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A CONVENIENT SYNTHESIS OF 2-BUTYL-4(5)-CHLORO-1H-IMIDAZOLE-5(4)-CARBOXALDEHYDE

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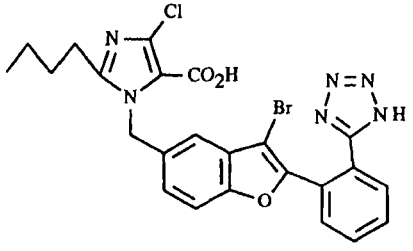
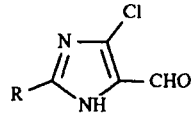
Abstract: A Convenient Synthesis of 2-Butyl-4(5)-chloro-1H-imidazole-5(4)-carboxaldehyde, starting from 2-butyl imidazole, has been developed.

As reported elsewhere[1], work in these laboratories has led to the identification of GR117289, a potent antagonist of the vasoconstrictor hormone angiotensin II.

The imidazole portion of GR117289 derives from the imidazole carboxaldehyde (1a). Thus, in order to prepare the large quantities of GR117289 required for clinical evaluation, a convenient process for the preparation of this aldehyde was required.

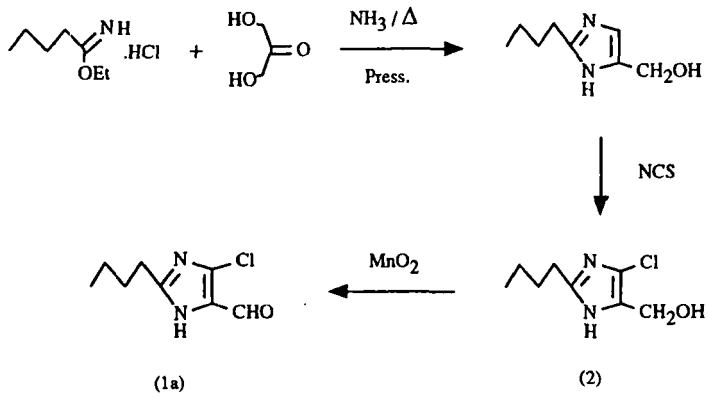


GR 117289



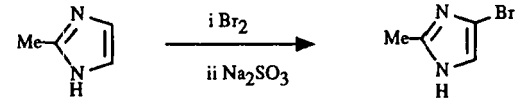
(1) a R = n-Bu
b R = Et

Scheme 1

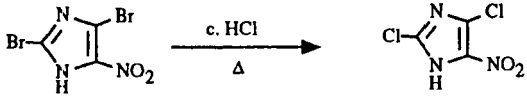


The aldehyde (1a) and the corresponding hydroxymethyl imidazole (2) have both been used in the syntheses of a number of other angiotensin II antagonists[2,3]. Hitherto we have prepared these imidazoles from ethyl valerimidate as depicted in scheme 1[2,4]. The first step in this sequence, the reaction of ethyl valerimidate, dihydroxyacetone and ammonia, requires elevated temperature and pressure and thus autoclave procedures. We found use of an autoclave unsuitable for large scale preparations (>100g) and hence sought an alternative convenient synthesis of aldehydes of type (1).

As they are readily available[5] 2-alkyl imidazoles represented attractive starting materials for the synthesis of aldehydes of type (1).

