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A New Direct Synthesis of Tertiary N-Acyloxymethylamide Prodrugs of Carboxylic Acid Drugs

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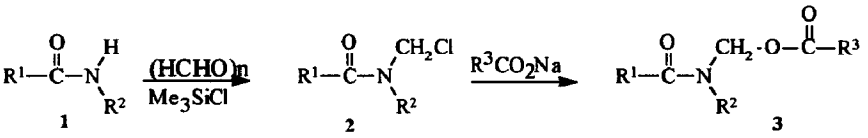
Abstract. N-Alkyl-N-chloromethylamides **2**, prepared from secondary amides, paraformaldehyde and chlorotrimethylsilane, react readily with carboxylate anions to generate the corresponding tertiary N-acyloxymethylamides **3** in good yield; the latter give rise to the parent carboxylic acids in aqueous media at pH 7.4 and 37 °C with half-lives between *ca.* 1 min and 42 h.

Drugs containing free carboxylic acid groups often have their therapeutic effectiveness greatly reduced after oral administration [1] A useful approach to overcome this problem is to transform the drug molecule into a prodrug by linking the carboxylic acid to an inactive carrier After absorption the prodrug must rapidly regenerate the bioactive compound, either with or without enzymatic activation [1]. We have recently reported that the tertiary N-acyloxymethylamides **3** are potential useful prodrugs for either carboxylic acids or secondary amides [2]. The use of amide moieties as carriers has also been recently recognized to be of particular interest in enhancing the dermal delivery of bioactive compounds [3]. The methods already available for synthesis of compounds **3** are: (a) acylation of tertiary N-hydroxymethylamides [4,5]; and (b) alkylation of the sodium salt of a secondary amide by the chloromethyl ester of a carboxylic acid [2]. The general non-availability of tertiary N-hydroxymethylamides [6,7] on one hand, with the necessity for the α-chloromethyl esters and a low yielding reaction on the other, are serious limitations of these methods for sensitive drug molecules. Clearly, there is a need for general method to allow the direct coupling of the $R^1CONR^2CH_2$ moiety to an R^3CO_2H drug.



1 **2** **3**

We now report a new and more efficient synthesis for tertiary N-acyloxymethylamides **3** which employs the N-alkyl-N-chloromethylamides **2** (equation) [8]. These are easily prepared by refluxing the appropriate secondary amide with paraformaldehyde in chlorotrimethylsilane for *ca.* 2 h.. After evaporation of the solvent, the N-alkyl-N-chloromethylamides **2** can be isolated in very good yield (Table 1). Compounds **2** are rather unstable, and regenerate the parent amide Nevertheless, their structures follow from their NMR and EI-MS

Table 1. N-Alkyl-N-chloromethylamides, 2, prepared by reacting secondary amides with paraformaldehyde/Me_3SiCl

Compound	R^1	R^2	Yield(%)	EI-MS(%) $(M+2)^+$	M^+	$(M-Cl)^+$
2a	Me	Me	100	123(7)	121(20)	86(72)
2b	Ph	Me	98	185(2)	183(6)	148(49)
2c	Ph	Pr^i	97	213(0.7)	211(2)	176(25) $(M-HCl)^+$
2d	Ph	CH_2Ph	99	261(1.7)	259(5)	224(28)
2e	Ph	CH_2CO_2Et	98	257(0.3)	255(1)	220(10)
2f	4-Cl-C_6H_4	Me	100	206(8)	204(25)	168(90)
2g	$CH_2CH_2CH_2$		93	131(7)	133(22)	98(70)

