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Practical Synthesis of N-Alkyl-N-alkyloxycarbonylaminomethyl Prodrug Derivatives of Acetaminophen, Theophylline, and 6-Mercaptopurine

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Abstract: We report a novel synthesis of N-alkyl-N-alkyloxycarbonylaminomethyl (NANAOCAM) prodrugs of acetaminophen, theophylline, and 6-mercaptopurine by alkylation of the corresponding drug molecule with N-alkyl-N-alkyloxycarbonylaminomethyl chlorides in good yield. Most of the alkylating agents were efficiently synthesized by chloromethylation of N-alkyl carbamic acid alkyl esters, which in turn were made from alkyl amines and alkyl chloroformates. In cases where the alkyl chloroformates were not available, synthesis of N-alkyl carbamic acid alkyl esters was accomplished by converting an alcohol to a chloroformate or to an activated acylating agent such as acyl imidazoles or p-nitrophenylcarbonate esters, followed by their reaction with alkyl amines.

Keywords: Prodrugs, acetaminophen, theophylline, 6-mercaptopurine, soft alkyl

INTRODUCTION

Prodrugs are biologically inactive derivatives of a drug that revert to the parent drug by either enzymatic or chemical hydrolysis. Most prodrugs are esters because they are easy to make, are economical, yield nontoxic side products, and are hydrolyzed to the corresponding acid and alcohol (either of which may be the parent drug) by esterases present in biological organs, tissues, and cells.

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Sometimes simple esters (alkyl derivatives of a carboxylic acid) are not labile, as in the case of penicillin esters.[1] Addition of a CH_2O spacer led to the generation of akylcarbonyloxymethyl (ACOM) or alkyloxycarbonyloxymethyl (AOCOM) esters of carboxylic acids. These ACOM and AOCOM esters are known as soft alkyl prodrugs because they are alkyl derivatives of the carboxylic acid but can undergo hydrolysis at the alkylcarbonyl or alkyloxycarbonyl functional group to leave a hydroxymethyl ester of the carboxylic acid, which undergoes fast chemical hydrolysis to give the active principle and formaldehyde.[2–4] Because formaldehyde is normally produced endogenously by various oxidative demethylation reactions catalyzed by CYP 450s, low levels of formaldehyde already exist in vivo and low levels of exogenous formaldehyde should be relatively safe.

NANAOCAM (N-alkyl-N-alkyloxycarbonylaminomethyl, ROCONR′ CH_2) derivatives can also be classed as soft alkyl prodrugs. However, the use of a NANAOCAM promoiety has only been reported for 6-mercaptopurine.[5] Since then it has been determined that NANAOCAM derivatives of phenols, carboxylic acids, and 6-mercaptopurine hydrolyse by a SN_1 type of mechanism.[6] We are interested in synthesizing prodrugs that would increase the absorption of drugs across the skin. 6-Mercaptopurine (6MP), theophylline (Th), and acetaminophen (APAP) are three drugs whose permeability across the skin is limited by their poor solubility properties (i.e., solubility in a lipid phase and solubility in an aqueous phase).[7] By transiently masking the hydrogen bonding groups like −SH in 6MP, −NH in Th, and −OH in APAP, it should be possible to increase their permeability across the skin.[7]

However, the synthesis of the NANAOCAM prodrugs of 6MP generally gave poor yields of the desired compounds. Here we report different approaches to their synthesis, which resulted in greatly improved yields.

SYNTHESIS OF ALKYLATING AGENT

The synthesis of NANAOCAM derivatives of APAP, Th, and 6MP involves the alkylation of the parent drug with N-alkyl-N-alkyloxycarbonylaminomethyl chloride (NANAOCAM-Cl).

