Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A convenient One-Pot Synthesis of an Unsymmetrical Propane-1,3-diamine BRL 61010A

Robin P Attrill [a] , Thomas W Ramsay [a] , Graham R Slater [a] & Paul Smith [a]
[a] Synthetic Chemistry SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue , Harlow, Essex, CM19 5AW
Published online: 17 Sep 2007.

To cite this article: Robin P Attrill , Thomas W Ramsay , Graham R Slater & Paul Smith (1999) A convenient One-Pot Synthesis of an Unsymmetrical Propane-1,3-diamine BRL 61010A, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:5, 827-833, DOI: 10.1080/00397919908086040

To link to this article: http://dx.doi.org/10.1080/00397919908086040

SYNTHETIC COMMUNICATIONS, 29(5), 827-833 (1999)

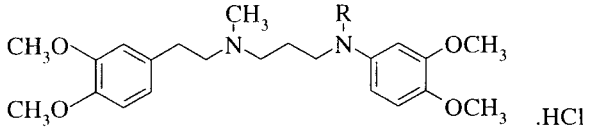
A CONVENIENT ONE-POT SYNTHESIS OF AN UNSYMMETRICAL PROPANE-1,3-DIAMINE BRL 61010A.

Robin P Attrill, Thomas W Ramsay*, Graham R Slater and Paul Smith
Synthetic Chemistry

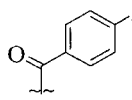
SmithKline Beecham Pharmaceuticals,
New Frontiers Science Park, Third Avenue, Harlow, Essex. CM19 5AW

Abstract: The one-pot condensation of N-methylhomoveratrylamine with acrolein followed by *in situ* reductive amination with 3,4-dimethoxyaniline to give an unsymmetrical propane 1,3-diamine in excellent yield is described.

The unsymmetrical propane 1,3-diamine, BRL 61010A (1a), is a key precursor in the synthesis of BRL 32872A (1b), a compound recently under development for the treatment of cardiac arrhythmia[1].



(1a) R= H; BRL 61010A

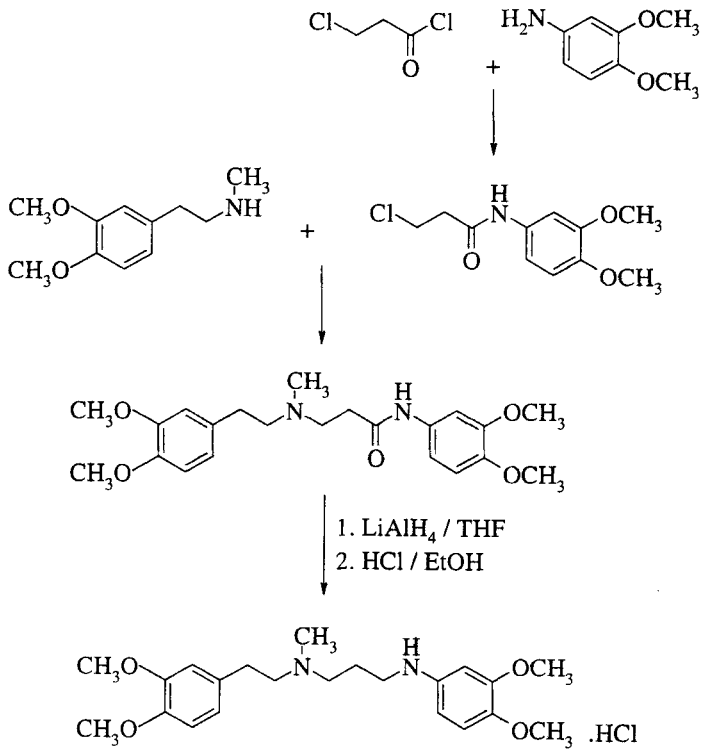
(1b) R=  ; BRL 32872A

* To whom correspondence should be addressed

BRL-61010A was initially synthesised by reacting 3,4-dimethoxyaniline with 3-chloropropionyl chloride and coupling the resulting chloropropylamide with N-methyl-3,4-dimethoxyphenethylamine under basic conditions. Reduction of the coupled product with lithium aluminium hydride followed by treatment with hydrogen chloride gas in ethanol gave BRL-61010A (see Scheme 1).

