Pergamon

Tetrahedron Letters 39 (1998) 1059–1062

TETRAHEDRON LETTERS

Solid Phase Synthesis of Tropane Derivatives

Daniel Jönsson, Håkan Molin† and Anders Undén*

Department of Neurochemistry & Neurotoxicology, Stockholm University, S-10691 Stockholm, Sweden

† Astra Pain Control AB, Preclinical Research, S-15185 Södertälje, Sweden

Received 23 September 1997; revised 21 November 1997; accepted 28 November 1997

Abstract: The azabicyclic moiety present in tropane alkaloids can be conveniently synthesized in high yield on solid phase using a modification of Robinson's tropinone synthesis.[1] The ε-amino group on a lysine residue attached to Tentagel® resin was treated with 10 eq excess of succinic dialdehyde and 1 eq of acetonedicarboxylic acid for 12 hours with a citric acid buffer of pH 4 as solvent, resulting in the formation of an 8-azabicyclo[3.2.1]octane structure on the ε-amino group of lysine in 93% yield.

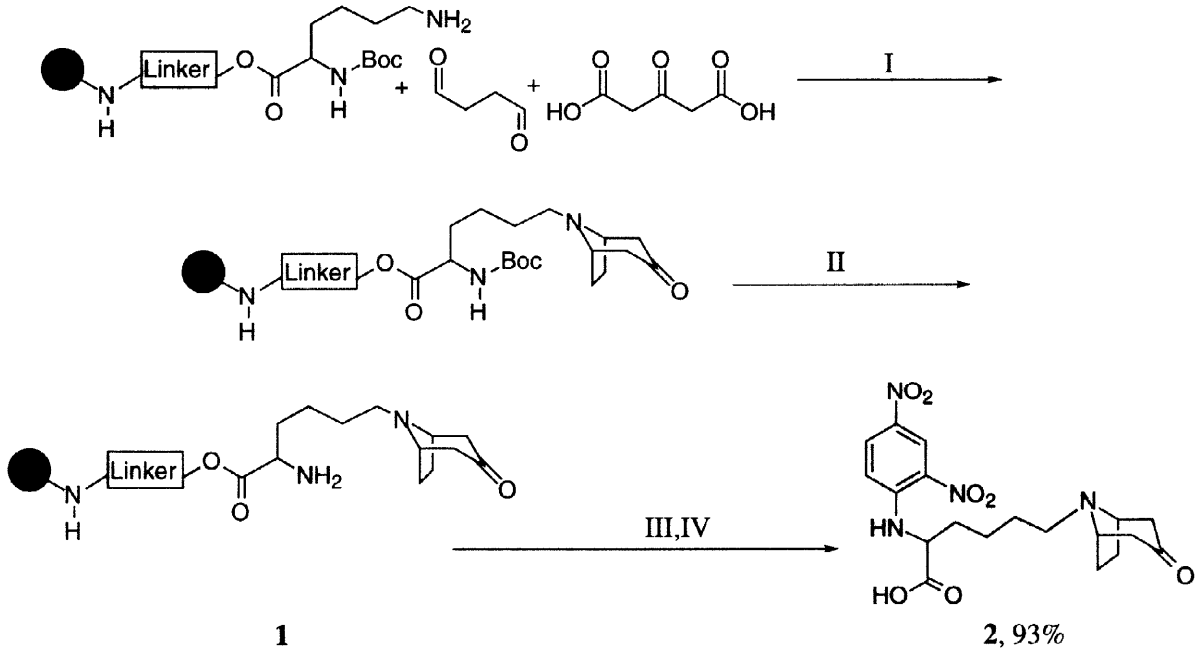
Tropane alkaloids such as cocaine and atropine are known to bind to structurally different proteins as monoamine transport proteins[2] and muscarinic acetylcholine receptors with high affinity.[3] The rigid 8-azabicyclo[3.2.1]octane structure of tropane alkaloids therefore represent an interesting rigid, so called, scaffold for the development of new pharmacologically active compounds by combinatorial organic chemistry. For this reason it could be of importance if methods were available that would permit the rapid synthesis of a large number of tropane derivatives on a small scale, compounds that could be used for testing in pharmacological assay systems. Tropane derivatives have been synthesized in solution by several routes,[3] e.g. oxalyl addition to pyrroles, amine addition to substituted dienones, nitrone induced cycloaddition, bisconjugate addition of a primary amine to a cycloheptadienone and nitrile oxide cycloaddition. The simplest and most commonly used route to tropane derivatives however is the classical tropinone synthesis reported by Robinson where a primary amine, acetonedicarboxylic acid and succinicdialdehyde are condensed in aqueous solution. In a recent studie a tropane derivative was attached to solid support with subsequent derivatisation.[4] In this communication we report a method for the solid phase synthesis of tropane derivatives using a modification of the Robinson tropinone synthesis starting from primary aliphatic amino groups attached to a solid support.