Method A

Siver et al.[5] reported the synthesis of NANAOCAM-Cl in two steps. 1,3,5-Trialkylhexahydrotriazene was synthesized from an equimolar amount of alkyl amine and formaldehyde in the presence of NaOH. The 1,3,5-trialkylhexahydrotriazene was treated with 3 equivalents of the appropriate alkyl chloroformate to generate NANAOCAM-C1 (RO-CO-NR′-CH_2-Cl), which was then used to derive the desired drug (Scheme 1). NANAOCAM-Cl, $R = CH_3$, $R' = CH_3$, was obtained in 90% yield using this protocol. We

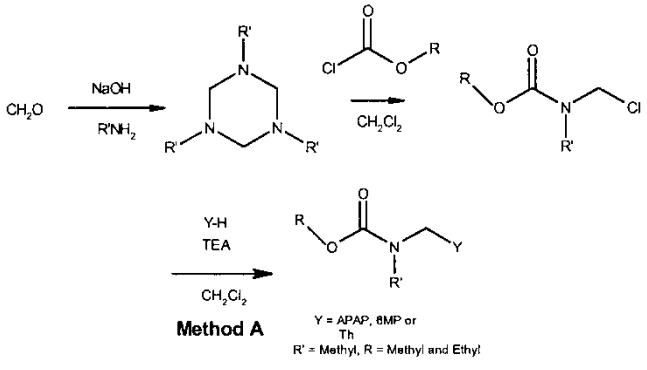
also found that the reaction of 1,3,5-trialkylhexahydrotriazenes with alkyl chloroformates in CH_2Cl_2 gave the corresponding bis-(N-alkyl-N-alkyloxycarbonylamino)methanes $(NANAOCA)_2M$, **2**, and unreacted alkyl chloroformate along with the desired NANAOCAM chlorides, **1**. The ratio of $(NANAOCA)_2M$ and unreacted alkyl chloroformate to NANAOCAM-Cl increased as the alkyloxy chain lengths grew longer (e.g., R = C_2H_5, C_3H_7, C_4H_9) (Table 1). It was difficult to remove these side products by trituration with hexanes or ether, and distillation was not possible because of decomposition of the products. The yields of the corresponding alkylated prodrugs were thus compromised because of the formation of acylated products along with the alkylated ones and the presence of $(NANAOCA)_2M$ in the reaction mixtures. Furthermore, isolation and purification of the desired prodrug by crystallization or column chromatography was a cumbersome process. Therefore alternative procedures for the synthesis of NANAOCAM-chlorides were developed. Characterizations of NANAOCAM-Cl synthesized by method A and used to alkylate APAP, Th, and 6MP with little contamination by **2** are as follows.

N-Methyl-N-methyloxycarbonylaminomethyl Chloride
Yield = 90%, ^{1}H NMR ($CDCl_3$): δ 2.9 (s, 3H), δ 3.75 (s, 3H), δ 5.3 (s, 2H).

N-Methyl-N-ethyloxycarbonylaminomethyl Chloride
Yield = 89%, ^{1}H NMR ($CDCl_3$): δ 1.3 (t, 3H), δ 2.9 (s, 3H), δ 4.22 (q, 2H), δ 5.33 (s, 2H).

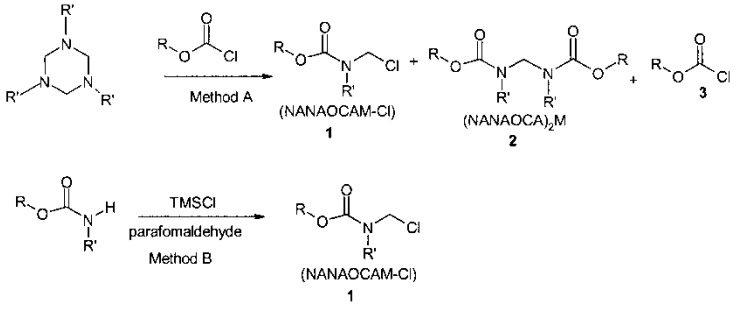
Method B

The synthesis of N-alkyl chloromethylamides has been reported by Moreira et al.[8] We have extrapolated from that synthesis of tertiary amides to the synthesis of tertiary carbamates. An alkyl chloroformate was reacted with alkyl amine in the presence of triethylamine in CH_2Cl_2 to give



Scheme 1.

