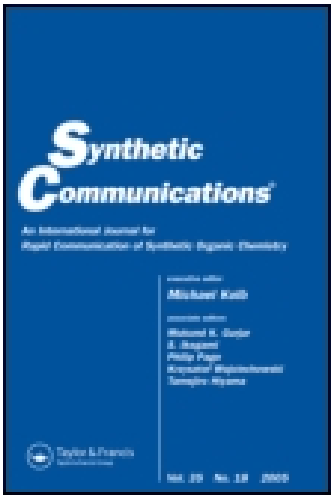

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Simple and Convenient Synthesis of 21-Thioalkylether Derivatives of Methyl 16-Prednisolone Carboxylates

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Simple and Convenient Synthesis of 21-Thioalkylether Derivatives of Methyl 16-Prednisolone Carboxylates

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Abstract: The antedrug approach for corticosteroids has been described as a fundamentally sound approach for the development of safer anti-inflammatory and anti-asthmatic therapy. However, the derivatization of prednisolone and its congeners have been considered to be major pitfalls, because their syntheses are complicated by the presence of numerous carboxylate esters and hydroxyl functions in the steroid nucleus. A simple and direct synthesis of 21-thioalkylether derivatives of methyl 16-prednisolonecarboxylates is described. The 21-mesylate of the methyl 16-prednisolonecarboxylate and 9-fluoro-17-dehydro methyl 16-prednisolonecarboxylate were reacted with Na-thioalkoxides to furnish the desired thioethers in good yields. A previously published method for the methanolysis of 16-cyanoprednisolone to methylcarboxylate has been reexamined, and the conditions are explained clearly. The reaction conditions for all these reactions were critical.

Keywords: antedrug, methanolysis, 16-methylcarboxylates, prednisolone 21-thioethers

In our continued effort to synthesize anti-inflammatory steroids on the basis of the antedrug concept,[1–3] metabolically labile groups at various strategic positions of potent corticosteroids, for example, prednisolone (**1**), were introduced.[4–6] An antedrug is a designed locally active drug that undergoes a predictable metabolic inactivation upon entry into the systemic circulation

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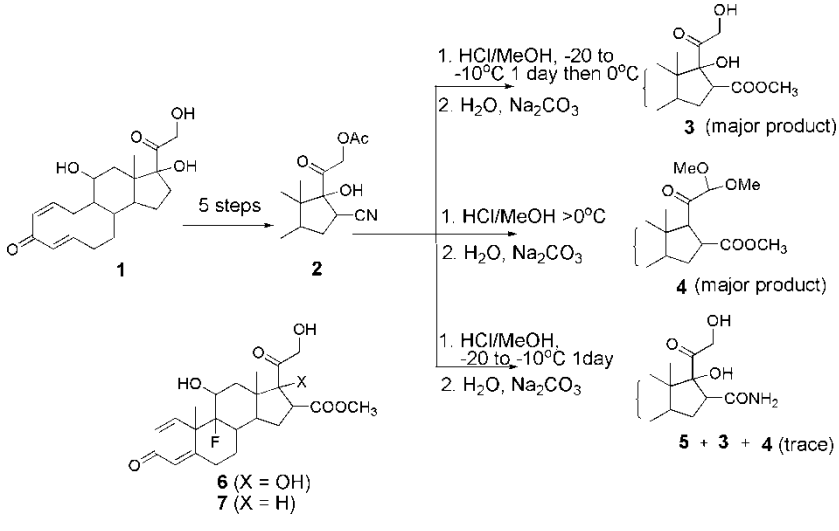
from the applied site. Thus, a true antedrug acts locally and is devoid of systemic toxicities. Various structural and pharmacological classes of antedrugs have been developed.[7] The synthesis of 16-cyanoprednisolone in five steps from prednisolone and its conversion to corresponding methyl-16α-prednisolonecarboxylates by methanolysis procedures have been reported by our group.[8–13] In methanolysis of 16-cyanoprednisolone, the conversion of the 16-cyano function to the corresponding 16-methylcarboxylate needs careful thermodynamic control of the reaction to suppress the mattox rearrangement[14,15] and or the side reaction leading to the amide (**5**).[16] The temperature for the reaction was described to be -20°C.[13]