An application of this synthetic route, where the reaction is carried out in aqueous solution, excludes the use of conventional crosslinked polystyrene as a solid support since most protic solvents and ions penetrate very poorly into the resin beads. In this report the tropane derivatives were therefore synthesized on Tentagel® amino resin,[5] a crosslinked polystyrene derivatized by polyethylene glycol that allows the penetration of both aprotic and protic solvents into the matrix.

The amino groups on the Tentagel® amino resin were acylated with p-(hydroxymethyl)-phenoxyacetic acid linker and Boc-Lys(Fmoc)OH was coupled with DCC/DMAP. Carboxylic acids attached to this linker have moderate stability to trifluoroacetic acid (TFA) and permits both cleavage of the Boc protection group

0040-4039/98/$19.00
PII: S0040-4039(97)10727-4

with 15 minutes treatment with TFA/CH_2Cl_2 (1:1) and cleavage of the product from the resin with neat TFA for 2 hours with marginal reduction in yield.[6] The Fmoc group on the ε-amino group of lysine was cleaved by 20% piperidine in DMF. After swelling of the resin in a citric acid buffer[7] of pH 4.4, 10 eq. succinicdialdehyde[8] and 1 eq. 1,3-acetonedicarboxylic acid were added, resulting in a modest gas evolution within 10 min (scheme 1). The reaction was monitored by removing samples of the resin and measuring the disappearance of amino groups by the ninhydrin test.[9] The rate of the reaction appeared to be of second order with a rapid disappearance of the amino groups and after 12 hours ninhydrin tests were negative.



Scheme 1. Solid phase synthesis of 2-(2,4-dinitroanilino)-6-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl) hexanoic acid **2**. I) Citric acid buffer (pH 4), rt,12h; II) TFA:CH_2Cl_2 1:1, 20min; III)1-fluoro-2,4-dinitrobenzene, DMF, 1 eq DIPEA, 1h; IV) TFA:CH_2Cl_2 95:5, 2h.

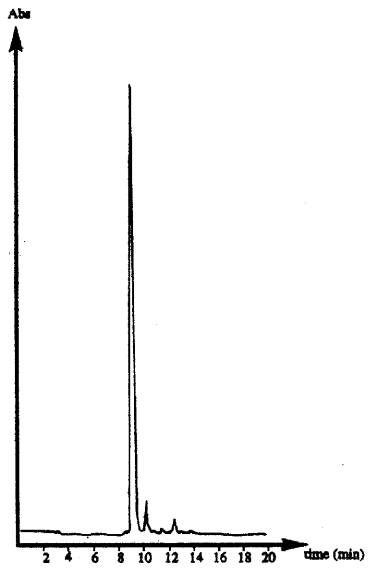


Figure 1. HPLC chromatogram at 420nm[10] of cleavage product after step IV.

If the product was cleaved from the resin after stage **II**, significant levels of unidentified side products, probably derived from resin or linker were visible with reversed phase HPLC at 215nm. Since desired product as well as possible side products in the condensation reaction are attached to a lysine, a more accurate estimation of the yield in the reaction **I** can be made by removing the Boc group of lysine with dilute TFA and arylate the N^{α}-amino groups with 2,4-dinitrofluorobenzene. By analyzing the relative amounts of products at 420 nm an accurate estimation of the yield in reaction **I** can be made.

The arylated products were cleaved from the resin with neat TFA and analysed with reversed phase HPLC. The elution profile revealed one major and two minor products accounting for app. 93.5, 3.5 and 2.9% of the absorption at 420nm (figure 1).

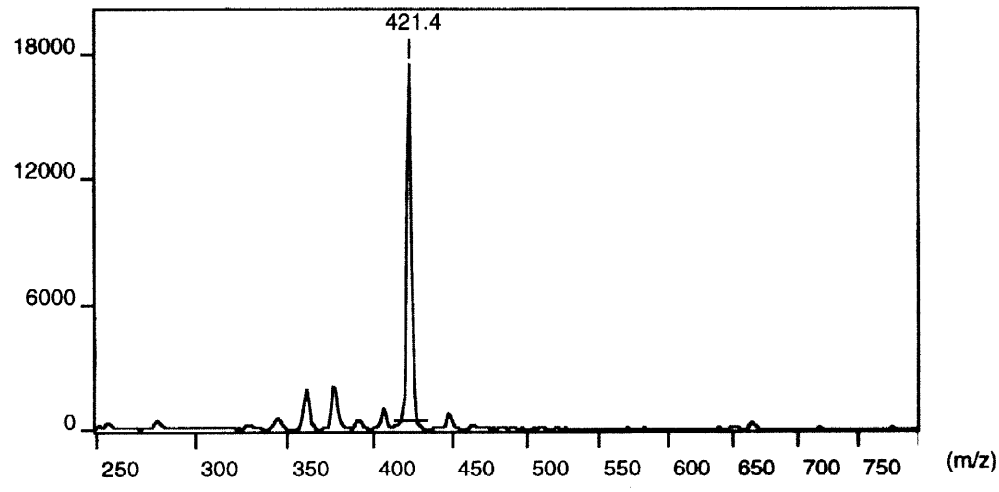


Figure 2. PDMS diagram of major product in figure 1. $C_{19}H_{24}N_4O_7$ (M+H)=421.4

