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SYNTHESIS OF (ALKOXYCARBONYLOXY)METHYL, (ACYLOXY)METHYL AND (OXODIOXOLENYL)METHYL CARBAMATES AS BIOREVERSIBLE PRODRUG MOIETIES FOR AMINES

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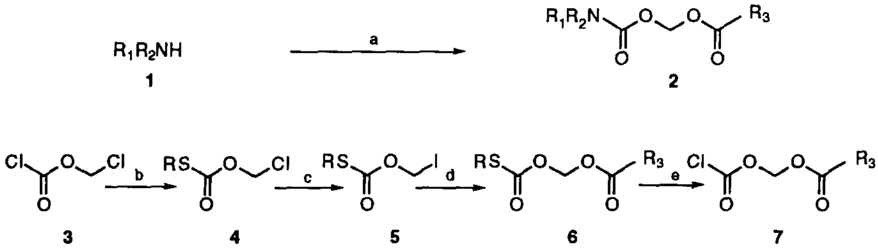
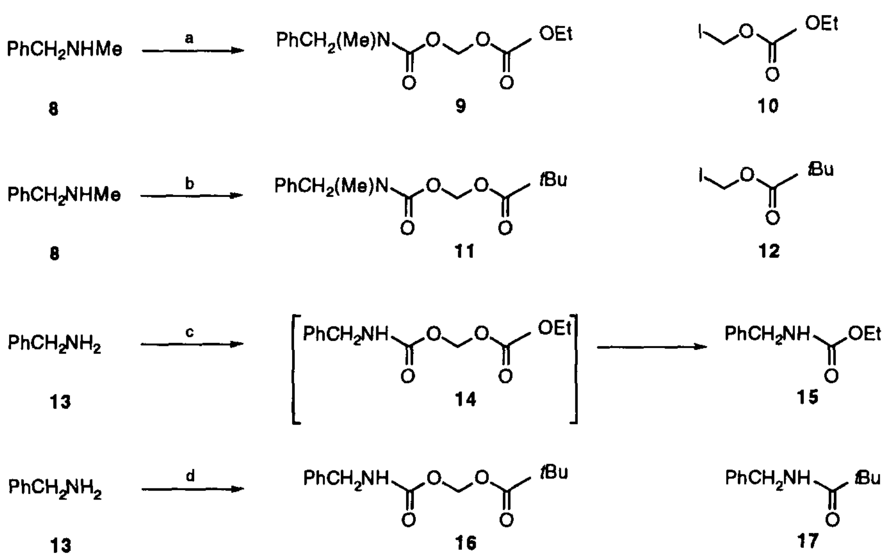
Abstract: Synthesis of (alkoxycarbonyloxy)methyl carbamates of secondary amines was developed, and it was extended to (acyloxy)methylation of benzylmethylamine and (oxodioxolenyl)methylation of benzylamine, benzylmethylamine, and L-phenylalanine. © 1997 Elsevier Science Ltd.

The pKa of primary and secondary alkylamines is generally in the range of 10 to 11.2.[1] In the intestine at pH of 7.2, only one-tenth of one percent of these amines is in the uncharged form. It is generally accepted that only the uncharged form of drugs containing these amines can diffuse through the phospholipid bilayer. Therefore, it is evident that these drugs can not be absorbed in the stomach and are poorly absorbed in the intestine. In addition, these amines are generally good nucleophiles and may also present chemical instability problem in the presence of labile groups in the molecule. Therefore, there is a need to prepare prodrugs of these amines to circumvent the problems of absorption and instability. Thus far, the (acyloxy)alkyl carbamylation of primary and secondary amino functions reported in the literature has been the most effective prodrug approach to circumvent these problems.[2,3] The prodrug group was introduced in one step involving nucleophilic attack of the primary or secondary amine **1** on acyloxymethyl chloroformate **7**, which was synthesized from chloromethyl chloroformate (**3**) in four steps (Scheme 1).[2b,4] The carbamate prodrugs **2** of secondary amines are chemically stable and are readily and quantitatively hydrolyzed by esterases to release the parent amines **1**. However, while the carbamate prodrugs **2** of primary amines released a major fraction of the parent amines **1** in the desired free form in plasma, a significant fraction of the undesired N-acetylated parent amines was also produced. Therefore, its utility as prodrugs of primary amines is more problematic and can not be predicted prior to in vivo studies for the individual compounds.[3] The reported prodrug synthesis is limited to the production of acyloxyalkyl carbamates (R_3 = alkyl or aryl).[2b,4] Since physicochemical properties of prodrugs, such as water solubility, chemical and enzymatic stability, and lipophilicity, are important factors for the success of an oral drug delivery,[5] we have been interested in developing the synthesis of (alkoxycarbonyloxy)methyl carbamate prodrugs (R_3 = alkoxy or aryloxy) for increasing water solubility and chemical stability.