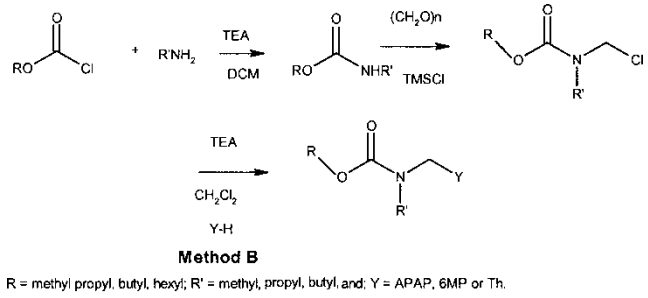
Table 1. Percentage yields of NANAOCAM-Cl (**1**) by methods A and B



Structure		Method A			Method B
N-R′	O-R	**1**	**2**	**3**	**1**
Methyl	Methyl	90	0	0	
Methyl	Ethyl	89	0	11	
Methyl	Propyl	33	18	49	85
Methyl	Butyl	17	27	56	82
Propyl	Butyl	55	13	18	93
Butyl	Methyl	60	12	22	92
Butyl	Propyl	35	19	36	90
Butyl	Butyl	42	18	28	82

N-alkylcarbamic acid alkyl esters. Chloromethylation of N-alkyl carbamic acid alkyl ester with paraformaldehyde and trimethylsilyl chloride under reflux conditions gave the desired NANAOCAM-Cl in excellent yields with no side products (Scheme 2 and Table 1). A comparison of the yields of the corresponding prodrug derivatives of APAP, Th, and 6MP using alkylating agents produced by the two protocols (method A and method B) is shown in Table 2. In all cases the yields improved substantially using method B because the reaction mixture containing the alkylating agent was not contaminated with any side products. The experimental protocol for the synthesis and characterization of NANAOCAM-Cl using method B are as follows.

One equivalent of triethylamine (0.033 mol) and alkyl amine (0.033 mol) was added dropwise to a solution of alkyl chloroformate (0.033 mol) in 75 mL of CH_2Cl_2 cooled with an ice bath. The reaction mixture was allowed to warm to room temperature and stirred overnight. The clear solution was washed with 3×10 mL of brine, and the organic layer was dried over Na_2SO_4, then concentrated to an oil. This oil was purified by trituration with hexane overnight. The suspension was filtered and the filtrate evaporated to give the corresponding N-alkyl carbamic acid alkyl ester as a yellow oil. A mixture of N-alkyl carbamic acid alkyl ester (0.02 mol), 1.7 equivalents of paraformaldehyde (0.034 mol), and 13 equivalents of trimethylsilyl chloride



Scheme 2.

(0.26 mol) was refluxed for 2.5 h over an oil bath using a $CaCl_2$ drying tube and a water-cooled reflux condenser. The suspension was diluted with 50 mL of CH_2Cl_2 and filtered to get rid of unreacted paraformaldehyde. The clear filterate was concentrated using a rotavapor at 40°C under reduced pressure. The yellow oil obtained was triturated with hexane overnight, the white suspension was filtered, and the filtrate was concentrated to give the desired alkylating agent.

N-Methyl-N-propyloxycarbonylaminomethyl chloride: yield = 85%, ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H), δ 1.7 (m, 2H), δ 3.0 (s, 3H), δ 4.12 (t, 2H), δ 5.35 (s, 2H).

Table 2. Percent yields of NANAOCAM derivatives by methods A and B and routes A, B and C

	Structure		Yields of prodrugs (%)				
Drug	N-R′	O-R	Method A	Method B	Route A	Route B	Route C
APAP	Methyl	Methyl	70				
APAP	Methyl	Ethyl	65				
APAP	Methyl	Propyl	28	76			
APAP	Methyl	Butyl	7	66			
APAP	Methyl	Hexyl			33	63	45
Th	Methyl	Methyl	73				
Th	Methyl	Ethyl	84				
Th	Methyl	Propyl	46	80			
Th	Methyl	Butyl	33	71			
Th	Methyl	Hexyl			39	77	59
6MP	Propyl	Butyl	25	78			
6MP	Butyl	Methyl	26	57			
6MP	Butyl	Propyl	5	68			
6MP	Butyl	Butyl	16	77			

N-Methyl-N-butyloxycarbonylaminomethyl chloride: yield = 82%, ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H), δ 1.41 (m, 2H), δ 1.65 (m, 2H), δ 3.0 (s, 3H), δ 4.17 (t, 2H), δ 5.33 (s, 2H).