Due to the length of the synthesis and its utilisation of lithium aluminium hydride methodology it was decided to investigate alternative routes to this key intermediate.

Scheme I

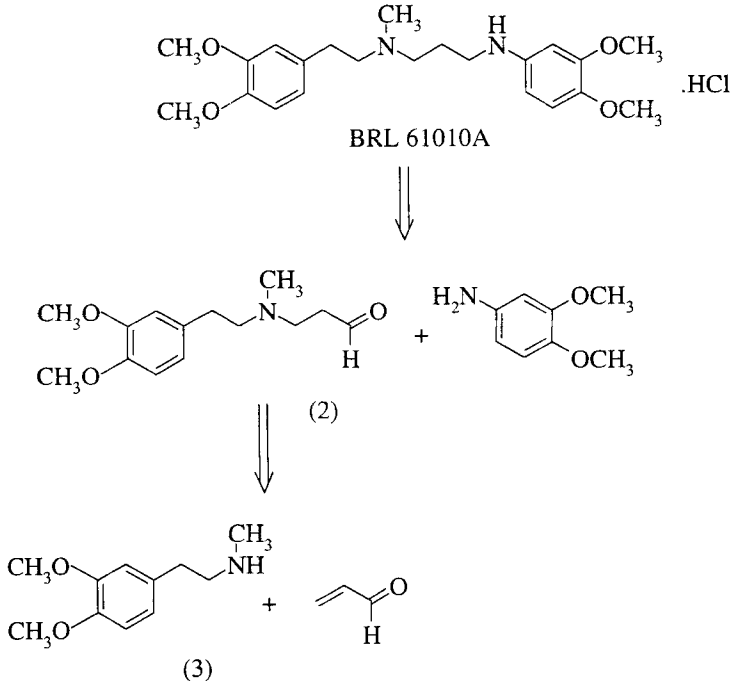


BRL 61010A (1a)

Retrosynthetic analysis suggested that BRL 61010A might be accessible via reductive alkylation of 3,4-dimethoxyaniline with a suitably substituted β-aminoaldehyde (2), derived in turn from the conjugate addition of N-methylhomoveratrylamine (3) to acrolein (Scheme II).

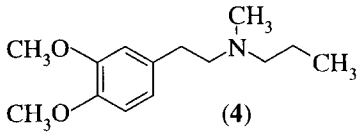
A survey of the literature revealed the findings of Marko and Chesney[2,3] who reported the clean condensation of acrolein with a range of secondary amines to afford the unstable β-aminoaldehydes in excellent *in situ* yield. These were not isolated but proved to be versatile intermediates with reduction, Wittig homologation and Grignard addition being reported to proceed smoothly in good to excellent yields.

Scheme II

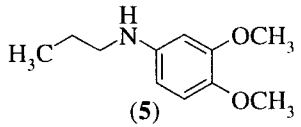


Whilst Marko and Chesney did not report reductive amination of the intermediate aminoaldehydes an earlier report by Finch *et al*[4] reported the reaction of acrolein with an excess of a range of amines to afford the intermediate enamines, without isolation of the intermediate β-aminoaldehydes, which could subsequently be reduced to give symmetrical 1,3-diamines in reasonable yields.

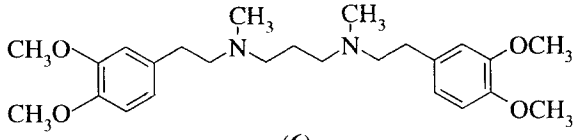
The condensation of N-methylhomoveratrylamine (3) with acrolein proceeds smoothly in tetrahydrofuran solution at -5°C to 0°C in the presence of a catalytic amount (1 mole %) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Optimum conversion is achieved after 30 minutes at which point proton nmr analysis indicates an *in situ* yield of ~70% of the desired intermediate aldehyde (2). [Chlorinated solvents are equally suitable for the β-aminoaldehyde formation but not for the subsequent reductive alkylation]. The solution of β-aminoaldehyde is then treated with 3,4-dimethoxyaniline (1equiv) and hydrogenated over 5% or 10% Pd/C at 50 psi and ambient temperature to afford the desired diamine in 60-65% in-pot yield. The product is conveniently isolated by treatment of the reaction mixture, after removal of the catalyst by filtration, with 0.7 molar equivalents of ethanolic hydrogen chloride to preferentially precipitate the product as its monohydrochloride salt in ca. 60% yield. The other principal reaction products which derive from the N-propylation of N-methylhomoveratrylamine (4), the N-propylation of 3,4-dimethoxyaniline (5) and the two to one adduct (6), arising from reaction of the intermediate aldehyde with homoveratrylamine, conveniently remain in solution.