Plasma desorbtion mass spectrometry (PDMS)[11] and NMR analysis[12] (^{1}H-NMR, ^{13}C-NMR, HMQC, DQFCOSY and APT) of the major product all confirmed the expected structure; 2-(2,4-dinitroanilino)-6-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)hexanoic acid **2**, but also indicated some contamination, possibly by polyethylene glycol-like structures. The slightly more hydrophobic by-product of 3.5% had a molecular weight of 478.60 u. We suggest that this product is 2-(2,4-dinitroanilino)-6-(2,5-di(2-oxopropyl)tetrahydro-1H-1-pyrrolyl)hexanoic acid (figure 3),[13] and that it was formed by the condensation of 1 eq. of amino groups with 1 eq. of succinicdialdehyde and 2 eq. of 1,3-acetonedicarboxylic acid. This assumption is corroborated by the fact that the relative amount of this side product was increased if the reaction was carried out with excess of acetonedicarboxylic acid.

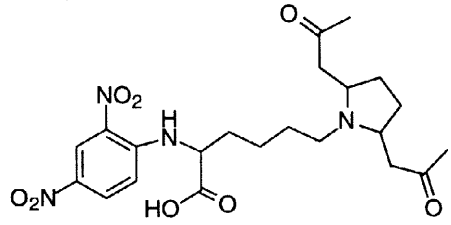


Figure 3. 2-(2,4-dinitroanilino)-6-(2,5-di(2-oxopropyl)tetrahydro-1H-1-pyrrolyl)hexanoic acid

The carbonyl group of **1** could be reduced by sodium borohydride in ethanol, but was accompanied by significant reduction of the ester bond linking to the resin. Instead, sodium cyanoborohydride in a pH 3 solution of ethanol and acetic acid was used at 50°C overnight. Preliminary results showed difficulties in the acetylation of the hydroxyl group thus generated, probably due to steric hindrance. The best result required a large excess of acetyl chloride/DMAP overnight in DMF:DCM 3:1.

In conclusion; we have demonstrated that the 8-azabicyclo[3.2.1]octane moiety present in tropane alkaloids can be rapidly and conveniently synthesized in high yields on solid phase in water, starting from primary amino groups linked to solid support. This method can therefore be used to give fast access to an array of tropane derivatives that can be assayed for pharmacological activity.

Acknowledgement.

This study was supported by a grant from the Swedish Research Council for Engineering Sciences to A. U.

References and Notes:

1. Robinson, R. *J. Chem. Soc.* **1917,** 111, 762-768.
2. Ritz, M. C. et al. *Science*, **1987**, 237, 1219-1223.
3. Manske, R. H. F, Ed. *The Alkaloids*, vol.16, 1977; Brossi, A, Ed. *The Alkaloids*, vol.33, 1988 and the references therein.
4. Koh, J.S., Ellman, J.A. *J. Org. Chem.* **1996**, 61, 4494-4495
5. Bayer, E. *Angew.Chem, Int. Ed. Engl.* **1991**, 30, 113-129.
6. Atherton, E. et al. *J. Chem. Soc., Perkin Trans. 1,* **1981**, 538-546.
7. The citric acid buffer was made by dissolving 2.94g of citric acid monohydrate and 3.23g of sodium citrate in 500ml of distilled water.
8. The succinicdialdehyde was prepared by hydrolysis of dimethoxytetrahydrofuran with 0.1 M H_2SO_4 at r.t. for 1 hour. The succinicdialdehyde was salted out with excess of NaCl, extracted with diethylether, dried and evaporated yielding a TLC-pure product that was immediately frozen to -90°C to prevent polymerisation.
9. Sarin, V. K. et al. *Anal.Bioch.* **1981**, 117, 147-157.
10. Purification and analyses of the products were performed on a Machery-Nagel 4x115mm C_{18} HPLC-column. The elution gradient was 15-65% of B in 15min. Solvent A was 0.1% TFA/H_2O and solvent B was 0.1% TFA /acetonitrile.
11. Molecular weight determination were made on an Applied Biosystems BIO-ION 20 plasma desorption mass spectrometer, using ^{252}Cf isotope as a source of fission fragments.
12. NMR spectra were obtained on a solution of 8mg of **2** in 0.6ml DMSO-d6 on a Varian UNITY Plus 400 MHz spectrometer. Analytical data for compound **2**: ^{1}H-NMR δ 1.35 m 2H, 1.7 m 2H, 1.8 d 2H, 1.95 d 2H, 2.2 d 2H, 2.4 t 2H, 2.9 d 2H, 3.1 t 2H, 4.1 s 2H, 4.7 q 1H, 7.2 d 1H, 8.3 d 1H, 8.85 s 1H, 8.95 d 1H. ^{13}C-NMR δ 21.71, 24.52, 25.39, 30.66, 43.76, 45.25, 55.01, 59.96, 115.81, 123.68, 130.27, 135.56, 147.09, 172.36, 203.70.
13. Schöpf, C., Lehmann, G. *Ann. Chem.* **1935**, 518, 17.