N-Propyl-N-butyloxycarbonylaminomethyl chloride: yield = 93%, ^{1}H NMR ($CDCl_3$): δ 0.90–0.95 (2t, 6H), δ 1.41 (m, 2H), δ 1.65 (m, 4H), δ 3.35 (t, 2H), δ 4.17 (t, 2H), δ 5.33 (s, 2H).

N-Butyl-N-methyloxycarbonylaminomethyl chloride: yield = 92%, ^{1}H NMR ($CDCl_3$): δ 0.94 (t, 3H), δ 1.35 (m, 2H), δ 1.59 (quintet, 2H), δ 3.36 (t, 2H), δ 3.78 (s, 3H), δ 5.33 (s, 2H).

N-Butyl-N-propyloxycarbonylaminomethyl chloride: yield = 90%, ^{1}H NMR ($CDCl_3$): δ 0.92 (2m, 6H), δ 1.32 (m, 2H), δ 1.6–1.71 (2m, 4H), δ 3.37 (t, 2H), δ 4.12 (t, 2H), δ 5.33 (s, 2H).

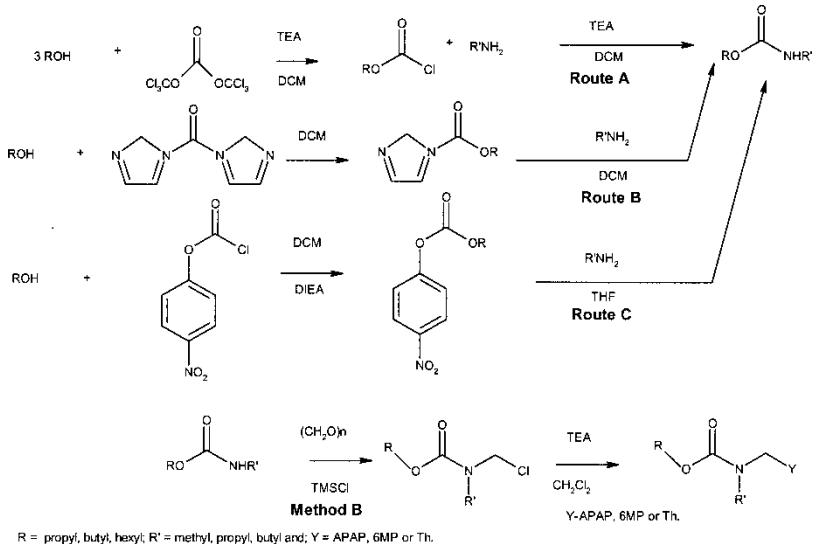
N-Butyl-N-butyloxycarbonylaminomethyl chloride: yield = 82%, ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), δ 1.3–1.36 (2m, 4H), δ 1.57–1.65 (2m, 4H), δ 3.36 (t, 2H), δ 4.16 (t, 2H), δ 5.32 (s, 2H).

Since methods A and B rely on the availability of alkyl chloroformates, other methods of making the chloroformate (route A) and activated acylating agents (routes B and C) were evaluated (Scheme 3). Routes A, B, and C illustrate alternate ways of synthesizing N-alkyl carbamic acid alkyl ester from an alcohol. The N-alkyl carbamic acid alkyl ester can then be converted to NANAOCAM-Cl using method B. We chose hexanol as our model alcohol for this purpose. A comparison of the yields obtained of the corresponding prodrug derivatives are reported in Table 2.

Route A

This method relies on the conversion of an alcohol to chloroformate. The chloroformate generated in situ is then reacted with alkyl amine to generate N-alkyl carbamic acid alkyl ester. The experimental protocol and characterization of NANAOCAM-Cl follows.

To an equivalent of triphosgene (2.96 g, 0.01 mol) in 140 mL of CH_2Cl_2 cooled with an ice bath, was added 3 equivalents of hexanol (3.06 g, 0.03 mol) and 3 equivalents triethylamine (3.03 g, 0.03 mol) in 10 mL of CH_2Cl_2 dropwise over a period of 15 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was again cooled with an ice bath and reacted with 3 equivalents of triethyl amine (3.03 g, 0.03 mol) and 3 equivalents of aqueous methyl amine (2.25 g, 0.03 mol). The reaction mixture was stirred overnight, then washed with 10 mL of 1 N HCl and 3 × 15 mL of water. The CH_2Cl_2 layer was dried



Scheme 3.

over Na_2SO_4, then concentrated to give the N-methyl carbamic acid hexyl ester as an oil. The corresponding NANAOCAM-Cl were made from the N-methyl carbamic acid hexyl ester by reacting it with trimethylsilyl chloride and paraformaldehyde as in method B. The alkylating agent was subsequently used to synthesize the desired prodrug (Scheme 3).