In the present study, we have examined the reaction further to reveal that the saturation of the methanol solution of the nitrile with HCl gas should be done at -20°C, then allow the temperature to reach and maintain -10°C overnight and then reach at 0°C slowly (over 5 h) to force the reaction to the completion, before pouring the solution into water and neutralizing with sodium carbonate powder to pH 3–4. Pouring the mixture in water for hydrolysis to occur at the final stage of the reaction at low temperature (-20 to -10°C) leads to the formation of a higher amount of amide (**5**) whereas allowing the temperature to be more than 0°C before pouring it into water causes the mattox rearrangement, furnishing compound **4**, and a careful balance of temperature is important to furnish the desired methyl ester (**3**) (Scheme 1). The same method was used to synthesize compound **6** from isofluprednisolone acetate in seven steps. The synthesis of 9-fluoro-17-dehydroprednisolone 16-methylcarboxylate (**7**) was performed in six steps employing the procedure described earlier.[17]

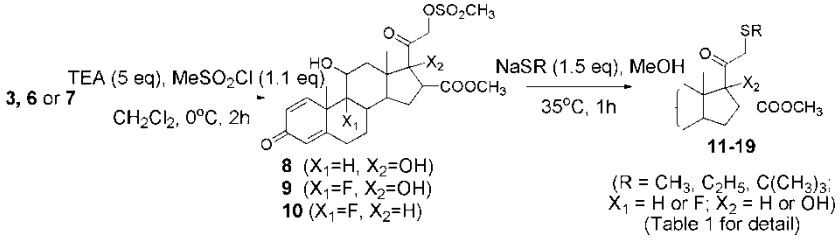


Scheme 1.

In an attempt to increase the potency of the methyl-16-carboxylates of prednisolone and analogs, we sought the substitution of 21-OH with thioalkyl ether to examine whether increased lipophilicity has any effect on localization of pharmacological activity and/or glucocorticoid receptor binding affinity. Compounds **3**, **6**, and **7** were used to synthesize the new 21-thioether derivatives according to the Scheme 2. In general, the mesylation of 21-OH was done using methyl sulfonylchloride and triethylamine as the base at 0°C for 2 h to furnish 70% isolated yields of compounds **8**, **9**, and **10**, respectively, after purification by column chromatography using ethylacetate–hexane (1:1).

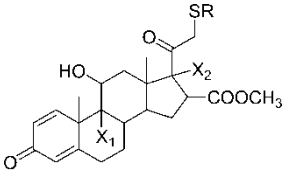
The substitution of a methyl sulfonate group with the desired thioalkyl group was critical in terms of reaction condition. At elevated temperature (70°C) using 5.0 or 2.0 equivalents of the Na-thioalkoxide for 2 h[18] in freshly distilled anhydrous methanol as solvent gave a very low yield of the product accompanied by several side products, which are supposed to be the hydrolytic products at the 16-ester linkage (as shown by highly polar products at the base of the thin-layer chromatography, TLC, plates) and some disubstituted products resulting from the formation of 21-thioalkylether with or without the 16-thioesters. A mild reaction condition, using 1.5 equivalents of the Na-thioalkoxide and 1.0 equivalent of the mesylate in anhydrous methanol at 35°C for 1 h loading the reaction mixture onto a silica-gel column, and eluting with 1:1 ethylacteate/hexane, furnished 60–75% of the pure thioethers as colorless crystals (Table 1) (**11**–**19**).[19] These conditions could lead to ~90% conversion to the desired product based on the TLC of the reaction mixture before column chromatography. The compounds were characterized by ^{1}H NMR and ^{13}C NMR, and the purity was checked by HPLC and C, H analyses. The HPLC system consisted of a Varian auto-sampler (9100), pump (9012), and UV detector (9050) set at a wavelength of 254 nm. The column was a Discovery-C18 (5 mm, 4.0 mm × 15 cm I.D.), coupled with a Pelliguard-C18 guard column (4.6 mm × 5 cm I.D.). The initial solvent conditions were set at 60% of water, 40% of methanol. After sample injection, there was a 10 min linear gradient change to 10% of water, 90% of methanol. Flow rate was maintained at 1.0 ml/min.

In conclusion, a new convenient process for the synthesis of 21-thioalkylether derivatives has been described. This provides a very facile method



Scheme 2.