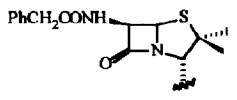
spectral data. The ^{1}H-NMR spectra of compounds **2** show a singlet at *ca* δ 5.2 corresponding to the NCH_2Cl group. Interestingly, compound **2a** appears to be a 1:1 mixture of *E* and *Z* rotamers, as shown by its ^{1}H and ^{13}C-NMR spectra [9]. The EI-MS spectra clearly exhibits the M^+ and $(M+2)^+$ peaks in a 3:1 ratio as expected for the presence of the NCH_2Cl group. The $(M-Cl)^+$ peak is also observable with variable intensity. As the N-chloromethylamides **2** appeared by NMR not to be contaminated with other products, they were used directly in the subsequent step. Typically, the synthesis of prodrugs **3a-g** (Table 2) was achieved by reacting the appropriate compound **2** (5 mmol) with the sodium salt of the carboxylic acid drug (5 mmol) in dry tetrahydrofuran (10 ml) at room temperature for 10-15 minutes. After evaporation of the solvent, the residue was suspended in dichloromethane or ethyl acetate, washed with sodium bicarbonate and subjected to column chromatography on silica gel (diethyl ether or ethyl acetate as eluant) to afford the desired product **3** in 50-90% (Table 2).

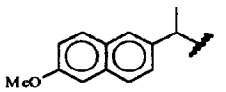
Despite the large range of the pK_a of carboxylic acids used (2.7 to 5.2), the reaction was generally completed within 10-15 minutes for all compounds. Moreover, changing to a better leaving group (by addition of NaI or Ag_2CO_3), brought no change in the yield nor did it shorten the reaction time. This behaviour contrasts sharply with α-haloalkyl esters, whose reactivity with different nucleophiles, including carboxylic acids, depends on the nature of the nucleophile and the halide leaving group ability [10].

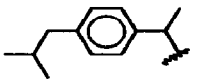
The structure of the tertiary N-acyloxymethylamides **3** follows from their spectroscopic and analytical data. When R^3=Ph (eg. **3g**), the ^{1}H-NMR spectra exhibits a singlet at *ca* δ 5.4 - 5.6 ppm due to the NCH_2O group. However, for derivatives **3a-f** the ^{1}H-NMR signal of the NCH_2O group indicates the diastereotopic nature of the two protons as a result of the chiral centre in the drug moiety Therefore a geminal coupling with *J ca* 11 - 12 Hz is observed The chemical shift range of the NCH_2O protons is very similar to that observed with secondary N-acyloxymethylamides [2]. When the amide moiety is ethyl hippurate (compounds **3e,f**, $R^2 = CH_2CO_2Et$), a second *AB* system is observed at *ca* δ 4.2-4.3 ppm, with $J = 17$ Hz, which corresponds to the CH_2 group. The CH_2 signal of the ethyl hippurate N-chloromethyl derivative, **2e**, appears as a singlet at δ 4.18 ppm. As expected, no significant change was observed to the proton chemical shifts corresponding to the drug moiety. As with compound **2a**, the derivative **3a** appears as 1:1 mixture of both rotamers [11]. The FAB-MS of compounds **3** present the $(M+1)^+$ peak as well as the $(M-OCOR)^+$ peak

Table 2. N-Acyloxymethylamides, 3, prepared from N-chloromethylamides 2.

Compound	R^1	R^2	R^3	Found (%) (required) C	H	N	m/z (%)[a] MH^+	Yield(%)	$t_{1/2}$[b]
3a	Me	Me	A	57.0 (57.3)	5.9 (6.0)	9.9 (10.0)	420 (2)	56	< 1 min
3b	Ph	Me	A	--	--	--	482 (1)	89	< 1 min
3c	4-Cl-C_6H_4	Me	A	58.5 (58.2)	4.9 (5.0)	8.3 (8.1)	516 (2)	50	2 min
3d	$CH_2CH_2CH_2$		A	59.0 (58.5)	6.0 (5.8)	9.5 (9.7)	432 (2)	79	2 min
3e	Ph	CH_2CO_2Et	B	69.3 (69.5)	5.9 (6.0)	3 0 (3.1)	450 (2)	45	42 h
3f	Ph	CH_2CO_2Et	C	70.3 (70 6)	7.4 (7.3)	3.2 (3.3)	426 (0.5)	46	35 h
3g	Ph	CH_2Ph	Ph	76 1 (76.5)	5.7 (5.5)	4.0 (4.1)	224 (16)	66	21 min

A: 

B: 

C: 

a) FAB-MS molecular ion (glycerol matrix); b) Half-life at pH 7.4 (phosphate buffer) and 37 °C. See reference 12 for the method.