N-Methyl-N-hexyloxycarbonylaminomethyl chloride: yield = 83%, ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H), δ 1.3 (m, 6H), δ 1.6 (m, 2H), δ 3.02 (s, 3H), δ 4.15 (t, 2H), δ 5.33 (s, 2H).

Route B

This method relies on the conversion of an alcohol to an activated acylating agent (acyl imidazole), which can subsequently be used to acylate an amine to generate N-alkyl carbamic acid alkyl ester. The experimental protocol follows.

Hexanol (3.06 g, 0.03 mol) was reacted with 1.1 equivalents of 1,1′-carbonyl diimidazole (5.34 g, 0.033 mol) in 50 mL of CH_2Cl_2 overnight at room temperature, The clear solution was diluted with 50 mL of CH_2Cl_2 and washed with 20 mL of 1 N HCl and 3 × 10 mL of water. The CH_2Cl_2 layer was dried over Na_2SO_4, then concentrated to an oil: hexyloxycarbonylimidazole. Coupling of the hexyloxycarbonylimidazole with 1.3 equivalents (2.94 g, 0.039 mol) of aqueous methyl amine in 2-propanol (10 mL) was

achieved by refluxing the reaction mixture overnight. The reaction mixture was then concentrated using a rotavapor under vacuum at 5°C. The oily residue obtained was dissolved in 50 mL of CH_2Cl_2 and washed with 10 mL of 1 N HCl and 5 × 3 mL of water. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated to an oil. The N-methyl carbamic acid hexylester was subsequently converted to the alkylating agent as reported in method B and used to generate the desired prodrug (Scheme 3).

Route C

This protocol relies on the conversion of an alcohol to its p-nitrophenylcarbonate ester, which is then reacted with alkyl amine to generate N-alkyl carbamic acid alkyl ester. The experimental protocol for synthesis of NANAOCAM-Cl follows.

Equimolar equivalents of hexanol(3.06 g, 0.03 mol), p-nitrophenylchloroformate (6.66 g, 0.033 mol), and diisopropylethylamine (4.26 g, 0.033 mol) were mixed in 50 mL of CH_2Cl_2, and reaction was run overnight. The clear solution that resulted was diluted with 25 mL of CH_2Cl_2 and washed with 10 mL of 1 N HCl, 10 mL of saturated $NaHCO_3$, and 3 × 10 mL of water. The CH_2Cl_2 layer was dried over Na_2SO_4 and then concentrated to give the p-nitrophenylcarbonate hexyl ester as an oil. Coupling of the p-nitrophenylcarbonate hexyl ester with 1.5 equivalents of methyl amine (3.48 g, 0.045 mol) in dry THF (10 mL) was carried out by refluxing the reaction mixture overnight. The reaction mixture was concentrated using a rotavapor under vacuum at 50°C. The oily residue obtained was resuspended in 50 mL of CH_2Cl_2 and washed with 10 mL of 1 N HCl and 3 × 5 mL with water. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated to give the N-methyl carbamic acid hexylester, which was subsequently converted to the alkylating agent as reported in method B and used to generate the desired prodrug.

SYNTHESIS OF EXAMPLES OF PRODRUGS OF ACETAMINOPHEN, THEOPHYLLINE, AND 6-MERCAPTOPURINE

Acetaminophen (APAP) Prodrugs

Equimolar amounts of APAP (0.01 mol) and triethylamine (0.01 mol) were refluxed for an hour in 20 mL of CH_2Cl_2 followed by the addition of 1.1 equivalents of the alkylating agent (0.01 mol, as determined by ^1H NMR). The contents were stirred overnight. The reaction mixture was diluted with 50 mL of CH_2Cl_2 followed by washing with 5 × 3 mL of water. The CH_2Cl_2 solution was dried over Na_2SO_4 for an hour and filtered.