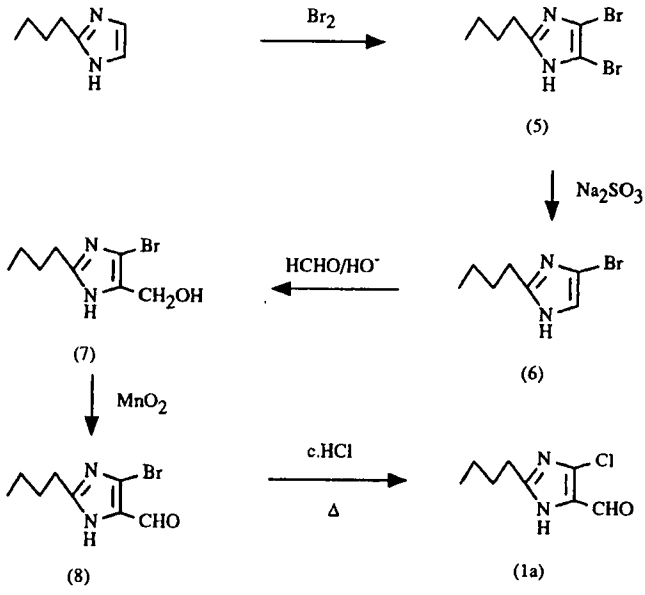


Equation 1



Equation 2

Scheme 2



Introduction of a single 4(5)-chlorine atom into imidazoles is problematical, however the synthesis of 2-alkyl-4(5)-bromo imidazoles is well known[6] (eqn. 1). Furthermore an imidazole 4(5)-bromine atom can be exchanged for chlorine in the presence of a powerful electron withdrawing substituent[7] (eqn. 2).

These two pieces of information lead us to develop the procedure depicted in scheme 2, whereby the aldehyde (1a) can be prepared from 2-butylimidazole in 5 steps in 24% overall yield. Treatment of 2-butylimidazole with bromine gives the dibromide (5) which, on reduction with sodium sulphite, affords the monobromo imidazole (6). Bromoimidazole (6) is successively hydroxymethylated and oxidized to give the bromoaldehyde (8) which on prolonged heating in concentrated hydrochloric acid affords 2-butyl-4(5)-chloroimidazole-5(4)-carboxaldehyde (1a).

The analogous 2-ethyl imidazolecarboxaldehyde (1b) can be similarly prepared in 30% overall yield from 2-ethylimidazole. Furthermore, in the case of 2-ethylimidazole, the bromination and debromination steps can be combined to

afford 4(5)-bromo-2-ethylimidazole in 35% yield in one pot. However these two steps cannot be combined for 2-butylimidazole as extensive contamination with valeric acid derivatives results.

Experimental Section

4,5-Dibromo-2-butyl-1H-imidazole (5)

Bromine (5.12ml,100mmol) was added dropwise to an ice-cooled, stirred, solution of 2-butylimidazole[5] (5.00g,40mmol) in chloroform (100ml). After ca. 1h. a copious amount of red precipitate had been formed. The mixture was stirred overnight at room temperature before the addition of 2N aqueous sodium hydroxide causing dissolution of the solid. The aqueous phase was separated and acidified to ca. pH 2 liberating some solid. 8% w/v Aqueous sodium hydrogen carbonate was added to ca. pH 8 and the mixture cooled in an ice bath. After 30 min. the precipitate liberated was collected by filtration, washed with distilled water and dried in vacuo to give the title compound as a grey powder (6.30g,56%). ^{1}H NMR (250MHz,DMSO-d_6):δ 0.89(t,3H)CH_3, 1.30(sex,2H) CH_3CH_2, 1.59(quin,2H)$CH_3CH_2CH_2$, 2.55(t,2H)$CH_3CH_2CH_2CH_2$. MS MH^+ = 280.9

4(5)-Bromo-2-butyl-1H-imidazole (6)

A suspension of the dibromide (5) (5.40g,19mmol) and sodium sulphite (25.0g 200mmol) in water (200ml) and ethanol (100ml) was warmed, to give a grey solution, and heated at reflux for 18h. The mixture was cooled and concentrated to ca. 200ml causing the separation of some oil/solid. The mixture was extracted with ethyl acetate (3x100ml) and the combined extracts boiled over charcoal (1g) for 10 min., filtered, dried, and concentrated in vacuo to give the title compound as a yellow waxy solid (3.25g,85%). ^{1}H NMR (250MHz,$CDCl_3$):δ 0.89(t,3H) CH_3, 1.33(sex,2H)CH_3CH_2, 1.68(quin,2H)$CH_3CH_2CH_2$, 2.74(t,2H) $CH_3CH_2CH_2CH_2$, 6.93(s,1H)4(5)-H. MS MH^+ = 203

4(5)-Bromo-2-butyl-1H-imidazole-5(4)-methanol (7)