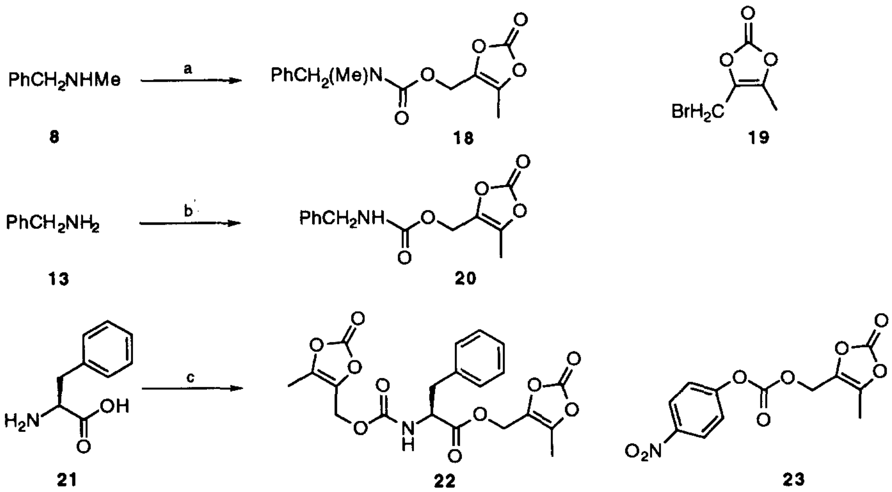
Scheme 1: (a) 7/DMF/r t; (b) RSH/TEA/0 °C; (c) NaI/$NaHCO_3$/acetone/40 °C; (d) R_3CO_2Na/DMF/0 °C; (e) SO_2Cl_2/0 °C.

Recently, it was reported that the reaction of benzylamine with carbon dioxide under an atmospheric pressure in the presence of benzyl chloride and Cs_2CO_3 gave a carbamate ester in good yield.[6] This information prompted us to investigate the carbamylation of benzylamine and benzylmethylamine in the presence of alkylating agents **10**[7] and **12**[8] under similar conditions. Indeed, we were able to obtain the desired prodrugs in excellentyields (87–89%) from benzylmethylamine but not from benzylamine.[9] In the case of benzylamine, carbamylation with **10** did not provide the desired product **14** which presumably further decomposed intramolecularly to give carbamate ester **15** in 31% yield. However, carbamylation of benzylamine with **12**



Scheme 2: (a) 10/CO_2/Cs_2CO_3/DMF/r t, 89%; (b) 12/CO_2/Cs_2CO_3/DMF/r t, 87%; (c) 10/CO_2/Cs_2CO_3/DMF/r t, 31%; (d) 12/CO_2/Cs_2CO_3/DMF/r t, 16%.

produced the desired product **16** in 16% yield and amide **17** was not obtained (Scheme 2). The reaction was further extended to (oxodioxolenyl)methyl carbamylation[10] of benzylmethyl amine, benzylamine, and L-phenylalanine (Scheme 3). Again, the desired products **18**, **20**, and **22** were obtained in excellent yields (70–90%).[9] Similar carbamylations have previously utilized **23**, available from **19** in three steps.[10]



Scheme 3: (a) 19/CO_2/Cs_2CO_3/DMF/r t, 90%; (b) 19/CO_2/Cs_2CO_3/DMF/r t, 70%; (c) 19/CO_2/Cs_2CO_3/DMF/r t, 84%.