The solution was concentrated using a rotavapor under vacuum at 40°C until it was solvent free. The resulting material was purified by recrystallization and, if necessary, column chromatography until a sharp melting point was obtained, a single spot was seen on thin-layer chromatography (TLC) and an ^{1}H NMR consistent with the desired product was obtained.

N-Methyl-N-methyloxycarbonylaminomethyl-APAP: Purified by recrystallization from CH_2Cl_2–hexane (1:3) twice to give white crystals. Yield 70%, mp 86–88°C, ^{1}H NMR ($CDCl_3$): δ 7.6 (s, lH), δ 7.39 (d, 2H), δ 6.96–6.87 (2d, 2H), δ 5.28–5.21 (2s, 2H), δ 3.72–3.7 (2s, 3H), δ 3.0–2.97 (2s, 3H), δ 2.0 (s, 3H). Anal. calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.1%. Found: C, 56.81; H, 6.34; N, 11.1.

N-Methyl-N-ethyloxycarbonylaminomethyl-APAP: Purified by trituration with hexane overnight to give yellow crystals, which were recrystallized from ethyl acetate–hexane (1:3) to give white crystals. Yield 65%, mp 75–77°C, ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H), δ 7.12 (s, 1H), δ 6.96 (2d, 2H), δ 5.3 (2s, 2H), δ 4.15 (2q, 2H), δ 3.0 (2s, 3H), δ 2.15 (s, 3H), δ 1.25 (2t, 3H). Anal. calcd. for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.53; H, 6.93; N, 10.47.

N-Methyl-N-propyloxycarbonylaminomethyl-APAP: Purified by silica-gel chromatography in ethyl acetate–hexane (3:2) followed by trituration in hexane overnight to give pale white crystals. These crystals were further recrystallized from ethyl acetate–hexane (3:2) to give white crystals. Yield 76%, mp 58–59°C, ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H), δ 7.14 (s, 1H), 6.96 (2d, 2H), δ 5.3 (2s, 2H), δ 4.05 (2t, 2H), δ 3.0 (2s, 3H), δ 2.15 (s, 3H), δ1.65 (m, 2H), δ 0.91 (2t, 3H). Anal. calcd. for $C_{14}H_{20}N_2O_4$: C, 60.01; H, 5.45; N, 12.73. Found: C, 60.1; H, 5.35; N, 12.58.

N-Methyl-N-butyloxycarbonylaminomethyl-APAP: Purified by silica-gel chromatography using 70% ethyl acetate–hexane as an eluent to give an yellow oil. Yield 66%, ^{1}H NMR ($CDCl_3$): δ 7.39 (d, 2H), δ 7.14 (s, lH), 6.97–6.88 (2d, 2H), δ 5.29–5.22 (2s, 2H), δ 4.10 (2t, 2H), δ 3.03–2.97 (2s, 3H), δ 2.15 (s, 3H), δ 1.65 (m, 2H), δ 1.4 (m, 2H), δ 0.91 (2t, 3H). Anal. calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.16; H, 7.65; N, 9.24.

N-Methyl-N-hexyloxycarbonylaminomethyl-APAP: Purified by silica-gel column chromatography in ethyl acetate–hexane (4:l) followed by trituration in hexane overnight to give a colorless oil. Yield 63%, ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H), δ 7.29 (s, 1H), δ 6.95–6.89 (2d, 2H), δ 5.29–5.23 (2s, 2H), δ 4.11–4.07 (m, 2H), δ 3.02–2.98 (2s, 3H), δ 2.15 (s, 3H), δ 1.63 (m, 2H), δ 1.3 (m, 6H), δ 0.89 (m, 3H). Anal. calcd. for $C_{17}H_{26}N_2O_4$: C, 62.33; H, 8.13; N, 8.69. Found: C, 61.96; H, 8.14; N, 8.36.