36% w/v Aqueous formaldehyde (11.1ml,13.7mmol) was added to a stirred solution of 4(5)-bromo-2-butylimidazole (6) (1.90g,9.41mmol) and 2N aqueous

sodium hydroxide (3.45ml,6.9mmol) in ethanol (50ml) and water (25ml). After stirring overnight at room temperature 2N hydrochloric acid (3.4ml) was added and the solution concentrated in vacuo. Water (100ml) was added and the mixture extracted with ethyl acetate (4 x 100ml). The combined extracts were washed with satd brine (100ml), dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid. Trituration with (1:1) ether/hexane gave the title compound as a light yellow powder (1.78g,78%). ^{1}H NMR (250MHz,$CDCl_3$):δ 0.93(t,3H)$C\underline{H}_3$, 1.36(sex,2H)$CH_3C\underline{H}_2$, 1.68(quin,2H)$CH_3CH_2C\underline{H}_2$, 2.65(t,2H) $CH_3CH_2CH_2C\underline{H}_2$, 4.52(s,2H)$C\underline{H}_2OH$,. Anal. Calcd. for $C_8H_{13}BrN_2O$: C,41.22; H,5.62; N,12.02. Found: C,41.55; H,5.66; N,11.90%.

4(5)-Bromo-2-butyl-1H-imidazole-5(4)-carboxaldehyde (8)

A suspension of the imidazolemethanol (**7**) (1.50g,6.47mmol) and manganese dioxide (4.77g,55mmol) in 1:1 dichloromethane/1,4-dioxan (50ml) was heated at reflux overnight. The mixture was filtered through hyflo and the filtrate concentrated in vacuo to afford a bright yellow solid. Trituration with hexane (15ml) gave the aldehyde as a light yellow powder (1.20g,81%). ^{1}H NMR (250MHz,$CDCl_3$):δ 0.94(t,3H)$C\underline{H}_3$, 1.40(sex,2H)$CH_3C\underline{H}_2$, 1.77(quin,2H) $CH_3CH_2C\underline{H}_2$, 2.83(t,2H)$CH_3CH_2CH_2C\underline{H}_2$, 9.55(s,1H)$C\underline{H}O$.Anal. Calcd. for $C_8H_{11}BrN_2O$: C,41.58; H,4.80; N,12.12. Found: C,41.17; H,4.79; N,11.91%.

2-Butyl-4(5)-chloro-1H-imidazole-5(4)-carboxaldehyde (1a)

A solution of the bromoaldehyde (**8**) (1.00g,43mmol) in conc. hydrochloric acid (25ml) was heated at reflux for 24h. The solution was cooled to room temperature,cautiously added to 8% w/v aqueous sodium hydrogen carbonate (150ml), and extracted with ethyl acetate (4x100ml). The combined extracts were boiled over charcoal (ca. 1g) for 10 min., filtered, dried ($MgSO_4$), and concentrated in vacuo to give a light yellow solid. Trituration with hexane (15ml) gave the title compound as a light yellow powder (0.70g,87%). ^{1}H NMR (250MHz,$CDCl_3$):δ 0.95(t,3H)$C\underline{H}_3$, 1.39(sex,2H)$CH_3C\underline{H}_2$, 1.77(quin,2H) $CH_3CH_2C\underline{H}_2$, 2.83(t,2H)$CH_3CH_2CH_2C\underline{H}_2$, 9.60(s,1H)$C\underline{H}O$. MS MH^+ = 187. Anal. Calcd. for $C_8H_{11}ClN_2O$: C,51.48; H,5.94; N,15.01. Found: C,51.38; H,6.03; N,14.78%.

4(5)-Bromo-2-ethyl-1H-imidazole

Bromine (10.24ml,200mmol) was added dropwise to a stirred, ice-cooled solution of 2-ethylimidazole[8] (8.54g,89mmol) in ethanol (150ml). After stirring at room temperature for ca. 3h. 5N aqueous sodium hydroxide (45ml) was added to give a solution of ca. pH. 6.5. A solution of sodium sulphite (120g,0.95ml) in water (1000ml) was added, followed by further ethanol (100ml) and water (100ml) to give, on warming to ca. 40°C, a yellow solution which was heated at reflux for 18h. The solution was then concentrated to ca. half its original volume and extracted with chloroform (3x250ml). The combined extracts were concentrated in vacuo to give the title compound as a white solid (6.1g,38%) ^{1}H NMR (250MHz,$CDCl_3$): δ 1.19(t,3H)C$\underline{H}_3$, 2.78(q,2H)C$\underline{H}_2$, 6.95(s,1H)4(5)-$\underline{H}$. Anal. Calcd. for $C_5H_7BrN_2$: C,34.31; H,4.03; N,16.01. Found: C,34.46; H,4.19; N,15.85%.

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