(4)



(5)



(6)

In conclusion BRL 61010A can be prepared in a convenient one-pot synthesis in 60% overall yield starting from N-methylhomoveratrylamine. The process is suitable for large scale synthesis and has been used to successfully prepare multi 100 kg quantities of the title compound (1a).

This methodology is being applied to other related systems to determine the scope of the process. These results will be reported at a later date.

Experimental

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-N'-(3,4-dimethoxyphenyl)-1,3-propanediamine hydrochloride (BRL 61010A)

Tetrahydrofuran (2.5L) was cooled to ca. 0° C under a nitrogen atmosphere and 90% acrolein[5] (152ml) was added. A solution of 3,4-dimethoxy-N-methylphenethylamine (400g) and DBU (3.2ml) in tetrahydrofuran (1L) was then added slowly with stirring and cooling over 23 mins maintaining the temperature below 5°C. A further amount of tetrahydrofuran (250ml) was used to wash in any

remaining solution in the addition funnel. The reaction mixture was stirred for 30mins at ca. 0° C then added to 3,4-dimethoxyaniline (315g) and 10% palladium on carbon (40g). The mixture was then hydrogenated at ambient temperature, 40-50 psi. pressure, for ca 20 hours. The catalyst was removed by filtration and the filtrate treated with 4.74 molar hydrogen chloride in ethanol (303ml). The solution was stirred for 1 hour then cooled at ca. 0° C for ca. 1.5 hours. The resulting suspension was filtered, washed with tetrahydrofuran and air dried to give N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-N'-(3,4-dimethoxyphenyl)-1,3-propanediamine hydrochloride as an off-white solid, 557g. A sample of the crude product (180g) was recrystallised from ethanol (1050ml) to give the desired product (170g, 60% overall yield) as an off white powder,.m.p. 153-155° C.

^{1}H NMR (DMSO, 400MHz): δ = 1.93-1.97 (m, 2H); 2.78 (s, 3H); 2.93-2.97 (m, 2H); 3.06 (t, J = 6.4 Hz, 2H); 3.19-3.26 (m, 4H); 3.62 (s, 3H); 3.70 (s, 3H); 3.72 (s, 3H); 3.75 (s, 3H); 6.07 (dd, J = 2.4, 8.4 Hz, 1H); 6.28 (d, J = 2.4 Hz, 1H); 6.72 (d, J = 8.4 Hz, 1H); 6.77 (dd, J = 1.6, 8.4 Hz, 1H); 6.88-6.90 (m, 2H)

^{13}C NMR (DMSO, 400MHz): δ = 23.0, 28.9, 39.2, 40.8, 53.0, 55.2, 55.4, 55.5, 55.8, 56.6, 98.7, 102.7, 111.9, 112.5, 114.5, 120.6, 129.3, 140.3, 143.7, 147.6, 148.7, 149.9

Anal. Calcd for $C_{22}H_{33}N_2O_4Cl$ (425.0): C 62.18, H 7.83, N 6.59, Cl 8.34. Found: C 62.14, H 8.15, N 6.62, Cl 8.37

References

[1] Bril, A., Gout, B., Bonhomme, M., Landias, L., Faivre, J-F., Linee, P., Poyser, R.H. and Ruffolo, R.R., *J. Pharmacol. Exp. Ther.*, **1996** *276*, 637.
[2] Chesney, A., Marko, I.E., *Synth. Comm.*, **1990**, *20*, 3167.
[3] Marko, I.E., Chesney, A., *Synthesis*, **1992**, 275.
[4] Finch, H., Peterson, E.A., Ballard, S.A., *J. Am. Chem..Soc.*, **1952**, *74*, 2016.
[5] Acrolein was obtained from Aldrich Chemical Company and was used without purification.

(Received in the USA 06 September 1998)