Theophylline Prodrugs

Equimolar amounts of theophylline (0.01 mol) and triethylamine (0.01 mol) in 20 mL of CH_2Cl_2 were stirred for 20 min. A white suspension was seen, and the alkylating agent (0.011 mol, as determined by ^1H NMR) was added to the suspension. An exothermic reaction occured, and the suspension cleared to give a solution, which was stirred overnight at room temperature. The reaction mixture was diluted with 40 mL of CH_2Cl_2 and extracted with 5 mL of 1 N HCl, 5 mL of $NaHCO_3$ saturated solution, and 5×3 mL of water. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated to give white solids, which were crystallized from CH_2Cl_2–ether or CH_2Cl_2–hexanes to give pure white crystals.

N^7-(N-Methyl-N-methyloxycarbonyl)aminomethyl theophylline: Purified by recrystallization with CH_2Cl_2–hexane (1:4) to give white crystals. Yield 73%, mp 165–166°C, NMR ($CDCl_3$): δ 7.98 (2s,lH), δ 5.8 (2s, 2H), δ 3.75 (2s, 3H), δ 3.61 (s, 3H), δ 3.43 (s, 3H), δ 3.0 (2s, 3H). Anal. calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.9. Found: C, 46.88; H, 5.22; N, 24.77.

N^7-(N-Methyl-N-ethyloxycarbonyl)aminomethyl theophylline: Purified by recrystallization with CH_2Cl_2–ether (1:4) followed by CH_2Cl_2–hexane (1:4) to give pure white crystals. Yield 84%, mp 115–117°C, ^1H NMR ($CDCl_3$): δ 7.99 (2s,lH), δ 5.8 (2s, 2H), δ 4.2 (2q, 3H), δ 3.61 (s, 3H), δ 3.43 (s, 3H), δ 3.1 (2s, 3H), δ 1.28 (t, 3H). Anal. calcd. for $C_{12}H_{17}N_5O_4$: C, 48.81; H, 5.8; N, 23.72. Found: C, 48.8; H, 5.84; N, 23.67.

N^7-(N-Methyl-N-propyloxycarbonyl)aminomethyl theophylline: Purified by recrystallization with CH_2Cl_2–hexane (1:4) followed by hot EtOH to give white crystals. Yield 80%, mp 128–129°C, ^1H NMR ($CDCl_3$): δ 7.98 (2s, lH), δ 5.8 (2s, 2H), δ 4.08 (2t, 2H), δ 3.6 (s, 3H), δ 3.43 (s, 3H), δ 3.1 (2s, 3H), δ 1.7 (m, 2H), δ 0.94 (2t, 3H). Anal. calcd. for $C_{13}H_{19}N_5O_4$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.60; H, 6.29; N, 22.62.

N^7-(N-Methyl-N-butyloxycarbonyl)aminomethyl theophylline: Purified by recrystallization with CH_2Cl_2–hexane (l:3) to give white crystals. Yield 71%, mp 103°C, ^1H NMR ($CDCl_3$): δ 7.98 (2s,1H), δ 5.8 (2s, 2H), δ 4.12 (2t, 2H)), δ 3.61 (s, 3H), δ 3.42 (s, 3H), δ 3.01 (2s, 3H), δ 1.63 (m, 2H), δ 1.39 (m, 2H), δ 0.94 (2t, 3H). Anal. calcd. for $C_{14}H_{21}N_5O_4$; C, 52.0; H, 6.55; N, 21.66. Found: C, 52.17; H, 6.73; N, 21.68.

N^7-(N-Methyl-N-hexyloxycarbonyl)aminomethyl theophylline: Purified by recrystallization with $CH_2Cl_2^-$petroleum ether (1:3) to give white crystals. Yield 77%, mp = 74–75°C, ^1H NMR($CDCl_3$): δ 7.99 (2s,1H), δ 5.8 (2s, 2H), δ 4.2–4.12 (2t, 2H), δ 3.61 (s, 3H), δ 3.42 (s, 3H), δ 3.01 (2s, 3H), δ

1.63 (m, 2H), δ 1.31 (m,6H), δ 0.89 (m, 3H). Anal. calcd. for $C_{16}H_{25}N_5O_4$: C, 54.6; H, 7.17; N, 19.93. Found: C, 54.18; H, 7.13; N, 19.53.