In summary, we have developed synthesis of heretofore unknown (alkoxycarbonyloxy)methyl carbamates of secondary amines, and the reaction was extended to (acyloxy)methylation of benzylmethylamine and (oxodioxolenyl)methylation of benzylamine, benzylmethylamine, and L-phenylalanine. Since the alkylating agents **12** and **19** are more readily obtained than the acylating agents 7 and **23**, this study provides a convenient method of making (acyloxy)methyl and (oxodioxolenyl)methyl carbamate prodrugs.[3] It is reasonable to assume that the hydrolysis of the new (alkoxycarbonyloxy)methyl carbamates by esterases is similar to that of (alkoxycarbonyloxy)alkyl esters.[2(a)]

References and Notes

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7. The alkylating agent **10** was synthesized by reaction of chloromethyl chloroformate with ethanol, followed by treatment with sodium iodide in acetonitrile.
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9. All new compounds were purified by SiO_2 flash column chromatography to greater than 95% purity and were fully characterized by ^{1}H NMR and ESIMS (electrospray ionization mass spectrometry) and by elemental analysis. Selected data for products are summarized as follows:
9: Calcd for $C_{13}H_{17}NO_5$: C,58.42; H 6.41; N, 5.24. Found: C, 58.44; H, 6.32; N, 5.22. ^{1}H NMR ($CDCl_3$; a mixture of rotamers): δ 7.3 (m, 5H); 5.84, 5.83 (2s, 2H); 4.50, 4.48 (2s, 2H); 4.22 (2q, 2H, *J* = 7.0 Hz); 2.92, 2.86 (2s, 3H); 1.32 (2t, 3H, *J* =7.0 Hz). IR (KBr): 1750 and 1720 cm^{-1}. ESIMS: *m/z* 268.2 $(M + H)^+$.
11: Calcd for $C_{15}H_{21}NO_4$: C,64.50; H 7.58; N, 5.01. Found: C, 64.52; H, 7.29; N, 4.95. ^{1}H NMR ($CDCl_3$; a mixture of rotamers): δ 7.3 (m, 5H); 5.83, 5.82 (2s, 2H); 4.50, 4.46 (2s, 2H); 2.92, 2.84 (2s, 3H); 1.23, 1.20 (2s, 9H). IR (KBr): 1750 and 1720 cm^{-1}. ESIMS: *m/z* 280.2 $(M + H)^+$.
15: ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 5H); 4.9 (br s, 1H); 4.37 (d, 2H); 4.25 (q, 2H, *J* = 6.5 Hz); 1.32 (t, 3H, *J* = 6.5 Hz). ESIMS: *m/z* 264.1 $(M + H)^+$.
16: Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H 7.22; N, 5.28. Found: C, 63.78; H, 7.25; N, 5.46. ^{1}H NMR ($CDCl_3$; a mixture of rotamers): δ 7.3 (m, 5H); 5.76 (s, 2H); 5.15 (bs, 1H); 4.47, 4.46 (2s, 3H); 1.22 (s, 9H). ESIMS: *m/z* 266.9 $(M + H)^+$.
18: Calcd for $C_{14}H_{15}NO_5$: C,60.65; H 5.45; N, 5.05. Found: C, 60.79; H, 5.50; N, 4.99. ^{1}H NMR ($CDCl_3$; a mixture of rotamers): δ 7.3 (m, 5H); 4.90 (s, 2H); 4.48, 4.45 (2s, 2H); 2.90, 2.85 (2s, 3H); 2.20, 2.18 (2s, 9H). IR (KBr): 1820 and 1710 cm^{-1}. ESIMS: *m/z* 278.1 $(M + H)^+$.
20: ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 5H); 5.1(br, 1H); 4.35 (s, 2H); 4.85 (s, 2H); 2.19 (s, 3H). ESIMS: *m/z* 264.1 $(M + H)^+$.
22: Calcd for $C_{20}H_{19}NO_{10}$: C,55.43; H 4.42; N, 3.23. Found: C, 54.81; H, 4.69; N, 2.84. ^{1}H NMR ($CDCl_3$): δ 7.2 (m, 5H); 5.30 (br s, 1H); 4.7–4.9 (m, 4H); 3.10 (d, 2H); 2.15 (s, 3H); 2.14, (s, 3H). IR (KBr): 1820 and 1740 cm^{-1}. ESIMS: *m/z* 434.2 $(M + H)^+$.
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