Table 1. Structures of the 21-thioalkylether derivatives of methyl 16-prednisolone carboxylates

	Compound	X_1	X_2	R	Yield (%)	Mp (°C)
	**11**	H	OH	CH_3	60	169–71
	12	H	OH	C_2H_5	72	128–30
	13	H	OH	$C(CH_3)_3$	66	142–4
	14	F	H	CH_3	60	138–40
	15	F	H	C_2H_5	73	108–10
	16	F	H	$C(CH_3)_3$	65	118–20
	17	F	OH	CH_3	65	178–80
	18	F	OH	C_2H_5	61	126–8
	19	F	OH	$C(CH_3)_3$	75	149–50

to synthesize numerous thioalkylether derivatives of various novel steroidal antedrugs in search of more potent yet safer anti-inflammatory and anti-asthmatic therapeutic agents.

EXPERIMENTAL

The chemicals and reagents were of high quality, purchased from Acros Organics and/or Aldrich. The procedures for each compound series are explained next.

Methanolysis of Nitrile

Compound **2** (1 g, 2.34 mmol) in 50 ml of dry anhydrous methanol was dissolved under stirring, cooled to −25°C, and then bubbled with HCl gas until completely saturated (as indicated by cloudy smoke or volume doubles). The temperature was adjusted to −20−10°C overnight. The mixture was allowed to warm up to 0°C over 5 h, poured into 250 ml of water, and slowly neutralized with sodium carbonate powder (∼40 g) to pH 3–4. The methyl ester product was then extracted into ethyl acetate. The product was purified by column chromatography over silica gel using benzene–acetone (4:1) as the mobile phase to yield 420 mg of the pure ester (**3**) (43%).

21-Mesylation

The 21-OH derivative of isofluoprednisolone (**3**) (1.5 g, 3.58 mmol) was dissolved in 30 ml of dry CH_2Cl_2 and 3.0 ml (21 mmol) of triethylamine. The mixture was stirred on cooling to −5°C under N_2, and CH_3SO_2Cl

(0.65 g, 5.67 mmol) was added to it slowly over 10 min. The mixture stirred for 1 h, more CH_2Cl_2 (200 ml) and was added. The mixture was taken to a separating funnel, washed consecutively with water, 2N HCl, saturated $NaHCO_3$, and brine; dried with Na_2SO_4; and evaporated to yield the crude product. The product was purified by column chromatography over silica gel using ethyl acetate–hexane (6:4) to yield 1.2 g of compound **8** (68%).

21-Thioalkylation

Compound **8** (150 mg, 0.30 mmol) and 30 mg (0.44 mmol) of Na-ethanethioate in 1 ml of methanol was warmed to 35°C and stirred for 1 h. The mixture was diluted with ethyl acetate, loaded onto the silica-gel column, and eluted with ethyl acetate–hexane (6:4) to yield 100 mg (72%) of the pure thialkylated product (**12**).

Chemical Data

Compound **11**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 1.0 (s, 3H, 10-CH_3), 1.46 (s, 3H, 13-CH_3), 2.14 (s, 3H, S-CH_3), 3.70 (s 3H, $COOCH_3$), 3.96–4.01 (bm, 1H, 11-CH), 4.49–4.68 (m, 2H, 21-CH_2), 6.02 (d, 1H, 4-CH), 6.27 (dd, 1H, 2-CH), 7.25 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 204, 187, 176, 170, 156, 128, 123, 70, 64, 56, 55, 52, 48, 45, 44(2), 42, 34, 32, 31, 29, 21, 17, 16; anal. ($C_{24}H_{32}O_6S$: C, calc. 64.26, found 64.04; H, calc. 7.19, found 7.28).

Compound **12**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 1.0 (s, 3H, 10-CH_3), 1.46 (s, 3H, 13-CH_3), 2.60 (q, 2H, S-CH_2), 1.27 (t, 3H, S-CH_2CH_3), 3.69 (s 3H, $COOCH_3$), 3.94–4.00 (bm, 1H, 11-CH), 4.49–4.70 (m, 2H, 21-CH_2), 6.02 (d, 1H, 4-CH), 6.27 (dd, 1H, 2-CH), 7.26 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 205, 187, 176, 170, 146, 128, 123, 91, 70, 55, 52, 51, 48, 46, 44, 40, 37, 34, 32, 31, 28, 26, 21, 17, 14; anal. ($C_{25}H_{34}O_6S$: C, calc. 64.91, found 64.78; H, calc. 7.48, found 7.76).