6-Mercaptopurine Prodrugs

To 6MP (0.01 mol) in 5 mL of DMSO was added N-alkyl-N-alkyloxycarbonylaminomethyl chloride (0.011 mol). The yellow solution was stirred at room temperature for 1.5 h. Triethyl amine (0.025 mol) and 15 mL of $CHCl_3$ were added, and stirring continued for one more hour. The reaction mixture was diluted with 100 mL of CH_2Cl_2 and was washed with 20 mL of 1 N HCl, 20 mL of saturated $NaHCO_3$ solution, and 15 × 3 mL of brine solution. The organic layer was dried over Na_2SO_4 and concentrated to give a yellow oil. The oil was triturated with petroleum ether to give yellow solids, which were further recrystallized with CH_2Cl_2–hexane or ethyl acetate–hexanes to give yellow crystals.

S-(N-Propyl-N-butyloxycarbonylaminomethyl)-6MP: Purified using ethyl acetate–hexane (1:3) to give yellow crystals. Yield 78%, mp 144–146°C (lit. mp = 143–144°C)[5]; ^{1}H NMR ($CDCl_3$): δ 8.76 (s,1H), δ 8.62–8.2 (2s,1H), δ 5.75 (2s, 2H), δ 4.24–4.17 (2t, 2H), δ 3.42–3.35 (2t, 2H), δ 1.68–1.61 (m,4H), δ 1.4–1.3 (m, 2H), δ 0.9 (m,6H). Anal. calcd. for $C_{14}H_{21}N_5O_2$: C, 51.99; H, 6.55; N, 21.65. Found: C, 52.09; H, 6.31; N, 21.69.

S-(N-Butyl-N-methyloxycarbonylaminomethyl)-6MP: Purified using ethyl acetate–hexane (1:1) to give yellow crystals. Yield 57%, mp 133–135°C (lit. mp = 134–135°C)[5]; ^{1}H NMR ($CDCl_3$): δ 8.71 (s, 1H), δ 8.42–8.2 (2s,1H), δ 5.68 (2s, 2H), δ 3.85–3.76 (2s, 3H), δ 3.47–3.38 (2t, 2H), δ 1.55–1.48 (m, 2H), δ 1.34–1.24 (m, 2H), δ 0.9 (t, 3H). Anal. calcd. for $C_{12}H_{17}N_5O_2$: C, 48.80; H, 5.8; N, 23.71. Found: C, 48.69; H, 5.78; N, 23.65.

S-(N-Butyl-N-propyloxycarbonylaminomethyl)-6MP: Purified using ethyl acetate–hexane (1:4) to give yellow crystals. Yield 68%, mp 75–77°C (lit. mp = 74–77°C)[5]; ^{1}H NMR ($CDCl_3$): δ 8.71 (s,1H), δ 8.42–8.2 (2s, 1H), δ 5.68 (2s, 2H), δ 4.19–4.1 (2t, 2H), δ 3.47–3.38 (2t, 2H), δ 1.78–1.64 (m, 2H), δ 1.54–1.51 (m, 2H), δ 1.28 (m, 2H), δ 1.0 (m, 6H). Anal. calcd. for $C_{14}H_{21}N_5O_2$: C, 51.99; H, 6.55; N, 21.65. Found: C, 51.76; H, 6.4; N, 21.57.

S-(N-Butyl-N-butyloxycarbonylaminomethyl)-6MP: purified using ethyl acetate–hexane (1:4) to give yellow crystals. Yield 77%, mp 85–87°C (lit. mp = 87–89°C);[5] ^{1}H NMR ($CDCl_3$): δ 8.72 (s,1H), δ 8.44–8.2 (2s,1H), δ 5.69 (2s, 2H), δ 4.23–4.15 (2t, 2H), δ 3.47–3.39 (2t, 2H), δ

1.7–1.2 (m, 8H), δ 0.9 (m, 6H). Anal. calcd. for $C_{14}H_{21}N_5O_2$: C, 53.39; H, 6.87; N, 20.75. Found: C, 53.42; H, 6.59; N, 20.77.

CONCLUSION

A practical general synthesis of N-alkyl-N-alkyloxycarbonylaminomethyl chlorides has been reported. The N-alkyl-N-alkyloxycarbonylaminomethyl chloride derivative can further be used to alkylate 6-MP, APAP, and Th to make useful prodrug derivatives whose purification and yields are higher than has been reported before.

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