Compounds **3** behave as true prodrugs, hydrolising quantitatively to the corresponding carboxylic acid in aqueous media at pH 7.4 in phosphate buffer and at 37 °C, with half-lives between *ca.* 1 min and 42 h (Table 2). These values were determined using an HPLC method [12] In the case of prodrugs **3a-d**, no product resultant of the β-lactam ring opening was detected.

In conclusion, this approach provides both a general synthesis for tertiary N-chloromethylamides **2** and, more importantly, enables the facile and mild synthesis of a variety of tertiary N-acyloxymethylamides **3** with a wide range of ester and amide substituents to be accomplished

General Procedure for the Preparation of N-Chloromethylamides 2. A suspension of the secondary amide (6 mmol) and paraformaldehyde (0.3 g) in chlorotrimethylsilane (20 ml) or in a 1:1 mixture of chlorotrimethylsilane and dry tetrahydrofuran (when $R^2 = CH_2CO_2Et$) was refluxed for 2 h. The solvent was removed under reduced pressure on a rotary evaporator to give the corresponding compound **2**.

General Procedure for the Preparation of N-Acyloxymethylamides 3. A solution of the N-chloromethylamide **2** (1 1 equiv.) in dry tetrahydrofuran (1 ml) was added to a suspension of the sodium salt of the appropriate carboxylic acid drug (5 mmol) in tetrahydrofuran (5 ml) at room temperature. After the reaction was completed, the solvent was removed under reduced pressure. When R^3 = A, the residue so formed, was treated with 50 ml of ice-water and extracted with 2x100 ml of ethyl acetate. The combined organic extracts were washed with ice-water, sodium bicarbonate, brine and dried over magnesium sulfate. Evaporation of the solvent gave the crude product which was further purified by column chromatography using ethyl acetate as eluant. For the other prodrugs, the residue was treated with 50 ml of water and extracted with 2x50 ml of dichloromethane. The combined extracts were washed with sodium bicarbonate, water and then evaporated to afford the crude product, which was purified by column chromatography using diethyl ether as eluant.

References and notes

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7. We were not able to reproduce the synthesis of N-alkyl-N-hydroxymethylbenzamide using the method described in ref. 6. The secondary amide, was always recovered quantitatively.
8. Another method for the synthesis of compounds **2** is described by Kritzler *et al.*,*Chem Abstr.*; **1963**, *59*, 9816, involving the reaction of 1,3,5-trialkylhexahydrotriazines with acyl chlorides. However, this method generates considerable amounts of dimer bisamidomethane.
9. ^{13}C-NMR of compound **2a**; δ_C: 20.1 and 21.2 (CH_3CO); 32.2 and 34.4 (CH_3N); 58.2 and 62.6 (NCH_2Cl);170.8 and 174.8 (CO).
10. Sloan,K.B.; Koch,S.M.; *J.Org.Chem.*, **1983**, *48*, 3777-83.
11. ^{13}C-NMR spectral data for compound **3a**; δ_C:22.2 and 22.6 (CH_3CO);28.0 (C2-CH_3);33.3 (C2-CH_3);35.5 and 38.2 (N-CH_3); 44.7 ($PhCH_2$); 60.2 (C-3); 65.7 (C-2); 69.4 (C-6); 71.7 (C-5);74.4 and 77.3 (NCH_2O); 129.1 and 130.6 (aromatic C-2,C-3 and C-4); 135.1 (aromatic C-1);168.9, 171.8,173.6 and 174.8 (CO)
12. The HPLC system consisted of a Shimadzu LC-9A pump, a SPD-6AV UV-vis detector set at 230 nm and a LiChrospher RP-8 5μm column (Merck); the mobile phase was methanol-water containing 0.04 M tetrabutylammonium phosphate (55:45 to 60:40%) for compounds **3a-d**, or acetonitrile-water containing 0.2 M sodium acetate buffer (55:45 to 70:30%) for compounds **3e-g**. The pseudo-first order rate constants were determined using the peak areas of either the prodrug or the parent drug.

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