Compound **13**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 1.0 (s, 3H, 10-CH_3), 1.45 (s, 3H, 13-CH_3), 1.34 (s, 9H, S-$C(CH_3)_3$), 3.69 (s 3H, $COOCH_3$), 3.93–3.98 (bm, 1H, 11-CH), 4.45–4.55 (m, 2H, 21-CH_2), 6.02 (d, 1H, 4-CH), 6.27 (dd, 1H, 2-CH), 7.27 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 205, 184, 173, 168, 154, 126, 120, 88, 68, 53, 50, 49, 46, 43, 42, 40, 38, 34, 31, 30, 29, 28(3), 26, 18, 15; anal. ($C_{27}H_{38}O_6S$: C, calc. 66.09, found 65.83; H, calc. 7.81, found 7.87).

Compound **14**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 0.97 (s, 3H, 10-CH_3), 1.46 (s, 3H, 13-CH_3), 2.06 (s, 3H, S-CH_3), 3.64 (s 3H, $COOCH_3$), 4.09–4.14 (bm, 1H, 11-CH), 4.43–4.45 (m, 2H, 21-CH_2), 6.02 (d, 1H, 4-CH), 6.27 (dd, 1H, 2-CH), 7.27 (d, 1H, 1-CH); anal. ($C_{24}H_{32}FO_5S$: C, calc. 63.98, found 64.22; H, calc. 6.93, found 7.04.

Compound **15**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 0.97 (s, 3H, 10-CH_3), 1.46 (s, 3H, 13-CH_3), 2.51 (q, 2H, S-CH_2), 1.24 (t, 3H, S-CH_2CH_3), 3.64 (s 3H, $COOCH_3$), 3.62–3.70 (bm, 1H, 11-CH), 4.43–4.47 (m, 2H, 21-CH_2), 6.02 (d, 1H, 4-CH), 6.27 (dd, 1H, 2-CH), 7.27 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 204, 186, 176, 170, 156, 128, 123, 70, 64, 56, 55, 52, 48, 45, 44, 41(2), 34, 32, 31, 29, 26, 21, 17, 14; anal. ($C_{25}H_{33}FO_5S$: C, calc. 64.63, found 64.89; H, calc. 7.16, found 7.15).

Compound **16**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 1.0 [s, 3H, 10-CH_3], 1.45 (s, 3H, 13-CH_3), 1.34 (s, 9H, S-$C(CH_3)_3$), 3.69 (s 3H, $COOCH_3$), 3.93–3.98 (bm, 1H, 11-CH), 4.45–4.55 (m, 2H, 21-CH_2), 6.02 (d, 1H, 4-CH), 6.27 (dd, 1H, 2-CH), 7.27 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 205, 187, 176, 170, 156, 128, 122, 70, 65, 56, 55, 52, 48, 45, 44, 43, 42, 40, 34, 32, 31, 30(3), 29, 21, 17; anal. ($C_{27}H_{37}FO_5S$: C, calc. 65.83, found 65.81; H, calc. 7.57, found 7.77).

Compound **17**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 1.00 (s, 3H, 10-CH_3), 1.55 (s, 3H, 13-CH_3), 2.14 (s, 3H, S-CH_3), 3.70 (s 3H, $COOCH_3$), 4.09–4.14 (bm, 1H, 11-CH), 4.35–4.68 (m, 2H, 21-CH_2), 6.12 (d, 1H, 4-CH), 6.33 (dd, 1H, 2-CH), 7.20 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 205, 186, 175, 166, 152, 130, 126, 91, 73, 72, 52, 48, 47, 44, 39, 37, 34, 31, 30, 27, 23, 17, 17, 14; anal. ($C_{24}H_{31}FO_6S$: C, calc. 61.78, found 61.87; H, calc. 6.70, found 6.94).

Compound **19**: ^{1}H NMR (δ_{ppm}, $CDCl_3$): 1.0 (s, 3H, 10-CH_3), 1.55 (s, 3H, 13-CH_3), 1.33 (s, 9H, S-$C(CH_3)_3$), 3.69 (s 3H, $COOCH_3$), 3.09–3.14 (bm, 1H, 11-CH), 4.38–4.87 (m, 2H, 21-CH_2), 6.12 (d, 1H, 4-CH), 6.33 (dd, 1H, 2-CH), 7.23 (d, 1H, 1-CH); ^{13}C NMR (δ_{ppm}, $CDCl_3$): 207, 187, 176, 167, 152, 130, 126, 91, 73, 72, 53, 48, 46, 44, 43, 37, 36, 34, 31(4), 30, 27, 23, 17, 14;anal. ($C_{27}H_{37}FO_6S$: C, calc. 63.76, found 63.81; H, calc. 7.33, found 7.37).

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