H); ^{13}C-NMR: 21.61 (CH_3), 30.45 (C-4), 67.87 (C-3), 70.83 (C-2), 74.24 (C-5), 98.84 (C-1), 145.30, 133.07, 127.80, 129.93 (aromatic-C), 155.39 (CO_2NH_2); IR (CCl_4+$CHCl_3$): 1178, 1192, 1425 (TsO), 1585, 1600, 1736, 3170, 3280, 3402, 3432, 3518, 3550 (CO_2NH_2) cm^{-1}.

12. (a) Katsuki T., Sharpless K.B.: J.Am.Chem.Soc. 102, 5974 (1980); for review see: (b) Sharpless K.B., Behrens C.H., Katsuki T., Lee A.W.M., Martin V.S., Takani M., Viti S.M., Walker F.J., Woodard S.S.: Pure Appl. Chem. 55, 589 (1983); (c) Behrens C.H., Sharpless K.B.: Aldrichim. Acta 16, 67 (1983); (d) Finn M.G., Sharpless K.B. in "Asymmetric Synthesis" (J. D. Morrison, ed.), Vol 5, p. 247, Academic Press, New York 1985; (e) Pfenninger A.: Synthesis 1985, 89; (f) Dryuk V.G.: Usp.Khim. 54, 1674 (1985); (g) Sharpless K.B.: Chem. in Britain 22, 38 (1986).

13. Wrobel J.E., Ganem B.: J.Org.Chem. 48, 3761 (1983).

14. Note that both the epoxides 6 and 9 are preferentially cleaved at the tertiary carbon in a $6(O)^{\pi,n}$ process (for notation see ref.[15]).

15. Kočovský P., Černý V., Synáčková M.: Collect.Czech.Chem.Commun. 44, 1483 (1979).

16. Kočovský P., Černý V.: ibid 44, 1496 (1979).

17. (a) Julia S., Fürer B.: Bull.Soc.Chim.Fr. 1966, 1106; (b) Masamune S., Ma P., Okumoto H., Ellingboe J.W., Ito Y.: J.Org.Chem. 49, 2834 (1984).

18. For hydroxyl-directed epoxidation see e.g.: (a) Henbest H.B., Wilson R.A.: J.Chem.Soc.1957, 1958; (b) Sharpless K.B., Michaelson R.C.: J.Am.Chem.Soc. 95, 6136 (1973); (c) Sharpless K.B., Michaelson R.C., Cuttings J.D., Tanaka S., Yamamoto H., Nozaki H.: J.Am.Chem.Soc. 96, 5254 (1974); (d) Rositer B.E., Verhoeven T.R., Sharpless K.B.: Tetrahed.Lett. 1979, 4733; (e) Itoh T., Kaneda K., Teranishi S.: J.Chem.Soc.Chem.Commun. 1976, 421; and reviews[1,12].

19. For ether-group-directed epoxidation see: McKittrick B.A., Ganem B.: Tetrahed.Lett. 26, 4895 (1985).

20. For examples employing N-benzyl carbamates see, e.g., ref.[2a-c].

(Received in UK 10 September 1986)